Azithromycin and Major Adverse Kidney Events in Critically Ill Patients with Sepsis-Associated Acute Kidney Injury

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Abstract

Background: Sepsis-associated acute kidney injury (SA-AKI) is associated with significant morbidity and mortality. Immune dysregulation is a hallmark of sepsis, with important contributions to organ dysfunction including injury and repair mechanisms in AKI. Macrolide antibiotics, such as azithromycin, have previously demonstrated in pre-clinical models a myriad of immunomodulatory effects that may benefit critically ill patients with SA-AKI. The aim of this study was to determine if early receipt of azithromycin in SA-AKI is associated with a reduction in major adverse kidney events (MAKE) at hospital discharge.

Methods: This was a single center, retrospective cohort study of critically ill adult patients with SA-AKI. Early exposure to azithromycin was defined as receipt of one or more doses within 48 hours of a hospital admission with SA-AKI. The primary outcome of MAKE assessed at hospital discharge was the composite of death, requirement for kidney replacement therapy, or a decline in estimated glomerular filtration rate of 25% or more. Multivariable logistic regression was used to account for potential confounders in the assessment.

Results: Of 737 included patients with SA-AKI, 152 (20.6%) received azithromycin. Patients that received early azithromycin were less likely to experience MAKE at hospital discharge when compared to those patients not receiving azithromycin: 38.8% versus 48.4% (p=0.035). In multivariable logistic regression, receipt of azithromycin was independently associated with a decreased odds of MAKE at hospital discharge (aOR 0.62, 95% CI 0.41–0.93).

Conclusions: Early exposure to azithromycin in SA-AKI is independently associated with lower odds of MAKE at hospital discharge.

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Introduction

Sepsis is a leading contributor to acute kidney injury (AKI) in hospitalized patients, identified as a risk factor in nearly 50% of AKI cases (1–4). Patients with sepsis-associated AKI (SA-AKI) often present with more severe AKI and are at higher risk of mortality compared to other etiologies of AKI (1). For those surviving hospitalization, SA-AKI is also associated with significant short- and long-term impairments in kidney function (5, 6).

SA-AKI is multifactorial, with potential intra-renal hemodynamic, metabolic, and immune pathologies influencing kidney injury and repair (7–10). Macrolide antibiotics, including azithromycin, have demonstrated a myriad of immunomodulatory effects in pre-clinical models that may prove beneficial for syndromes of immune dysregulation in critically ill patients such as SA-AKI (11). Azithromycin is a Food and Drug Administration approved antibiotic and widely used clinically in various respiratory conditions that trigger an inflammatory response including cystic fibrosis, community-acquired pneumonia, and chronic obstructive pulmonary disease (11).

Given its significant morbidity and lack of therapeutic agents for SA-AKI, we sought to evaluate the effect of early azithromycin exposure on kidney outcomes and mortality in a cohort of critically ill patients with SA-AKI.

Materials and Methods

Study Design

This was a retrospective, single center, cohort study conducted at a tertiary care, academic medical center. Patients admitted from January 1, 2013 to July 31, 2020 were screened for study eligibility and included if they were 18 years of age or older, initially admitted to the medical intensive care unit (ICU), and diagnosed with sepsis or septic shock and AKI at the time of ICU admission. Sepsis and septic shock diagnoses were identified based on International Classification of Diseases (ICD)-9 and ICD-10 codes. AKI was defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 1 or higher based on the serum creatinine component (12). Exclusion criteria consisted of the following: outside hospital transfer, death within 24 hours of admission, end-stage kidney disease, or history of kidney transplantation. For patients with multiple ICU admissions during the study period, only the first ICU admission was evaluated.

Demographic data and baseline characteristics were collected on ICU admission including severity of illness indicators such as the Sepsis-related Organ Failure Assessment (SOFA) score (13). Baseline comorbidities were identified using ICD-9 and ICD-10 codes. The presence of septic shock was classified based on the need for vasopressor support within the first 48 hours of admission. To assess baseline kidney function, the most recent serum creatinine within six months prior to admission was collected when available.

Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (14).

Exposure to azithromycin was defined as one or more doses of oral or intravenous azithromycin within 48 hours of ICU admission. In order to distinguish if sepsis was secondary to a suspected community or hospital source, antibiotic administration within the first 48 hours of ICU admission was assessed. Patients receiving anti-Pseudomonal antibiotic coverage (cefepime, piperacillin/tazobactam, or meropenem) for more than one day were classified as a suspected hospital source and all other patients were classified as a suspected community source. The study was approved by the University of Kentucky Institutional Review Board (#61174) with a waiver of informed consent due to the retrospective nature.

Study Outcomes

The primary outcome was Major Adverse Kidney Events (MAKE) at hospital discharge, a composite of death, need for kidney replacement therapy (KRT), or decrease in eGFR 25% from baseline (15). Secondary outcomes included KRT or death within 1 week of admission, development of acute kidney disease (AKD), serum creatinine and eGFR at discharge in survivors not requiring KRT, ICU length of stay, and hospital length of stay. AKD was defined per the Acute Disease Quality Initiative consensus definition (16).

Statistical Analysis

Continuous data are presented as medians with interquartile range and compared using the Wilcoxon rank-sum test. Categorical data are presented as counts with associated percentages and compared using a chi-square test. For patients who did not have a baseline serum creatinine available prior to admission, multiple imputations were conducted using SAS 9.4 Proc MI (SAS Institute Inc), fully conditional specification, with 50 imputed data sets. Variables included for imputation were age, sex, race, diabetes and hypertension as they have been validated in previous studies of serum creatinine imputation (17, 18). The average creatinine value from the 50 imputations was used to classify screened patients with sepsis or septic shock as having AKI or not.

Multivariable logistic regression was used to model MAKE at hospital discharge. Variables for the model were defined *a priori* and hypothesized by the investigators to influence both the receipt of azithromycin and the MAKE outcome. These variables included: age, sex, baseline eGFR, diabetes, hypertension, heart failure, liver disease, chronic kidney disease, KDIGO AKI stage 1–3 on admission, serum lactate on admission, admission SOFA, and anti-Pseudomonal antibiotic coverage as a surrogate for suspect hospital vs. community-acquired infection. Four separate sensitivity analyses of this model were conducted: 1) examination of an alternative MAKE definition using a 50% reduction in eGFR rather than a 25% reduction; 2) examination of patients with a measured (non-imputed) baseline serum creatinine; 3) examination of a composite outcome of death or KRT (removing eGFR component from MAKE); and 4) examination of patients with severe SA-AKI limited to those with KDIGO stage 2 or 3 AKI. An E-value was calculated to determine the minimum strength of association required by an unmeasured confounder to explain away

the relationship observed between azithromycin and MAKE (19). A p-value <0.05 was considered statistically significant. Statistical analyses were performed in Stata (StataCorp. 2019. Stata Statistical Software: Release 16; StataCorp LLC, College Station, Texas, USA).

Results

Over the study period, 4,810 patients were admitted to the medical ICU with a diagnosis of sepsis or septic shock. After exclusion criteria were applied, 1,205 patients remained, and of those, 737 had AKI present on admission (Figure 1). One-hundred fifty-two patients received early azithromycin and the remaining 585 were considered non-exposed or control patients (10 of these patients received azithromycin at some point later in the admission beyond 48 hours). Based on the timing of the evaluation period, three patients tested positive for severe acute respiratory coronavirus 2 (SARS-CoV-2). All three patients had bacterial co-infections and were included in the cohort of SA-AKI patients.

Baseline demographics are presented in Table 1. Patients in the azithromycin group were slightly older, more commonly male, and with a lower baseline eGFR. Comorbidities were similar between groups except for heart failure which was more common in the azithromycin group. Patients prescribed azithromycin tended to have less severe AKI on admission with more stage 1 and less stage 3 AKI compared to the non-exposed group. Patients receiving azithromycin were also less likely to receive anti-Pseudomonal antibiotic coverage compared to the non-exposed group. Both groups demonstrated similar severity of illness as assessed by admission SOFA score and vasopressor requirement in the first 48 hours of ICU admission. The median duration of receipt of azithromycin was 3 (2–5) days.

The primary outcome of MAKE at hospital discharge occurred in 59 (38.8%) patients in the azithromycin group and in 283 (48.4%) patients in the non-exposed group (p=0.035) (Table 2). The individual components of the MAKE outcome were all numerically less frequent in the azithromycin group (Figure 2) but were not statistically significant as a single criterion. There were no differences in any of the secondary outcomes assessed.

When controlling for potential confounders in multivariable logistic regression, exposure to azithromycin was independently associated with a reduction in MAKE at hospital discharge (aOR 0.62 [95% CI 0.41–0.93]; p=0.020) (Table 3). In sensitivity analysis (eTables 1–4) azithromycin retained a statistically significant association on reducing the odds of MAKE at discharge when the eGFR threshold for the MAKE outcome was changed to 50% reduction from baseline and when analyzing the composite outcome of death or KRT at discharge without accounting for the eGFR reduction. Azithromycin exposure was not significantly associated with a reduction of MAKE at discharge when limited to patients with a documented (non-imputed) baseline serum creatinine or when limited to patients with KDIGO stage 2–3 AKI. Using the adjusted odds ratio for MAKE at discharge from the primary model, the E-value was determined to be 1.86, indicating an unmeasured confounder would need an odds ratio of 1.86 to explain away the observed benefit of azithromycin exposure seen in the primary analysis (eFigure 1).

Discussion

To our knowledge, this is the first study to assess the clinical effects of azithromycin on kidney-related outcomes in critically ill patients with SA-AKI. We observed an independent association between receipt of azithromycin within the first 48-hours of ICU admission and a reduction in the risk of MAKE at hospital discharge in critically ill adults with SA-AKI. Results were consistent when adjusted for identified confounders and across several sensitivity analyses.

Macrolides have previously been studied as anti-infective or potential immunomodulatory adjuncts in critically ill patients, with a focus on primarily respiratory conditions including pneumonia and acute respiratory distress syndrome yielding mixed results (20–33). In the largest randomized trial of macrolides in critically ill patients (n=600 patients), Giamarellos-Bourboulis et al evaluated clarithromycin versus placebo in gram-negative sepsis (34). Although there was no difference in 28-day mortality, of the 54 patients with septic shock and multiple organ dysfunction, 15/28 (53.6%) randomized to clarithromycin died compared to 19/26 (73.1%) receiving placebo (p=0.020) (34). Although this was a subset of the entire trial population, the results are consistent with analysis from a smaller pilot trial performed by the same group of investigators studying clarithromycin versus placebo in ventilator-associated pneumonia (27). In this smaller trial of 200 patients, clarithromycin was also associated with mortality reduction compared to placebo in the subgroup of patients with septic shock and multiple organ dysfunction (27). These subgroup analyses from prior trials of macrolides in critical illness suggest that any potential benefit present may be driven by those patients with septic shock and a significant degree of organ dysfunction. With nearly 3 out of 4 patients requiring vasopressor support within 48 hours of admission, a median SOFA score of 9, and all patients in our cohort with SA-AKI, the patients from our study represent this type of acute illness phenotype.

Although the design of our study does not allow for evaluation of any potential immunomodulatory or other mechanisms for the protective association observed with azithromycin, pre-clinical data suggest several possible mechanisms whereby azithromycin may be beneficial in patients with infection or sepsis, including: reversal of immune suppression and endotoxin tolerance in sepsis and facilitating return of innate immune cell function (11, 28, 29), induction of a shift to more tolerogenic immune cell phenotypes such as T-helper-2 and M2-macrophages (35, 36), alteration of the microbiome and its interaction with the immune system (37), impaired Toll-like receptor signaling and reduced inflammasome activation (38–40), reduction of inflammatory chemokines and cytokines (41), inhibition of CD4 T-cell proliferation (42), enhancement of phagocytosis (43) and efferocytosis (44), enhancement of apoptosis in neutrophils contributing to excessive inflammation (45), enhancement of bacterial killing (46) and/or synergism with other antimicrobials, and inhibition of quorum sensing (47), among other potential mechanisms. Readers are referred to an excellent review by Reijnders and colleagues for an in-depth discussion of these potential mechanisms (11).

Potential advantages of azithromycin include: 1.) It is a commonly prescribed antibiotic available in multiple formulations and with a well-defined safety profile; 2.) It has extensive

tissue distribution (48), with tissue concentrations exceeding those observed in serum anywhere from 10–100 fold, including lung and kidney tissue (49); and 3.) It achieves rapid, high, and prolonged intracellular concentrations in many cell lines (50, 51).

Our study has several strengths. First, we included a relatively large sample size with consideration of the many potential confounders in critical care nephrology research. Our E-value of 1.86 suggests that an unmeasured confounder of this magnitude could theoretically move the confidence interval to the null, but the unmeasured confounder would have to be approximately similar in magnitude to CKD or liver disease (Table 3), which we anticipate being unlikely. Second, the outcome of MAKE is clinically relevant, accounts for the competing risk of mortality, and is garnering increased support as a universal endpoint in critical care nephrology research (15). Lastly, we conducted several sensitivity analyses including more specific GFR thresholds for the MAKE outcome that also demonstrated a protective association of azithromycin.

Our study also has notable limitations. First, as a single center, retrospective, observational study, there may be inherent biases including information bias and selection bias that affected our results. Second, culture data were not available for all patients in our study, so we were unable to assess what proportion of patients had a respiratory versus non-respiratory source of infection. Third, baseline serum creatinine was missing for approximately half of the patient population. Although imputation was used to estimate missing values and define our cohort of SA-AKI patients, this may have biased the true baseline kidney function for a significant portion of our cohort. The sensitivity analysis in documented (non-imputed) baseline serum creatinine was not significant for azithromycin's association with MAKE, but was also reduced in power by approximately 50%. Fourth, azithromycin is predominantly used for community-acquired infections or to provide antibiotic coverage for atypical pathogens which may have introduced indication bias in our study with less illness severity in the azithromycin group. Although we used anti-Pseudomonal antibiotic coverage as a surrogate for hospital versus community source of infection as well as adjusted for numerous other relevant potential confounders, we may have been unable to fully control for any potential bias. Fifth, over 50% of patients in the azithromycin group were diagnosed with KDIGO Stage 1 AKI on admission. Although we controlled for KDIGO severity stage, and even though the azithromycin group had lower baseline eGFR, this could indicate less kidney injury on admission in the azithromycin group that may not be adequately controlled for with multivariable regression modeling which may have led to more favorable outcomes in patients receiving azithromycin. Finally, the design of our study did not allow the opportunity to study immune parameters and specific immunomodulatory effects of azithromycin in SA-AKI. While we hypothesize that the immunomodulatory properties shown in other conditions may be beneficial in SA-AKI (52–54), further research is required.

Our study found that early exposure to azithromycin in critically ill adult patients with SA-AKI was associated with a reduction in MAKE at hospital discharge compared to patients not receiving azithromycin. Additional investigation of macrolide antibiotics or derivatives in SA-AKI is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

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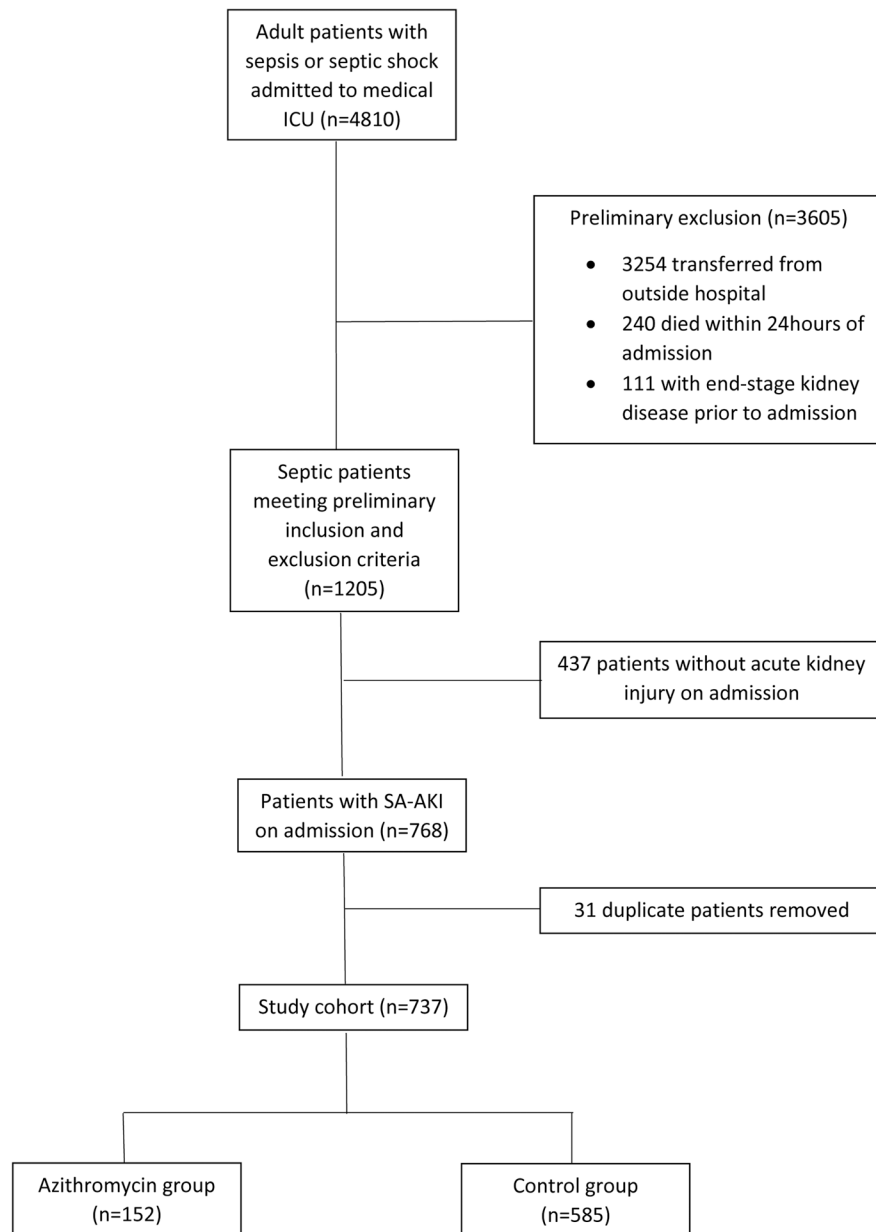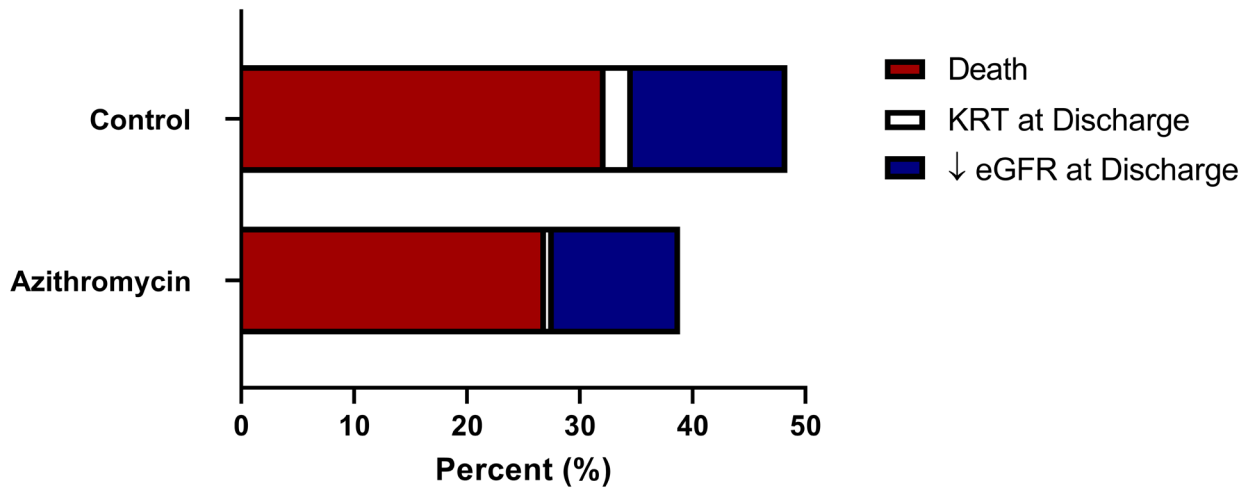Author Manuscript

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Figure 1.
Study Flow Diagram

Figure 2.
Component Outcomes of Major Adverse Kidney Events Between Cohorts

Table 1.

Patient Demographics

Demographic	Azithromycin (n=152)	Control (n=585)	p-value
Prior to admission			
Age (years)	61 (50–70)	56 (45–66)	0.001
Sex (% male)	98 (64.5%)	313 (53.5%)	0.015
Race (% white)	132 (86.8%)	519 (88.7%)	0.685
Height (cm)	173 (165–180)	173 (163–178)	0.185
Weight (kg)	83 (70–100)	81 (68–100)	0.239
Baseline serum creatinine (mg/dl)	1.0 (0.8–1.1)	0.9 (0.7–1.0)	0.011
Baseline eGFR (ml/min/1.73 m^2)	77 (64–97)	87 (67–105)	0.016
Diabetes (%)	48 (31.6%)	202 (34.5%)	0.494
Hypertension (%)	99 (65.1%)	376 (64.3%)	0.844
Coronary artery disease (%)	54 (35.5%)	183 (31.3%)	0.318
Heart failure (%)	48 (31.6%)	132 (22.6%)	0.021
Liver disease (%)	40 (26.3%)	182 (31.1%)	0.251
Chronic kidney disease (%)	39 (25.7%)	127 (21.7%)	0.299
Hospital admission			
KDIGO AKI stage			<0.001
1	84 (55.3%)	223 (38.1%)	
2	37 (24.3%)	156 (26.7%)	
3	31 (20.4%)	206 (35.2%)	
Serum lactate (mmol/l)	0.9 (0.4–1.9)	1.0 (0.5–3.3)	0.03
SOFA score	9 (6–13)	9 (6–13)	0.393
Anti-pseudomonal antibiotic coverage (%)	103 (67.8%)	444 (75.9%)	0.041
Vasopressor requirement within 48 hours of admission (%)	109 (71.7%)	438 (74.9%)	0.427
Duration of azithromycin treatment (days)	3 (2–5)	0 (0–0)	<0.001

eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease Improving Global Outcomes; SOFA=Sequential Organ Failure Assessment

Table 2.

Study Outcomes

Outcome	Azithromycin (n=152)	Control (n=585)	p-value
Major Adverse Kidney Events (%)	59 (38.8%)	283 (48.4%)	0.035
Hospital mortality	41 (27.0%)	189 (32.3%)	0.206
KRT at discharge	1 (0.7%)	14 (2.4%)	0.177
eGFR decrease ≥ 25% at discharge	17 (11.2%)	80 (13.7%)	0.418
KRT within one week of admission (%)	19 (12.5%)	85 (14.5%)	0.522
Death within one week of admission (%)	23 (15.1%)	103 (17.6%)	0.470
Incident Acute Kidney Disease (%)	37 (24.3%)	157 (26.8%)	0.534
Death or Incident Acute Kidney Disease (%)	60 (39.5%)	260 (44.4%)	0.271
ICU mortality (%)	30 (19.7%)	147 (25.1%)	0.166
Serum creatinine at discharge, survivors without KRT (mg/dl)	0.9 (0.7–1.1)	0.8 (0.7–1.2)	0.888
eGFR at discharge, survivors without KRT (ml/min/1.73 m^2)	92 (64–108)	89 (61–110)	0.777
ICU length of stays (days)	5.8 (2.9–12.1)	5.5 (2.9–11.1)	0.499
Hospital length of stay (days)	10.3 (5.2–18.6)	9.5 (5.1–18.7)	0.879

KRT=kidney replacement therapy; eGFR=estimated glomerular filtration rate; ICU=intensive care unit

Table 3.

Multivariable Logistic Regression for Major Adverse Kidney Events at Discharge

Variable	Odds Ratio (95% Confidence Interval	p-value
Azithromycin	0.62 (0.41–0.93)	0.020
Age (per 1-year)	1.01 (0.99–1.02)	0.224
Sex (male vs. female)	1.43 (1.03–1.98)	0.031
Baseline eGFR (per 1 ml/min/1.73 m^2)	0.99 (0.98–1.00)	0.155
Diabetes	0.83 (0.58–1.18)	0.299
Hypertension	0.62 (0.42–0.92)	0.016
Heart failure	1.09 (0.75–1.59)	0.641
Liver disease	1.93 (1.35–2.77)	<0.001
Chronic kidney disease	2.29 (1.51–3.49)	<0.001
KDIGO AKI stage (vs. stage 1)		
Stage 2	0.99 (0.66–1.47)	0.946
Stage 3	1.33 (0.90–1.97)	0.146
Lactate (per 1 mmol/l)	1.02 (0.98–1.07)	0.261
SOFA (per 1-unit)	1.10 (1.06–1.14)	<0.001
Anti-pseudomonal antibiotic coverage	0.76 (0.53–1.10)	0.148

eGFR=estimated glomerular filtration rate; KDIGO=Kidney Disease Improving Global Outcomes; SOFA=Sequential Organ Failure Assessment score