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## Intestinal carriage of carbapenem-resistant *Acinetobacter baumannii* among patients in the intensive care unit: risk factors and the impact on subsequent infection

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Complete List of Authors:	<p>Qiao, Fu; Sichuan University West China Hospital, Department of Infection Control</p> <p>Huang, Wenzhi; Sichuan University West China Hospital, Department of Infection Control</p> <p>Gao, Shan; Zhengzhou University First Affiliated Hospital, Department of Infection Control</p> <p>Cai, Lin; Sichuan University West China Hospital, Intensive Care Unit</p> <p>Zhu, Shichao; Sichuan University West China Hospital, Department of Infection Control</p> <p>Wei, Li; Sichuan University West China Hospital, Department of Infection Control</p> <p>Kang, Yan</p> <p>Tao, Chuanmin; Sichuan University West China Hospital, Department of Laboratory Medicine</p> <p>Zong, Zhiyong; Sichuan University West China Hospital, Department of Infection Control; Sichuan University West China Hospital, Center of Infectious Disease</p>
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4 1 **Intestinal carriage of carbapenem-resistant *Acinetobacter baumannii***  
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7 2 **among patients in the intensive care unit: risk factors and the**  
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9 3 **impact on subsequent infection**  
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12 4 Fu Qiao<sup>1</sup>, Wenzhi Huang<sup>1</sup>, Shan Gao<sup>2</sup>, Lin Cai<sup>3</sup>, Shichao Zhu<sup>1</sup>, Li Wei<sup>1</sup>, Yan Kang<sup>3</sup>,  
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14  
15 5 Chuanmin Tao<sup>4\*</sup>, Zhiyong Zong<sup>1,5\*</sup>  
16

17 6 <sup>1</sup> Department of Infection Control, West China Hospital, Sichuan University, Chengdu, China.  
18

19 7 <sup>2</sup> Department of Infection Control, The First Affiliated Hospital of Zhengzhou University,  
20

21 8 Zhengzhou, China. <sup>3</sup> Intensive Care Unit, West China Hospital, Sichuan University, Chengdu,  
22

23 9 China. <sup>4</sup> Department of Laboratory Medicine, West China Hospital, Sichuan University,  
24

25 10 Chengdu, China. <sup>5</sup> Center of Infectious Disease, West China Hospital, Sichuan University,  
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27 11 Chengdu, China  
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33 13 **Running title: intestinal carriage of CRAB in ICU**  
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42 17 **\*Co-corresponding author**  
43

44 18 Dr. Chuanmin Tao, Department of Laboratory Medicine, West China Hospital, Sichuan  
45

46 19 University, Chengdu, China. Email: [taocm@scu.edu.cn](mailto:taocm@scu.edu.cn)  
47

48 20 Dr. Zhiyong Zong, Center of Infectious Diseases, West China Hospital (Huaxi), Guoxuexiang 37,  
49

50 21 Chengdu 610041, China. Phone: 86-28-8542-2637. Fax: 86-28-8542-3212. E-mail:  
51

52 22 [zongzhiyong@gmail.com](mailto:zongzhiyong@gmail.com)  
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## 23 Abstract

24 **Objectives:** To assess the incidence and the impact of carbapenem-resistant *Acinetobacter*  
25 *baumannii* (CRAB) intestinal carriage on subsequent CRAB infection and to study risk factors of  
26 acquiring CRAB intestinal carriage among patients in intensive care unit (ICU).

27 **Design:** Observational study including a case control study and a retrospective cohort study.

28 **Setting:** A 50-bed general ICU of a university hospital, China.

29 **Methods:** From May 2017 to April 2018, an observational study was conducted in a 50-bed  
30 general ICU of a university hospital in China. Rectal swabs were collected from ICU patients on  
31 admission and thereafter weekly. Risk factors of acquiring CRAB intestinal carriage were analyzed  
32 using multiple logistic regression. Patients with CRAB intestinal carriage were then compared to  
33 those without for the incidence of subsequent CRAB infection using Kaplan–Meier survival and  
34 COX multivariate analyses.

35 **Results:** CRAB intestinal carriage was detected in 6.87% (66/961; 95% CI 5.27%–8.47%) of  
36 patients on ICU admission, whereas 11.97% (115/961; 95% CI 9.91%–14.02%) of patients  
37 acquired CRAB intestinal carriage during the ICU stay. Pancreatitis (OR 2.16, 95% CI 1.28–3.67),  
38 hematological disease (OR 2.26, 95% CI 1.42–3.58), gastric tube feeding (OR 3.35, 95% CI 2.03–  
39 5.51), and use of carbapenems (OR 1.84, 95% CI 1.11–3.07) were independent risk factors for  
40 acquiring CRAB intestinal carriage. The incidence of subsequent CRAB infection was 1.75-fold  
41 in patients with CRAB intestinal carriage compared to that in patients without (95% CI 1.16–2.62,  
42 P=0.007).

43 **Conclusion:** More patients acquired CRAB intestinal carriage during their ICU stay than had on  
44 admission. Severity of illness, acute pancreatitis, tube feeding, and use of carbapenems were  
45 independent risk factors of acquisition of CRAB intestinal carriage. Patients with CRAB intestinal

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3 46 carriage are more likely to develop CRAB infection.  
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8 48 **Strengths and limitations of this study**  
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10 49 A case control study was performed to analyze risk factors of the acquisition of CRAB intestinal  
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12 50 carriage in ICU.  
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14 51 A retrospective cohort study was performed to address whether intestinal CRAB carriage could  
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17 52 lead to an increased likelihood of subsequent CRAB infection.  
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19 53 Most influencing factors were considered in the study.  
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21 54 Not all screened CRABs were confirmed using Vitek II or other methods.  
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## 56 Background

57 *Acinetobacter baumannii* is one of the most common nosocomial pathogens[1]. A  
58 systematic review has revealed that *A. baumannii* accounted for 11.28% of nosocomial infections  
59 in general hospitals in China, making it the third most common nosocomial pathogen[2].  
60 Carbapenems such as meropenem and imipenem are a class of potent antimicrobial agents for  
61 treating severe infections caused by Gram-negative bacteria including *A. baumannii*. However,  
62 carbapenem-resistant *A. baumannii* (CRAB) has emerged worldwide. As early as 2013, the US  
63 Centers for Disease Control and Prevention listed multi-drug resistant *A. baumannii* (MDRAB)  
64 including CRAB as a serious threat[3], and the World Health Organization listed CRAB as one of  
65 the three most critical threats in a global drug-resistant warning in 2017[4]. The prevalence of *A.*  
66 *baumannii* and its resistance to carbapenems varies from country to country. For instance, the  
67 European Bacterial Resistance Surveillance Report shows that the rate of *Acinetobacter* resistant  
68 to carbapenem in Europe in 2017 was 33.4% (95% CI 32%–35%), but it was as high as 96.2% in  
69 Croatia (95% CI 92%–98%) [5]. In the US, 49.5% of *A. baumannii* is resistant to carbapenems,  
70 while in Singapore, India, and Pakistan, it is 50%, 85%, and 62-100%, respectively[6,7]. The  
71 prevalence of CRAB is also very high in China. The surveillance data released by CHINET (China  
72 Antimicrobial Surveillance Network; <http://chinets.com/Chinet>), a national network in China,  
73 have shown that *A. baumannii* isolates ranked the 5th in the number of microbial isolates from all  
74 types of clinical samples in 2018, with 77.1% and 78.1% of *A. baumannii* isolates resistant to  
75 imipenem and meropenem, respectively[8].

76 Infections caused by CRAB can lead to serious consequences. A previous study has  
77 demonstrated that patients with CRAB infection had longer average length of stay (LOS) in ICUs  
78 (13.1 vs. 10.5 days) and \$11,359 higher average in-hospital costs than those with carbapenem-

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3 79 susceptible *A. baumannii* (CSAB) infection[9]. Another previous study has found that the  
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5 80 mortality rate of patients with CRAB infection is 2.22-fold that of patients with CSAB  
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7 81 infection[10]. A case-control study conducted by our team have also showed that the 28-day  
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9 82 survival rate of patients with bloodstream CRAB infection was 66.17%, lower than the 96.95% of  
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11 83 those with bloodstream CSAB infection[11].  
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15 84 It is well known that *A. baumannii* including CRAB usually colonized in the respiratory tract  
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17 85 of hospitalized patients, in particular those with mechanical ventilation[12,13]. The colonization  
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19 86 of CRAB in the respiratory tract has been found as a major risk factor for subsequent CRAB  
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21 87 infection[14]. However, ICU patients may carry CRAB in intestine on admission or acquire CRAB  
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23 88 during the ICU stay[15]. Patients with intestinal carriage of multi-drug resistant organisms  
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25 89 (MDRO), in particular carbapenem-resistant *Enterobacteriaceae* (CRE), may sever as a reservoir  
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27 90 for further dissemination in ICU[16] and could be associated with be associated with an increased  
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29 91 risk of subsequent MDRO infections[17]. Therefore, active screening the carriage of CRE, which  
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31 92 is usually performed using rectal swabs, has been recommended as a core component of the  
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33 93 infection control bundle[7]. However, by contrast to CRE, the prevalence of CRAB intestinal  
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35 94 carriage among ICU patients is much less studied and the risk factors of acquisition of CRAB  
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37 95 intestinal carriage remains largely unknown. In addition, it remains to be determined whether  
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39 96 CRAB intestinal carriage leads to increased risks of subsequent CRAB infection. To address these  
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41 97 questions, we therefore conducted this study.  
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## 49 99 **Methods**

### 50 51 52 100 **Study settings**

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54 101 An observational study was conducted in a 50-bed general ICU of a 4,300-bed university  
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3 102 hospital in China. From May 2017 to April 2018, all patients admitted to the ICU were subjected  
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5 103 to collecting a rectal swab within 48 h of admission and thereafter weekly. For patients hospitalized  
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8 104 for less than 3 days, a rectal swab was collected only once within 48 h of admission.  
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### 11 12 106 **Inclusion and exclusion criteria**

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15 107 Inclusion criteria: This study included all patients who were  $\geq 18$  years of age, admitted to  
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17 108 the ICU, and underwent collection of rectal swabs.

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19 109 Exclusion criteria: 1) patients who did not receive a rectal swab within 48 h of admission to  
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21 110 ICU; or 2) patients who were eligible for weekly follow-up collection of rectal swabs but did not  
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24 111 receive subsequent sampling; or 3) patients with CRAB infection on admission.  
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### 27 28 113 **Patient and public involvement**

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31 114 Patients were involved in this study.  
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### 34 35 116 **Definitions**

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38 117 Patients with CRAB intestinal carriage were defined as those with CRAB isolated from a  
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40 118 rectal swab, while patient without CRAB intestinal carriage referred to those whose swabs were  
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42 119 all negative for CRAB during the ICU stay. Patients with CRAB isolated from a rectal swab  
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44 120 collected within 48 h of ICU admission were defined as those with CRAB intestinal carriage on  
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47 121 ICU admission. The acquisition of CRAB intestinal carriage referred to a patient who had a CRAB-  
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49 122 negative rectal swab collected within 48 h of ICU admission but had CRAB from a swab collected  
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51 123 after 48 h. CRAB infection was defined as the growth of CRAB from clinical specimens in the  
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54 124 presence of clinical manifestations of infection[18]. Subsequent CRAB infection referred to  
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3 125 CRAB infection developed after the collection of a CRAB-positive rectal swab for patients with  
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5 126 CRAB intestinal carriage and CRAB infection developed after 48 h admission to the ICU for  
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8 127 patients without CRAB intestinal carriage.  
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### 10 128 **Screening for CRAB by rectal swabs**

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12 129 For collecting rectal swabs, ready-to-use transport medium swabs (HBPT004; Hopebio  
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14 130 Biotechnology, Qingdao, China) was inserted about 2–3 cm into the patient's anus and then gently  
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17 131 rotated. After sampling, the swab was inserted into the ready-to-use transport medium and  
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19 132 transported to the laboratory within 2 h. Rectal swabs were inoculated onto modified CHROMagar  
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21 133 *Acinetobacter* colorimetric plates (Chromagar; Paris, France) containing 2 mg/L meropenem using  
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24 134 the partition-and-streaking method[19,20]. Plates were then cultured at 37°C for 18–24 h[20].  
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### 28 136 **Data collection and statistical analysis**

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31 137 In this study, the patient's demographic data, underlying diseases, invasive procedures,  
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33 138 medical orders, and use of antimicrobial agents were retrieved from the electronic medical record  
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35 139 system. Two professional statisticians collaborated to clean the data.  
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37  
38 140 We performed two types of comparison. First, a case control study was performed to analyze  
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40 141 risk factors of the acquisition of CRAB intestinal carriage in ICU. Patients with ICU acquisition  
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42 142 of CRAB intestinal carriage were assigned to the case group, while those without CRAB intestinal  
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44 143 carriage during their ICU stay were assigned to the control group. All potential factors were  
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47 144 initially subjected to the univariate analysis. Quantitative data were described by the median  
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49 145 (interquartile range) and were then analyzed using a rank-sum test. Qualitative data were described  
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51 146 by number of cases (composition ratio) and were then analyzed using the chi-square test or Fisher  
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54 147 exact probability method when applied. All variables showing *P* value less than 0.2 in the  
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3 148 univariate analysis were then included into the multiple logistic regression using the forward  
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5 149 selection stepwise regression method[21,22]. Odds ratio (OR) and 95% confidence interval (CI)  
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8 150 were calculated. The Hosmer-Lemeshow method was used to test the goodness-of-fit of the  
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10 151 multiple logistic model[23].

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12 152 Second, a retrospective cohort study was performed to address whether intestinal CRAB  
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14 153 carriage could lead to an increased likelihood of subsequent CRAB infection. In this cohort study,  
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16 154 the exposed group comprised patients with CRAB intestinal carriage either detected on ICU  
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18 155 admission or acquired during the ICU stay, while the non-exposed group consisted of those without  
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20 156 CRAB intestinal carriage. As the impact of CRAB intestinal carriage on subsequent infection may  
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22 157 also be influenced by other factors such as patient demographics, underlying diseases,  
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24 158 antimicrobial use and medical operations, we included these factors for analysis instead of  
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26 159 evaluating CRAB carriage alone. Survival curves (probability of CRAB infection) in patients with  
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28 160 and without CRAB intestinal carriage were mapped using the Kaplan–Meier method[24,25]. After  
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30 161 introducing the interaction term of time and each variable ( $X \cdot \ln(T)$ ) into the COX model [24,25],  
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32 162 the proportional hazards hypothesis was tested, and the results showed no statistical significance  
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34 163 ( $P < 0.05$ ). Therefore, the COX regression (proportional hazards model) was used for univariate  
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36 164 and multivariate analyses. Hazard ratio (HR) and 95% CI were calculated to explore whether  
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38 165 CRAB intestinal carriage was a risk factor for subsequent CRAB infection. The Omnibus method  
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40 166 was used to test the goodness-of-fit of the multivariate COX model[26]. We also performed  
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42 167 subgroup analyses to investigate whether CRAB intestinal carriage on ICU admission and that  
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44 168 acquired in ICU had different impact on subsequent CRAB infection using the same statistical  
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46 169 method as describe above. For the subgroup analysis, patients with CRAB intestinal carriage on  
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48 170 ICU admission and those with ICU acquisition of CRAB intestinal carriage were assigned to two  
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171 exposed subgroups, respectively, while those without CRAB intestinal carriage were assigned to  
172 the non-exposed group.

173 All statistical analyses were performed using SPSS 21.0 (IBM–SPSS Inc; Armonk, NY, US)  
174 with a 0.05 two-sided test level.

175

## 176 **Results**

### 177 **Some patients (6.87%) had CRAB intestinal carriage on ICU admission and more (12.85%)** 178 **acquired in ICU**

179 From May 1, 2017 to April 30, 2018, a total of 1,605 patients were admitted to the ICU, of  
180 which 382 (23.8%) were not screened during their hospital stay. Of which the 382 patients, 323  
181 (84.55%) stayed in the ICU for no more than 2 days, while the other 59 (15.45%) patients were  
182 missed for sampling. In addition, 118 patients (118/1,605, 7.4%) were excluded due to  
183 inappropriate or incomplete sampling including 104 patients whose first rectal swab was collected  
184 48 h after admission and 14 patients who were not screened weekly. A total of 144 (144/1,605,  
185 8.97%) had CRAB infection on ICU admission and were therefore also excluded. Taken together,  
186 a total of 961 patients (620 males, 64.52% and 341 female 35.48%) were included in the analysis,  
187 with an average age of 54 (44–68) years (Figure 1).

188 Among the 961 patients, 66 (6.87%, 95% CI 5.27%–8.47%) had CRAB intestinal carriage on  
189 ICU admission. For the remaining 895 patients, 115 acquired (12.85%, 95% CI 10.66%–15.04%)  
190 CRAB intestinal carriage during their ICU stay with an average age of 51 (40–70) and a 1.61  
191 male/female ratio (71 male and 44 female).

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### 193 **Multiple risks factors of acquiring CRAB intestinal carriage were identified**

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3 194 The univariate analysis showed that APACHE II score (the patient's disease severity),  
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5 195 respiratory failure, renal dysfunction, hematological disease, acute pancreatitis, indwelling central  
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8 196 venous catheter, gastric tube feeding, nebulization, and use of vancomycin, aminoglycosides,  
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10 197 carbapenems, tigecycline, and antifungal agents are risk factors for the acquisition of CRAB  
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12 198 intestinal carriage in the ICU. Multiple logistic regression including all variables with  $P < 0.2$  in  
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15 199 the univariate analysis showed that APACHE II score, pancreatitis, hematological diseases, gastric  
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17 200 tube feeding, and use of carbapenems were independent risk factors for acquiring CRAB intestinal  
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19 201 carriage during the ICU stay (Table 1). For APACHE II score, the model estimated that the  
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21 202 increase of the score by 1 point would lead to a 4% increase of the risk of acquiring CRAB  
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24 203 intestinal carriage in the ICU. Hosmer-Lemeshow test generated a 0.73 P value ( $\chi^2=5.25$ ,  $df=8$ ),  
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26 204 suggesting adequate goodness-of-fit of the multiple logistic model.  
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### 31 206 **CRAB intestinal carriage led to increased risks of subsequent CRAB infection**

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33 207 During the study period, 112 of the 961 patients (11.65%, 95% CI 9.63%–13.68%) developed  
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35 208 CRAB infections during the ICU stay. As for the infection type, lower respiratory tract infections  
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38 209 were the most common ( $n=82$ , 73.21%), followed by bloodstream infections ( $n=9$ , 8.04%),  
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40 210 surgical site infection ( $n=8$ , 7.14%), while 13 patients (11.61%) had infections at other sites.  
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42 211 CRAB intestinal carriage was a risk factor for subsequent CRAB infection (HR 2.69, 95% CI  
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45 212 1.85–3.92;  $P < 0.001$ ; Figure 2). The 90-day cumulative probability of no CRAB infection in  
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47 213 patients with and without CRAB intestinal carriage was 68.0% (95% CI 60.3%–75.7%) and 24.6%  
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49 214 (95% CI 12.2%–37.0%), respectively ( $P < 0.001$ ). In the univariate analysis, CRAB intestinal  
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51 215 carriage, APACHE II score, respiratory failure, hepatic insufficiency, hematological disease,  
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54 216 pancreatitis, mechanical ventilation, placement of a central venous catheter, gastric tube feeding,  
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3 217 and the use of carbapenems were identified as risk factors for subsequent CRAB infection. In the  
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5 218 COX multivariate analysis, CRAB intestinal carriage was also found to be an independent risk  
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8 219 factor for subsequent CRAB infection (HR 1.75, 95% CI 1.16–2.62; Table 2). Omnibus test  
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10 220 showed a log likelihood difference of 79.82 and generated a less than 0.001 P value, suggesting  
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12 221 adequate goodness-of-fit of the COX model.

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15 222 To evaluate whether CRAB intestinal carriage on admission and that acquired during the ICU  
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17 223 stay has different impact on subsequent CRAB, we performed subgroup analyses. In the subgroup  
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19 224 COX multivariate analysis, both CRAB intestinal carriage on admission and that acquired during  
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21 225 the ICU stay were an independent risk factor for subsequent CRAB infection (HR 2.08, 95% CI  
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23 226 1.17–3.68 for carriage on admission, Table S1 in the Supplementary file; HR 1.81, 95% CI 1.14–  
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25 227 2.88 for acquired carriage, Table S2). Omnibus test showed log likelihood difference of 66.06 and  
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27 228 74.18, respectively, and generated a less than 0.001 P value in the subgroup analysis, suggesting  
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29 229 adequate goodness-of-fit of the COX model.

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33 230 In addition to CRAB intestinal carriage, the use of ventilator (HR 2.37, 95% CI 1.15–4.89),  
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35 231 liver dysfunction (HR 2.23, 95% CI 1.29–3.85), and the use of carbapenems (HR 2.75, 95% CI  
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37 232 1.74–4.35), were also identified as independent risk factors of subsequent CRAB infection, while  
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39 233 the use of cephalosporins (HR 0.44, 95% CI 0.27–0.73) and cephamycins (HR 0.49, 95% CI 0.28–  
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41 234 0.84) were protective factors (Table 2).

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## 46 47 236 **Discussion**

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49 237 In this study, we found that in a region with a high CRAB prevalence, 6.87% of patients  
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51 238 (83.3% of those patients were transferred from other hospitals and 25.8% of them were stayed in  
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53 239 emergency ICU before admitted to the ICU) admitted to the ICU had CRAB intestinal carriage on

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3 240 ICU admission, while an additional 11.97% of patients acquired CRAB intestinal carriage during  
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5 241 the ICU stay. The overall CRAB intestinal carriage rate was therefore 18.84%. This rate was  
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7 242 similar with a study conduct in Thailand, in which 5.45% (15/275) of patients had intestinal  
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9 243 carriage on ICU admission and 13.59% (28/206) patients acquired CRAB during their ICU  
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11 244 stay[15] and with another study in Italy[27], in which 18.92%(74/391) of patients carried CRAB  
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13 245 during ICU stay. However, the rate was significantly higher than those in Turkey (7.22%,  
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15 246 55/762)[28], Brazil (13.23%, 43/325)[29], USA (13.46%, 49/364)[30], and South Korea (15.06%,  
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17 247 168/1,115)[14], although other sites such as respiratory secretions were also screened in these  
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19 248 studies. This difference may be related to the local CRAB prevalence.  
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24 249 Interestingly, we found that gastric tube feeding is a risk factor for both acquiring CRAB  
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26 250 intestinal carriage of CRAB in ICU, which is consistent with the findings of Kiddee et al[15], in  
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28 251 which tube feeding was also a high-risk factor for carriage of Gram-negative bacilli. This may  
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30 252 suggest an entry point of CRAB into human intestine. In this study, 73.0% (84/115) of patients  
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32 253 who acquired CRAB intestinal carriage using tube feeding. During the study, we performed a one-  
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34 254 day snapshot sampling of the feeding tubes (at the tube port), feeding contents and containers for  
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36 255 preparing feeding contents in the ICU and found the presence of CRAB in the tube feeding content  
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38 256 (24.0%, 6/25), at the tube port (33.3%, 3/9) and the tube feeding containers (7.1%, 1/14), indicating  
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40 257 contamination. This may be a key point for intervention in the ICU.  
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45 258 We also found that patients with CRAB intestinal carriage were more likely to develop  
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47 259 subsequent CRAB infection than those without carriage. The survival curve in this study showed  
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49 260 that the cumulative infection rates in 90 days in patients with and without CRAB intestinal carriage  
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51 261 were 75.4% and 32%, respectively, similar to those reported in other studies[30]. However, the  
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53 262 HR was 1.75, which is much lower than those in previous studies[15,30,31]. This may be due to  
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3 263 the fact that healthcare associated infections in our ICU were mainly caused by lower respiratory  
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5 264 infections, which accounting for more than 70% of infections, while we only screened the  
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8 265 colonization of the intestines. Interestingly, we found that the use of cephalosporins and  
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10 266 cephamycins led to lower risks of subsequent CRAB infection, while carbapenem use led to  
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12 267 increased risks. The association between CRAB and carbapenem use has been documented  
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15 268 before[30,32]. CRAB is usually resistant to cephalosporins and cephamycins. The use of  
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17 269 cephalosporins and cephamycins may reflect the fact that patients did not receive carbapenems  
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19 270 and could therefore result in reduced selection pressure for CRAB.

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22 271 There are a few limitations in this study. First, this is a single center study and the findings  
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24 272 may not be generalized. Second, we used a modified CHROMagar *Acinetobacter* chromogenic  
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26 273 plate to screen CRAB from rectal swabs. Not all screened CRABs were confirmed using Vitek II  
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28 274 or other methods and there may be false negative results. Nonetheless, at the beginning of this  
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31 275 study, we confirmed that the 58 CRAB strains grown on the chromogenic medium were indeed all  
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33 276 *A. baumannii* by MALDI-TOF-MS and were all non-susceptible to imipenem or meropenem as  
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35 277 determined using the agar dilution method recommended by the Clinical and Laboratory Standards  
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38 278 Institute (CLSI)[20]. Third, we only collected the patients' rectal swabs for investigating CRAB  
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40 279 carriage. Studies have shown concurrent swab collection of skin, oropharyngeal, and airway  
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42 280 secretions in addition to rectal swabs, may improve sensitivity. However, the sample sizes in these  
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45 281 studies were small with only 21 and 34 cases, respectively[12,33]. Nonetheless, for practical  
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47 282 reasons and the aim to study CRAB intestinal carriage, we only collected rectal swabs. Last, this  
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49 283 study failed to collect for the first rectal swab specimen within 48 h of ICU admission from 23.8%  
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51 284 of the patients. Nonetheless, 84.55% of these patients stayed in the ICU for less than 48 h.

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3 286 In conclusion, some patients had CRAB intestinal carriage but more acquired during their ICU  
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5 287 stay. Severity of illness, acute pancreatitis, tube feeding, and use of carbapenems were independent  
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7 288 risk factors of the acquisition of CRAB intestinal carriage. Patients with CRAB intestinal carriage  
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10 289 were more likely to have subsequent CRAB infection than those without.  
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### 23 295 **Author contributions**

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26 296 Fu Qiao, Zhiyong Zong and Chuanmin Tao contributed to study conception and design. Shichao  
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28 297 Zhu and Yan Kang contributed to acquisition of data. Lin Cai collected rectal swabs and  
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30 298 transported to the laboratory. Fu Qiao, Wenzhi Huang and Shan Gao analyzed and interpreted data.  
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32  
33 299 Li Wei inoculated rectal swabs onto plates cultured for 18-24h. Fu Qiao, Zhiyong Zong and  
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35 300 Chuanmin Tao drafted the manuscript. All authors revised the manuscript for important intellectual  
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37 301 content. All authors read and approved the final manuscript.  
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39 302

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3 **309 Competing interests**  
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5 310 The authors declare that they have no competing interests.  
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10 **312 Patient consent for publication**  
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12 313 Not required.  
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17 **315 Ethics approval**  
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19 316 This project was approved by the Ethics Committee of West China Hospital of Sichuan University.  
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24 **318 Availability of data and materials**  
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26 319 The datasets during the current study available from the corresponding author on reasonable  
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28 320 request.  
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3 **426 Figure legends**  
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6 **427 Figure 1.** Patient selection flow algorithm  
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8 **428 Figure 2.** Survival curves of patients with and without CRAB intestinal carriage (cumulative  
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10 probability of no CRAB infection). The solid line represents patients with CRAB intestinal  
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12 carriage, while the dashed line represents those without.  
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Table 1 Risk factors for the acquisition of CRAB intestinal carriage during the ICU stay

Characteristics	Patients with acquiring CRAB intestinal carriage		Univariate analysis		Multivariate analysis	
	Yes (n=115)	No (n=780)	OR (95% CI)	P	OR (95% CI)	P
<b>Demographics</b>						
Sex, male	71 (61.74%)	502 (64.36%)	1.12 (0.75–1.68)	0.590		
Ethnicity, Han Chinese	108 (93.91%)	712 (91.28%)	1.47 (0.66–3.29)	0.338		
Age (median)	51 (40–70)	56 (45–68)	/	0.207		
<b>Underlying disease</b>						
Myocardial infarction	1 (0.87%)	4 (0.51%)	1.7 (0.19–15.36)	0.500		
Peripheral vascular disease	11 (9.57%)	62 (7.95%)	1.22 (0.62–2.40)	0.550		
Cerebrovascular disease	4 (3.48%)	36 (4.62%)	0.74 (0.26–2.13)	0.582		
Dementia	1 (0.87%)	0 (0%)	/	0.130		
Connective tissue disease	1 (0.87%)	12 (1.54%)	0.56 (0.07–4.36)	0.887		
Peptic Ulcer	5 (4.35%)	25 (3.21%)	1.37 (0.51–3.66)	0.720		
Hemiplegia	0 (0%)	1 (0.13%)	/	1.000		
Hypertension	36 (31.30%)	180 (23.08%)	1.52 (0.99–2.33)	0.054		
Tuberculosis	1 (0.87%)	12 (1.54%)	0.56 (0.07–4.36)	0.887		
COPD	10 (8.70%)	54 (6.92%)	1.28 (0.63–2.59)	0.490		

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3	Respiratory failure	40 (34.78%)	163 (20.90%)	2.02 (1.33–3.07)	<b>0.001</b>		
4							
5	Kidney failure	11 (9.57%)	31 (3.97%)	2.56 (1.25–5.24)	<b>0.010</b>		
6							
7	Heart failure	7 (6.09%)	19 (2.44%)	2.99 (1.28–7.01)	0.060		
8							
9	Diabetes	21 (18.26%)	102 (13.08%)	1.48 (0.89–2.49)	0.132		
10							
11	Liver dysfunction	5 (4.35%)	37 (4.74%)	0.91 (0.35–2.37)	0.850		
12							
13	<b>Hematological disease</b>	<b>71 (61.74%)</b>	<b>268 (34.36%)</b>	<b>3.08 (2.06–4.62)</b>	<b>&lt;0.001</b>	<b>2.26 (1.42–3.58)</b>	<b>0.001</b>
14							
15	<b>Pancreatitis</b>	<b>35 (30.43%)</b>	<b>77 (9.87%)</b>	<b>3.99 (2.52–6.34)</b>	<b>&lt;0.001</b>	<b>2.16 (1.28–3.67)</b>	<b>0.004</b>
16							
17	Medical operation						
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19	<b>Surgery</b>	<b>82 (71.30%)</b>	<b>645 (82.69%)</b>	<b>0.52 (0.33–0.81)</b>	<b>0.004</b>	<b>0.40 (0.24–0.68)</b>	<b>0.001</b>
20							
21	CVC	78 (67.83%)	424 (54.36%)	1.77 (1.17–2.68)	<b>0.010</b>		
22							
23	Ventilator	101 (87.83%)	666 (85.38%)	1.23 (0.68–2.23)	0.490		
24							
25	Indwelling catheter	110 (95.65%)	742 (95.13%)	1.13 (0.43–2.92)	0.810		
26							
27	<b>Tube feeding</b>	<b>84 (73.04%)</b>	<b>280 (35.90%)</b>	<b>4.84 (3.13–7.49)</b>	<b>&lt;0.001</b>	<b>3.35 (2.03–5.51)</b>	<b>&lt;0.001</b>
28							
29	Nebulizer fiberoptic	73 (63.48%)	368 (47.18%)	1.95 (1.30–2.92)	<b>0.001</b>		
30							
31	Bronchoscope	1 (0.87%)	21 (2.69%)	0.32 (0.04–2.38)	0.390		
32							
33	Antimicrobial use						
34							
35	<b>Cephalosporin</b>	<b>35 (30.43%)</b>	<b>312 (40.00%)</b>	<b>0.66 (0.43–1.00)</b>	<b>0.049</b>	<b>0.59 (0.37–0.95)</b>	<b>0.029</b>
36							
37	Vancomycin	13 (11.30%)	32 (4.10%)	2.98 (1.51–5.86)	<b>0.001</b>		
38							
39	Aminoglycosides	12 (10.43%)	31 (3.97%)	2.81 (1.40–5.65)	<b>0.002</b>		
40							
41	<b>Carbapenems</b>	<b>82 (71.30%)</b>	<b>295 (37.82%)</b>	<b>4.09 (2.66–6.27)</b>	<b>&lt;0.001</b>	<b>1.84 (1.11–3.07)</b>	<b>0.018</b>
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Fluoroquinolones	26 (22.61%)	137 (17.56%)	1.37 (0.85–2.20)	0.190		
Antifungal agents	49 (42.61%)	138 (17.69%)	3.45 (2.29–5.22)	<b>&lt;0.001</b>		
Cephamycins	16 (13.91%)	253 (32.44%)	0.34 (0.19–0.58)	<b>&lt;0.001</b>		
Lincomycin	3 (2.61%)	61 (7.82%)	0.32 (0.10–1.02)	<b>0.040</b>		
Tigecycline	19 (16.52%)	69 (8.85%)	2.04 (1.18–3.54)	<b>0.010</b>		
<b>APACHE II</b>	<b>21.5 (17–26)</b>	<b>17 (12–22)</b>	/	<b>&lt;0.001</b>	<b>1.04 (1.01–1.07)</b>	<b>0.013</b>
Charlson score	2 (1–5)	3 (2–4)	/	0.063		
Sharing room with other patients with	20 (17.39%)	153 (19.62%)	0.86 (0.52–1.44)	0.573		
CRAB intestinal carriage						

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with  $P < 0.05$  in the multiple logistic analysis are highlighted in bold.



Table 2 Variables associated with developing subsequent CRAB infection during the ICU stay

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=112)	No (n=849)	HR (95% CI)	P	HR (95% CI)	P
<b>CRAB intestinal carriage</b>	<b>51 (45.54%)</b>	<b>130 (15.31%)</b>	<b>2.69 (1.85–3.92)</b>	<b>&lt;0.001</b>	<b>1.75 (1.16–2.62)</b>	<b>0.007</b>
Demographics						
Sex, male	72 (64.29%)	548 (64.55%)	1.01 (0.68–1.48)	0.979		
Ethnicity, Han Chinese	106 (94.64%)	774 (91.38%)	1.68 (0.74–3.83)	0.215		
Age (median)	53 (42–67)	55 (44–68)	1.00 (0.99–1.01)	0.940		
APACHE II	21 (17–26)	17 (12–22)	1.06 (1.03–1.08)	<b>&lt;0.001</b>		
Charlson score	3 (1–5)	3 (1.5–4)	0.99 (0.90–1.09)	0.869		
Underlying disease						
Myocardial infarction	0 (0%)	6 (0.71%)	0.05 (0–6037.12)	0.615		
Peripheral vascular disease	13 (11.61%)	66 (7.77%)	1.27 (0.71–2.27)	0.418		
Cerebrovascular disease	4 (3.57%)	36 (4.24%)	1.02 (0.37–2.77)	0.971		
Dementia	0 (0%)	1 (0.12%)	0.05 (0–5419.76)	0.609		
Connective tissue disease	1 (0.89%)	12 (1.41%)	0.72 (0.10–5.12)	0.739		
Peptic ulcer	4 (3.57%)	27 (3.18%)	1.07 (0.39–2.91)	0.891		
Hemiplegia	1 (0.89%)	0 (0%)	5.24 (0.73–37.73)	0.100		
Hypertension	28 (25.00%)	199 (23.44%)	1.06 (0.69–1.63)	0.792		
Tuberculosis	2 (1.79%)	12 (1.41%)	1.12 (0.28–4.54)	0.874		
COPD	11 (9.82%)	55 (6.48%)	1.46 (0.79–2.73)	0.231		
Respiratory failure	47 (41.96%)	170 (20.02%)	2.14 (1.47–3.12)	<b>&lt;0.001</b>		
Kidney failure	9 (8.04%)	42 (4.95%)	1.61 (0.81–3.18)	0.171		
Heart failure	4 (3.57%)	27 (3.18%)	1.28 (0.47–3.47)	0.631		
Diabetes	15 (13.39%)	118 (13.90%)	0.85 (0.50–1.47)	0.570		
<b>Liver dysfunction</b>	<b>17 (15.18%)</b>	<b>34 (4.00%)</b>	<b>3.07 (1.83–5.15)</b>	<b>&lt;0.001</b>	<b>2.23 (1.29–3.85)</b>	<b>0.004</b>
Hematological disease	60 (53.57%)	314 (36.98%)	1.71 (1.18–2.49)	<b>0.005</b>		
Pancreatitis	29 (25.89%)	107 (12.60%)	1.85 (1.21–2.83)	<b>0.004</b>		
Medical operation						

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Surgery	83 (74.11%)	711 (83.75%)	0.76 (0.49–1.16)	0.199		
CVC	83 (74.11%)	470 (55.36%)	2.03 (1.33–3.10)	<b>0.001</b>		
<b>Ventilator</b>	<b>103 (91.96%)</b>	<b>719 (84.69%)</b>	<b>2.15 (1.09–4.26)</b>	<b>0.027</b>	<b>2.37 (1.15–4.89)</b>	<b>0.019</b>
Indwelling catheter	109 (97.32%)	808 (95.17%)	1.91 (0.61–6.03)	0.269		
Tube feeding	80 (71.43%)	332 (39.10%)	2.40 (1.58–3.62)	<b>&lt;0.001</b>		
Nebulizer fiberoptic	72 (64.29%)	413 (48.65%)	1.13 (0.76–1.67)	0.542		
Bronchoscope	5 (4.46%)	18 (2.12%)	1.31 (0.53–3.21)	0.561		
Antimicrobial use						
<b>Cephalosporin</b>	<b>20 (17.86%)</b>	<b>236 (27.80%)</b>	<b>0.51 (0.31–0.82)</b>	<b>0.006</b>	<b>0.44 (0.27–0.73)</b>	<b>0.001</b>
Vancomycin	3 (2.68%)	35 (4.12%)	0.67 (0.21–2.12)	0.496		
Aminoglycosides	1 (0.89%)	23 (2.71%)	0.25 (0.04–1.82)	0.173		
<b>Carbapenems</b>	<b>82 (73.21%)</b>	<b>351 (41.34%)</b>	<b>3.05 (2.01–4.64)</b>	<b>&lt;0.001</b>	<b>2.75 (1.74–4.35)</b>	<b>&lt;0.001</b>
Fluoroquinolones	32 (28.57%)	154 (18.14%)	1.00 (0.66–1.52)	0.986		
Antifungal agents	23 (20.54%)	157 (18.49%)	1.02 (0.64–1.61)	0.944		
<b>Cephamycins</b>	<b>16 (14.29%)</b>	<b>196 (23.09%)</b>	<b>0.48 (0.28–0.81)</b>	<b>0.006</b>	<b>0.49 (0.28–0.84)</b>	<b>0.010</b>
Lincomycin	5 (4.46%)	35 (4.12%)	0.94 (0.38–2.31)	0.897		
Tigecycline	13 (11.61%)	65 (7.66%)	1.40 (0.78–2.49)	0.259		

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.

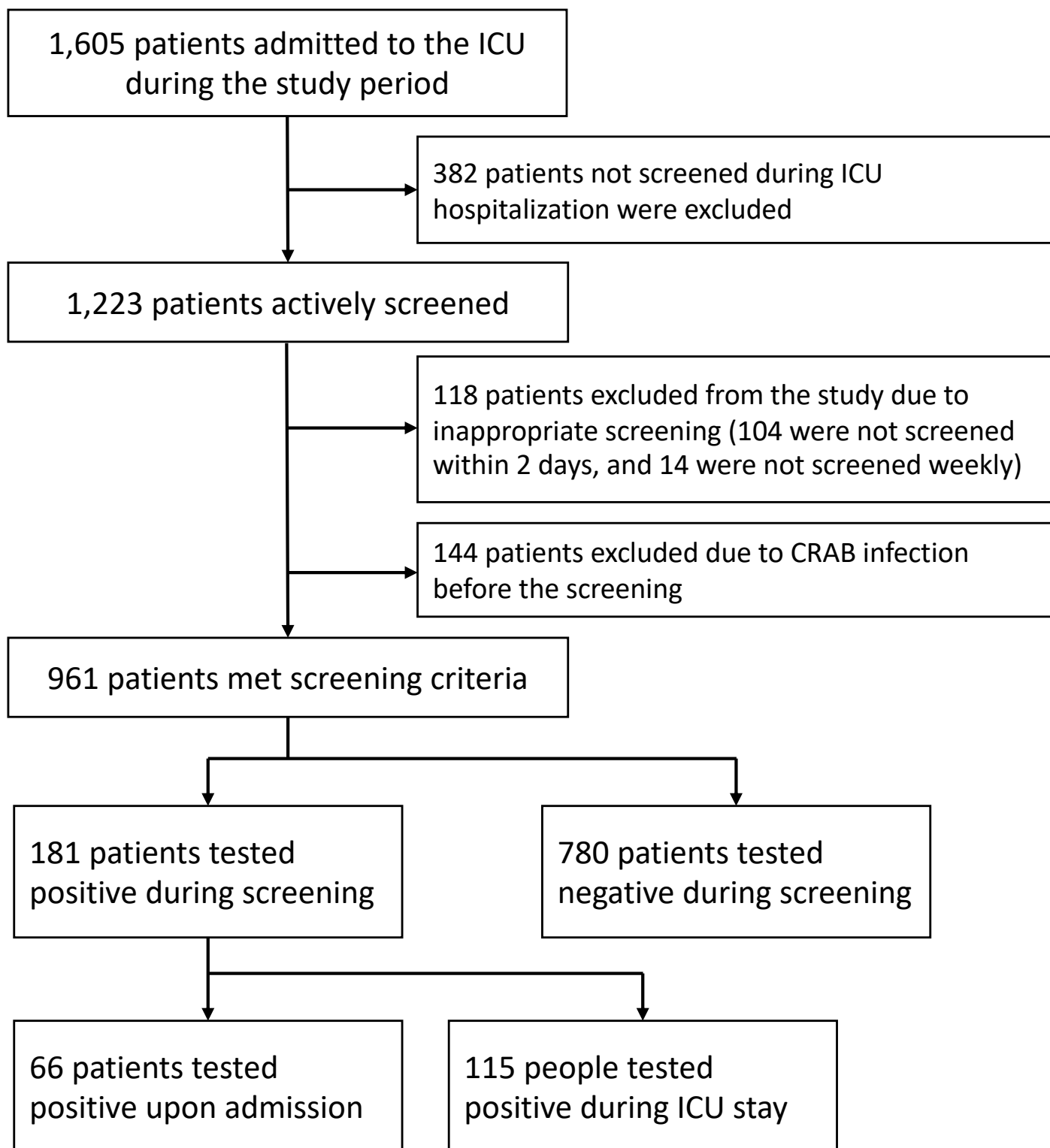
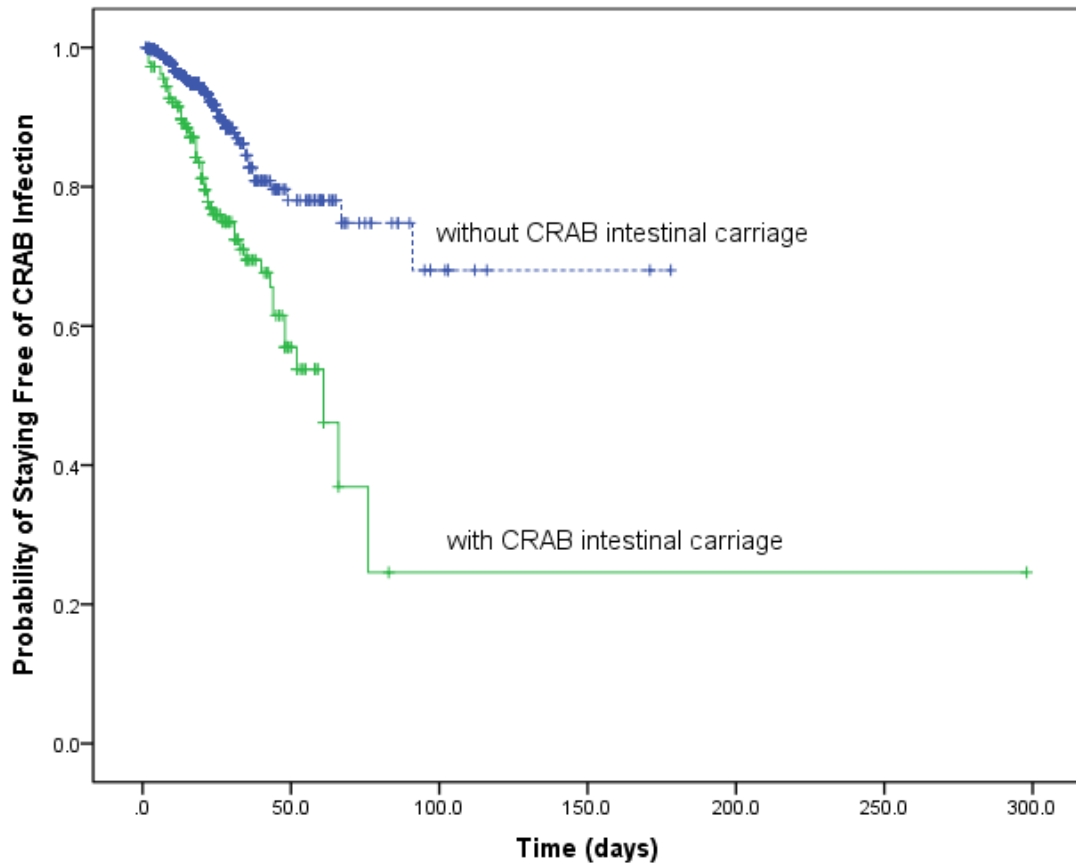


Figure 1. Patient selection flow algorithm



**Figure 2.** Survival curves of patients with and without CRAB intestinal carriage (cumulative probability of no CRAB infection). The solid line represents patients with CRAB intestinal carriage, while the dashed line represents those without.

## Supplementary files

Table S1 Variables associated with developing subsequent CRAB infection during the ICU stay (exposed group was those patients with intestinal carriage on ICU admission)

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=80)	No (n=766)	HR (95% CI)	P	HR (95% CI)	P
<b>CRAB intestinal carriage</b>	<b>19 (23.75%)</b>	<b>47 (6.14%)</b>	<b>2.98 (1.78-5.00)</b>	<b>&lt;0.001</b>	<b>2.08 (1.17-3.68)</b>	<b>0.012</b>
Demographics						
Sex, male	50 (62.50%)	499 (65.14%)	1.09 (0.70-1.72)	0.696		
Ethnicity, Han Chinese	77 (96.25%)	697 (90.99%)	2.66 (0.84-8.45)	0.096		
Age (median)	54 (42-68)	55 (44-68)	1.00 (0.99-1.02)	0.527		
<b>APACHE II</b>	<b>20 (15-26)</b>	<b>17 (12-22)</b>	<b>1.07 (1.04-1.10)</b>	<b>&lt;0.001</b>	<b>1.04 (1.01-1.07)</b>	<b>0.020</b>
Charlson score	3 (1-5)	3 (2-4)	1.03 (0.91-1.15)	0.659		
Underlying disease						
Myocardial infarction	0 (0%)	5 (0.65%)	0.93 (0.23-3.80)	0.923		
Peripheral vascular disease	11 (13.75%)	57 (7.44%)	1.61 (0.85-3.04)	0.143		
Cerebrovascular disease	3 (3.75%)	33 (4.31%)	1.01 (0.32-3.21)	0.983		
Dementia	0 (0%)	0 (0%)	/	/		
Connective tissue disease	1 (1.25%)	11 (1.44%)	0.91 (0.13-6.52)	0.921		
Peptic ulcer	3 (3.75%)	23 (3.00%)	1.06 (0.33-3.36)	0.923		
Hemiplegia	1 (1.25%)	0 (0%)	4.30 (0.59-31.23)	0.149		
Hypertension	18 (22.50%)	173 (22.58%)	1.07 (0.63-1.80)	0.810		
Tuberculosis	1 (1.25%)	12 (1.57%)	0.65 (0.09-4.68)	0.669		
<b>COPD</b>	<b>11 (13.75%)</b>	<b>45 (5.87%)</b>	<b>2.19 (1.16-4.13)</b>	<b>0.016</b>	<b>2.42 (1.23-4.76)</b>	<b>0.011</b>

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5	Respiratory failure	34 (42.50%)	143 (18.67%)	2.52 (1.61-3.93)	<0.001		
6	Kidney failure	5 (6.25%)	35 (4.57%)	1.22 (0.49-3.02)	0.667		
7	Heart failure	2 (2.50%)	21 (2.74%)	0.93 (0.23-3.80)	0.923		
8	Diabetes	11 (13.75%)	101 (13.19%)	1.00 (0.53-1.89)	0.998		
9	Liver dysfunction	<b>14 (17.50%)</b>	<b>32 (4.18%)</b>	<b>3.42 (1.92-6.11)</b>	<b>&lt;0.001</b>	<b>2.12 (1.15-3.93)</b>	<b>0.016</b>
10	Hematological disease	42 (52.50%)	261 (34.07%)	2.05 (1.32-3.18)	0.001		
11	Pancreatitis	17 (21.25%)	84 (10.97%)	1.78 (1.04-3.05)	0.035		
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14	Medical operation						
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16	Surgery	62 (77.50%)	638 (83.29%)	0.94 (0.56-1.60)	0.830		
17	CVC	61 (76.25%)	414 (54.05%)	2.18 (1.30-3.65)	0.003		
18	Ventilator	72 (90.00%)	648 (84.60%)	1.80 (0.87-3.74)	0.115		
19	Indwelling catheter	78 (97.50%)	729 (95.17%)	2.03 (0.50-8.28)	0.325		
20	Tube feeding	54 (67.50%)	265 (34.60%)	2.34 (1.46-3.75)	<0.001		
21	Nebulizer fiberoptic	51 (63.75%)	349 (45.56%)	1.34 (0.85-2.12)	0.213		
22	Bronchoscope	5 (6.25%)	17 (2.22%)	2.39 (0.97-5.93)	0.060		
23							
24	Antimicrobial use						
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26	Cephalosporin	15 (18.75%)	210 (27.42%)	0.57 (0.33-1.00)	0.051		
27	Vancomycin	2 (2.50%)	28 (3.66%)	0.70 (0.17-2.84)	0.615		
28	Aminoglycosides	1 (1.25%)	15 (1.96%)	0.46 (0.06-3.32)	0.443		
29	Carbapenems	<b>58 (72.50%)</b>	<b>284 (37.08%)</b>	<b>3.77 (2.30-6.16)</b>	<b>&lt;0.001</b>	<b>2.70 (1.56-4.67)</b>	<b>&lt;0.001</b>
30	Fluoroquinolones	21 (26.25%)	127 (16.58%)	1.29 (0.78-2.14)	0.316		
31	Antifungal agents	17 (21.25%)	123 (16.06%)	1.19 (0.70-2.04)	0.525		
32	Cephamycins	12 (15.00%)	179 (23.37%)	0.54 (0.29-1.00)	0.049		
33	Lincomycin	3 (3.75%)	32 (4.18%)	0.75 (0.24-2.39)	0.632		
34	Tigecycline	8 (10.00%)	53 (6.92%)	1.34 (0.64-2.77)	0.438		
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COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with  $P < 0.05$  in the multivariate COX analysis are highlighted in bold.

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Table S2. Variables associated with developing subsequent CRAB infection during the ICU stay (exposed group was those patients with ICU acquisition of CRAB intestinal carriage)

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=93)	No (n=802)	HR (95% CI)	P	HR (95% CI)	P
<b>CRAB intestinal carriage</b>	<b>32 (34.41%)</b>	<b>83 (10.35%)</b>	<b>3.02 (1.97-4.64)</b>	<b>&lt;0.001</b>	<b>1.81 (1.14-2.88)</b>	<b>0.012</b>
Demographics						
Sex, male	60 (64.52%)	513 (63.97%)	0.99 (0.65-1.51)	0.954		
Ethnicity, Han Chinese	87 (93.55%)	731 (91.15%)	1.01 (0.99-1.02)	0.398		
Age (median)	54 (44-68)	55 (45-68)	1.42 (0.62-3.24)	0.410		
<b>APACHE II</b>	<b>21 (18-26)</b>	<b>17 (12-22)</b>	<b>1.07 (1.05-1.10)</b>	<b>&lt;0.001</b>	<b>1.04 (1.01-1.07)</b>	<b>0.016</b>
Charlson score	3 (1-5)	3 (2-4)	1.04 (0.93-1.15)	0.490		
Underlying disease						
Myocardial infarction	0 (0%)	5 (0.62%)	0.05 (0-28290)	0.656		
Peripheral vascular disease	11 (11.83%)	62 (7.73%)	1.36 (0.72-2.54)	0.344		
Cerebrovascular disease	4 (4.30%)	36 (4.49%)	1.11 (0.41-3.03)	0.835		
Dementia	0 (0%)	1 (0.12%)	0.05 (0-24060)	0.651		
Connective tissue disease	1 (1.08%)	12 (1.50%)	0.75 (0.10-5.35)	0.770		
Peptic ulcer	4 (4.30%)	26 (3.24%)	1.31 (0.48-3.58)	0.597		
Hemiplegia	1 (1.08%)	0 (0%)	3.99 (0.55-28.87)	0.17		
Hypertension	25 (26.88%)	191 (23.82%)	1.22 (0.77-1.92)	0.405		
Tuberculosis	2 (2.15%)	11 (1.37%)	1.19 (0.29-4.85)	0.805		



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5	COPD	10 (10.75%)	54 (6.73%)	1.44 (0.75-2.78)	0.275		
6	<b>Respiratory failure</b>	<b>44 (47.31%)</b>	<b>159 (19.83%)</b>	<b>2.70 (1.79-4.07)</b>	<b>&lt;0.001</b>	<b>1.99 (1.29-3.06)</b>	<b>0.002</b>
7	Kidney failure	7 (7.53%)	35 (4.36%)	1.92 (0.89-4.15)	0.097		
8	Heart failure	3 (3.23%)	24 (2.99%)	1.52 (0.48-4.83)	0.475		
9	Diabetes	11 (11.83%)	112 (13.97%)	0.74 (0.40-1.39)	0.351		
10	Liver dysfunction	13 (13.98%)	29 (3.62%)	3.11 (1.73-5.61)	<0.001		
11	Hematological disease	49 (52.69%)	290 (36.16%)	1.91 (1.27-2.87)	0.002		
12	Pancreatitis	20 (21.51%)	92 (11.47%)	1.81 (1.10-2.97)	0.019		
13							
14	Medical operation						
15							
16	Surgery	70 (75.27%)	666 (83.04%)	0.90 (0.56-1.45)	0.658		
17	CVC	68 (73.12%)	434 (54.11%)	1.86 (1.17-2.94)	0.008		
18	Ventilator	85 (91.40%)	683 (85.16%)	1.93 (0.94-4.00)	0.075		
19	Indwelling catheter	91 (97.85%)	761 (94.89%)	2.34 (0.58-9.52)	0.235		
20	Tube feeding	67 (72.04%)	300 (37.41%)	2.72 (1.72-4.29)	<0.001		
21	Nebulizer fiberoptic	64 (68.82%)	388 (48.38%)	1.56 (1.00-2.42)	0.050		
22	Bronchoscope	5 (5.38%)	18 (2.24%)	2.00 (0.81-4.93)	0.133		
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24	Antimicrobial use						
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26	Cephalosporin	18 (19.35%)	213 (26.56%)	0.66 (0.40-1.11)	0.114		
27	Vancomycin	2 (2.15%)	33 (4.11%)	0.52 (0.13-2.12)	0.363		
28	Aminoglycosides	0 (0%)	16 (2.00%)	0.05 (0.00-14.57)	0.297		
29	<b>Carbapenems</b>	<b>68 (73.12%)</b>	<b>319 (39.78%)</b>	<b>3.50 (2.21-5.54)</b>	<b>&lt;0.001</b>	<b>2.17 (1.30-3.63)</b>	<b>0.003</b>
30	Fluoroquinolones	28 (30.11%)	144 (17.96%)	1.49 (0.96-2.33)	0.079		
31	Antifungal agents	16 (17.20%)	141 (17.58%)	0.92 (0.53-1.57)	0.749		
32	Cephamecins	15 (16.13%)	187 (23.32%)	0.57 (0.33-1.00)	0.049		
33	Lincomycin	4 (4.30%)	34 (4.24%)	0.82 (0.30-2.24)	0.703		
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5 Tigecycline 7 (7.53%) 57 (7.11%) 1.03 (0.47-2.22) 0.947

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6 COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

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8 Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.

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For peer review only

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

	Reporting Item	Page Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	<a href="#">#1b</a> Provide in the abstract an informative and balanced summary of what was done and what	2

was found

## Introduction

Background / [#2](#) Explain the scientific background and rationale for 4-5  
 rationale the investigation being reported

Objectives [#3](#) State specific objectives, including any 5  
 prespecified hypotheses

## Methods

Study design [#4](#) Present key elements of study design early in the 7-8  
 paper

Setting [#5](#) Describe the setting, locations, and relevant dates, 5-6  
 including periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and 6  
 methods of selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and n/a  
 number of exposed and unexposed  
 Not matched studies

Variables [#7](#) Clearly define all outcomes, exposures, predictors, 6-8  
 potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Data sources / [#8](#) For each variable of interest give sources of data 6-8  
 measurement and details of methods of assessment

(measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for exposed and unexposed groups if applicable.

Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8
Study size	<a href="#">#10</a>	Explain how the study size was arrived at	n/a
			Including all the patients admitted to the ICU in the study period.
Quantitative variables	<a href="#">#11</a>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	<a href="#">#12a</a>	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	<a href="#">#12b</a>	Describe any methods used to examine subgroups and interactions	8
Statistical methods	<a href="#">#12c</a>	Explain how missing data were addressed	n/a
			No missing data.
Statistical methods	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	n/a
			Not applicable

1	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a
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3	methods			Not done.
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7	<b>Results</b>			
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10	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of	9
11			study—eg numbers potentially eligible, examined	
12			for eligibility, confirmed eligible, included in the	
13			study, completing follow-up, and analysed. Give	
14			information separately for for exposed and	
15			unexposed groups if applicable.	
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25	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	9
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28	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	Figure 1
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31	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg	19-23
32			demographic, clinical, social) and information on	
33			exposures and potential confounders. Give	
34			information separately for exposed and unexposed	
35			groups if applicable.	
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43	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data	n/a
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49	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total	Figure 2
50			amount)	
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55	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary	19-23
56			measures over time. Give information separately	
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1		for exposed and unexposed groups if applicable.	
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4	Main results	<a href="#">#16a</a> Give unadjusted estimates and, if applicable,	19-23
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6		confounder-adjusted estimates and their precision	
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8		(eg, 95% confidence interval). Make clear which	
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10		confounders were adjusted for and why they were	
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16	Main results	<a href="#">#16b</a> Report category boundaries when continuous	n/a
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21			were not categorized.
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24	Main results	<a href="#">#16c</a> If relevant, consider translating estimates of	n/a
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26		relative risk into absolute risk for a meaningful time	
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32	Other analyses	<a href="#">#17</a> Report other analyses done—e.g., analyses of	Supplementary files
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34		subgroups and interactions, and sensitivity	
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36		analyses	
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39	<b>Discussion</b>		
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42	Key results	<a href="#">#18</a> Summarise key results with reference to study	11-13
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44		objectives	
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48	Limitations	<a href="#">#19</a> Discuss limitations of the study, taking into account	13
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50		sources of potential bias or imprecision. Discuss	
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52		both direction and magnitude of any potential bias.	
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55	Interpretation	<a href="#">#20</a> Give a cautious overall interpretation considering	11-13
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1 results from similar studies, and other relevant

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6 Generalisability [#21](#) Discuss the generalisability (external validity) of 13  
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11 Other

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13 Information

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16 Funding [#22](#) Give the source of funding and the role of the 14  
17 funders for the present study and, if applicable, for  
18 the original study on which the present article is  
19 based  
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26 None The STROBE checklist is distributed under the terms of the Creative Commons Attribution  
27 License CC-BY. This checklist can be completed online using <https://www.goodreports.org/>, a tool  
28 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Intestinal carriage of carbapenem-resistant *Acinetobacter baumannii* among patients in the intensive care unit: risk factors and the impact on subsequent infection

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035893.R1
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Complete List of Authors:	Qiao, Fu; Sichuan University West China Hospital, Department of Infection Control Huang, Wenzhi; Sichuan University West China Hospital, Department of Infection Control Gao, Shan; Zhengzhou University First Affiliated Hospital, Department of Infection Control Cai, Lin; Sichuan University West China Hospital, Intensive Care Unit Zhu, Shichao; Sichuan University West China Hospital, Department of Infection Control Wei, Li; Sichuan University West China Hospital, Department of Infection Control Kang, Yan; Sichuan University West China Hospital, Intensive Care Unit Tao, Chuanmin; Sichuan University West China Hospital, Department of Laboratory Medicine Zong, Zhiyong; Sichuan University West China Hospital, Department of Infection Control; Sichuan University West China Hospital, Center of Infectious Disease
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4 1 **Intestinal carriage of carbapenem-resistant *Acinetobacter baumannii***  
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7 2 **among patients in the intensive care unit: risk factors and the**  
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9 3 **impact on subsequent infection**  
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12 4 Fu Qiao<sup>1</sup>, Wenzhi Huang<sup>1</sup>, Shan Gao<sup>2</sup>, Lin Cai<sup>3</sup>, Shichao Zhu<sup>1</sup>, Li Wei<sup>1</sup>, Yan Kang<sup>3</sup>,  
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14  
15 5 Chuanmin Tao<sup>4\*</sup>, Zhiyong Zong<sup>1,5\*</sup>  
16

17 6 <sup>1</sup> Department of Infection Control, West China Hospital, Sichuan University, Chengdu, China.

18  
19 7 <sup>2</sup> Department of Infection Control, The First Affiliated Hospital of Zhengzhou University,

20  
21 8 Zhengzhou, China. <sup>3</sup> Intensive Care Unit, West China Hospital, Sichuan University, Chengdu,

22  
23 9 China. <sup>4</sup> Department of Laboratory Medicine, West China Hospital, Sichuan University,

24  
25 10 Chengdu, China. <sup>5</sup> Center of Infectious Disease, West China Hospital, Sichuan University,

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27 11 Chengdu, China  
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33 13 **Running title: intestinal carriage of CRAB in ICU**  
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42 17 **\*Co-corresponding author**  
43

44 18 Dr. Chuanmin Tao, Department of Laboratory Medicine, West China Hospital, Sichuan  
45  
46

47 19 University, Chengdu, China. Email: [taocm@scu.edu.cn](mailto:taocm@scu.edu.cn)  
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49 20 Dr. Zhiyong Zong, Center of Infectious Diseases, West China Hospital (Huaxi), Guoxuexiang 37,  
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51 21 Chengdu 610041, China. Phone: 86-28-8542-2637. Fax: 86-28-8542-3212. E-mail:  
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54 22 [zongzhiyong@gmail.com](mailto:zongzhiyong@gmail.com)  
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## 23 Abstract

24 **Objectives:** To assess the incidence and the impact of carbapenem-resistant *Acinetobacter*  
25 *baumannii* (CRAB) intestinal carriage on subsequent CRAB infection and to study risk factors of  
26 acquiring CRAB intestinal carriage among patients in intensive care unit (ICU).

27 **Design:** Observational study including a case control study and a retrospective cohort study.

28 **Setting:** A 50-bed general ICU of a university hospital, China.

29 **Methods:** From May 2017 to April 2018, an observational study was conducted in a 50-bed  
30 general ICU of a university hospital in China. Rectal swabs were collected from ICU patients on  
31 admission and thereafter weekly. A case control study was performed to analyze risk factors of the  
32 acquisition of CRAB intestinal carriage in ICU using multiple logistic regression. A retrospective  
33 cohort study was performed to address whether intestinal CRAB carriage could lead to an  
34 increased likelihood of subsequent CRAB infection using sub-distribution hazard model  
35 regarding death in the ICU as a competing risk event.

36 **Results:** CRAB intestinal carriage was detected in 6.87% (66/961; 95% CI 5.27%–8.47%) of  
37 patients on ICU admission, whereas 11.97% (115/961; 95% CI 9.91%–14.02%) of patients  
38 acquired CRAB intestinal carriage during the ICU stay. Pancreatitis (OR 2.16, 95% CI 1.28–3.67),  
39 hematological disease (OR 2.26, 95% CI 1.42–3.58), gastric tube feeding (OR 3.35, 95% CI 2.03–  
40 5.51), and use of carbapenems (OR 1.84, 95% CI 1.11–3.07) were independent risk factors for  
41 acquiring CRAB intestinal carriage. The incidence of subsequent CRAB infection was 2.24-fold  
42 in patients with CRAB intestinal carriage compared to that in patients without (95% CI 1.48–3.39,  
43  $P<0.001$ ).

44 **Conclusion:** More patients acquired CRAB intestinal carriage during their ICU stay than had on  
45 admission. Severity of illness, acute pancreatitis, tube feeding, and use of carbapenems were

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3 46 independent risk factors of acquisition of CRAB intestinal carriage. Patients with CRAB intestinal  
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5 47 carriage are more likely to develop CRAB infection.  
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10 49 **Strengths and limitations of this study**

11  
12 50 A case control study was performed to analyze risk factors of the acquisition of CRAB intestinal  
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14 51 carriage in ICU.  
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17 52 A retrospective cohort study was performed to address whether intestinal CRAB carriage was  
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19 53 associated with subsequent CRAB infection.  
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21 54 Most influencing factors were considered in the study.  
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23  
24 55 Not all screened CRABs were confirmed using Vitek II or other methods.  
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## 57 **Background**

58 *Acinetobacter baumannii* is one of the most common nosocomial pathogens in Asia and  
59 South America[1]. A systematic review has revealed that *A. baumannii* accounted for 11.28% of  
60 nosocomial infections in general hospitals in China, making it the third most common nosocomial  
61 pathogen[2]. And carbapenem-resistant *A. baumannii* (CRAB) has emerged worldwide. As early  
62 as 2013, the US Centers for Disease Control and Prevention listed multi-drug resistant *A.*  
63 *baumannii* (MDRAB) including CRAB as a serious threat[3], and the World Health Organization  
64 listed CRAB as one of the three most critical threats in a global drug-resistant warning in 2017[4].  
65 The prevalence of *A. baumannii* and its resistance to carbapenems varies from country to country.  
66 For instance, the European Bacterial Resistance Surveillance Report shows that the rate of  
67 *Acinetobacter* resistant to carbapenem in Europe in 2017 was 33.4% (95% CI 32%–35%), but it  
68 was as high as 96.2% in Croatia (95% CI 92%–98%) [5]. In the US, 49.5% of *A. baumannii* is  
69 resistant to carbapenems, while in Singapore, India, and Pakistan, it is 50%, 85%, and 62-100%,  
70 respectively[6,7]. The prevalence of CRAB is also very high in China. The surveillance data  
71 released by CHINET (China Antimicrobial Surveillance Network; <http://chinets.com/Chinet>), a  
72 national network in China, have shown that 77.1% and 78.1% of *A. baumannii* isolates resistant to  
73 imipenem and meropenem, respectively[8].

74 Infections caused by CRAB can lead to serious consequences. A previous study has  
75 demonstrated that patients with CRAB infection had longer average length of stay (LOS) in ICUs  
76 (13.1 vs. 10.5 days) and \$11,359 higher average in-hospital costs than those with carbapenem-  
77 susceptible *A. baumannii* (CSAB) infection[9]. Another previous study has found that the  
78 mortality rate of patients with CRAB infection is 2.22-fold that of patients with CSAB  
79 infection[10]. A case-control study conducted by our team have also showed that the 28-day

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3 80 survival rate of patients with bloodstream CRAB infection was 66.17%, lower than the 96.95% of  
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5 81 those with bloodstream CSAB infection[11].  
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8 82 It is well known that *A. baumannii* including CRAB may colonized in the respiratory tract of  
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10 83 hospitalized patients, in particular those with mechanical ventilation[12,13]. The colonization of  
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12 84 CRAB in the respiratory tract has been found as a major risk factor for subsequent CRAB  
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14 85 infection[14]. However, ICU patients may carry CRAB in intestine on admission or acquire CRAB  
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16 86 during the ICU stay[15]. Patients with intestinal carriage of multi-drug resistant organisms  
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18 87 (MDRO), in particular carbapenem-resistant *Enterobacteriaceae* (CRE), may sever as a reservoir  
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20 88 for further dissemination in ICU[16] and could be associated with be associated with an increased  
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22 89 risk of subsequent MDRO infections[17]. Therefore, active screening the carriage of CRE, which  
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24 90 is usually performed using rectal swabs, has been recommended as a core component of the  
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26 91 infection control bundle[7]. However, by contrast to CRE, the prevalence of CRAB intestinal  
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28 92 carriage among ICU patients is much less studied and the risk factors of acquisition of CRAB  
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30 93 intestinal carriage remains largely unknown. In addition, it remains to be determined whether  
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32 94 CRAB intestinal carriage leads to increased risks of subsequent CRAB infection. To address these  
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34 95 questions, we therefore conducted this study.  
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## 42 97 **Methods**

### 43 98 **Study settings**

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45 99 An observational study was conducted in a 50-bed general ICU of a 4,300-bed university  
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47 100 hospital in China. From May 2017 to April 2018, all patients admitted to the ICU were subjected  
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49 101 to collecting a rectal swab within 48 h of admission and thereafter weekly. For patients hospitalized  
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51 102 for less than 3 days, a rectal swab was collected only once within 48 h of admission.  
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**104 Inclusion and exclusion criteria**

105 Inclusion criteria: This study included all patients who were  $\geq 18$  years of age, admitted to  
106 the ICU, and underwent collection of rectal swabs.

107 Exclusion criteria: 1) patients who did not receive a rectal swab within 48 h of admission to  
108 ICU; or 2) patients who were eligible for weekly follow-up collection of rectal swabs but did not  
109 receive subsequent sampling; or 3) patients with CRAB infection on admission.

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**112 Definitions**

113 Patients with CRAB intestinal carriage were defined as those with CRAB isolated from a  
114 rectal swab, while patient without CRAB intestinal carriage referred to those whose swabs were  
115 all negative for CRAB during the ICU stay. Patients with CRAB isolated from a rectal swab  
116 collected within 48 h of ICU admission were defined as those with CRAB intestinal carriage on  
117 ICU admission. The acquisition of CRAB intestinal carriage referred to a patient who had a CRAB-  
118 negative rectal swab collected within 48 h of ICU admission but had CRAB from a swab collected  
119 after 48 h. CRAB infection was defined as the growth of CRAB from clinical specimens in the  
120 presence of clinical manifestations of infection[18]. Subsequent CRAB infection referred to  
121 CRAB infection developed after the collection of a CRAB-positive rectal swab for patients with  
122 CRAB intestinal carriage and CRAB infection developed after 48 h admission to the ICU for  
123 patients without CRAB intestinal carriage.

**124 Screening for CRAB by rectal swabs**

125 For collecting rectal swabs, ready-to-use transport medium swabs (HBPT004; Hopebio



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3 126 Biotechnology, Qingdao, China) was inserted about 2–3 cm into the patient's anus and then gently  
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5 127 rotated. After sampling, the swab was inserted into the ready-to-use transport medium and  
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8 128 transported to the laboratory within 2 h. Rectal swabs were inoculated onto modified CHROMagar  
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10 129 *Acinetobacter* colorimetric plates (Chromagar; Paris, France) containing 2 mg/L meropenem using  
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12 130 the partition-and-streaking method[19,20]. Plates were then cultured at 37°C for 18–24 h[20].  
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### 17 132 **Data collection and statistical analysis**

19 133 In this study, the patient's demographic data, underlying diseases, invasive procedures,  
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21 134 medical orders, and use of antimicrobial agents were retrieved from the electronic medical record  
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24 135 system. Two professional statisticians collaborated to clean the data.  
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26 136 We performed two types of comparison. First, a case control study was performed to analyze  
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28 137 risk factors of the acquisition of CRAB intestinal carriage in ICU. Patients with ICU acquisition  
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30 138 of CRAB intestinal carriage were assigned to the case group, while those without CRAB intestinal  
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33 139 carriage during their ICU stay were assigned to the control group. All potential factors were  
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35 140 initially subjected to the univariate analysis. Quantitative data were described by the median  
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38 141 (interquartile range) and were then analyzed using a rank-sum test. Qualitative data were described  
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40 142 by number of cases (composition ratio) and were then analyzed using the chi-square test or Fisher  
41  
42 143 exact probability method when applied. All variables showing *P* value less than 0.2 in the  
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44 144 univariate analysis were then included into the multiple logistic regression using the forward  
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47 145 selection stepwise regression method[21,22]. Odds ratio (OR) and 95% confidence interval (CI)  
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49 146 were calculated. The Hosmer-Lemeshow method was used to test the goodness-of-fit of the  
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51 147 multiple logistic model[23].  
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54 148 Second, a retrospective cohort study was performed to address whether intestinal CRAB  
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3 149 carriage could lead to an increased likelihood of subsequent CRAB infection. In this cohort study,  
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5 150 the exposed group comprised patients with CRAB intestinal carriage either detected on ICU  
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8 151 admission or acquired during the ICU stay, while the non-exposed group consisted of those without  
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10 152 CRAB intestinal carriage. As the impact of CRAB intestinal carriage on subsequent infection may  
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12 153 also be influenced by other factors such as patient demographics, underlying diseases,  
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14 154 antimicrobial use and medical operations, we included these factors for analysis instead of  
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17 155 evaluating CRAB carriage alone. Survival curves (probability of CRAB infection) in patients with  
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19 156 and without CRAB intestinal carriage were mapped using the Fine and Gray model regarding death  
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22 157 in the ICU as a competing risk event [24,25]. After introducing the interaction term of time and  
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24 158 each variable ( $X \cdot \ln(T)$ ) into the COX model [24,25], the proportional hazards hypothesis was  
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26 159 tested, and the results showed no statistical significance ( $P < 0.05$ ). Therefore, sub-distribution  
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28 160 hazard model was used to obtain sub-distribution hazard ratios (SDHRs) and to explore whether  
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31 161 CRAB intestinal carriage was a risk factor for subsequent CRAB infection for competing events  
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33 162 (R package “cmprsk”)The Akaike information criteria (AIC) was used to select the multivariate  
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35 163 model[26]. We also performed subgroup analyses to investigate whether CRAB intestinal carriage  
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38 164 on ICU admission and that acquired in ICU had different impact on subsequent CRAB infection  
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40 165 using the same statistical method as describe above. For the subgroup analysis, patients with  
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42 166 CRAB intestinal carriage on ICU admission and those with ICU acquisition of CRAB intestinal  
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45 167 carriage were assigned to two exposed subgroups, respectively, while those without CRAB  
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47 168 intestinal carriage were assigned to the non-exposed group.

49 169 All statistical analyses were performed using SPSS 21.0 (IBM–SPSS Inc; Armonk, NY, US)  
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51 170 and R version 3.5.3 with a 0.05 two-sided test level.

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## 172 **Patient and public involvement**

173 Patients were not involved in this study.

## 175 **Results**

### 176 **Some patients (6.87%) had CRAB intestinal carriage on ICU admission and more (12.85%)** 177 **acquired in ICU**

178 From May 1, 2017 to April 30, 2018, a total of 1,605 patients were admitted to the ICU, of  
179 which 382 (23.8%) were not screened during their hospital stay. Of which the 382 patients, 323  
180 (84.55%) stayed in the ICU for no more than 2 days, while the other 59 (15.45%) patients were  
181 missed for sampling. In addition, 118 patients (118/1,605, 7.4%) were excluded due to  
182 inappropriate or incomplete sampling including 104 patients whose first rectal swab was collected  
183 48 h after admission and 14 patients who were not screened weekly. A total of 144 (144/1,605,  
184 8.97%) had CRAB infection on ICU admission and were therefore also excluded. Taken together,  
185 a total of 961 patients (620 males, 64.52% and 341 female 35.48%) were included in the analysis,  
186 with an average age of 54 (44–68) years (Figure 1).

187 Among the 961 patients, 66 (6.87%, 95% CI 5.27%–8.47%) had CRAB intestinal carriage on  
188 ICU admission. For the remaining 895 patients, 115 acquired (12.85%, 95% CI 10.66%–15.04%)  
189 CRAB intestinal carriage during their ICU stay with an average age of 51 (40–70) and a 1.61  
190 male/female ratio (71 male and 44 female).

### 192 **Multiple risks factors of acquiring CRAB intestinal carriage were identified**

193 The univariate analysis showed that APACHE II score (the patient's disease severity),  
194 respiratory failure, renal dysfunction, hematological disease, acute pancreatitis, indwelling central

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3 195 venous catheter, gastric tube feeding, nebulization, and use of vancomycin, aminoglycosides,  
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5 196 carbapenems, tigecycline, and antifungal agents are risk factors for the acquisition of CRAB  
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8 197 intestinal carriage in the ICU. Multiple logistic regression including all variables with  $P < 0.2$  in  
9  
10 198 the univariate analysis showed that APACHE II score, pancreatitis, hematological diseases, gastric  
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12 199 tube feeding, and use of carbapenems were independent risk factors for acquiring CRAB intestinal  
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14 200 carriage during the ICU stay (Table 1). For APACHE II score, the model estimated that the  
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16 201 increase of the score by 1 point would lead to a 4% increase of the risk of acquiring CRAB  
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18 202 intestinal carriage in the ICU. Hosmer-Lemeshow test generated a 0.73 P value ( $\chi^2=5.25$ ,  $df=8$ ),  
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21 203 suggesting adequate goodness-of-fit of the multiple logistic model.  
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### 205 **CRAB intestinal carriage led to increased risks of subsequent CRAB infection**

206 During the study period, 112 of the 961 patients (11.65%, 95% CI 9.63%–13.68%) developed  
207 CRAB infections during the ICU stay. As for the infection type, lower respiratory tract infections  
208 were the most common ( $n=82$ , 73.21%), followed by bloodstream infections ( $n=9$ , 8.04%),  
209 surgical site infection ( $n=8$ , 7.14%), while 13 patients (11.61%) had infections at other sites.  
210 CRAB intestinal carriage was a risk factor for subsequent CRAB infection (HR 2.82, 95% CI  
211 1.94–4.09;  $P < 0.001$ ; Figure 2). The 90-day cumulative probability of no CRAB infection in  
212 patients with and without CRAB intestinal carriage was 69.5.0% (95% CI 43.5%–95.5%) and  
213 22.3% (95% CI 14.7%–29.9%), respectively ( $P < 0.001$ ). In the univariate analysis, CRAB  
214 intestinal carriage, APACHE II score, respiratory failure, liver dysfunction, hematological disease,  
215 pancreatitis, mechanical ventilation, placement of a central venous catheter, gastric tube feeding,  
216 and the use of carbapenems were identified as risk factors for subsequent CRAB infection. In the  
217 COX multivariate analysis, CRAB intestinal carriage was also found to be an independent risk

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3 218 factor for subsequent CRAB infection (HR 2.24, 95% CI 1.48–3.39; Table 2). Omnibus test  
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5 219 showed a log likelihood difference of 79.82 and generated a less than 0.001 P value, suggesting  
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7 220 adequate goodness-of-fit of the COX model.  
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10 221 To evaluate whether CRAB intestinal carriage on admission and that acquired during the ICU  
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12 222 stay has different impact on subsequent CRAB, we performed subgroup analyses. In the subgroup  
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14 223 COX multivariate analysis, both CRAB intestinal carriage on admission and that acquired during  
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16 224 the ICU stay were an independent risk factor for subsequent CRAB infection (HR 3.42, 95% CI  
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18 225 1.88–6.22 for carriage on admission, Table S1 in the Supplementary file; HR 1.81, 95% CI 1.15–  
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20 226 2.86 for acquired carriage, Table S2). Omnibus test showed log likelihood difference of 66.06 and  
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22 227 74.18, respectively, and generated a less than 0.001 P value in the subgroup analysis, suggesting  
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24 228 adequate goodness-of-fit of the COX model.  
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28 229 In addition to CRAB intestinal carriage, liver dysfunction (HR 2.33, 95% CI 1.30–4.17), and  
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30 230 the use of carbapenems (HR 2.21, 95% CI 1.40–3.49), were also identified as independent risk  
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32 231 factors of subsequent CRAB infection, while the use of cephalosporins (HR 0.45, 95% CI 0.28–  
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34 232 0.73) and cephamycins (HR 0.53, 95% CI 0.31–0.90) were protective factors (Table 2).  
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## 39 234 **Discussion**

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42 235 In this study, we found that in a region with a high CRAB prevalence, 6.87% of patients  
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44 236 (83.3% of those patients were transferred from other hospitals and 25.8% of them were stayed in  
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46 237 emergency ICU before admitted to the ICU) admitted to the ICU had CRAB intestinal carriage on  
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48 238 ICU admission, while an additional 11.97% of patients acquired CRAB intestinal carriage during  
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50 239 the ICU stay. The overall CRAB intestinal carriage rate was therefore 18.84%. This rate was  
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52 240 similar with a study conduct in Thailand, in which 5.45% (15/275) of patients had intestinal  
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3 241 carriage on ICU admission and 13.59% (28/206) patients acquired CRAB during their ICU  
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5 242 stay[15] and with another study in Italy[27], in which 18.92%(74/391) of patients carried CRAB  
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7 243 during ICU stay. However, the rate was significantly higher than those in Turkey (7.22%,  
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9 244 55/762)[28], Brazil (13.23%, 43/325)[29], USA (13.46%, 49/364)[30], and South Korea (15.06%,  
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11 245 168/1,115)[14], although other sites such as respiratory secretions were also screened in these  
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13 246 studies. This difference may be related to the local CRAB prevalence.  
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17 247 Interestingly, we found that gastric tube feeding is a risk factor for both acquiring CRAB  
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19 248 intestinal carriage of CRAB in ICU, which is consistent with the findings of Kiddee et al[15], in  
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21 249 which tube feeding was also a high-risk factor for carriage of Gram-negative bacilli. This may  
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23 250 suggest an entry point of CRAB into human intestine. In this study, 73.0% (84/115) of patients  
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25 251 who acquired CRAB intestinal carriage using tube feeding. During the study, we performed a one-  
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27 252 day snapshot sampling of the feeding tubes (at the tube port), feeding contents and containers for  
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29 253 preparing feeding contents in the ICU and found the presence of CRAB in the tube feeding content  
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31 254 (24.0%, 6/25), at the tube port (33.3%, 3/9) and the tube feeding containers (7.1%, 1/14), indicating  
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33 255 contamination. This may be a key point for intervention in the ICU.  
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37 256 We also found that patients with CRAB intestinal carriage were more likely to develop  
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39 257 subsequent CRAB infection than those without carriage. The survival curve in this study showed  
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41 258 that the cumulative infection rates in 90 days in patients with and without CRAB intestinal carriage  
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43 259 were 69.5% and 22.3%, respectively, similar to those reported in other studies[30]. However, the  
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45 260 HR was 2.24, which is much lower than those in previous studies[15,30,31]. This may be due to  
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47 261 the fact that healthcare associated infections in our ICU were mainly caused by lower respiratory  
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49 262 infections, which accounting for more than 70% of infections, while we only screened the  
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51 263 colonization of the intestines. Interestingly, we found that the use of cephalosporins and  
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3 264 cephamycins led to lower risks of subsequent CRAB infection, while carbapenem use led to  
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5 265 increased risks. The association between CRAB and carbapenem use has been documented  
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7 266 before[30,32]. CRAB is usually resistant to cephalosporins and cephamycins. The use of  
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10 267 cephalosporins and cephamycins may reflect the fact that patients did not receive carbapenems  
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12 268 and could therefore result in reduced selection pressure for CRAB.

14  
15 269 There are a few limitations in this study. First, this is a single center study and the findings  
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17 270 may not be generalized. Second, we used a modified CHROMagar *Acinetobacter* chromogenic  
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19 271 plate to screen CRAB from rectal swabs. Not all screened CRABs were confirmed using Vitek II  
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21 272 or other methods and there may be false negative results. Nonetheless, at the beginning of this  
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23 273 study, we confirmed that the 58 CRAB strains grown on the chromogenic medium were indeed all  
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25 274 *A. baumannii* by MALDI-TOF-MS and were all non-susceptible to imipenem or meropenem as  
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27 275 determined using the agar dilution method recommended by the Clinical and Laboratory Standards  
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29 276 Institute (CLSI)[20]. Third, we only collected the patients' rectal swabs for investigating CRAB  
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31 277 carriage. Studies have shown concurrent swab collection of skin, oropharyngeal, and airway  
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33 278 secretions in addition to rectal swabs, may improve sensitivity. However, the sample sizes in these  
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35 279 studies were small with only 21 and 34 cases, respectively[12,33]. Nonetheless, for practical  
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37 280 reasons and the aim to study CRAB intestinal carriage, we only collected rectal swabs. Fourth, due  
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39 281 to the poor sensitivity of rectal swabbing, a single negative test result could overlook carriers.  
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41 282 Moreover, no molecular strain typing was performed. Though reasonable, it was not proven that  
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43 283 CRAB isolated from intestinal colonization and site of nosocomial infection were identical. Last,  
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45 284 this study failed to collect for the first rectal swab specimen within 48 h of ICU admission from  
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47 285 23.8% of the patients. Nonetheless, 84.55% of these patients stayed in the ICU for less than 48 h.

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3 287 In conclusion, some patients had CRAB intestinal carriage but more acquired during their ICU  
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5 288 stay. Severity of illness, acute pancreatitis, tube feeding, and use of carbapenems were independent  
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7 289 risk factors of the acquisition of CRAB intestinal carriage. Patients with CRAB intestinal carriage  
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10 290 were more likely to have subsequent CRAB infection than those without.  
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### 23 296 **Author contributions**

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26 297 Fu Qiao, Zhiyong Zong and Chuanmin Tao contributed to study conception and design. Shichao  
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28 298 Zhu and Yan Kang contributed to acquisition of data. Lin Cai collected rectal swabs and  
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30 299 transported to the laboratory. Fu Qiao, Wenzhi Huang and Shan Gao analyzed and interpreted data.  
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32 300 Li Wei inoculated rectal swabs onto plates cultured for 18-24h. Fu Qiao, Zhiyong Zong and  
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34 301 Chuanmin Tao drafted the manuscript. All authors revised the manuscript for important intellectual  
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36 302 content. All authors read and approved the final manuscript.  
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### 310 **Competing interests**

311 The authors declare that they have no competing interests.

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### 313 **Patient consent for publication**

314 Not required.

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### 316 **Ethics approval**

317 This project was approved by the Ethics Committee of West China Hospital of Sichuan University.

318 We confirm that consents were not obtained from the patients. First, active screening is part of the

319 routine care for ICU patients in our hospital. In other words, no matter whether we analyzed the

320 data, the patients would receive the screening. Second, this is a retrospective study, in which we

321 looked back the patients' data and did not perform any interventions. Third, before we performed

322 this study, we have obtained ethical approval from the Ethical Committee and inform consents

323 were waived due to the retrospective nature of this study.

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### 325 **Availability of data and materials**

326 The datasets during the current study available from the corresponding author on reasonable

327 request.

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3 **432 Figure legends**  
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6 **433 Figure 1.** Patient selection flow algorithm  
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8 **434 Figure 2.** Survival curves of patients with and without CRAB intestinal carriage  
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Table 1 Risk factors for the acquisition of CRAB intestinal carriage during the ICU stay

Characteristics	Patients with acquiring CRAB intestinal carriage		Univariate analysis		Multivariate analysis	
	Yes (n=115)	No (n=780)	OR (95% CI)	P	OR (95% CI)	P
<b>Demographics</b>						
Sex, male	71 (61.74%)	502 (64.36%)	1.12 (0.75–1.68)	0.59		
Ethnicity, Han Chinese	108 (93.91%)	712 (91.28%)	1.47 (0.66–3.29)	0.34		
Age (median)	51 (40–70)	56 (45–68)	/	0.21		
<b>Underlying disease</b>						
Myocardial infarction	1 (0.87%)	4 (0.51%)	1.7 (0.19–15.36)	0.50		
Peripheral vascular disease	11 (9.57%)	62 (7.95%)	1.22 (0.62–2.40)	0.55		
Cerebrovascular disease	4 (3.48%)	36 (4.62%)	0.74 (0.26–2.13)	0.58		
Dementia	1 (0.87%)	0 (0%)	/	0.13		
Connective tissue disease	1 (0.87%)	12 (1.54%)	0.56 (0.07–4.36)	0.89		
Peptic Ulcer	5 (4.35%)	25 (3.21%)	1.37 (0.51–3.66)	0.72		
Hemiplegia	0 (0%)	1 (0.13%)	/	1.00		
Hypertension	36 (31.30%)	180 (23.08%)	1.52 (0.99–2.33)	0.05		
Tuberculosis	1 (0.87%)	12 (1.54%)	0.56 (0.07–4.36)	0.89		
COPD	10 (8.70%)	54 (6.92%)	1.28 (0.63–2.59)	0.49		
Respiratory failure	40 (34.78%)	163 (20.90%)	2.02 (1.33–3.07)	<b>0.001</b>		

Kidney failure	11 (9.57%)	31 (3.97%)	2.56 (1.25–5.24)	<b>0.01</b>		
Heart failure	7 (6.09%)	19 (2.44%)	2.99 (1.28–7.01)	0.06		
Diabetes	21 (18.26%)	102 (13.08%)	1.48 (0.89–2.49)	0.13		
Liver dysfunction	5 (4.35%)	37 (4.74%)	0.91 (0.35–2.37)	0.85		
<b>Hematological disease</b>	<b>71 (61.74%)</b>	<b>268 (34.36%)</b>	<b>3.08 (2.06–4.62)</b>	<b>&lt;0.001</b>	<b>2.26 (1.42–3.58)</b>	<b>0.001</b>
<b>Pancreatitis</b>	<b>35 (30.43%)</b>	<b>77 (9.87%)</b>	<b>3.99 (2.52–6.34)</b>	<b>&lt;0.001</b>	<b>2.16 (1.28–3.67)</b>	<b>0.004</b>
Medical operation						
<b>Surgery</b>	<b>82 (71.30%)</b>	<b>645 (82.69%)</b>	<b>0.52 (0.33–0.81)</b>	<b>0.004</b>	<b>0.40 (0.24–0.68)</b>	<b>0.001</b>
CVC	78 (67.83%)	424 (54.36%)	1.77 (1.17–2.68)	<b>0.01</b>		
Ventilator	101 (87.83%)	666 (85.38%)	1.23 (0.68–2.23)	0.49		
Indwelling catheter	110 (95.65%)	742 (95.13%)	1.13 (0.43–2.92)	0.81		
<b>Tube feeding</b>	<b>84 (73.04%)</b>	<b>280 (35.90%)</b>	<b>4.84 (3.13–7.49)</b>	<b>&lt;0.001</b>	<b>3.35 (2.03–5.51)</b>	<b>&lt;0.001</b>
Nebulizer fiberoptic	73 (63.48%)	368 (47.18%)	1.95 (1.30–2.92)	<b>0.001</b>		
Bronchoscope	1 (0.87%)	21 (2.69%)	0.32 (0.04–2.38)	0.39		
Antimicrobial use						
<b>Cephalosporin</b>	<b>35 (30.43%)</b>	<b>312 (40.00%)</b>	<b>0.66 (0.43–1.00)</b>	<b>0.05</b>	<b>0.59 (0.37–0.95)</b>	<b>0.03</b>
Vancomycin	13 (11.30%)	32 (4.10%)	2.98 (1.51–5.86)	<b>0.001</b>		
Aminoglycosides	12 (10.43%)	31 (3.97%)	2.81 (1.40–5.65)	<b>0.002</b>		
<b>Carbapenems</b>	<b>82 (71.30%)</b>	<b>295 (37.82%)</b>	<b>4.09 (2.66–6.27)</b>	<b>&lt;0.001</b>	<b>1.84 (1.11–3.07)</b>	<b>0.02</b>

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Fluoroquinolones	26 (22.61%)	137 (17.56%)	1.37 (0.85–2.20)	0.19	
Antifungal agents	49 (42.61%)	138 (17.69%)	3.45 (2.29–5.22)	<b>&lt;0.001</b>	
Cephamycins	16 (13.91%)	253 (32.44%)	0.34 (0.19–0.58)	<b>&lt;0.001</b>	
Lincomycin	3 (2.61%)	61 (7.82%)	0.32 (0.10–1.02)	<b>0.04</b>	
Tigecycline	19 (16.52%)	69 (8.85%)	2.04 (1.18–3.54)	<b>0.01</b>	
<b>APACHE II</b>	<b>21.5 (17–26)</b>	<b>17 (12–22)</b>	/	<b>&lt;0.001</b>	<b>1.04 (1.01–1.07) 0.01</b>
Charlson score	2 (1–5)	3 (2–4)	/	0.06	
Sharing room with other patients with	20 (17.39%)	153 (19.62%)	0.86 (0.52–1.44)	0.57	
CRAB intestinal carriage					

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multiple logistic analysis are highlighted in bold.



Table 2 Variables associated with developing subsequent CRAB infection during the ICU stay using sub-distribution hazard model

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=112)	No (n=849)	SDHR (95% CI)	P	SDHR (95% CI)	P
<b>CRAB intestinal carriage</b>	<b>51 (45.54%)</b>	<b>130 (15.31%)</b>	2.82(1.94-4.09)	<0.001	<b>2.24 (1.48–3.39)</b>	<b>&lt;0.001</b>
Demographics						
Sex, male	72 (64.29%)	548 (64.55%)	1.03(0.70-1.52)	0.87		
Ethnicity, Han Chinese	106 (94.64%)	774 (91.38%)	1.62(0.70-3.74)	0.26		
Age (median)	53 (42–67)	55 (44–68)	1.00(0.99-1.01)	0.71		
APACHE II	21 (17–26)	17 (12–22)	1.05(1.03-1.07)	<0.001		
Charlson score	3 (1–5)	3 (1.5–4)	0.98(0.88-1.08)	0.66		
Underlying disease						
Peripheral vascular disease	13 (11.61%)	66 (7.77%)	1.30(0.72-2.34)	0.38		
Cerebrovascular disease	4 (3.57%)	36 (4.24%)	0.89(0.34-2.33)	0.81		
Connective tissue disease	1 (0.89%)	12 (1.41%)	0.60(0.08-4.48)	0.62		
Peptic ulcer	4 (3.57%)	27 (3.18%)	1.11(0.46-2.71)	0.81		
Hypertension	28 (25.00%)	199 (23.44%)	1.02(0.67-1.57)	0.92		
Tuberculosis	2 (1.79%)	12 (1.41%)	1.22(0.28-5.27)	0.79		
COPD	11 (9.82%)	55 (6.48%)	1.35(0.70-2.59)	0.37		
Respiratory failure	47 (41.96%)	170 (20.02%)	2.02(1.38-2.96)	<0.001		
Kidney failure	9 (8.04%)	42 (4.95%)	1.42(0.73-2.75)	0.30		
Heart failure	4 (3.57%)	27 (3.18%)	1.22(0.48-3.11)	0.68		
Diabetes	15 (13.39%)	118 (13.90%)	0.87(0.50-1.49)	0.61		
<b>Liver dysfunction</b>	<b>17 (15.18%)</b>	<b>34 (4.00%)</b>	<b>3.15(1.86-5.35)</b>	<0.001	<b>2.33 (1.30–4.17)</b>	<b>0.005</b>
Hematological disease	60 (53.57%)	314 (36.98%)	1.61(1.11-2.34)	0.012		
Pancreatitis	29 (25.89%)	107 (12.60%)	1.94(1.29-2.92)	0.002		
Medical operation						

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Surgery	83 (74.11%)	711 (83.75%)	0.70(0.45-1.07)	0.099		
CVC	83 (74.11%)	470 (55.36%)	1.85(1.21-2.81)	0.004		
<b>Ventilator</b>	<b>103 (91.96%)</b>	<b>719 (84.69%)</b>	<b>2.02(1.04-3.93)</b>	0.038		
Indwelling catheter	109 (97.32%)	808 (95.17%)	1.84(0.62-5.52)	0.27		
Tube feeding	80 (71.43%)	332 (39.10%)	2.44(1.62-3.69)	<0.001		
Nebulizer fiberoptic	72 (64.29%)	413 (48.65%)	1.18(0.80-1.73)	0.40		
Bronchoscope	5 (4.46%)	18 (2.12%)	1.44(0.59-3.52)	0.43		
Antimicrobial use						
<b>Cephalosporin</b>	<b>20 (17.86%)</b>	<b>236 (27.80%)</b>	<b>0.50(0.31-0.81)</b>	0.005	<b>0.45 (0.28–0.73)</b>	<b>0.001</b>
Vancomycin	3 (2.68%)	35 (4.12%)	0.68(0.21-2.15)	0.51		
Aminoglycosides	1 (0.89%)	23 (2.71%)	0.24(0.03-1.71)	0.15		
<b>Carbapenems</b>	<b>82 (73.21%)</b>	<b>351 (41.34%)</b>	<b>2.84(1.87-4.32)</b>	<0.001	<b>2.21(1.40–3.49)</b>	<b>&lt;0.001</b>
Fluoroquinolones	32 (28.57%)	154 (18.14%)	1.04(0.69-1.56)	0.84		
Antifungal agents	23 (20.54%)	157 (18.49%)	0.96(0.61-1.5)	0.85		
<b>Cephamycins</b>	<b>16 (14.29%)</b>	<b>196 (23.09%)</b>	<b>0.51(0.30-0.86)</b>	0.011	<b>0.53 (0.31–0.90)</b>	<b>0.018</b>
Lincomycin	5 (4.46%)	35 (4.12%)	1.01(0.41-2.48)	0.99		
Tigecycline	13 (11.61%)	65 (7.66%)	1.33(0.76-2.34)	0.32		

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.

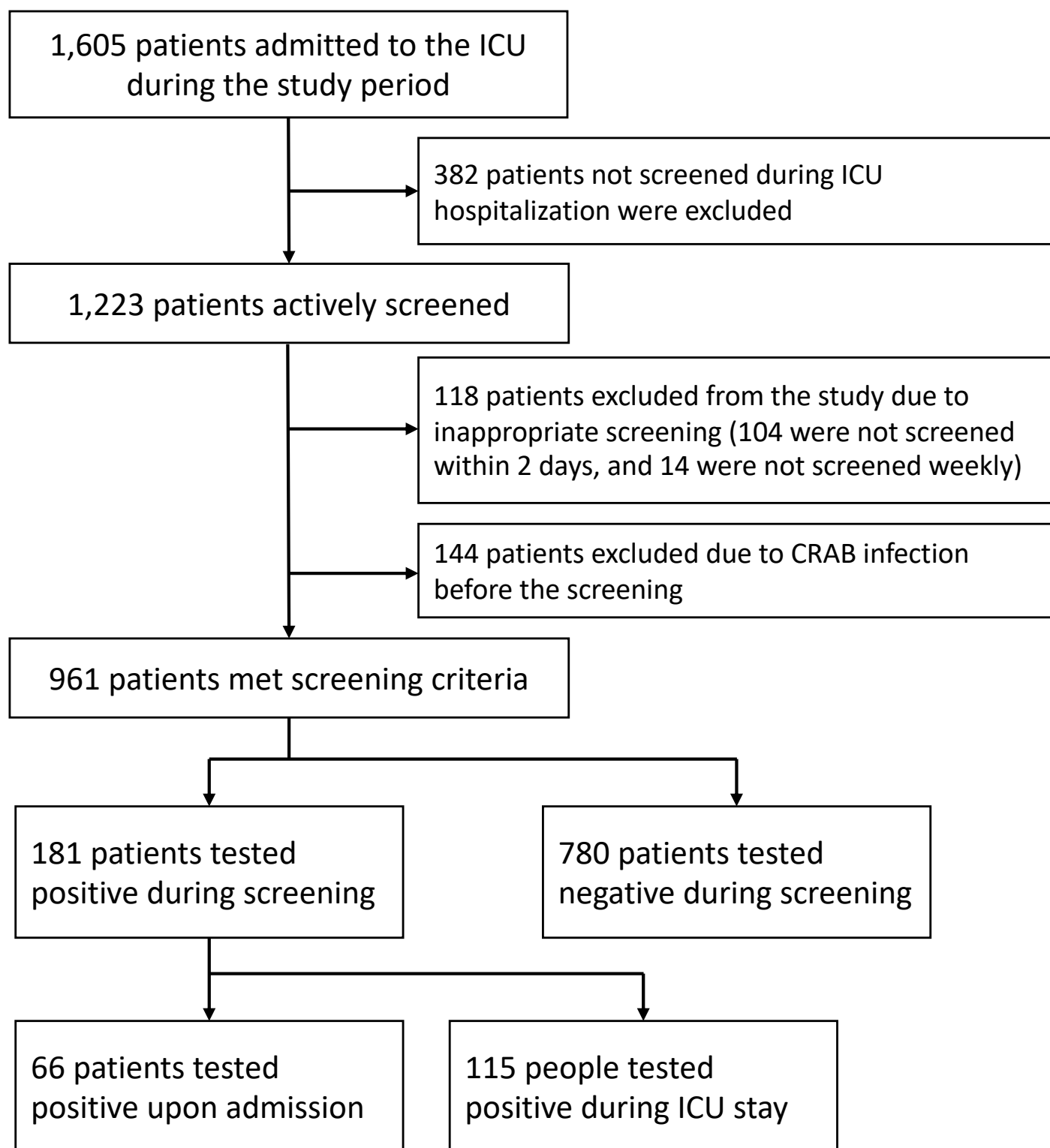
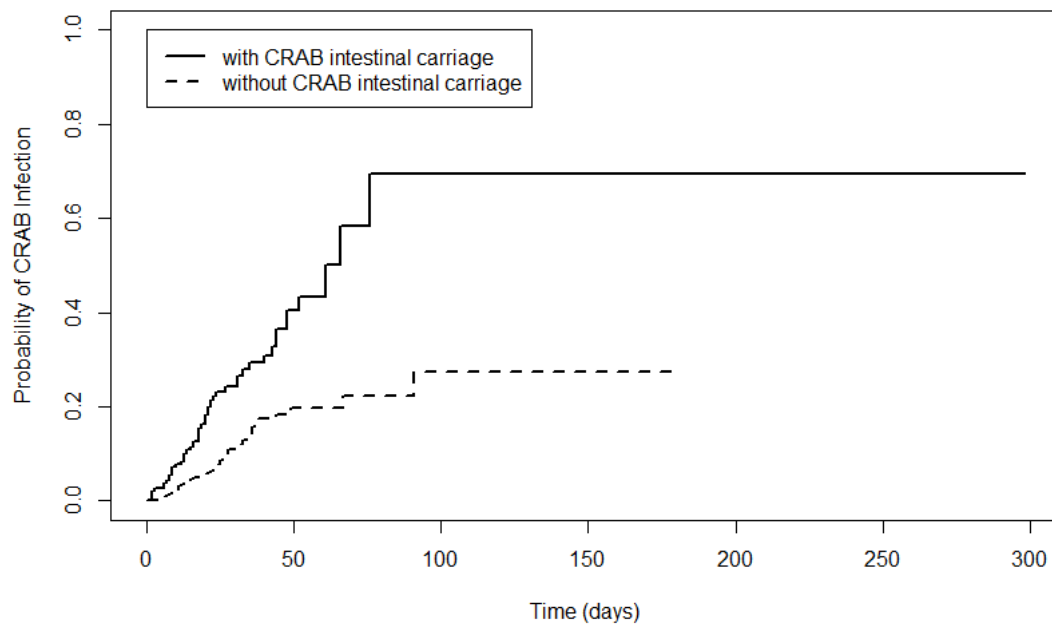


Figure 1. Patient selection flow algorithm



**Figure 2.** Survival curves of patients with and without CRAB intestinal carriage

(cumulative probability of CRAB infection). Death in the ICU is considered as a competing event, not drawn in the figure. The solid line represents patients with CRAB intestinal carriage, while the dashed line represents those without. In patients with CRAB intestinal carriage, Day 0 corresponds to the day of the first positive rectal sample. While in patients without CRAB intestinal carriage, Day 0 corresponds to the day of the first rectal sample.

## Supplementary files

Table S1 Variables associated with developing subsequent CRAB infection during the ICU stay using sub-distribution hazard model (exposed group was those patients with intestinal carriage on ICU admission)

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=80)	No (n=766)	<i>SDHR (95% CI)</i>	<i>P</i>	<i>SDHR (95% CI)</i>	<i>P</i>
<b>CRAB intestinal carriage</b>	<b>19 (23.75%)</b>	<b>47 (6.14%)</b>	3.78(2.20-6.49)	<b>&lt;0.001</b>	<b>3.42 (1.88-6.22)</b>	<b>&lt;0.001</b>
Demographics						
Sex, male	50 (62.50%)	499 (65.14%)	1.15(0.73-1.80)	0.55		
Ethnicity, Han Chinese	77 (96.25%)	697 (90.99%)	2.54(0.78-8.24)	0.12		
Age (median)	54 (42-68)	55 (44-68)	1.00(0.99-1.02)	0.85		
<b>APACHE II</b>	<b>20 (15-26)</b>	<b>17 (12-22)</b>	<b>1.06(1.03-1.08)</b>	<b>&lt;0.001</b>	<b>1.03 (1.00-1.05)</b>	<b>0.045</b>
Charlson score	3 (1-5)	3 (2-4)	1.00(0.88-1.13)	1.00		
Underlying disease						
Peripheral vascular disease	11 (13.75%)	57 (7.44%)	1.62(0.85-3.10)	0.14		
Cerebrovascular disease	3 (3.75%)	33 (4.31%)	0.87(0.29-2.66)	0.81		
Connective tissue disease	1 (1.25%)	11 (1.44%)	0.78(0.11-5.73)	0.80		
Peptic ulcer	3 (3.75%)	23 (3.00%)	1.19(0.41-3.46)	0.74		
Hypertension	18 (22.50%)	173 (22.58%)	0.97(0.58-1.64)	0.91		
Tuberculosis	1 (1.25%)	12 (1.57%)	0.72(0.10-5.37)	0.75		
<b>COPD</b>	<b>11 (13.75%)</b>	<b>45 (5.87%)</b>	<b>2.21(1.15-4.24)</b>	<b>0.017</b>	<b>2.71 (1.40-5.24)</b>	<b>0.003</b>
Respiratory failure	34 (42.50%)	143 (18.67%)	2.38(1.52-3.72)	<b>&lt;0.001</b>		
Kidney failure	5 (6.25%)	35 (4.57%)	1.13(0.474-2.7)	0.78		
Heart failure	2 (2.50%)	21 (2.74%)	1.05(0.28-3.92)	0.95		

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5	Diabetes	11 (13.75%)	101 (13.19%)	1.03(0.54-1.98)	0.92		
6	Liver dysfunction	<b>14 (17.50%)</b>	<b>32 (4.18%)</b>	<b>3.59(2.00-6.45)</b>	<b>&lt;0.001</b>	<b>2.35 (1.30-4.25)</b>	<b>0.005</b>
7	Hematological disease	42 (52.50%)	261 (34.07%)	1.84(1.19-2.85)	<b>0.006</b>		
8	Pancreatitis	17 (21.25%)	84 (10.97%)	1.91(1.13-3.22)	<b>0.016</b>		
9							
10	Medical operation						
11	Surgery	62 (77.50%)	638 (83.29%)	0.83(0.49-1.42)	0.50		
12	CVC	61 (76.25%)	414 (54.05%)	2.23(1.33-3.74)	<b>0.002</b>		
13	Ventilator	72 (90.00%)	648 (84.60%)	1.62(0.80-3.25)	0.18		
14	Indwelling catheter	78 (97.50%)	729 (95.17%)	1.91(0.53-6.94)	0.32		
15	Tube feeding	54 (67.50%)	265 (34.60%)	2.71(1.69-4.34)	<b>&lt;0.001</b>		
16	Nebulizer fiberoptic	51 (63.75%)	349 (45.56%)	1.35(0.86-2.12)	0.19		
17	Bronchoscope	5 (6.25%)	17 (2.22%)	1.85(0.77-4.46)	0.17		
18							
19	Antimicrobial use						
20	Cephalosporin	<b>15 (18.75%)</b>	<b>210 (27.42%)</b>	<b>0.54(0.31-0.95)</b>	<b>0.032</b>	<b>0.43(0.24-0.78)</b>	<b>0.006</b>
21	Vancomycin	2 (2.50%)	28 (3.66%)	0.70(0.16-2.98)	0.63		
22	Aminoglycosides	1 (1.25%)	15 (1.96%)	0.50(0.07-3.52)	0.48		
23	Carbapenems	<b>58 (72.50%)</b>	<b>284 (37.08%)</b>	<b>3.57(2.18-5.85)</b>	<b>&lt;0.001</b>	<b>2.61(1.53-4.46)</b>	<b>&lt;0.001</b>
24	Fluoroquinolones	21 (26.25%)	127 (16.58%)	1.07(0.66-1.74)	0.79		
25	Antifungal agents	17 (21.25%)	123 (16.06%)	1.26(0.74-2.12)	0.39		
26	Cephamecins	12 (15.00%)	179 (23.37%)	0.52(0.28-0.96)	<b>0.036</b>		
27	Lincomycin	3 (3.75%)	32 (4.18%)	0.84(0.26-2.68)	0.76		
28	Tigecycline	8 (10.00%)	53 (6.92%)	1.36(0.67-2.76)	0.39		

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.

Table S2. Variables associated with developing subsequent CRAB infection during the ICU stay using sub-distribution hazard model (exposed group was those patients with ICU acquisition of CRAB intestinal carriage)

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=93)	No (n=802)	<i>SDHR (95% CI)</i>	<i>P</i>	<i>SDHR (95% CI)</i>	<i>P</i>
CRAB intestinal carriage	<b>32 (34.41%)</b>	<b>83 (10.35%)</b>	<b>2.35(1.56-3.55)</b>	<b>&lt;0.001</b>	<b>1.81 (1.15-2.86)</b>	<b>0.011</b>
Demographics						
Sex, male	60 (64.52%)	513 (63.97%)	1.01(0.66-1.55)	0.95		
Ethnicity, Han Chinese	87 (93.55%)	731 (91.15%)	1.32(0.56-3.08)	0.52		
Age (median)	54 (44-68)	55 (45-68)	1.00(0.99-1.01)	0.70		
APACHE II	21 (18-26)	17 (12-22)	1.05(1.03-1.07)	<0.001		
Charlson score	3 (1-5)	3 (2-4)	1.01(0.91-1.13)	0.80		
Underlying disease						
Peripheral vascular disease	11 (11.83%)	62 (7.73%)	1.34(0.71-2.53)	0.37		
Cerebrovascular disease	4 (4.30%)	36 (4.49%)	1.03(0.39-2.73)	0.96		
Connective tissue disease	1 (1.08%)	12 (1.50%)	0.68(0.09-5.07)	0.70		
Peptic ulcer	4 (4.30%)	26 (3.24%)	1.39(0.58-3.33)	0.46		
Hypertension	25 (26.88%)	191 (23.82%)	1.10(0.69-1.74)	0.70		
Tuberculosis	2 (2.15%)	11 (1.37%)	1.41(0.32-6.29)	0.65		
COPD	10 (10.75%)	54 (6.73%)	1.37(0.69-2.75)	0.37		
Respiratory failure	<b>44 (47.31%)</b>	<b>159 (19.83%)</b>	<b>2.42(1.59-3.69)</b>	<b>&lt;0.001</b>	<b>1.84 (1.17-2.90)</b>	<b>0.009</b>
Kidney failure	7 (7.53%)	35 (4.36%)	1.56(0.75-3.28)	0.24		

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5	Heart failure	3 (3.23%)	24 (2.99%)	1.34(0.47-3.82)	0.58		
6	Diabetes	11 (11.83%)	112 (13.97%)	0.75(0.40-1.39)	0.36		
7	Liver dysfunction	<b>13 (13.98%)</b>	<b>29 (3.62%)</b>	<b>3.18(1.74-5.81)</b>	<b>&lt;0.001</b>	<b>2.13(1.05-4.32)</b>	<b>0.037</b>
8	Hematological disease	49 (52.69%)	290 (36.16%)	1.60(1.06-2.40)	0.025		
9	Pancreatitis	20 (21.51%)	92 (11.47%)	1.71(1.06-2.76)	0.028		
10							
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12	Medical operation						
13	Surgery	70 (75.27%)	666 (83.04%)	0.78(0.49-1.27)	0.32		
14	CVC	68 (73.12%)	434 (54.11%)	1.82(1.15-2.88)	0.011		
15	Ventilator	85 (91.40%)	683 (85.16%)	1.83(0.89-3.76)	0.10		
16	Indwelling catheter	91 (97.85%)	761 (94.89%)	2.37(0.58-9.63)	0.23		
17	Tube feeding	67 (72.04%)	300 (37.41%)	2.64(1.67-4.18)	<0.001		
18	Nebulizer fiberoptic	64 (68.82%)	388 (48.38%)	1.42(0.92-2.20)	0.11		
19	Bronchoscope	5 (5.38%)	18 (2.24%)	1.60(0.64-3.99)	0.31		
20							
21							
22	Antimicrobial use						
23							
24	Cephalosporin	<b>18 (19.35%)</b>	<b>213 (26.56%)</b>	<b>0.60(0.36-1.00)</b>	<b>0.051</b>	<b>0.59(0.35-1.00)</b>	<b>0.048</b>
25	Vancomycin	2 (2.15%)	33 (4.11%)	0.53(0.13-2.15)	0.38		
26	Carbapenems	<b>68 (73.12%)</b>	<b>319 (39.78%)</b>	<b>2.92(1.84-4.64)</b>	<b>&lt;0.001</b>	<b>2.11 (1.27-3.50)</b>	<b>0.004</b>
27	Fluoroquinolones	28 (30.11%)	144 (17.96%)	1.11(0.71-1.72)	0.65		
28	Antifungal agents	16 (17.20%)	141 (17.58%)	0.82(0.48-1.39)	0.46		
29	Cephamycins	15 (16.13%)	187 (23.32%)	0.56(0.33-0.98)	0.042		
30	Lincomycin	4 (4.30%)	34 (4.24%)	0.90(0.34-2.44)	0.84		
31	Tigecycline	7 (7.53%)	57 (7.11%)	0.91(0.43-1.96)	0.82		
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COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.



# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

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	Reporting Item	Page Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	<a href="#">#1b</a> Provide in the abstract an informative and balanced summary of what was done and what	2

was found

## Introduction

Background / [#2](#) Explain the scientific background and rationale for 4-5  
 rationale the investigation being reported

Objectives [#3](#) State specific objectives, including any 5  
 prespecified hypotheses

## Methods

Study design [#4](#) Present key elements of study design early in the 7-8  
 paper

Setting [#5](#) Describe the setting, locations, and relevant dates, 5-6  
 including periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and 6  
 methods of selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and n/a  
 number of exposed and unexposed  
 Not matched studies

Variables [#7](#) Clearly define all outcomes, exposures, predictors, 6-8  
 potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Data sources / [#8](#) For each variable of interest give sources of data 6-8  
 measurement and details of methods of assessment

(measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.

Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8
Study size	<a href="#">#10</a>	Explain how the study size was arrived at	n/a
			Including all the patients admitted to the ICU in the study period.
Quantitative variables	<a href="#">#11</a>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	<a href="#">#12a</a>	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	<a href="#">#12b</a>	Describe any methods used to examine subgroups and interactions	8
Statistical methods	<a href="#">#12c</a>	Explain how missing data were addressed	n/a
			No missing data.
Statistical methods	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	n/a
			Not applicable

1	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a
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3	methods			Not done.
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7	<b>Results</b>			
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10	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of	9
11			study—eg numbers potentially eligible, examined	
12			for eligibility, confirmed eligible, included in the	
13			study, completing follow-up, and analysed. Give	
14			information separately for for exposed and	
15			unexposed groups if applicable.	
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25	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	9
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28	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	Figure 1
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31	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg	19-23
32			demographic, clinical, social) and information on	
33			exposures and potential confounders. Give	
34			information separately for exposed and unexposed	
35			groups if applicable.	
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43	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data	n/a
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49	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total	Figure 2
50			amount)	
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55	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary	19-23
56			measures over time. Give information separately	
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1		for exposed and unexposed groups if applicable.	
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4	Main results	<a href="#">#16a</a> Give unadjusted estimates and, if applicable,	19-23
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6		confounder-adjusted estimates and their precision	
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8		(eg, 95% confidence interval). Make clear which	
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10		confounders were adjusted for and why they were	
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12		included	
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16	Main results	<a href="#">#16b</a> Report category boundaries when continuous	n/a
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18		variables were categorized	
19			Continuous variables
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21			were not categorized.
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24	Main results	<a href="#">#16c</a> If relevant, consider translating estimates of	n/a
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26		relative risk into absolute risk for a meaningful time	
27			Not applicable
28		period	
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32	Other analyses	<a href="#">#17</a> Report other analyses done—e.g., analyses of	Supplementary files
33			
34		subgroups and interactions, and sensitivity	
35			
36		analyses	
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39	<b>Discussion</b>		
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42	Key results	<a href="#">#18</a> Summarise key results with reference to study	11-13
43			
44		objectives	
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48	Limitations	<a href="#">#19</a> Discuss limitations of the study, taking into account	13
49			
50		sources of potential bias or imprecision. Discuss	
51			
52		both direction and magnitude of any potential bias.	
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55	Interpretation	<a href="#">#20</a> Give a cautious overall interpretation considering	11-13
56			
57		objectives, limitations, multiplicity of analyses,	
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1 results from similar studies, and other relevant  
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3 evidence.  
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6 Generalisability [#21](#) Discuss the generalisability (external validity) of 13  
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8 the study results  
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## 10 11 Other

### 12 13 Information

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16 Funding [#22](#) Give the source of funding and the role of the 14  
17  
18 funders for the present study and, if applicable, for  
19 the original study on which the present article is  
20  
21 based  
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# BMJ Open

## Risk factor of intestinal carriage of carbapenem-resistant *Acinetobacter baumannii* and the impact on subsequent infection among patients in an intensive care unit: an observational study

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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	EPIDEMIOLOGY, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Infection control < INFECTIOUS DISEASES

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4 1 **Risk factor of intestinal carriage of carbapenem-resistant**  
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7 2 **Acinetobacter baumannii and the impact on subsequent infection**  
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10 3 **among patients in an intensive care unit: an observational study**

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12 4 Fu Qiao<sup>1</sup>, Wenzhi Huang<sup>1</sup>, Shan Gao<sup>2</sup>, Lin Cai<sup>3</sup>, Shichao Zhu<sup>1</sup>, Li Wei<sup>1</sup>, Yan Kang<sup>3</sup>,  
13  
14  
15 5 Chuanmin Tao<sup>4\*</sup>, Zhiyong Zong<sup>1,5\*</sup>

16  
17 6 <sup>1</sup> Department of Infection Control, West China Hospital, Sichuan University, Chengdu, China.

18  
19 7 <sup>2</sup> Department of Infection Control, The First Affiliated Hospital of Zhengzhou University,

20  
21 8 Zhengzhou, China. <sup>3</sup> Intensive Care Unit, West China Hospital, Sichuan University, Chengdu,

22  
23 9 China. <sup>4</sup> Department of Laboratory Medicine, West China Hospital, Sichuan University,

24  
25 10 Chengdu, China. <sup>5</sup> Center of Infectious Disease, West China Hospital, Sichuan University,

26  
27 11 Chengdu, China

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33 13 **Running title: intestinal carriage of CRAB in ICU**

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40 16 Word count: 3147

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42 17 **\*Co-corresponding author**

43  
44 18 Dr. Chuanmin Tao, Department of Laboratory Medicine, West China Hospital, Sichuan

45  
46 19 University, Chengdu, China. Email: [taocm@scu.edu.cn](mailto:taocm@scu.edu.cn)

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48 20 Dr. Zhiyong Zong, Center of Infectious Diseases, West China Hospital (Huaxi), Guoxuexiang 37,

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50 21 Chengdu 610041, China. Phone: 86-28-8542-2637. Fax: 86-28-8542-3212. E-mail:

51  
52 22 [zongzhiyong@gmail.com](mailto:zongzhiyong@gmail.com)

## 23 Abstract

24 **Objectives:** To assess the incidence and the impact of carbapenem-resistant *Acinetobacter*  
25 *baumannii* (CRAB) intestinal carriage on subsequent CRAB infection and to study risk factors of  
26 acquiring CRAB intestinal carriage among patients in intensive care unit (ICU).

27 **Design:** Observational study including a case control study and a retrospective cohort study.

28 **Setting:** A 50-bed general ICU of a university hospital, China.

29 **Methods:** From May 2017 to April 2018, an observational study was conducted in a 50-bed  
30 general ICU of a university hospital in China. Rectal swabs were collected from ICU patients on  
31 admission and thereafter weekly. A case control study was performed to analyze risk factors of the  
32 acquisition of CRAB intestinal carriage in ICU using multiple logistic regression. A retrospective  
33 cohort study was performed to address whether intestinal CRAB carriage could lead to an  
34 increased likelihood of subsequent CRAB infection using sub-distribution hazard model  
35 regarding death in the ICU as a competing risk event.

36 **Results:** CRAB intestinal carriage was detected in 6.87% (66/961; 95% CI 5.27%–8.47%) of  
37 patients on ICU admission, whereas 11.97% (115/961; 95% CI 9.91%–14.02%) of patients  
38 acquired CRAB intestinal carriage during the ICU stay. Pancreatitis (OR 2.16, 95% CI 1.28–3.67),  
39 hematological disease (OR 2.26, 95% CI 1.42–3.58), gastric tube feeding (OR 3.35, 95% CI 2.03–  
40 5.51), and use of carbapenems (OR 1.84, 95% CI 1.11–3.07) were independent risk factors for  
41 acquiring CRAB intestinal carriage. The incidence of subsequent CRAB infection was 2.24-fold  
42 in patients with CRAB intestinal carriage compared to that in patients without (95% CI 1.48–3.39,  
43  $P<0.001$ ).

44 **Conclusion:** More patients acquired CRAB intestinal carriage during their ICU stay than had on  
45 admission. Severity of illness, acute pancreatitis, tube feeding, and use of carbapenems were

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3 46 independent risk factors of acquisition of CRAB intestinal carriage. Patients with CRAB intestinal  
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5 47 carriage are more likely to develop CRAB infection.  
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10 49 **Strengths and limitations of this study**

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12 50 This observational study contains a combination of a case control study for analyzing risk factors  
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14 51 of the acquisition of CRAB intestinal carriage in ICU and a retrospective cohort study to address  
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16 52 whether intestinal CRAB carriage was associated with subsequent CRAB infection.  
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19 53 The competing risk of death in ICU was considered using a well-established model.  
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21 54 This is a single-unit study and the findings may not be generalized.  
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23 55 A culture-based method to screen CRAB, which is less sensitive than PCR-based methods.  
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26 56 Only rectal swabs were collected for screening CRAB and some CRAB carriers might have been  
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28 57 missed.  
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## 58 Background

59 *Acinetobacter baumannii* is one of the most common nosocomial pathogens in Asia and  
60 South America[1]. A systematic review has revealed that *A. baumannii* accounted for 11.28% of  
61 nosocomial infections in general hospitals in China, making it the third most common nosocomial  
62 pathogen[2]. And carbapenem-resistant *A. baumannii* (CRAB) has emerged worldwide. As early  
63 as 2013, the US Centers for Disease Control and Prevention listed multi-drug resistant *A.*  
64 *baumannii* (MDRAB) including CRAB as a serious threat[3], and the World Health Organization  
65 listed CRAB as one of the three most critical threats in a global drug-resistant warning in 2017[4].  
66 The prevalence of *A. baumannii* and its resistance to carbapenems varies from country to country.  
67 For instance, the European Bacterial Resistance Surveillance Report shows that the rate of  
68 *Acinetobacter* resistant to carbapenem in Europe in 2017 was 33.4% (95% CI 32%–35%), but it  
69 was as high as 96.2% in Croatia (95% CI 92%–98%) [5]. In the US, 49.5% of *A. baumannii* is  
70 resistant to carbapenems, while in Singapore, India, and Pakistan, it is 50%, 85%, and 62-100%,  
71 respectively[6,7]. The prevalence of CRAB is also very high in China. The surveillance data  
72 released by CHINET (China Antimicrobial Surveillance Network; <http://chinets.com/Chinet>), a  
73 national network in China, have shown that 77.1% and 78.1% of *A. baumannii* isolates resistant to  
74 imipenem and meropenem, respectively[8].

75 Infections caused by CRAB can lead to serious consequences. A previous study has  
76 demonstrated that patients with CRAB infection had longer average length of stay (LOS) in ICUs  
77 (13.1 vs. 10.5 days) and \$11,359 higher average in-hospital costs than those with carbapenem-  
78 susceptible *A. baumannii* (CSAB) infection[9]. Another previous study has found that the  
79 mortality rate of patients with CRAB infection is 2.22-fold that of patients with CSAB  
80 infection[10]. A case-control study conducted by our team have also showed that the 28-day

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3 81 survival rate of patients with bloodstream CRAB infection was 66.17%, lower than the 96.95% of  
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5 82 those with bloodstream CSAB infection[11].  
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8 83 It is well known that *A. baumannii* including CRAB may colonized in the respiratory tract of  
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10 84 hospitalized patients, in particular those with mechanical ventilation[12,13]. The colonization of  
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12 85 CRAB in the respiratory tract has been found as a major risk factor for subsequent CRAB  
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14 86 infection[14]. However, ICU patients may carry CRAB in intestine on admission or acquire CRAB  
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16 87 during the ICU stay[15]. Patients with intestinal carriage of multi-drug resistant organisms  
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18 88 (MDRO), in particular carbapenem-resistant *Enterobacteriaceae* (CRE), may sever as a reservoir  
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20 89 for further dissemination in ICU[16] and could be associated with be associated with an increased  
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22 90 risk of subsequent MDRO infections[17]. Therefore, active screening the carriage of CRE, which  
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24 91 is usually performed using rectal swabs, has been recommended as a core component of the  
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26 92 infection control bundle[7]. However, by contrast to CRE, the prevalence of CRAB intestinal  
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28 93 carriage among ICU patients is much less studied and the risk factors of acquisition of CRAB  
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30 94 intestinal carriage remains largely unknown. In addition, it remains to be determined whether  
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32 95 CRAB intestinal carriage leads to increased risks of subsequent CRAB infection. To address these  
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34 96 questions, we therefore conducted this study.  
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## 42 98 **Methods**

### 43 99 **Study settings**

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47 100 An observational study was conducted in a 50-bed general ICU of a 4,300-bed university  
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49 101 hospital in China. From May 2017 to April 2018, all patients admitted to the ICU were subjected  
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51 102 to collecting a rectal swab within 48 h of admission and thereafter weekly. For patients hospitalized  
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53 103 for less than 3 days, a rectal swab was collected only once within 48 h of admission.  
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**105 Inclusion and exclusion criteria**

106 Inclusion criteria: This study included all patients who were  $\geq 18$  years of age, admitted to  
107 the ICU, and underwent collection of rectal swabs.

108 Exclusion criteria: 1) patients who did not receive a rectal swab within 48 h of admission to  
109 ICU; or 2) patients who were eligible for weekly follow-up collection of rectal swabs but did not  
110 receive subsequent sampling; or 3) patients with CRAB infection on admission.

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**113 Definitions**

114 Patients with CRAB intestinal carriage were defined as those with CRAB isolated from a  
115 rectal swab, while patient without CRAB intestinal carriage referred to those whose swabs were  
116 all negative for CRAB during the ICU stay. Patients with CRAB isolated from a rectal swab  
117 collected within 48 h of ICU admission were defined as those with CRAB intestinal carriage on  
118 ICU admission. The acquisition of CRAB intestinal carriage referred to a patient who had a CRAB-  
119 negative rectal swab collected within 48 h of ICU admission but had CRAB from a swab collected  
120 after 48 h. CRAB infection was defined as the growth of CRAB from clinical specimens in the  
121 presence of clinical manifestations of infection[18]. Subsequent CRAB infection referred to  
122 CRAB infection developed after the collection of a CRAB-positive rectal swab for patients with  
123 CRAB intestinal carriage and CRAB infection developed after 48 h admission to the ICU for  
124 patients without CRAB intestinal carriage.

**125 Screening for CRAB by rectal swabs**

126 For collecting rectal swabs, ready-to-use transport medium swabs (HBPT004; Hopebio

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3 127 Biotechnology, Qingdao, China) was inserted about 2–3 cm into the patient's anus and then gently  
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5 128 rotated. After sampling, the swab was inserted into the ready-to-use transport medium and  
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8 129 transported to the laboratory within 2 h. Rectal swabs were inoculated onto modified CHROMagar  
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10 130 *Acinetobacter* colorimetric plates (Chromagar; Paris, France) containing 2 mg/L meropenem using  
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12 131 the partition-and-streaking method[19,20]. Plates were then cultured at 37°C for 18–24 h[20].  
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### 17 133 **Data collection and statistical analysis**

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19 134 In this study, the patient's demographic data, underlying diseases, invasive procedures,  
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21 135 medical orders, and use of antimicrobial agents were retrieved from the electronic medical record  
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24 136 system. Two professional statisticians collaborated to clean the data.  
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26 137 We performed two types of comparison. First, a case control study was performed to analyze  
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28 138 risk factors of the acquisition of CRAB intestinal carriage in ICU. Patients with ICU acquisition  
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30 139 of CRAB intestinal carriage were assigned to the case group, while those without CRAB intestinal  
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33 140 carriage during their ICU stay were assigned to the control group. All potential factors were  
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35 141 initially subjected to the univariate analysis. Quantitative data were described by the median  
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38 142 (interquartile range) and were then analyzed using a rank-sum test. Qualitative data were described  
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40 143 by number of cases (composition ratio) and were then analyzed using the chi-square test or Fisher  
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42 144 exact probability method when applied. All variables showing *P* value less than 0.2 in the  
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45 145 univariate analysis were then included into the multiple logistic regression using the forward  
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47 146 selection stepwise regression method[21,22]. Odds ratio (OR) and 95% confidence interval (CI)  
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49 147 were calculated. The Hosmer-Lemeshow method was used to test the goodness-of-fit of the  
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51 148 multiple logistic model[23].  
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54 149 Second, a retrospective cohort study was performed to address whether intestinal CRAB  
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3 150 carriage could lead to an increased likelihood of subsequent CRAB infection. In this cohort study,  
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5 151 the exposed group comprised patients with CRAB intestinal carriage either detected on ICU  
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7 152 admission or acquired during the ICU stay, while the non-exposed group consisted of those without  
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10 153 CRAB intestinal carriage. As the impact of CRAB intestinal carriage on subsequent infection may  
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12 154 also be influenced by other factors such as patient demographics, underlying diseases,  
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14 155 antimicrobial use and medical operations, we included these factors for analysis instead of  
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16 156 evaluating CRAB carriage alone. Survival curves (probability of CRAB infection) in patients with  
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18 157 and without CRAB intestinal carriage were mapped using the Fine and Gray model regarding death  
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20 158 in the ICU as a competing risk event [24,25]. After introducing the interaction term of time and  
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22 159 each variable ( $X \cdot \ln(T)$ ) into the COX model [24,25], the proportional hazards hypothesis was  
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24 160 tested, and the results showed no statistical significance ( $P < 0.05$ ). Therefore, sub-distribution  
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26 161 hazard model was used to obtain sub-distribution hazard ratios (SDHRs) and to explore whether  
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28 162 CRAB intestinal carriage was a risk factor for subsequent CRAB infection for competing events  
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31 163 (R package “cmprsk”)The Akaike information criteria (AIC) was used to select the multivariate  
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33 164 model[26]. We also performed subgroup analyses to investigate whether CRAB intestinal carriage  
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35 165 on ICU admission and that acquired in ICU had different impact on subsequent CRAB infection  
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37 166 using the same statistical method as describe above. For the subgroup analysis, patients with  
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39 167 CRAB intestinal carriage on ICU admission and those with ICU acquisition of CRAB intestinal  
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41 168 carriage were assigned to two exposed subgroups, respectively, while those without CRAB  
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43 169 intestinal carriage were assigned to the non-exposed group.  
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49 170 All statistical analyses were performed using SPSS 21.0 (IBM–SPSS Inc; Armonk, NY, US)  
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51 171 and R version 3.5.3 with a 0.05 two-sided test level.  
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## 173 **Patient and public involvement**

174 Patients were not involved in this study.

## 176 **Results**

### 177 **Some patients (6.87%) had CRAB intestinal carriage on ICU admission and more (12.85%)** 178 **acquired in ICU**

179 From May 1, 2017 to April 30, 2018, a total of 1,605 patients were admitted to the ICU, of  
180 which 382 (23.8%) were not screened during their hospital stay. Of which the 382 patients, 323  
181 (84.55%) stayed in the ICU for no more than 2 days, while the other 59 (15.45%) patients were  
182 missed for sampling. In addition, 118 patients (118/1,605, 7.4%) were excluded due to  
183 inappropriate or incomplete sampling including 104 patients whose first rectal swab was collected  
184 48 h after admission and 14 patients who were not screened weekly. A total of 144 (144/1,605,  
185 8.97%) had CRAB infection on ICU admission and were therefore also excluded. Taken together,  
186 a total of 961 patients (620 males, 64.52% and 341 female 35.48%) were included in the analysis,  
187 with an average age of 54 (44–68) years (Figure 1).

188 Among the 961 patients, 66 (6.87%, 95% CI 5.27%–8.47%) had CRAB intestinal carriage on  
189 ICU admission. For the remaining 895 patients, 115 acquired (12.85%, 95% CI 10.66%–15.04%)  
190 CRAB intestinal carriage during their ICU stay with an average age of 51 (40–70) and a 1.61  
191 male/female ratio (71 male and 44 female).

### 193 **Multiple risks factors of acquiring CRAB intestinal carriage were identified**

194 The univariate analysis showed that APACHE II score (the patient's disease severity),  
195 respiratory failure, renal dysfunction, hematological disease, acute pancreatitis, indwelling central

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3 196 venous catheter, gastric tube feeding, nebulization, and use of vancomycin, aminoglycosides,  
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5 197 carbapenems, tigecycline, and antifungal agents are risk factors for the acquisition of CRAB  
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7 198 intestinal carriage in the ICU. Multiple logistic regression including all variables with  $P < 0.2$  in  
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10 199 the univariate analysis showed that APACHE II score, pancreatitis, hematological diseases, gastric  
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12 200 tube feeding, and use of carbapenems were independent risk factors for acquiring CRAB intestinal  
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14 201 carriage during the ICU stay (Table 1). For APACHE II score, the model estimated that the  
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16 202 increase of the score by 1 point would lead to a 4% increase of the risk of acquiring CRAB  
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18 203 intestinal carriage in the ICU. Hosmer-Lemeshow test generated a 0.73 P value ( $\chi^2=5.25$ ,  $df=8$ ),  
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21 204 suggesting adequate goodness-of-fit of the multiple logistic model.  
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### 206 **CRAB intestinal carriage led to increased risks of subsequent CRAB infection**

207 During the study period, 112 of the 961 patients (11.65%, 95% CI 9.63%–13.68%) developed  
208 CRAB infections during the ICU stay. As for the infection type, lower respiratory tract infections  
209 were the most common ( $n=82$ , 73.21%), followed by bloodstream infections ( $n=9$ , 8.04%),  
210 surgical site infection ( $n=8$ , 7.14%), while 13 patients (11.61%) had infections at other sites.  
211 CRAB intestinal carriage was a risk factor for subsequent CRAB infection (HR 2.82, 95% CI  
212 1.94–4.09;  $P < 0.001$ ; Figure 2). The 90-day cumulative probability of no CRAB infection in  
213 patients with and without CRAB intestinal carriage was 69.5.0% (95% CI 43.5%–95.5%) and  
214 22.3% (95% CI 14.7%–29.9%), respectively ( $P < 0.001$ ). In the univariate analysis, CRAB  
215 intestinal carriage, APACHE II score, respiratory failure, liver dysfunction, hematological disease,  
216 pancreatitis, mechanical ventilation, placement of a central venous catheter, gastric tube feeding,  
217 and the use of carbapenems were identified as risk factors for subsequent CRAB infection. In the  
218 COX multivariate analysis, CRAB intestinal carriage was also found to be an independent risk

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3 219 factor for subsequent CRAB infection (HR 2.24, 95% CI 1.48–3.39; Table 2). Omnibus test  
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5 220 showed a log likelihood difference of 79.82 and generated a less than 0.001 P value, suggesting  
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7 221 adequate goodness-of-fit of the COX model.

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10 222 To evaluate whether CRAB intestinal carriage on admission and that acquired during the ICU  
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12 223 stay has different impact on subsequent CRAB, we performed subgroup analyses. In the subgroup  
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14 224 COX multivariate analysis, both CRAB intestinal carriage on admission and that acquired during  
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16 225 the ICU stay were an independent risk factor for subsequent CRAB infection (HR 3.42, 95% CI  
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18 226 1.88–6.22 for carriage on admission, Table S1 in the Supplementary file; HR 1.81, 95% CI 1.15–  
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20 227 2.86 for acquired carriage, Table S2). Omnibus test showed log likelihood difference of 66.06 and  
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22 228 74.18, respectively, and generated a less than 0.001 P value in the subgroup analysis, suggesting  
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24 229 adequate goodness-of-fit of the COX model.

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27 230 In addition to CRAB intestinal carriage, liver dysfunction (HR 2.33, 95% CI 1.30–4.17), and  
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29 231 the use of carbapenems (HR 2.21, 95% CI 1.40–3.49), were also identified as independent risk  
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31 232 factors of subsequent CRAB infection, while the use of cephalosporins (HR 0.45, 95% CI 0.28–  
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33 233 0.73) and cephamycins (HR 0.53, 95% CI 0.31–0.90) were protective factors (Table 2).

## 34 35 36 37 38 39 40 235 **Discussion**

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42 236 In this study, we found that in a region with a high CRAB prevalence, 6.87% of patients  
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44 237 (83.3% of those patients were transferred from other hospitals and 25.8% of them were stayed in  
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46 238 emergency ICU before admitted to the ICU) admitted to the ICU had CRAB intestinal carriage on  
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48 239 ICU admission, while an additional 11.97% of patients acquired CRAB intestinal carriage during  
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50 240 the ICU stay. The overall CRAB intestinal carriage rate was therefore 18.84%. This rate was  
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52 241 similar with a study conduct in Thailand, in which 5.45% (15/275) of patients had intestinal  
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3 242 carriage on ICU admission and 13.59% (28/206) patients acquired CRAB during their ICU  
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5 243 stay[15] and with another study in Italy[27], in which 18.92%(74/391) of patients carried CRAB  
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7 244 during ICU stay. However, the rate was significantly higher than those in Turkey (7.22%,  
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9 245 55/762)[28], Brazil (13.23%, 43/325)[29], USA (13.46%, 49/364)[30], and South Korea (15.06%,  
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11 246 168/1,115)[14], although other sites such as respiratory secretions were also screened in these  
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15 247 studies. This difference may be related to the local CRAB prevalence.

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17 248 Interestingly, we found that gastric tube feeding is a risk factor for both acquiring CRAB  
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19 249 intestinal carriage of CRAB in ICU, which is consistent with the findings of Kiddee et al[15], in  
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21 250 which tube feeding was also a high-risk factor for carriage of Gram-negative bacilli. This may  
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23 251 suggest an entry point of CRAB into human intestine. In this study, 73.0% (84/115) of patients  
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25 252 who acquired CRAB intestinal carriage using tube feeding. During the study, we performed a one-  
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27 253 day snapshot sampling of the feeding tubes (at the tube port), feeding contents and containers for  
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29 254 preparing feeding contents in the ICU and found the presence of CRAB in the tube feeding content  
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31 255 (24.0%, 6/25), at the tube port (33.3%, 3/9) and the tube feeding containers (7.1%, 1/14), indicating  
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33 256 contamination. This may be a key point for intervention in the ICU.

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37 257 We also found that patients with CRAB intestinal carriage were more likely to develop  
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39 258 subsequent CRAB infection than those without carriage. The survival curve in this study showed  
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41 259 that the cumulative infection rates in 90 days in patients with and without CRAB intestinal carriage  
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43 260 were 69.5% and 22.3%, respectively, similar to those reported in other studies[30]. However, the  
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45 261 HR was 2.24, which is much lower than those in previous studies[15,30,31]. This may be due to  
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47 262 the fact that healthcare associated infections in our ICU were mainly caused by lower respiratory  
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49 263 infections, which accounting for more than 70% of infections, while we only screened the  
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51 264 colonization of the intestines. Interestingly, we found that the use of cephalosporins and  
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3 265 cephamycins led to lower risks of subsequent CRAB infection, while carbapenem use led to  
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5 266 increased risks. The association between CRAB and carbapenem use has been documented  
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7 267 before[30,32]. CRAB is usually resistant to cephalosporins and cephamycins. The use of  
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9 268 cephalosporins and cephamycins may reflect the fact that patients did not receive carbapenems  
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11 269 and could therefore result in reduced selection pressure for CRAB.

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14 270 There are a few limitations in this study. First, this is a single center study and the findings  
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16 271 may not be generalized. Second, we used a modified CHROMagar *Acinetobacter* chromogenic  
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18 272 plate to screen CRAB from rectal swabs. Not all screened CRABs were confirmed using Vitek II  
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20 273 or other methods and there may be false negative results. Nonetheless, at the beginning of this  
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22 274 study, we confirmed that the 58 CRAB strains grown on the chromogenic medium were indeed all  
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24 275 *A. baumannii* by MALDI-TOF-MS and were all non-susceptible to imipenem or meropenem as  
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26 276 determined using the agar dilution method recommended by the Clinical and Laboratory Standards  
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28 277 Institute (CLSI)[20]. Third, we only collected the patients' rectal swabs for investigating CRAB  
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30 278 carriage. Studies have shown concurrent swab collection of skin, oropharyngeal, and airway  
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32 279 secretions in addition to rectal swabs, may improve sensitivity. However, the sample sizes in these  
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34 280 studies were small with only 21 and 34 cases, respectively[12,33]. Nonetheless, for practical  
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36 281 reasons and the aim to study CRAB intestinal carriage, we only collected rectal swabs. Fourth, due  
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38 282 to the poor sensitivity of rectal swabbing, a single negative test result could overlook carriers.  
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40 283 Moreover, no molecular strain typing was performed. Though reasonable, it was not proven that  
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42 284 CRAB isolated from intestinal colonization and site of nosocomial infection were identical. Last,  
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44 285 this study failed to collect for the first rectal swab specimen within 48 h of ICU admission from  
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46 286 23.8% of the patients. Nonetheless, 84.55% of these patients stayed in the ICU for less than 48 h.

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3 288 In conclusion, some patients had CRAB intestinal carriage but more acquired during their ICU  
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5 289 stay. Severity of illness, acute pancreatitis, tube feeding, and use of carbapenems were independent  
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7 290 risk factors of the acquisition of CRAB intestinal carriage. Patients with CRAB intestinal carriage  
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10 291 were more likely to have subsequent CRAB infection than those without.  
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12 292

### 14 293 **Acknowledgments**

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16  
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18  
19 295 of Electronic Medical Record system of West China Hospital.  
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### 23 297 **Author contributions**

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26 298 Fu Qiao, Zhiyong Zong and Chuanmin Tao contributed to study conception and design. Shichao  
27  
28 299 Zhu and Yan Kang contributed to acquisition of data. Lin Cai collected rectal swabs and  
29  
30 300 transported to the laboratory. Fu Qiao, Wenzhi Huang and Shan Gao analyzed and interpreted data.  
31  
32 301 Li Wei inoculated rectal swabs onto plates cultured for 18-24h. Fu Qiao, Zhiyong Zong and  
33  
34 302 Chuanmin Tao drafted the manuscript. All authors revised the manuscript for important intellectual  
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36 303 content. All authors read and approved the final manuscript.  
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49  
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3 311 **Competing interests**  
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5 312 The authors declare that they have no competing interests.  
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10 314 **Patient consent for publication**  
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12 315 Not required.  
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17 317 **Ethics approval**  
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19 318 This project was approved by the Ethics Committee of West China Hospital of Sichuan University.  
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21 319 We confirm that consents were not obtained from the patients. First, active screening is part of the  
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23 320 routine care for ICU patients in our hospital. In other words, no matter whether we analyzed the  
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25 321 data, the patients would receive the screening. Second, this is a retrospective study, in which we  
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27 322 looked back the patients' data and did not perform any interventions. Third, before we performed  
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29 323 this study, we have obtained ethical approval from the Ethical Committee and inform consents  
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31 324 were waived due to the retrospective nature of this study.  
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37 326 **Availability of data and materials**  
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39 327 The datasets during the current study available from the corresponding author on reasonable  
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41 328 request.  
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47 330 **References**  
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3 **433 Figure legends**  
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6 **434 Figure 1.** Patient selection flow algorithm  
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8 **435 Figure 2.** Survival curves of patients with and without CRAB intestinal carriage  
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Table 1 Risk factors for the acquisition of CRAB intestinal carriage during the ICU stay

Characteristics	Patients with acquiring CRAB intestinal carriage		Univariate analysis		Multivariate analysis	
	Yes (n=115)	No (n=780)	OR (95% CI)	P	OR (95% CI)	P
<b>Demographics</b>						
Sex, male	71 (61.74%)	502 (64.36%)	1.12 (0.75–1.68)	0.59		
Ethnicity, Han Chinese	108 (93.91%)	712 (91.28%)	1.47 (0.66–3.29)	0.34		
Age (median)	51 (40–70)	56 (45–68)	/	0.21		
<b>Underlying disease</b>						
Myocardial infarction	1 (0.87%)	4 (0.51%)	1.7 (0.19–15.36)	0.50		
Peripheral vascular disease	11 (9.57%)	62 (7.95%)	1.22 (0.62–2.40)	0.55		
Cerebrovascular disease	4 (3.48%)	36 (4.62%)	0.74 (0.26–2.13)	0.58		
Dementia	1 (0.87%)	0 (0%)	/	0.13		
Connective tissue disease	1 (0.87%)	12 (1.54%)	0.56 (0.07–4.36)	0.89		
Peptic Ulcer	5 (4.35%)	25 (3.21%)	1.37 (0.51–3.66)	0.72		
Hemiplegia	0 (0%)	1 (0.13%)	/	1.00		
Hypertension	36 (31.30%)	180 (23.08%)	1.52 (0.99–2.33)	0.05		
Tuberculosis	1 (0.87%)	12 (1.54%)	0.56 (0.07–4.36)	0.89		
COPD	10 (8.70%)	54 (6.92%)	1.28 (0.63–2.59)	0.49		
Respiratory failure	40 (34.78%)	163 (20.90%)	2.02 (1.33–3.07)	<b>0.001</b>		

Kidney failure	11 (9.57%)	31 (3.97%)	2.56 (1.25–5.24)	<b>0.01</b>		
Heart failure	7 (6.09%)	19 (2.44%)	2.99 (1.28–7.01)	0.06		
Diabetes	21 (18.26%)	102 (13.08%)	1.48 (0.89–2.49)	0.13		
Liver dysfunction	5 (4.35%)	37 (4.74%)	0.91 (0.35–2.37)	0.85		
<b>Hematological disease</b>	<b>71 (61.74%)</b>	<b>268 (34.36%)</b>	<b>3.08 (2.06–4.62)</b>	<b>&lt;0.001</b>	<b>2.26 (1.42–3.58)</b>	<b>0.001</b>
<b>Pancreatitis</b>	<b>35 (30.43%)</b>	<b>77 (9.87%)</b>	<b>3.99 (2.52–6.34)</b>	<b>&lt;0.001</b>	<b>2.16 (1.28–3.67)</b>	<b>0.004</b>
Medical operation						
<b>Surgery</b>	<b>82 (71.30%)</b>	<b>645 (82.69%)</b>	<b>0.52 (0.33–0.81)</b>	<b>0.004</b>	<b>0.40 (0.24–0.68)</b>	<b>0.001</b>
CVC	78 (67.83%)	424 (54.36%)	1.77 (1.17–2.68)	<b>0.01</b>		
Ventilator	101 (87.83%)	666 (85.38%)	1.23 (0.68–2.23)	0.49		
Indwelling catheter	110 (95.65%)	742 (95.13%)	1.13 (0.43–2.92)	0.81		
<b>Tube feeding</b>	<b>84 (73.04%)</b>	<b>280 (35.90%)</b>	<b>4.84 (3.13–7.49)</b>	<b>&lt;0.001</b>	<b>3.35 (2.03–5.51)</b>	<b>&lt;0.001</b>
Nebulizer fiberoptic	73 (63.48%)	368 (47.18%)	1.95 (1.30–2.92)	<b>0.001</b>		
Bronchoscope	1 (0.87%)	21 (2.69%)	0.32 (0.04–2.38)	0.39		
Antimicrobial use						
<b>Cephalosporin</b>	<b>35 (30.43%)</b>	<b>312 (40.00%)</b>	<b>0.66 (0.43–1.00)</b>	<b>0.05</b>	<b>0.59 (0.37–0.95)</b>	<b>0.03</b>
Vancomycin	13 (11.30%)	32 (4.10%)	2.98 (1.51–5.86)	<b>0.001</b>		
Aminoglycosides	12 (10.43%)	31 (3.97%)	2.81 (1.40–5.65)	<b>0.002</b>		
<b>Carbapenems</b>	<b>82 (71.30%)</b>	<b>295 (37.82%)</b>	<b>4.09 (2.66–6.27)</b>	<b>&lt;0.001</b>	<b>1.84 (1.11–3.07)</b>	<b>0.02</b>

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Fluoroquinolones	26 (22.61%)	137 (17.56%)	1.37 (0.85–2.20)	0.19		
Antifungal agents	49 (42.61%)	138 (17.69%)	3.45 (2.29–5.22)	<b>&lt;0.001</b>		
Cephamycins	16 (13.91%)	253 (32.44%)	0.34 (0.19–0.58)	<b>&lt;0.001</b>		
Lincomycin	3 (2.61%)	61 (7.82%)	0.32 (0.10–1.02)	<b>0.04</b>		
Tigecycline	19 (16.52%)	69 (8.85%)	2.04 (1.18–3.54)	<b>0.01</b>		
<b>APACHE II</b>	<b>21.5 (17–26)</b>	<b>17 (12–22)</b>	/	<b>&lt;0.001</b>	<b>1.04 (1.01–1.07)</b>	<b>0.01</b>
Charlson score	2 (1–5)	3 (2–4)	/	0.06		
Sharing room with other patients with	20 (17.39%)	153 (19.62%)	0.86 (0.52–1.44)	0.57		
CRAB intestinal carriage						

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multiple logistic analysis are highlighted in bold.

Table 2 Variables associated with developing subsequent CRAB infection during the ICU stay using sub-distribution hazard model

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=112)	No (n=849)	SDHR (95% CI)	P	SDHR (95% CI)	P
<b>CRAB intestinal carriage</b>	<b>51 (45.54%)</b>	<b>130 (15.31%)</b>	2.82(1.94-4.09)	<0.001	<b>2.24 (1.48–3.39)</b>	<b>&lt;0.001</b>
Demographics						
Sex, male	72 (64.29%)	548 (64.55%)	1.03(0.70-1.52)	0.87		
Ethnicity, Han Chinese	106 (94.64%)	774 (91.38%)	1.62(0.70-3.74)	0.26		
Age (median)	53 (42–67)	55 (44–68)	1.00(0.99-1.01)	0.71		
APACHE II	21 (17–26)	17 (12–22)	1.05(1.03-1.07)	<0.001		
Charlson score	3 (1–5)	3 (1.5–4)	0.98(0.88-1.08)	0.66		
Underlying disease						
Peripheral vascular disease	13 (11.61%)	66 (7.77%)	1.30(0.72-2.34)	0.38		
Cerebrovascular disease	4 (3.57%)	36 (4.24%)	0.89(0.34-2.33)	0.81		
Connective tissue disease	1 (0.89%)	12 (1.41%)	0.60(0.08-4.48)	0.62		
Peptic ulcer	4 (3.57%)	27 (3.18%)	1.11(0.46-2.71)	0.81		
Hypertension	28 (25.00%)	199 (23.44%)	1.02(0.67-1.57)	0.92		
Tuberculosis	2 (1.79%)	12 (1.41%)	1.22(0.28-5.27)	0.79		
COPD	11 (9.82%)	55 (6.48%)	1.35(0.70-2.59)	0.37		
Respiratory failure	47 (41.96%)	170 (20.02%)	2.02(1.38-2.96)	<0.001		
Kidney failure	9 (8.04%)	42 (4.95%)	1.42(0.73-2.75)	0.30		
Heart failure	4 (3.57%)	27 (3.18%)	1.22(0.48-3.11)	0.68		
Diabetes	15 (13.39%)	118 (13.90%)	0.87(0.50-1.49)	0.61		
<b>Liver dysfunction</b>	<b>17 (15.18%)</b>	<b>34 (4.00%)</b>	<b>3.15(1.86-5.35)</b>	<0.001	<b>2.33 (1.30–4.17)</b>	<b>0.005</b>
Hematological disease	60 (53.57%)	314 (36.98%)	1.61(1.11-2.34)	0.012		
Pancreatitis	29 (25.89%)	107 (12.60%)	1.94(1.29-2.92)	0.002		
Medical operation						

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Surgery	83 (74.11%)	711 (83.75%)	0.70(0.45-1.07)	0.099		
CVC	83 (74.11%)	470 (55.36%)	1.85(1.21-2.81)	0.004		
<b>Ventilator</b>	<b>103 (91.96%)</b>	<b>719 (84.69%)</b>	<b>2.02(1.04-3.93)</b>	0.038		
Indwelling catheter	109 (97.32%)	808 (95.17%)	1.84(0.62-5.52)	0.27		
Tube feeding	80 (71.43%)	332 (39.10%)	2.44(1.62-3.69)	<0.001		
Nebulizer fiberoptic	72 (64.29%)	413 (48.65%)	1.18(0.80-1.73)	0.40		
Bronchoscope	5 (4.46%)	18 (2.12%)	1.44(0.59-3.52)	0.43		
Antimicrobial use						
<b>Cephalosporin</b>	<b>20 (17.86%)</b>	<b>236 (27.80%)</b>	<b>0.50(0.31-0.81)</b>	0.005	<b>0.45 (0.28–0.73)</b>	<b>0.001</b>
Vancomycin	3 (2.68%)	35 (4.12%)	0.68(0.21-2.15)	0.51		
Aminoglycosides	1 (0.89%)	23 (2.71%)	0.24(0.03-1.71)	0.15		
<b>Carbapenems</b>	<b>82 (73.21%)</b>	<b>351 (41.34%)</b>	<b>2.84(1.87-4.32)</b>	<0.001	<b>2.21(1.40–3.49)</b>	<b>&lt;0.001</b>
Fluoroquinolones	32 (28.57%)	154 (18.14%)	1.04(0.69-1.56)	0.84		
Antifungal agents	23 (20.54%)	157 (18.49%)	0.96(0.61-1.5)	0.85		
<b>Cephamycins</b>	<b>16 (14.29%)</b>	<b>196 (23.09%)</b>	<b>0.51(0.30-0.86)</b>	0.011	<b>0.53 (0.31–0.90)</b>	<b>0.018</b>
Lincomycin	5 (4.46%)	35 (4.12%)	1.01(0.41-2.48)	0.99		
Tigecycline	13 (11.61%)	65 (7.66%)	1.33(0.76-2.34)	0.32		

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.



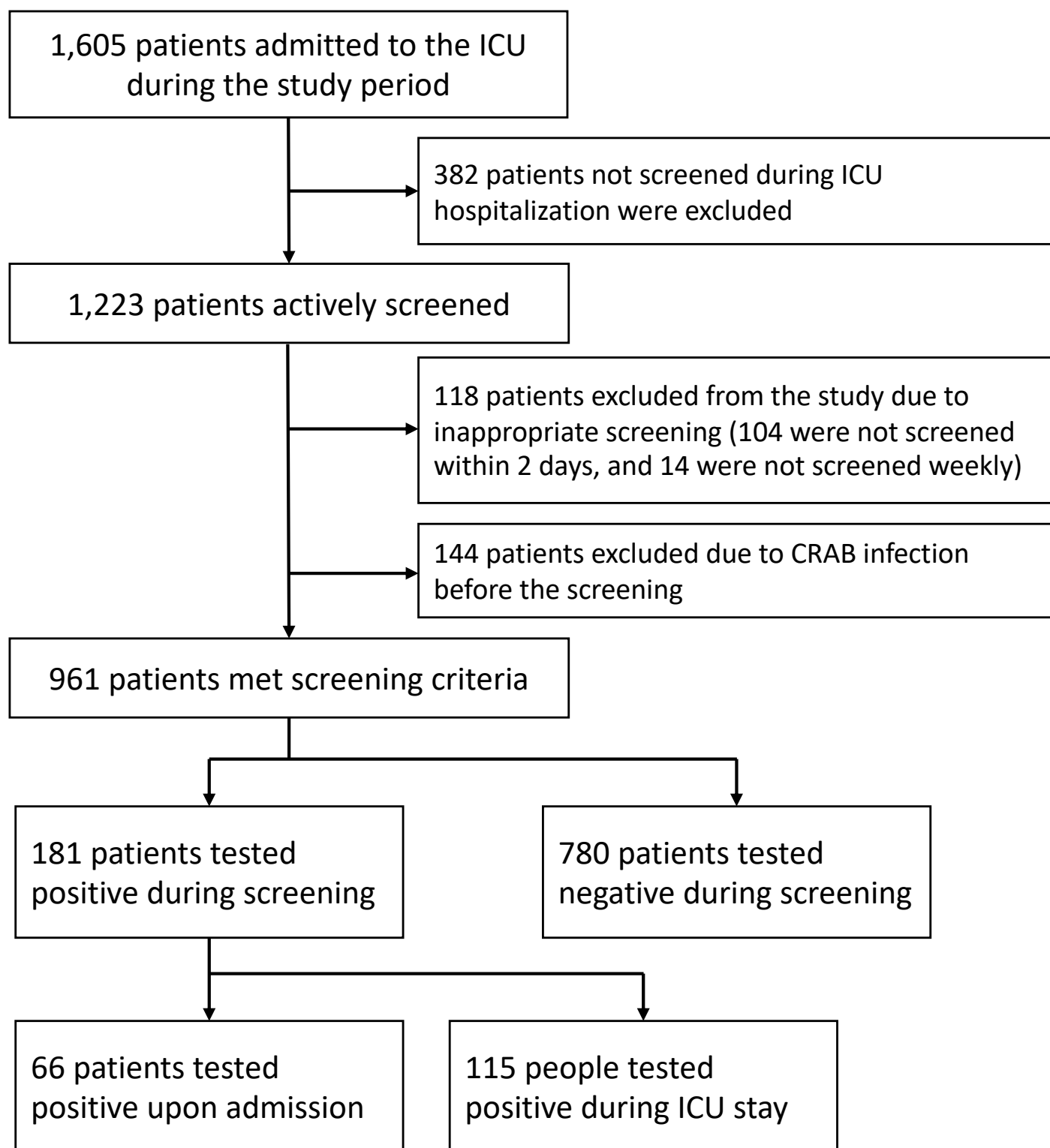
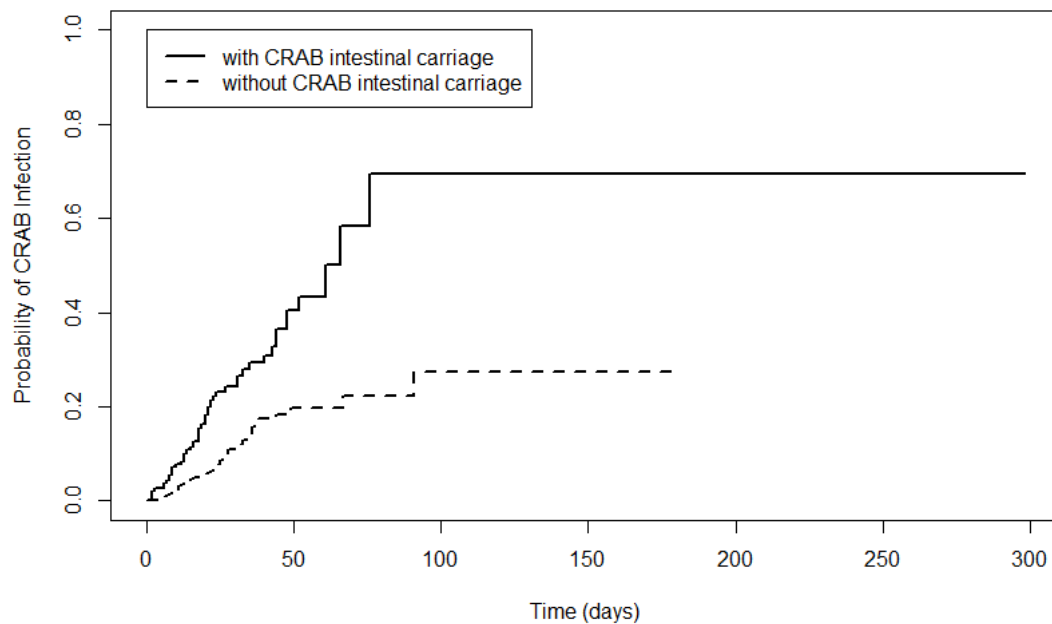


Figure 1. Patient selection flow algorithm



**Figure 2.** Survival curves of patients with and without CRAB intestinal carriage

(cumulative probability of CRAB infection). Death in the ICU is considered as a competing event, not drawn in the figure. The solid line represents patients with CRAB intestinal carriage, while the dashed line represents those without. In patients with CRAB intestinal carriage, Day 0 corresponds to the day of the first positive rectal sample. While in patients without CRAB intestinal carriage, Day 0 corresponds to the day of the first rectal sample.

## Supplementary files

Table S1 Variables associated with developing subsequent CRAB infection during the ICU stay using sub-distribution hazard model (exposed group was those patients with intestinal carriage on ICU admission)

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=80)	No (n=766)	<i>SDHR (95% CI)</i>	<i>P</i>	<i>SDHR (95% CI)</i>	<i>P</i>
<b>CRAB intestinal carriage</b>	<b>19 (23.75%)</b>	<b>47 (6.14%)</b>	3.78(2.20-6.49)	<b>&lt;0.001</b>	<b>3.42 (1.88-6.22)</b>	<b>&lt;0.001</b>
Demographics						
Sex, male	50 (62.50%)	499 (65.14%)	1.15(0.73-1.80)	0.55		
Ethnicity, Han Chinese	77 (96.25%)	697 (90.99%)	2.54(0.78-8.24)	0.12		
Age (median)	54 (42-68)	55 (44-68)	1.00(0.99-1.02)	0.85		
<b>APACHE II</b>	<b>20 (15-26)</b>	<b>17 (12-22)</b>	<b>1.06(1.03-1.08)</b>	<b>&lt;0.001</b>	<b>1.03 (1.00-1.05)</b>	<b>0.045</b>
Charlson score	3 (1-5)	3 (2-4)	1.00(0.88-1.13)	1.00		
Underlying disease						
Peripheral vascular disease	11 (13.75%)	57 (7.44%)	1.62(0.85-3.10)	0.14		
Cerebrovascular disease	3 (3.75%)	33 (4.31%)	0.87(0.29-2.66)	0.81		
Connective tissue disease	1 (1.25%)	11 (1.44%)	0.78(0.11-5.73)	0.80		
Peptic ulcer	3 (3.75%)	23 (3.00%)	1.19(0.41-3.46)	0.74		
Hypertension	18 (22.50%)	173 (22.58%)	0.97(0.58-1.64)	0.91		
Tuberculosis	1 (1.25%)	12 (1.57%)	0.72(0.10-5.37)	0.75		
<b>COPD</b>	<b>11 (13.75%)</b>	<b>45 (5.87%)</b>	<b>2.21(1.15-4.24)</b>	<b>0.017</b>	<b>2.71 (1.40-5.24)</b>	<b>0.003</b>
Respiratory failure	34 (42.50%)	143 (18.67%)	2.38(1.52-3.72)	<b>&lt;0.001</b>		
Kidney failure	5 (6.25%)	35 (4.57%)	1.13(0.474-2.7)	0.78		
Heart failure	2 (2.50%)	21 (2.74%)	1.05(0.28-3.92)	0.95		

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5	Diabetes	11 (13.75%)	101 (13.19%)	1.03(0.54-1.98)	0.92		
6	Liver dysfunction	<b>14 (17.50%)</b>	<b>32 (4.18%)</b>	<b>3.59(2.00-6.45)</b>	<b>&lt;0.001</b>	<b>2.35 (1.30-4.25)</b>	<b>0.005</b>
7	Hematological disease	42 (52.50%)	261 (34.07%)	1.84(1.19-2.85)	<b>0.006</b>		
8	Pancreatitis	17 (21.25%)	84 (10.97%)	1.91(1.13-3.22)	<b>0.016</b>		
9							
10	Medical operation						
11	Surgery	62 (77.50%)	638 (83.29%)	0.83(0.49-1.42)	0.50		
12	CVC	61 (76.25%)	414 (54.05%)	2.23(1.33-3.74)	<b>0.002</b>		
13	Ventilator	72 (90.00%)	648 (84.60%)	1.62(0.80-3.25)	0.18		
14	Indwelling catheter	78 (97.50%)	729 (95.17%)	1.91(0.53-6.94)	0.32		
15	Tube feeding	54 (67.50%)	265 (34.60%)	2.71(1.69-4.34)	<b>&lt;0.001</b>		
16	Nebulizer fiberoptic	51 (63.75%)	349 (45.56%)	1.35(0.86-2.12)	0.19		
17	Bronchoscope	5 (6.25%)	17 (2.22%)	1.85(0.77-4.46)	0.17		
18							
19	Antimicrobial use						
20	Cephalosporin	<b>15 (18.75%)</b>	<b>210 (27.42%)</b>	<b>0.54(0.31-0.95)</b>	<b>0.032</b>	<b>0.43(0.24-0.78)</b>	<b>0.006</b>
21	Vancomycin	2 (2.50%)	28 (3.66%)	0.70(0.16-2.98)	0.63		
22	Aminoglycosides	1 (1.25%)	15 (1.96%)	0.50(0.07-3.52)	0.48		
23	Carbapenems	<b>58 (72.50%)</b>	<b>284 (37.08%)</b>	<b>3.57(2.18-5.85)</b>	<b>&lt;0.001</b>	<b>2.61(1.53-4.46)</b>	<b>&lt;0.001</b>
24	Fluoroquinolones	21 (26.25%)	127 (16.58%)	1.07(0.66-1.74)	0.79		
25	Antifungal agents	17 (21.25%)	123 (16.06%)	1.26(0.74-2.12)	0.39		
26	Cephamecins	12 (15.00%)	179 (23.37%)	0.52(0.28-0.96)	<b>0.036</b>		
27	Lincomycin	3 (3.75%)	32 (4.18%)	0.84(0.26-2.68)	0.76		
28	Tigecycline	8 (10.00%)	53 (6.92%)	1.36(0.67-2.76)	0.39		

COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.

Table S2. Variables associated with developing subsequent CRAB infection during the ICU stay using sub-distribution hazard model (exposed group was those patients with ICU acquisition of CRAB intestinal carriage)

Item	Subsequent CRAB infection during the ICU stay		Univariate analysis		Multivariate analysis	
	Yes (n=93)	No (n=802)	<i>SDHR (95% CI)</i>	<i>P</i>	<i>SDHR (95% CI)</i>	<i>P</i>
CRAB intestinal carriage	<b>32 (34.41%)</b>	<b>83 (10.35%)</b>	<b>2.35(1.56-3.55)</b>	<b>&lt;0.001</b>	<b>1.81 (1.15-2.86)</b>	<b>0.011</b>
Demographics						
Sex, male	60 (64.52%)	513 (63.97%)	1.01(0.66-1.55)	0.95		
Ethnicity, Han Chinese	87 (93.55%)	731 (91.15%)	1.32(0.56-3.08)	0.52		
Age (median)	54 (44-68)	55 (45-68)	1.00(0.99-1.01)	0.70		
APACHE II	21 (18-26)	17 (12-22)	1.05(1.03-1.07)	<0.001		
Charlson score	3 (1-5)	3 (2-4)	1.01(0.91-1.13)	0.80		
Underlying disease						
Peripheral vascular disease	11 (11.83%)	62 (7.73%)	1.34(0.71-2.53)	0.37		
Cerebrovascular disease	4 (4.30%)	36 (4.49%)	1.03(0.39-2.73)	0.96		
Connective tissue disease	1 (1.08%)	12 (1.50%)	0.68(0.09-5.07)	0.70		
Peptic ulcer	4 (4.30%)	26 (3.24%)	1.39(0.58-3.33)	0.46		
Hypertension	25 (26.88%)	191 (23.82%)	1.10(0.69-1.74)	0.70		
Tuberculosis	2 (2.15%)	11 (1.37%)	1.41(0.32-6.29)	0.65		
COPD	10 (10.75%)	54 (6.73%)	1.37(0.69-2.75)	0.37		
Respiratory failure	<b>44 (47.31%)</b>	<b>159 (19.83%)</b>	<b>2.42(1.59-3.69)</b>	<b>&lt;0.001</b>	<b>1.84 (1.17-2.90)</b>	<b>0.009</b>
Kidney failure	7 (7.53%)	35 (4.36%)	1.56(0.75-3.28)	0.24		

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5	Heart failure	3 (3.23%)	24 (2.99%)	1.34(0.47-3.82)	0.58		
6	Diabetes	11 (11.83%)	112 (13.97%)	0.75(0.40-1.39)	0.36		
7	Liver dysfunction	<b>13 (13.98%)</b>	<b>29 (3.62%)</b>	<b>3.18(1.74-5.81)</b>	<b>&lt;0.001</b>	<b>2.13(1.05-4.32)</b>	<b>0.037</b>
8	Hematological disease	49 (52.69%)	290 (36.16%)	1.60(1.06-2.40)	0.025		
9	Pancreatitis	20 (21.51%)	92 (11.47%)	1.71(1.06-2.76)	0.028		
10							
11							
12	Medical operation						
13	Surgery	70 (75.27%)	666 (83.04%)	0.78(0.49-1.27)	0.32		
14	CVC	68 (73.12%)	434 (54.11%)	1.82(1.15-2.88)	0.011		
15	Ventilator	85 (91.40%)	683 (85.16%)	1.83(0.89-3.76)	0.10		
16	Indwelling catheter	91 (97.85%)	761 (94.89%)	2.37(0.58-9.63)	0.23		
17	Tube feeding	67 (72.04%)	300 (37.41%)	2.64(1.67-4.18)	<0.001		
18	Nebulizer fiberoptic	64 (68.82%)	388 (48.38%)	1.42(0.92-2.20)	0.11		
19	Bronchoscope	5 (5.38%)	18 (2.24%)	1.60(0.64-3.99)	0.31		
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21							
22	Antimicrobial use						
23							
24	Cephalosporin	<b>18 (19.35%)</b>	<b>213 (26.56%)</b>	<b>0.60(0.36-1.00)</b>	<b>0.051</b>	<b>0.59(0.35-1.00)</b>	<b>0.048</b>
25	Vancomycin	2 (2.15%)	33 (4.11%)	0.53(0.13-2.15)	0.38		
26	Carbapenems	<b>68 (73.12%)</b>	<b>319 (39.78%)</b>	<b>2.92(1.84-4.64)</b>	<b>&lt;0.001</b>	<b>2.11 (1.27-3.50)</b>	<b>0.004</b>
27	Fluoroquinolones	28 (30.11%)	144 (17.96%)	1.11(0.71-1.72)	0.65		
28	Antifungal agents	16 (17.20%)	141 (17.58%)	0.82(0.48-1.39)	0.46		
29	Cephamycins	15 (16.13%)	187 (23.32%)	0.56(0.33-0.98)	0.042		
30	Lincomycin	4 (4.30%)	34 (4.24%)	0.90(0.34-2.44)	0.84		
31	Tigecycline	7 (7.53%)	57 (7.11%)	0.91(0.43-1.96)	0.82		
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COPD, chronic obstructive pulmonary disease. CVC, central venous catheter.

Variables with P < 0.05 in the multivariate COX analysis are highlighted in bold.

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

	Reporting Item	Page Number
<b>Title and abstract</b>		
Title	<a href="#">#1a</a> Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	<a href="#">#1b</a> Provide in the abstract an informative and balanced summary of what was done and what	2

was found

## Introduction

Background / [#2](#) Explain the scientific background and rationale for 4-5  
 rationale the investigation being reported

Objectives [#3](#) State specific objectives, including any 5  
 prespecified hypotheses

## Methods

Study design [#4](#) Present key elements of study design early in the 7-8  
 paper

Setting [#5](#) Describe the setting, locations, and relevant dates, 5-6  
 including periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and 6  
 methods of selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and n/a  
 number of exposed and unexposed  
 Not matched studies

Variables [#7](#) Clearly define all outcomes, exposures, predictors, 6-8  
 potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

Data sources / [#8](#) For each variable of interest give sources of data 6-8  
 measurement and details of methods of assessment



(measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for exposed and unexposed groups if applicable.

Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	8
Study size	<a href="#">#10</a>	Explain how the study size was arrived at	n/a
			Including all the patients admitted to the ICU in the study period.
Quantitative variables	<a href="#">#11</a>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	<a href="#">#12a</a>	Describe all statistical methods, including those used to control for confounding	7-8
Statistical methods	<a href="#">#12b</a>	Describe any methods used to examine subgroups and interactions	8
Statistical methods	<a href="#">#12c</a>	Explain how missing data were addressed	n/a
			No missing data.
Statistical methods	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	n/a
			Not applicable

1	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a
2				
3	methods			Not done.
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7	<b>Results</b>			
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10	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of	9
11			study—eg numbers potentially eligible, examined	
12			for eligibility, confirmed eligible, included in the	
13			study, completing follow-up, and analysed. Give	
14			information separately for for exposed and	
15			unexposed groups if applicable.	
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25	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	9
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28	Participants	<a href="#">#13c</a>	Consider use of a flow diagram	Figure 1
29				
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31	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg	19-23
32			demographic, clinical, social) and information on	
33			exposures and potential confounders. Give	
34			information separately for exposed and unexposed	
35			groups if applicable.	
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43	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data	n/a
44			for each variable of interest	
45				No missing data.
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49	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total	Figure 2
50			amount)	
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55	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary	19-23
56			measures over time. Give information separately	
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1		for exposed and unexposed groups if applicable.	
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4	Main results	<a href="#">#16a</a> Give unadjusted estimates and, if applicable,	19-23
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6		confounder-adjusted estimates and their precision	
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8		(eg, 95% confidence interval). Make clear which	
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10		confounders were adjusted for and why they were	
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12		included	
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16	Main results	<a href="#">#16b</a> Report category boundaries when continuous	n/a
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18		variables were categorized	
19			Continuous variables
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21			were not categorized.
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24	Main results	<a href="#">#16c</a> If relevant, consider translating estimates of	n/a
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26		relative risk into absolute risk for a meaningful time	
27			Not applicable
28		period	
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32	Other analyses	<a href="#">#17</a> Report other analyses done—e.g., analyses of	Supplementary files
33			
34		subgroups and interactions, and sensitivity	
35			
36		analyses	
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39	<b>Discussion</b>		
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41			
42	Key results	<a href="#">#18</a> Summarise key results with reference to study	11-13
43			
44		objectives	
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48	Limitations	<a href="#">#19</a> Discuss limitations of the study, taking into account	13
49			
50		sources of potential bias or imprecision. Discuss	
51			
52		both direction and magnitude of any potential bias.	
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55	Interpretation	<a href="#">#20</a> Give a cautious overall interpretation considering	11-13
56			
57		objectives, limitations, multiplicity of analyses,	
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1 results from similar studies, and other relevant  
2  
3 evidence.  
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6 Generalisability [#21](#) Discuss the generalisability (external validity) of 13  
7  
8 the study results  
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## 10 11 Other

### 12 13 Information

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15  
16 Funding [#22](#) Give the source of funding and the role of the 14  
17  
18 funders for the present study and, if applicable, for  
19 the original study on which the present article is  
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21 based  
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