Survival analysis of antibiotics in patients undergoing cardiopulmonary bypass in the intensive care unit: A study based on the Medical Information Mart for Intensive Care-IV database

Keywords
antibiotics, survival analysis, cardiopulmonary bypass, Medical Information Mart for Intensive Care-IV

Abstract

Introduction
This project was designed to evaluate the influence of antibiotics on the survival of patients in the intensive care unit (ICU) undergoing cardiopulmonary bypass (CPB) treatment.

Material and methods
This retrospective cohort study included data of 7,296 patients who underwent CPB surgery and were admitted to the ICU from MIMIC-IV database. Patients with CPB were grouped according to their survival time of more than 30 days or less after admission and whether antibiotics were used, with baseline characteristics analyzed. Survival differences were demonstrated by utilizing Kaplan-Meier (K-M) curves.

Results
In CPB patients grouped according to survival time, great differences were detected in laboratory indexes, comorbidities, and treatment information. In terms of disease severity scores, vital signs, and comorbidity, there were notable differences in the data in CPB patients grouped by whether antibiotics were administrated. K-M curves manifested that the use of antibiotics substantially increased the 30-day survival rate of all CPB patients as well as CPB patients without sepsis complications. Landmark analysis indicated that the use of antibiotics greatly heightened the survival rates of all CPB patients and CPB patients without sepsis complications at 7 and 14 days after ICU admission.

Conclusions
In CPB patients admitted to the ICU, the rational use of antibiotics for treatment and prophylaxis can remarkably minimize the risk of patient mortality. These findings proffer essential references for clinical practice, assisting healthcare professionals to better assess and manage CPB patients in the ICU and formulate appropriate treatment plans to improve patient survival rates.

Survival analysis of antibiotics in patients undergoing cardiopulmonary bypass in the intensive care unit: A study based on the Medical Information Mart for Intensive Care-IV database

Short title: Impact of antibiotics on survival in patients undergoing CPB in the ICU

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Abstract:

Objective: This project was designed to evaluate the influence of antibiotics on the survival of patients in the intensive care unit (ICU) undergoing cardiopulmonary bypass (CPB) treatment.

Method: This retrospective cohort study included data of 7,296 patients who underwent CPB surgery and were admitted to the ICU from MIMIC-IV database. Patients with CPB were grouped according to their survival time of more than 30 days or less after admission and whether antibiotics were used, with baseline characteristics analyzed. Survival differences were demonstrated by utilizing Kaplan-Meier (K-M)

curves. Inter-group survival differences before and after specific time points were assessed by Landmark analysis. Three models were constructed by adjusting for different covariates. Cox regression analysis assisted with the association analysis between antibiotic use and the mortality risk in CPB patients. According to subgroup analysis, survival differences between distinct subgroups of CPB patients were compared.

Results: In CPB patients grouped according to survival time, great differences were detected in laboratory indexes, comorbidities, and treatment information. In terms of disease severity scores, vital signs, and comorbidity, there were notable differences in the data in CPB patients grouped by whether antibiotics were administrated. K-M curves manifested that the use of antibiotics substantially increased the 30-day survival rate of all CPB patients as well as CPB patients without sepsis complications. Landmark analysis indicated that the use of antibiotics greatly heightened the survival rates of all CPB patients and CPB patients without sepsis complications at 7 and 14 days after ICU admission. Cox regression analysis uncovered that the mortality risk of patients using antibiotics was tellingly reduced in all CPB patients and CPB patients without sepsis complications. The mortality risk was considerably lower in CPB patients with SOFA scores in the range of (-1, 5] (HR: 0.28, 95%CI: 0.21-0.37, P<0.001), ICU stay ≤3 days ((0，2]: HR: 0.22, 95%CI: 0.15-0.32, P<0.001; (2，3]: HR: 0.33, 95%CI: 0.21-0.53, P<0.001), and those who did not receive renal replacement therapy (RRT) (HR: 0.37, 95%CI: 0.29-0.47, P<0.001).

Conclusion: In CPB patients admitted to the ICU, the rational use of antibiotics for treatment and prophylaxis can remarkably minimize the risk of patient mortality. These findings proffer essential references for clinical practice, assisting healthcare professionals to better assess and manage CPB patients in the ICU and formulate appropriate treatment plans to improve patient survival rates.

Keywords: antibiotics; cardiopulmonary bypass; Medical Information Mart for Intensive Care-IV; survival analysis

1. Introduction

Cardiopulmonary bypass (CPB) represents a commonly utilized surgical technique in cardiac surgery, which temporarily replaces the functions of the heart and lungs through mechanical devices to maintain the body's blood circulation and oxygen supply, furnishing a stable surgical environment and reducing the burden on the patient's heart and lungs[1, 2]. Notably, although strict aseptic techniques during the CPB procedure, contact between blood and the CPB system may trigger complex immune reactions, such as complement system activation and declined levels of immunoglobulins[3, 4], elevating the risk of complications such as infections, organ dysfunction, and coagulation disorders[5-8]. Therefore, patients undergoing CPB need to stay in the Intensive Care Unit (ICU) postoperatively for close monitoring and intervention of any changes in their condition[9]. One particular concern is the persistent bacterial infections following CPB surgery that can advance the development of sepsis[10-12], considerably heightening the in-hospital mortality rate of patients[13, 14].

Searching for effective preventive and treatment modalities for infectious complications in CPB is instrumental. Antibiotics, as prevalent infection control drugs in cardiac surgery, play a pivotal role in refining the survival and prognosis of infected patients as well as effectively treating severe infectious diseases such as sepsis[15-17]. Canonical antibiotic drugs include vancomycin, cephalosporins, and aminoglycosides[18]. However, the pharmacokinetic parameters of antibiotics in CPB patients are influenced by multiple factors[19], such as physiological changes induced by the connection of patients to the CPB circuit and substitution of blood loss and intraoperative bleeding[11, 20]. Therefore, there is uncertainty about whether antibiotics in CPB can also effectively refine patient prognosis and survival.

Large-scale data was utilized in the exploration of the microbial patterns of infections in patients after prolonged CPB, with corresponding antibiotic treatment regimens formulated[5, 21]. However, there is a lack of large-scale studies to clarify the actual efficacy of antibiotics in CPB patients. The purpose of this study was to evaluate the effect of antibiotics on the survival of ICU patients treated with CPB. Therefore,

this project used Medical Information Mart for Intensive Care (MIMIC)-IV to evaluate factors affecting the prognosis of CPB patients and assess the survival impact of antibiotics, aiming to optimize the use of antibiotics in CPB patients, avert misuse and unnecessary use, and advance further development of clinical management and treatment protocols.

2. Methods

2.1 MIMIC-IV

The present retrospective analysis was based on the large publicly available MIMIC-IV database, which contained complete clinical data of ICU patients treated at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. The data covered detailed information on each patient during hospitalization, including laboratory test results and medication use (https://physionet.org/content/mimiciv/2.2/). Since the data in this database has been made publicly available and de-identified, individual informed consent was not required.

2.2 Patient selection

We screened 299,712 patients from the MIMIC-IV database. 8,270 patients who received CPB treatment were selected based on the International Classification of Diseases (ICD) codes (ICD-9: 39.61 and ICD-10: 5A1221Z). Subsequently, samples were excluded based on the following criteria: (1) those who were not the first admission to the ICU; (2) those who had ICU stay <1 day or death within 1 day of ICU admission; (3) those who aged <18 or >90 years old upon admission; (4) those who had duplicate clinical records. In the end, we included clinical data from 7,297 patients who underwent CPB for the first time upon ICU admission for analysis (Figure. 1).

2.3 Data collection

Clinical information of patients was collected from the MIMIC-IV database, which was categorized into six major classes: (1) demographic information, including gender, age, race, and marital status. (2) disease severity scores, including Sequential Organ Failure Assessment (SOFA), Glasgow Coma Scale (GCS), Systemic

Inflammatory Response Syndrome (SIRS), and Simplified Acute Physiology Score II (SAPS II). (3) comorbidity, including Acute Kidney Injury (AKI)[22], sepsis, chronic lung disease, Congestive Heart Failure (CHF), kidney disease, and liver disease. (4) vital signs including mean blood pressure (MBP), heart rate (HR), respiratory rate, and temperature. (5) Laboratory parameters including saturation of peripheral oxygen (SpO_2), blood glucose concentration, bicarbonate concentration, anion gap, chloride concentration, hematocrit, platelet count, hemoglobin, potassium ion concentrations, partial thromboplastin time (PTT), international normalized ratio (INR), prothrombin time (PT), sodium ion concentration, red blood cell (RBC) count, blood urea nitrogen (BUN), white blood cell (WBC) count, partial pressure of oxygen (pO_2), Potential of hydrogen (pH), partial pressure of carbon dioxide (pCO_2), mean corpuscular hemoglobin (MCH), base excess, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and creatinine levels. (6) treatment information including the use of antibiotics, use of vasopressors within 24 h of ICU admission and continued for more than 48 h (dopamine, epinephrine, norepinephrine, vasopressin, and phenylephrine)[23], mechanical ventilation, platelet transfusion, renal replacement therapy (RRT), RBC transfusion, and antiplatelet therapy.

2.4 Main outcomes

The main outcome of samples in this project included survival time (in days: D), length of stay (LOS) in the ICU, and survival status within 30 days after ICU admission (alive, deceased).

2.5 Statistical analysis

Continuous variables were presented as mean and standard deviation (SD), and differences between groups were determined by *t*-test. Categorical variables were presented as percentages, and differences between groups were compared with the chi-square test. Statistical significance was set at $P < 0.05$. Kaplan-Meier (K-M) curves were applied in the comparison of the trends of survival probability over time. The Landmark analysis was employed to evaluate inter-group survival differences before and after specific time points. We resorted to the Cox regression model to measure the

association between antibiotic use and the risk of death in CPB patients and set up three different models based on adjusted covariates (Model 1: Unadjusted; Model 2: Adjusted for age, gender, and race; Model 3: Adjusted for marital status, LOS, anion gap, platelets, PTT, sodium concentration, urea, WBC count, pCO_2, base excess, RDW, MCV, RTT, AKI, CHF, chronic lung disease, kidney disease, liver disease, RBC transfusion, and antiplatelet therapy on the basis of Model 2. We also compared the survival differences among different subgroups of CPB patients based on gender, age, race, marital status, SOFA, mechanical ventilation, and AKI. For all analyses, bilateral *p* values <0.05 were deemed statistically significant. We excluded variables with missing values exceeding 20% of the total sample size in life characteristics and biochemical indicators and handled other missing variables using the Random Forest (RF) method. Data analysis was performed using R (version 4.3.1) software, with R packages including *mice*[24] and *survival*[25].

3. Results

3.1 Baseline characteristics

The characteristics of patients undergoing CPB surgery are outlined in Table 1. Two groups were classified based on survival time with a cutoff of 30 days. Among the 7,296 CPB surgery patients admitted to the ICU, 6,604 survived for more than 30 days, while 692 survived for less than 30 days. Compared to patients with a survival time greater than 30 days, those with a survival time less than 30 days were more likely to be females (37.6% vs. 28.5%, *P*<0.001), had a higher average age (70.01 vs. 66.72, *P*<0.001), a lower proportion of other or unknown races (19.4% vs. 22.7%, *P*=0.037), a longer LOS (4.69 (5.09) vs. 2.97 (4.33), *P*<0.001), and were not likely to be married (51.7% vs. 61.7%, *P*=0.001). In terms of vital signs, there were notable differences between the two groups in all data except for average HR (*P*=0.308), MBP (*P*=0.353), and lowest body temperature (*P*=0.63) (*P*<0.05). Laboratory indicators varied substantially between the two groups (*P*<0.05). For example, patients with less than 30 days of survival had a lower average SpO_2 (97.58 vs. 97.72, $P = 0.014$) and a higher

maximum INR (1.62 vs. 1.45, $P < 0.001$) compared to patients with more than 30 days of survival. Similarly, the two groups exhibited telling differences in terms of comorbidity and treatment information ($P < 0.05$). For example, in the group without the use of antibiotics, CPB patients with a survival time of less than 30 days were more than those with a survival time of more than 30 days (11.0% vs. 4.4%, $P < 0.001$). In addition, in the disease severity score of the two groups, except for GCS ($P = 0.054$) and SIRS ($P = 0.206$), other scores were also remarkably different ($P < 0.05$).

As shown in Table 2, among 7,296 CPB patients, 6,932 patients used antibiotics, while 364 patients did not use antibiotics. In terms of demographic information, compared to patients who did not use antibiotics, those who used antibiotics were less likely to be Black (4.0% vs. 10.7%, $P<0.001$), more likely to be married (61.2% vs. 51.9%, $P=0.001$), and had a longer LOS (4.53 vs. 1.71, $P=0.006$). Patients of the two groups were greatly different in severity scores, vital signs, and comorbidity data ($P<0.05$). For example, in comorbidity, the incidence of sepsis differed dramatically between the two groups ($P<0.001$), with 60% of patients using antibiotics developing sepsis while none of the patients not using antibiotics developing sepsis. In terms of laboratory indicators, except for blood glucose ($P=0.635$), highest potassium ion concentration ($P=0.089$), maximum INR ($P=0.429$), maximum PT ($P=0.429$), lowest pO_2 ($P=0.37$), lowest MCH ($P=0.404$), lowest MCHC ($P=0.6$), and lowest MCV ($P=0.94$) exhibiting no remarkable differences, other indicators demonstrated significant differences ($P<0.05$). In terms of treatment information, except for the use of vasopressin ($P=0.117$), dopamine ($P=0.896$), and antiplatelet therapy ($P=0.137$), there were dramatic differences in other treatment information ($P<0.05$).

3.2 Survival analysis

Among all patients undergoing CPB surgery, patients using antibiotics had tellingly better survival than those not using antibiotics ($P<0.0001$) (Figure 2A). Specifically, the survival rates of patients not using antibiotics at 3 days, 5 days, 10 days, and 30 days were 82.1%, 79.7%, 79.4%, and 79.1% respectively (Table S1), while the corresponding survival rates of patients using antibiotics were 94.5%, 94.5%, 92.0%,

and 91.1% respectively (Table S1). In further studies, we probed into the survival role of antibiotics in patients without sepsis, illuminating whether prophylactic use of antibiotics was necessary for CPB patients to reduce the occurrence of severe complications. Similarly, among patients undergoing CPB surgery without sepsis, those using antibiotics had substantially higher 30-day survival rates than those not receiving antibiotics (P<0.0001) (Figure 2B). Landmark analysis uncovered that the use of antibiotics considerably elevated the survival status of all CPB surgery patients (Figure 3A-B) and CPB patients without sepsis complications (Figure 3C-D) at 7 and 14 days (P<0.001).

3.3 Cox regression analysis

The results of Cox regression analysis delineated that in all three models, the risk of death dramatically declined in all patients treated with antibiotics compared to those not using antibiotics (Model 1: HR: 0.383, 95%CI: 0.302-0.486, P<0.001; Model 2: HR: 0.391, 95%CI: 0.308-0.497, P<0.001; Model 3: HR: 0.439, 95%CI: 0.326-0.59, P<0.001) (Table 3). Based on Cox model regression analysis on CPB patients without sepsis, in three different covariate-adjusted models, patients treated with antibiotics had a strikingly lower risk of death compared to those not using antibiotics (Model 1: HR: 0.247, 95%CI: 0.188-0.324, P<0.001; Model 2: HR: 0.258, 95%CI: 0.196-0.340, P<0.001; Model 3: HR: 0.461, 95%CI: 0.327-0.648, P<0.001) (Table 4).

3.4 Subgroup analysis

Subgroup analysis in Figure 4 revealed a remarkably lower risk of death in subgroups of CPB patients with SOFA scores ranging from (− 1, 5] (HR: 0.28, 95% CI: 0.21-0.37, P < 0.001), ICU admission ≤ 3 days ((0, 2]: HR: 0.22, 95% CI: 0.15-0.32, P < 0.001; (2, 3]: HR: 0.33, 95% CI: 0.21-0.53, P < 0.001), and no RRT (HR: 0.37, 95% CI: 0.29-0.47, P < 0.001).

4. Discussion

In this study, we observed that 60% of CPB patients receiving antibiotic treatment developed sepsis. After comprehensive statistical analysis, we found that antibiotic

treatment considerably reduced the risk of death for all CPB patients and CPB patients without sepsis (P<0.001). Moreover, the subgroup of CPB patients with SOFA scores ranging from (-1, 5], ICU stay ≤3 days and those not undergoing RRT had a remarkably lower risk of death (P<0.001). These results emphasized the critical role of antibiotics in reducing the risk of death in CPB patients.

The findings of this project indicated that antibiotic treatment has obvious benefits for the survival of patients undergoing CPB treatment. Although patients undergoing cardiac surgery with CPB have established conventional treatment strategies to control the initial high inflammatory response, persistent immunosuppression remains a clinical challenge, making patients susceptible to postoperative infections and increasing the mortality risk[26, 27]. Observational studies have demonstrated that infections following CPB cardiac surgery include sternal wound infections, mediastinitis, endocarditis, or device-related infections, and are tightly linked with adverse outcomes and rising treatment costs[28, 29]. Early diagnosis and appropriate antibiotic use to control infections can aid in reducing mortality from postoperative complications, shortening hospital stays, and improving outcomes for cardiac surgery patients[15]. Patients with bloodstream infections following CPB are likely to be infected with Gram-negative bacilli[5, 21]. Oral antibiotics, especially those with high bioavailability, possess impactful efficacy in eradicating Gram-negative bloodstream infections[30]. Additionally, antibiotic therapy can effectively heighten the survival rate and shorten the treatment time for infected patients in the ICU[31]. A retrospective study on patients progressing from sepsis to septic shock in the ICU also manifested that antibiotic treatment regimens containing at least two extracorporeal active antibiotics can improve survival rates[32]. Combining our results, antibiotics are instrumental in treating postoperative infections including sepsis in ICU patients undergoing CPB, greatly promoting patient survival rates.

In the samples of this project, 60% of CPB patients receiving antibiotic treatment developed sepsis, while 40% did not have this complication. Sepsis, as a severe systemic infection complication after CPB cardiac surgery, is one of the important risk factors affecting patient prognosis[12, 33, 34]. Timely administration of antibiotics to septic

patients can refine patient survival[35, 36]. Furthermore, we further dissected the survival effect of antibiotics in CPB patients without sepsis to evaluate the necessity of prophylactic antibiotic use in this population. The results uncovered that antibiotics greatly reduced the mortality risk in such patients. This result may be attributed to the effective prevention and control of infections by antibiotics. For example, perioperative antibiotic prophylaxis is one of the most essential measures to prevent surgical site infections in cardiac surgery, which can reduce the incidence of surgical site infections in cardiac surgery and other surgeries, thereby minimizing the occurrence rates of related complications and mortality[18, 37]. In conclusion, the rational use of antibiotics for CPB patients can help improve patient survival.

We unearthed that the risk of death was considerably elevated for CPB patients with ICU stays exceeding three days. The result is in line with previous research findings, which delineated that in cardiac surgery patients, those with ICU stays of more than 3 days had dramatically elevated ICU, in-hospital, and long-term mortality rates compared to those with stays of 3 days or less, mainly due to organ failure[38]. The SOFA score has been validated in cardiac surgery patients as an objective indicator for assessing the severity of organ dysfunction[39, 40]. This scoring system aims to quantitatively assess the severity of dysfunction in six organ systems, including the respiratory system, circulatory system, renal system, hematological system, liver, and central nervous system, having a pivotal impact on the recuperation process following heart surgery[41]. Former studies have illuminated that patients undergoing cardiac surgery may develop organ dysfunction, which can further deteriorate and affect the prognosis of patients[42]. In the population undergoing cardiac surgery, the SOFA score has demonstrated good discriminative ability in predicting in-hospital mortality[43]. A large-scale study based on the MIMIC-III database confirmed that cardiac surgery patients with higher SOFA scores (SOFA score $\geq$ 7) have a higher risk of adverse clinical outcomes, including higher in-hospital mortality, 28-day mortality, 90-day mortality, and 1-year mortality, as well as longer ICU stay[42]. This is harmonized with the trend in our project, where the mortality risk in CPB patients with SOFA scores of -1 to 5 was tellingly higher than in CPB patients with scores of 5 to 21. Therefore, the

present work not only underscored that a longer ICU nursing time may indicate a slow treatment response and adverse prognosis in CPB patients but also supplied further data support to reiterate the importance of organ failure in assessing prognosis for CPB patients. By timely and comprehensive assessment of the organ function status of CPB patients, clinicians can more accurately predict the patients' survival probability and propose timely treatment and management strategies. The results of this project also demonstrated that CPB patients who received RRT had an elevated risk of death. An investigation into the long-term survival rate, possibility, and timeline of kidney function recovery in cardiac surgery patients requiring postoperative RRT uncovered that postoperative RRT is an independent risk factor for patient mortality[44]. In another multinational study report, the incidence of acute renal failure requiring RRT in ICU patients ranged from 5% to 6%, greatly associated with a high in-hospital mortality rate[45]. Therefore, for critically ill CPB patients who have undergone RRT, close monitoring of their kidney function recovery is necessary to adjust treatment plans promptly.

To our knowledge, this is the first project to excavate the relationship between antibiotics and survival in critically ill CPB patients, providing new insights into the postoperative management of CPB patients. Antibiotic therapy is not only beneficial for patients who have already developed an infection, but also has a significant effect on preventing postoperative infections. Based on the results of the study, we suggest that the following improvements should be considered for implementation in daily clinical practice for post-CPB patients: 1. Prophylactic antibiotic use should be considered for all post-CPB patients, even when there are no signs of infection, in order to minimize the risk of infection. 2. Enhanced monitoring of post-CPB patients should be performed to allow for early diagnosis of infection and timely initiation of antibiotic therapy. 3. Patient-specific circumstances, including the type of possible infection and the pharmacokinetic properties of the antibiotic, should be taken into account when selecting antibiotics.

Certain limitations persist in our project. First of all, the exclusion of variables with missing values exceeding 20% of the total sample size in vital signs and

biochemical indicators may exert some impact on results. In addition, sample size limitations may affect the statistical significance and external validity of the results. Although we used the MIMIC-IV database for our analyses, the patient population in this database may not be fully representative of all CPB patients, especially since there may be differences in treatment practices across hospitals and regions. Second, the acquisition and quality of the data may have influenced the study results. Since this study relied on observational data, there may be information bias or omissions, especially the lack of specific dose, start time, and total number of days of antibiotic administration. These factors may have led to an underestimation or overestimation of antibiotic efficacy. Additionally, the study failed to control for all potential confounders, which may have affected patient survival and prognosis. Therefore, although the results show a significant benefit of antibiotic treatment on survival in patients with CPB, caution should be exercised in interpreting these results. Finally, because this study was conducted based on an observational database and thus lacked a randomized controlled trial design, potential bias could not be completely excluded. Therefore, prospective randomized controlled trials should be considered for future studies to verify the actual efficacy of antibiotics in CPB patients and to further explore the optimal antibiotic use strategy.

Declaration

Author contribution

Conceptualization: Xian Ma

Data curation: Jiangmin Liu

Formal Analysis: Xian Ma

Investigation: Jiangmin Liu

Methodology: Jie He

Project administration: Congna Zi

Supervision: Xian Ma

Validation: Jie He

Writing – original draft: Jie He

Writing – review & editing: Congna Zi

Ethics approval and consent to participate

Before data from this study were included in the MIMIC-IV public database, all participants signed informed consent forms, adhered to the principles outlined in the Declaration of Helsinki, and were reviewed and approved by the NCHS Ethical Review Board.

Consent for publication

Not applicable.

Availability of data and materials

The data and materials in the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare no conflicts of interest.

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Figure legends

Figure 1 Inclusion and exclusion criteria

Figure 2 Survival analysis of patients with CPB based on whether antibiotics were used or not.

A-B: K-M survival curves in 30 days for all patients (A) and non-septic patients (B), respectively.

Figure 3 Landmark analysis of patients with CPB of use antibiotic or not.

A-B: K-M survival curves for all patients with cutoffs set at 7 days (A) and 14 days (B), respectively.

C-D: K-M survival curves for patients without sepsis, with cutoffs set at 7 days (C) and 14 days (D), respectively.

Figure 4 Subgroup analysis of patients who underwent CPB

Antibiotics Enhance Survival in ICU Patients Undergoing Cardiopulmonary Bypass

Data sources: Medical Information Mart for Intensive Care-IV database 2008-2019

Method:
Patients: ICU admissions post-CPB surgery
Grouping: Based on survival ≥30 days vs. <30 days
Antibiotic prophylaxis: Assessed impact on survival
Statistical analyses: Kaplan-Meier, Landmark, and Cox regression
Key variables: SOFA score, ICU stay, Renal Replacement Therapy
Outcome: 30-day survival rate

Result:
1. Antibiotic use associated with significantly reduced mortality risk.
2. Landmark analysis confirmed survival benefits at 7 and 14 days.
3. Adjusted for demographics, clinical variables, and key indicators such as SOFA score, ICU stay, and RRT.
4. Subgroup analysis: SOFA score and ICU stay as significant modifiers.

- Antibiotic treatment in CPB patients significantly reduced the risk of mortality.
- Prophylactic use of antibiotics is associated with improved survival outcomes.
- Early administration of antibiotics post-CPB surgery is crucial for better patient prognosis.
- Further studies are warranted to optimize antibiotic regimens in CPB patients.

Table1. Baseline Table of patients with cardiopulmonary bypass surgery divided by patient survival at 30 days

Variable	Total	Survival longer than 30 days	Survival less than 30 days	P-value
Number of patients	7296	6604	692	
Gender (%)				<0.001
Female	2140 (29.3)	1880 (28.5)	260 (37.6)	
Male	5156 (70.7)	4724 (71.5)	432 (62.4)	
Age (mean (SD))	67.03 (11.54)	66.72 (11.41)	70.01 (12.29)	<0.001
Race (%)				0.037
Black	315 (4.3)	276 (4.2)	39 (5.6)	
White	1636 (22.4)	4826 (73.1)	519 (75.0)	
Other/Unkown	5345 (73.3)	1502 (22.7)	134 (19.4)	
Marital status (%)				0.001
Married	4431 (60.7)	4073 (61.7)	358 (51.7)	
Unmarried/Unkown	2865 (39.3)	2531 (38.3)	334 (48.3)	
LOS,(mean (SD))	3.13 (4.43)	2.97 (4.33)	4.69 (5.09)	<0.001
Heart rate mean,(mean (SD))	81.97 (10.02)	81.93 (9.86)	82.34 (11.50)	0.308
MBP mean,(mean (SD))	74.62 (6.73)	74.64 (6.49)	74.39 (8.75)	0.353
Respiratory rate mean,(mean (SD))	17.84 (2.76)	17.79 (2.71)	18.32 (3.16)	<0.001
Temperature min,(mean (SD))	36.01 (0.78)	36.00 (0.79)	36.02 (0.67)	0.63
SpO_2 mean,(mean (SD))	97.70 (1.44)	97.72 (1.37)	97.58 (1.96)	0.014
GCS min,(mean (SD))	13.30 (3.61)	13.27 (3.64)	13.55 (3.32)	0.054
SAPSII,(mean (SD))	37.46 (11.79)	37.07 (11.63)	41.25 (12.69)	<0.001
SOFA,(mean (SD))	5.23 (2.78)	5.14 (2.69)	6.18 (3.39)	<0.001
Aniongap max,(mean (SD))	13.26 (3.28)	13.08 (3.07)	14.97 (4.53)	<0.001
Bicarbonate min,(mean (SD))	22.32 (2.50)	22.39 (2.37)	21.69 (3.49)	<0.001
Chloride max,(mean (SD))	108.74 (4.18)	108.83 (4.00)	107.90 (5.51)	<0.001
Hematocrit min,(mean (SD))	27.49 (4.79)	27.61 (4.72)	26.34 (5.28)	<0.001
Hemoglobin min,(mean (SD))	9.28 (1.66)	9.32 (1.64)	8.83 (1.81)	<0.001
Lactate max,(mean (SD))	2.87 (1.55)	2.82 (1.41)	3.36 (2.45)	<0.001
Platelets min,(mean (SD))	141.90 (57.70)	141.38 (56.33)	146.84 (69.30)	0.018
Potassium max,(mean (SD))	4.63 (0.58)	4.62 (0.57)	4.77 (0.72)	<0.001
PTT max,(mean (SD))	42.51 (24.20)	41.63 (23.15)	50.94 (31.35)	<0.001
INR max,(mean (SD))	1.47 (0.45)	1.45 (0.39)	1.62 (0.82)	<0.001
PT max,(mean (SD))	16.16 (5.34)	15.99 (4.64)	17.81 (9.64)	<0.001
Sodium min,(mean (SD))	137.11 (3.04)	137.13 (2.96)	136.86 (3.76)	0.026
Bun max,(mean (SD))	20.20 (12.30)	19.25 (10.54)	29.34 (21.02)	<0.001
WBC max,(mean (SD))	16.26 (7.53)	16.34 (7.59)	15.52 (6.93)	0.006
RBC min,(mean (SD))	3.07 (0.57)	3.08 (0.56)	2.95 (0.63)	<0.001
PO_2 min,(mean (SD))	103.46 (43.11)	104.26 (42.39)	95.78 (48.82)	<0.001
PCO_2 max,(mean (SD))	48.67 (7.64)	48.53 (7.26)	50.01 (10.51)	<0.001
ph min,(mean (SD))	7.31 (0.06)	7.31 (0.06)	7.29 (0.09)	<0.001
Base excess min,(mean (SD))	-3.13 (2.94)	-3.03 (2.70)	-4.05 (4.55)	<0.001
MCH min,(mean (SD))	29.96 (2.10)	30.00 (2.08)	29.64 (2.26)	<0.001

MCHC min,(mean (SD))	33.15 (1.34)	33.18 (1.32)	32.83 (1.48)	<0.001
MCV min,(mean (SD))	89.25 (5.35)	89.30 (5.28)	88.83 (5.94)	0.027
RDW max,(mean (SD))	14.22 (1.59)	14.10 (1.50)	15.30 (1.99)	<0.001
Creatinine max,(mean (SD))	1.17 (1.08)	1.09 (0.87)	1.88 (2.12)	<0.001
Mechanical ventilation,(%)				<0.001
No	6825 (93.5)	6257 (94.7)	568 (82.1)	
Yes	471 (6.5)	347 (5.3)	124 (17.9)	
Norepinephrine (%)				<0.001
No	7082 (97.1)	6450 (97.7)	632 (91.3)	
Yes	214 (2.9)	154 (2.3)	60 (8.7)	
Epinephrine (%)				<0.001
No	7161 (98.1)	6515 (98.7)	646 (93.4)	
Yes	135 (1.9)	89 (1.3)	46 (6.6)	
Phenylephrine (%)				<0.001
No	6936 (95.1)	6315 (95.6)	621 (89.7)	
Yes	360 (4.9)	289 (4.4)	71 (10.3)	
Dopamine (%)				0.001
No	7284 (99.8)	6597 (99.9)	687 (99.3)	
Yes	12 (0.2)	7 (0.1)	5 (0.7)	
Vasopressin (%)				<0.001
No	7199 (98.7)	6540 (99.0)	659 (95.2)	
Yes	97 (1.3)	64 (1.0)	33 (4.8)	
Use pressor drugs (%)				<0.001
No	6688 (91.7)	6135 (92.9)	553 (79.9)	
Yes	608 (8.3)	469 (7.1)	139 (20.1)	
Antibiotic use (%)				<0.001
No	364 (5.0)	288 (4.4)	76 (11.0)	
Yes	6932 (95.0)	6316 (95.6)	616 (89.0)	
RRT (%)				<0.001
No	7225 (99.0)	6569 (99.5)	656 (94.8)	
Yes	71 (1.0)	35 (0.5)	36 (5.2)	
AKI (%)				<0.001
No	1554 (21.3)	1482 (22.4)	72 (10.4)	
Yes	5742 (78.7)	5122 (77.6)	620 (89.6)	
SEPSIS (%)				<0.001
No	3136 (43.0)	2902 (43.9)	234 (33.8)	
Yes	4160 (57.0)	3702 (56.1)	458 (66.2)	
Congestive heart failure (%)				<0.001
No	5230 (71.7)	4882 (73.9)	348 (50.3)	
Yes	2066 (28.3)	1722 (26.1)	344 (49.7)	
Chronic pulmonary disease (%)				<0.001
No	5714 (78.3)	5243 (79.4)	471 (68.1)	
Yes	1582 (21.7)	1361 (20.6)	221 (31.9)	
Renal disease (%)				<0.001

No	6106 (83.7)	5656 (85.6)	450 (65.0)	
Yes	1190 (16.3)	948 (14.4)	242 (35.0)	
Liver disease (%)				<0.001
No	7003 (96.0)	6380 (96.6)	623 (90.0)	
Yes	293 (4.0)	224 (3.4)	69 (10.0)	
Platelet transfusion (%)				<0.001
No	6149 (84.3)	5630 (85.3)	519 (75.0)	
Yes	1147 (15.7)	974 (14.7)	173 (25.0)	
RBC transfusion (%)				<0.001
No	5013 (68.7)	4705 (71.2)	308 (44.5)	
Yes	2283 (31.3)	1899 (28.8)	384 (55.5)	
Anti-platelet				<0.001
No	33 (0.5)	23 (0.3)	10 (1.4)	
Yes	7263 (99.5)	6581 (99.7)	682 (98.6)	
SIRS				0.206
0	30 (0.4)	27 (0.4)	3 (0.4)	
1	552 (7.6)	491 (7.4)	61 (8.8)	
2	2063 (28.3)	1848 (28.0)	215 (31.1)	
3	3364 (46.1)	3061 (46.4)	303 (43.8)	
4	1287 (17.6)	1177 (17.8)	110 (15.9)	

Note: GCS, Glasgow Coma Scale; LOS, length of stay in ICU; MBP, mean blood pressure; SAPS II, simplified acute physiology score (SAPS) II; PTT, partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; WBC, white blood cell; RBC, red blood cell.

Table 2 Baseline Table of patients with cardiopulmonary bypass surgery for patients taking antibiotics or not

Variable	No antibiotics used	Use antibiotics	P-value
Number of patients	364	6932	
Gender (%)			0.302
Female	116 (31.9)	2024 (29.2)	
Male	248 (68.1)	4908 (70.8)	
Age (mean (SD))	66.85 (12.60)	67.04 (11.48)	0.761
Race (%)			<0.001
Black	39 (10.7)	276 (4.0)	
White	263 (72.3)	5082 (73.3)	
Other/Unkown	62 (17.0)	1574 (22.7)	
Marital status (%)			0.001
Married	189 (51.9)	4242 (61.2)	
Unmarried/Unkown	175 (48.1)	2690 (38.8)	
LOS,(mean (SD))	2.51 (1.71)	3.16 (4.53)	0.006
Heart rate mean,(mean (SD))	80.50 (13.79)	82.05 (9.78)	0.004
MBP mean,(mean (SD))	78.94 (10.54)	74.39 (6.39)	<0.001
Respiratory rate mean,(mean (SD))	18.52 (3.05)	17.81 (2.74)	<0.001
Temperature min,(mean (SD))	36.24 (0.54)	35.99 (0.79)	<0.001
SpO_2 mean,(mean (SD))	96.87 (1.64)	97.75 (1.41)	<0.001
Glucose mean,(mean (SD))	144.04 (46.69)	204.50 (2431.40)	0.635
GCS min,(mean (SD))	13.90 (2.97)	13.27 (3.64)	0.001
SAPSII,(mean (SD))	33.10 (12.39)	37.69 (11.72)	<0.001
SOFA,(mean (SD))	3.55 (2.71)	5.32 (2.76)	<0.001
Anion gap max,(mean (SD))	15.30 (4.15)	13.15 (3.19)	<0.001
Bicarbonate min,(mean (SD))	22.92 (3.61)	22.29 (2.43)	<0.001
Chloride max,(mean (SD))	105.15 (5.39)	108.93 (4.02)	<0.001
Hematocrit min,(mean (SD))	31.51 (6.58)	27.28 (4.58)	<0.001
Hemoglobin min,(mean (SD))	10.61 (2.25)	9.21 (1.60)	<0.001
Lactate max,(mean (SD))	2.40 (1.24)	2.90 (1.56)	<0.001
Platelets min,(mean (SD))	189.60 (78.01)	139.40 (55.31)	<0.001
Potassium max,(mean (SD))	4.58 (0.71)	4.64 (0.58)	0.089
PTT max,(mean (SD))	52.80 (36.12)	41.97 (23.28)	<0.001
INR max,(mean (SD))	1.45 (0.72)	1.47 (0.43)	0.429
PT max,(mean (SD))	15.87 (6.99)	16.17 (5.24)	0.298
Sodium min,(mean (SD))	136.37 (4.39)	137.15 (2.95)	<0.001
Bun max,(mean (SD))	28.80 (21.41)	19.75 (11.45)	<0.001
WBC max,(mean (SD))	12.50 (5.76)	16.46 (7.56)	<0.001
RBC min,(mean (SD))	3.54 (0.78)	3.04 (0.54)	<0.001
PO_2 min,(mean (SD))	105.43 (65.89)	103.36 (41.57)	0.37
PCO_2 max,(mean (SD))	45.72 (8.14)	48.83 (7.58)	<0.001
ph min,(mean (SD))	7.35 (0.07)	7.31 (0.06)	<0.001
Base excess min,(mean (SD))	-1.85 (3.32)	-3.19 (2.91)	<0.001
MCH min,(mean (SD))	29.87 (2.23)	29.97 (2.09)	0.404

MCHC min,(mean (SD))	33.19 (1.37)	33.15 (1.34)	0.6
MCV min,(mean (SD))	89.23 (5.98)	89.26 (5.32)	0.94
RDW max,(mean (SD))	14.61 (1.50)	14.20 (1.59)	<0.001
Creatinine max,(mean (SD))	1.66 (1.87)	1.14 (1.01)	<0.001
Mechanical ventilation,(%)			0.004
No	354 (97.3)	6471 (93.3)	
Yes	10 (2.7)	461 (6.7)	
Norepinephrine (%)			0.022
No	361 (99.2)	6721 (97.0)	
Yes	3 (0.8)	211 (3.0)	
Epinephrine (%)			0.037
No	363 (99.7)	6798 (98.1)	
Yes	1 (0.3)	134 (1.9)	
Phenylephrine (%)			0.002
No	359 (98.6)	6577 (94.9)	
Yes	5 (1.4)	355 (5.1)	
Dopamine (%)			0.896
No	364 (100.0)	6920 (99.8)	
Yes	0 (0.0)	12 (0.2)	
Vasopressin (%)			0.117
No	363 (99.7)	6836 (98.6)	
Yes	1 (0.3)	96 (1.4)	
Use pressor drugs (%)			<0.001
No	356 (97.8)	6332 (91.3)	
Yes	8 (2.2)	600 (8.7)	
RRT (%)			0.001
No	354 (97.3)	6871 (99.1)	
Yes	10 (2.7)	61 (0.9)	
AKI (%)			0.026
No	95 (26.1)	1459 (21.0)	
Yes	269 (73.9)	5473 (79.0)	
SEPSIS (%)			<0.001
No	364 (100.0)	2772 (40.0)	
Yes	0 (0.0)	4160 (60.0)	
Congestive heart failure (%)			<0.001
No	185 (50.8)	5045 (72.8)	
Yes	179 (49.2)	1887 (27.2)	
Chronic pulmonary disease (%)			0.022
No	267 (73.4)	5447 (78.6)	
Yes	97 (26.6)	1485 (21.4)	
Renal disease (%)			<0.001
No	260 (71.4)	5846 (84.3)	
Yes	104 (28.6)	1086 (15.7)	
Liver disease (%)			<0.001

No	336 (92.3)	6667 (96.2)	
Yes	28 (7.7)	265 (3.8)	
Platelet transfusion (%)			<0.001
No	343 (94.2)	5806 (83.8)	
Yes	21 (5.8)	1126 (16.2)	
RBC transfusion (%)			<0.001
No	296 (81.3)	4717 (68.0)	
Yes	68 (18.7)	2215 (32.0)	
Anti-platelet			0.137
No	4 (1.1)	29 (0.4)	
Yes	360 (98.9)	6903 (99.6)	
SIRS			0.009
0	1 (0.3)	29 (0.4)	
1	42 (11.5)	510 (7.4)	
2	114 (31.3)	1949 (28.1)	
3	157 (43.1)	3207 (46.3)	
4	50 (13.7)	1237 (17.8)	

Note: GCS, Glasgow Coma Scale; LOS, length of stay in ICU; MBP, mean blood pressure; SAPS II, simplified acute physiology score (SAPS) II; PTT, partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; BUN, blood urea nitrogen; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW, red cell distribution width; WBC, white blood cell; RBC, red blood cell.

Table 3 Cox model in all participants

Cox regression model	Hazard Ratio(95%CI)	P-value
Model1	0.383(0.302-0.486)	<0.001
Model2	0.391(0.308-0.497)	<0.001
Model3	0.439(0.326-0.59)	<0.001

Model 1: unadjusted

Model 2: adjusted for model 1 plus age, gender, race

Model 3: adjusted for model 2 plus marry status, LOS, anion gap, platelets, PTT, sodium, BUN, WBC, pCO_2, base excess, RDW, MCV, RTT, AKI, sepsis, congestive heart failure, chronic pulmonary disease, renal disease, liver disease, RBC transfusion, anti-platelet

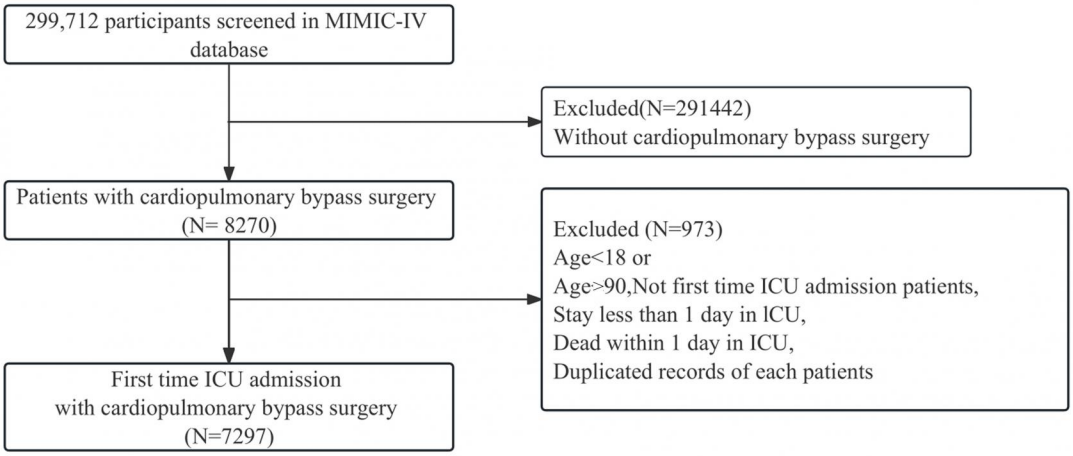
Table 4 Cox model in participants without further diagnosed sepsis

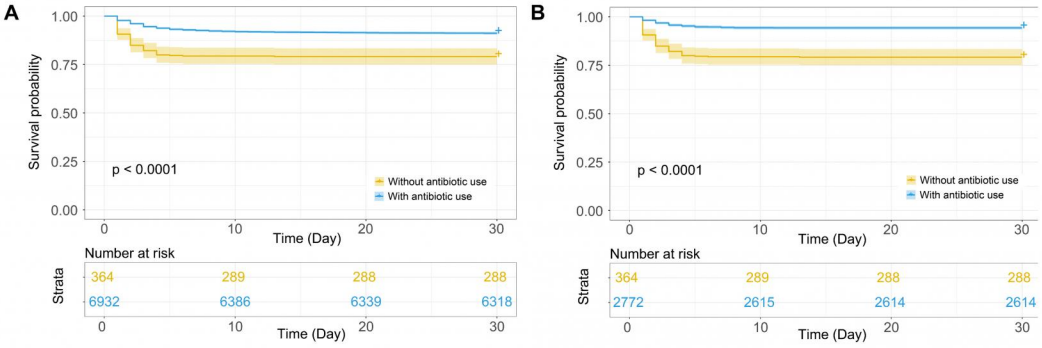
Cox regression model	Hazard Ratio(95%CI)	P-value
Model1	0.247(0.188-0.324)	<0.001
Model2	0.258(0.196-0.340)	<0.001
Model3	0.461(0.327-0.648)	<0.001

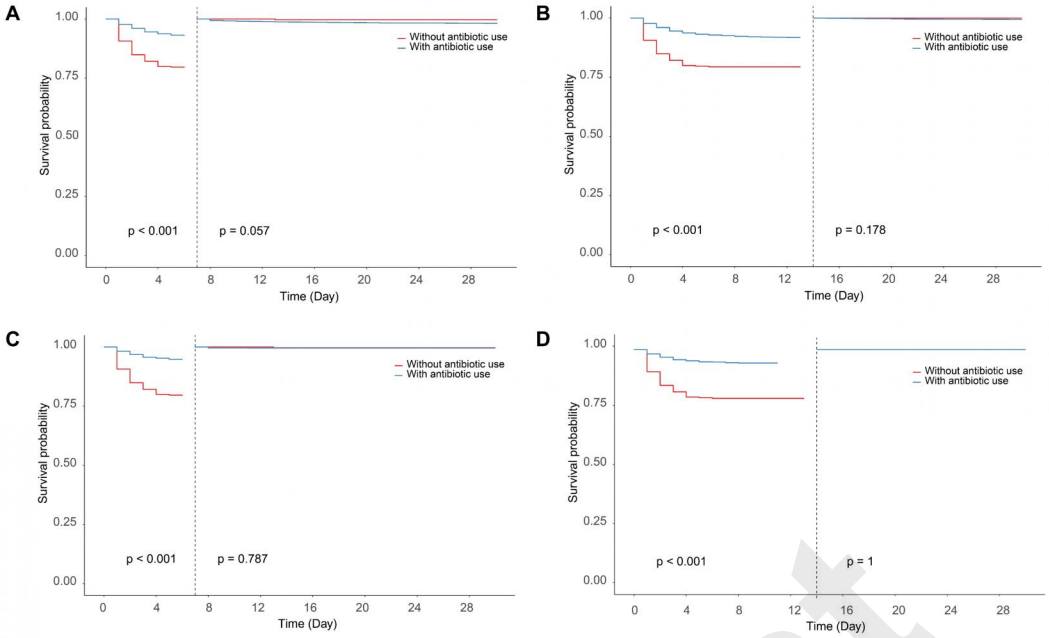
Model 1: unadjusted

Model 2: adjusted for model 1 plus age, gender, race

Model 3: adjusted for model 2 plus marry status, LOS, anion gap, platelets, PTT, sodium, BUN, WBC, pCO_2, base excess, RDW, MCV, RTT, AKI, congestive heart failure, chronic pulmonary disease, renal disease, liver disease, RBC transfusion, anti-platelet


299,712 participants screened in MIMIC-IV database
Excluded(N=291442)
Without cardiopulmonary bypass surgery
Patients with cardiopulmonary bypass surgery (N= 8270)
Excluded (N=973)
Age<18 or
Age>90,Not first time ICU admission patients,
Stay less than 1 day in ICU,
Dead within 1 day in ICU,
Duplicated records of each patients
First time ICU admission with cardiopulmonary bypass surgery (N=7297)


A
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
Without antibiotic use
With antibiotic use
0
10
20
30
Time (Day)
Number at risk
Strata
364
289
288
288
6932
6386
6339
6318
0
10
20
30
Time (Day)
B
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
Without antibiotic use
With antibiotic use
0
10
20
30
Time (Day)
Number at risk
Strata
364
289
288
288
2772
2615
2614
2614
0
10
20
30
Time (Day)


A
1.00
0.75
0.50
0.25
0.00
Survival probability
Without antibiotic use
With antibiotic use
p < 0.001
p = 0.057
0
4
8
12
16
20
24
28
Time (Day)
B
1.00
0.75
0.50
0.25
0.00
Survival probability
Without antibiotic use
With antibiotic use
p < 0.001
p = 0.178
0
4
8
12
16
20
24
28
Time (Day)
C
1.00
0.75
0.50
0.25
0.00
Survival probability
Without antibiotic use
With antibiotic use
p < 0.001
p = 0.787
0
4
8
12
16
20
24
28
Time (Day)
D
1.00
0.75
0.50
0.25
0.00
Survival probability
Without antibiotic use
With antibiotic use
p < 0.001
p = 1
0
4
8
12
16
20
24
28
Time (Day)

Variable	Count	Percent	HR (95% CI)	P value	P for interaction
Overall	7296	100	0.38 (0.30 to 0.49)	<0.001	
age_level					0.717
(18,64]	2785	38.2	0.40 (0.26 to 0.62)	<0.001	
(64,90]	4511	61.8	0.37 (0.27 to 0.49)	<0.001	
gender					0.734
F	2140	29.3	0.37 (0.25 to 0.53)	<0.001	
M	5156	70.7	0.40 (0.29 to 0.54)	<0.001	
race					0.96
Black	315	4.3	0.43 (0.20 to 0.90)	0.026	
Other/Unkown	1636	22.4	0.41 (0.22 to 0.75)	0.004	
White	5345	73.3	0.38 (0.29 to 0.51)	<0.001	
sofa_level1					0.019
(−1,5]	4249	58.2	0.28 (0.21 to 0.37)	<0.001	
(5,21]	3047	41.8	0.56 (0.33 to 0.95)	0.031	
los_level					<0.001
(0,2]	3627	49.7	0.22 (0.15 to 0.32)	<0.001	
(2,3]	1465	20.1	0.33 (0.21 to 0.53)	<0.001	
(3,100]	2204	30.2	0.69 (0.45 to 1.08)	0.105	
rrt					0.006
0	7225	99	0.37 (0.29 to 0.47)	<0.001	
1	71	1	2.02 (0.62 to 6.60)	0.243	
aki					0.295
0	1554	21.3	0.28 (0.15 to 0.51)	<0.001	
1	5742	78.7	0.38 (0.30 to 0.50)	<0.001