BMC Infectious Diseases

RESEARCH

Open Access

Incidence and predictors of vancomycin nephrotoxicity and mortality in patients with chronic liver disease: a two-center retrospective cohort study

Reem F. Bamogaddam[1†], Ahmad Alamer[2†], Shatha Alqarni[3,4], Mohammed M. Almotairi[5], Ali A. Almakrami[5], Alwaleed M. Alharbi[5], Raghad Alamri[3,4], Manar Altamimi[3,4], Amal Alkhulaif[3,4], Raghad Alanazi[3,4], Omar A. Almohammed[6,7] and Majed S. Al Yami[3,4,8*]

Abstract

Background Patients with liver disease express multiple pathophysiological variations that alter the pharmacokinetics of numerous drugs. At this time, there is insufficient evidence about the proper dosing of vancomycin in patients with liver disease. This study aimed to assess the risk of acute kidney injury (AKI) during vancomycin therapy and identify predictors of AKI and all-cause mortality among patients with varying degrees of liver dysfunction.

Methods A retrospective cohort study was conducted including patients with chronic liver disease who used vancomycin during hospitalization from January 2016 to January 2024 in two Saudi hospitals. Patients were grouped by the severity of the liver disease (mild liver disease [MLD] or moderate-to-severe liver disease [MSLD] based on the Child–Pugh score). The incidence of AKI, vancomycin mean trough level, and all-cause mortality were compared between the two groups. A multivariable logistic regression model was employed to identify predictors of AKI and mortality.

Results A total of 110 patients treated with vancomycin were included in this study (28 had MLD and 82 had MSLD). A higher incidence of AKI in patients with MSLD than those with MLD was observed (28% vs. 14.3%, respectively; $p=0.1440$), but the difference was statistically insignificant. The vancomycin mean trough levels (12.9 ± 5.2 µmol/L vs. 10.2 ± 4.7 µmol/L, $p=0.0143$) and the percentage of patients with vancomycin trough level > 13.8 µmol/L (35.4% vs. 10.7%, $p=0.0131$) were significantly higher in the MSLD group compared to the MLD group. Having a Creatinine Clearance (CrCl) between 15.1–29.9 ml/min (adjusted Odds ratio [aOR]: 45.5; 95% Confidence interval [CI] 4.99–414.8), and a vancomycin mean trough level > 13.8 µmol/L (aOR: 7.67; 95%CI 2.49–23.63) were associated with a higher risk of AKI development. Similarly, mortality was significantly higher in the MSLD group than in the MLD (23.2% vs. 3.6%, respectively; $p=0.0203$). The risk of mortality was associated with having a body mass index (BMI) between 25–29.9 kg/m^2 (sOR 6.69; 95%CI 1.73–25.8), an albumin level < 25 g/L (aOR: 4.33; 95%CI 1.36–13.8), and a vancomycin mean trough level > 13.8 µmol/L (aOR: 6.13; 95%CI 1.82–20.6).

[†]Reem F. Bamogaddam and Ahmad Alamer contributed equally to the work, and therefore are considered to be first co-authors for this paper.

*Correspondence:
Majed S. Al Yami
yamim@ksau-hs.edu.sa
Full list of author information is available at the end of the article

Conclusion Patients who had MSLD had a higher trough vancomycin levels and mortality than patients who had MLD; and this risk increases as liver disease progresses. Thus, the existence of chronic liver disease should be considered when monitoring toxicity from vancomycin to minimize the risk of adverse outcomes and mortality. Larger studies are needed to closely quantify the risk of vancomycin toxicity among patients with chronic liver disease.

Keywords Vancomycin, Vancomycin trough level, Toxicity, Liver disease, Creatinine clearance, Acute kidney injury, Mortality, Albumin

Introduction

Vancomycin is a glycopeptide antibiotic that was first discovered in 1953 [1]. It exhibits bactericidal activity by disrupting bacterial cell wall synthesis through interference with the polymerization of peptidoglycans [2]. Thus, it is used to treat gram-positive severe infections caused by bacteria resistant to other antibiotics, such as methicillin-resistant staphylococci. Historically, impurities in the initial formulations of vancomycin were predominantly associated with many safety issues, especially nephrotoxicity. Nevertheless, despite the advancement of refined formulations, the incidence of nephrotoxicity can range from 5 to 43% depending on accompanying risk factors: overdose and higher trough concentrations greater than 10.35 µmol/L, chronic kidney disease, obesity, dehydration, and use of other nephrotoxic medications as aminoglycosides [1, 3]. Vancomycin has a narrow therapeutic index and requires therapeutic drug monitoring during administration [2]. The most accurate method for dosing and monitoring vancomycin is by the area under the curve to minimum inhibitory concentration (AUC: MIC) ratio. The recommended AUC: MIC ratio target is 400 to 600 mg*hr/ L [4]. However, due to practicality issues, many institutions use serum vancomycin trough concentrations and target trough concentrations between 10.35 and 13.8 µmol/L for serious infections as a substitute for the optimal vancomycin AUC: MIC ratio [4].

The liver is the primary organ in the body for metabolism and detoxification. Hence, liver disease causes multiple pathophysiological changes that alter the pharmacokinetics of several drugs [5, 6]. Furthermore, due to the reduced muscle mass and compromised enzymatic metabolism of creatine to creatinine in many patients with severe hepatic disease, estimates of creatinine clearance (CrCl) based on serum creatinine (Scr) measures (e.g., Cockroft-Gault method) are frequently misleading and overestimated [7]. For this reason, dosage adjustments are necessary, not only in drugs that are extensively hepatically metabolized but may also be advised for renally-cleared drugs such as vancomycin [5, 8]. Additionally, patients with cirrhosis, the last stage of chronic liver disease, are more prone to developing acute kidney injury (AKI) than those without [9, 10].

Currently, knowledge about how to adjust vancomycin doses in patients with liver disease is scarce. Brown et al. investigated the effects of liver damage on vancomycin pharmacokinetics in 15 cancer patients. They found that patients with poor hepatic function had a much longer half-life and lower vancomycin clearance than patients with normal hepatic function [11]. Moreover, individuals with severe hypoalbuminemia have a longer half-life for vancomycin and a higher rate of nephrotoxicity [12]. These findings suggest that hypoalbuminemia in severe liver disease can affect the concentration of vancomycin unbound free form and lengthen its half-life.

To look for the influence of chronic liver disease in patients treated with vancomycin on the risk of nephrotoxicity, Brunetti et al. conducted a retrospective cohort study involving more than 400 patients. They noticed a significantly higher incidence of supratherapeutic vancomycin exposure among patients with moderate to severe liver dysfunction (MSLD) compared to patients with no to mild liver dysfunction (NMLD). Furthermore, AKI developed more frequently in patients with MSLD, although the difference was not statistically significant [13].

Renal function is often considered when choosing a vancomycin dosing strategy; nevertheless, liver function is rarely counted. The influence of renal function on vancomycin pharmacokinetics has been extensively studied. On the other hand, little is known about the role of hepatic dysfunction on vancomycin pharmacokinetics [7, 11, 13–16]. The current manufacturer's labeling does not recommend any dosage adjustment for vancomycin in patients with hepatic impairment [17]. Therefore, this study aims to assess the incidence and identify predictors of AKI and all-cause mortality in patients with varying degrees of liver dysfunction during vancomycin therapy.

Methods

Study design, population and settings

This was a retrospective cohort study conducted at the hepatology ward and internal medicine general wards in two centers in Saudi Arabia: King Abdulaziz Medical City (KAMC) in Riyadh and King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia. We included patients

with a documented diagnosis of chronic liver disease who were ≥ 18 years old, received vancomycin IV therapy of at least two days, had stable kidney function upon admission with a baseline CrCl > 15 ml/min (calculated using the Cockroft-Gault equation) [8], and had a vancomycin trough concentration obtained at steady state. Patients who had liver transplant, critical illness (e.g. shock, disseminated intravascular coagulation), burn injuries, or pregnancy were excluded from the study. Study approval was granted by the Institutional Review Boards at KAMC (IRB: 1755/23) and KFMC (IRB: 24–015).

Data collection methods, instruments used, and measurements

We performed a retrospective chart review of patients with chronic liver disease who used vancomycin during hospitalization from January 2016 to January 2024. All patients were screened according to the inclusion and exclusion criteria and grouped based on the severity of their liver disease into patients with mild liver disease (MLD) or moderate to severe liver disease (MSLD). The severity of liver dysfunction was based on the Child–Pugh score (Child–Pugh score ≤ 6: mild [A]; Child–Pugh score 7–9: moderate [B]; Child–Pugh score 10–15: severe [C]) [8].

All data for the included cohort were extracted retrospectively from the electronic health records. Extracted data included demographic characteristics [age, weight, height, body mass index (BMI), and gender], comorbidities were assessed and scored according to the Charlson Comorbidity Index (CCI) [18], the etiology of the liver disease, Child–Pugh scores, infection type, lab parameters [albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin, international normalized ratio (INR), serum creatinine (Scr), and blood urea nitrogen (BUN)], vancomycin dosing and duration of use, vancomycin mean trough levels, concomitant use of other nephrotoxic medications, and mortality during admission.

Study outcomes

The primary outcome was the incidence of AKI during vancomycin therapy in patients with MLD compared to patients with MSLD. AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines as "an increase in Scr by ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 h, or an increase in Scr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days, or a urine volume < 0.5 mL/kg/hour for six hours" [19]. Secondary outcomes included mortality rate, mean vancomycin trough level during treatment, proportion of patients with a vancomycin trough level > 13.8 µmol/L, and series of Scr levels, BUN levels, and CrCl during vancomycin therapy, as well as predictors of AKI and mortality.

Statistical analysis

Continuous data were presented using means with standard deviations (± SD), and categorical data were presented using frequencies with percentages. For normally distributed continuous variables, the Student's t-test was used, and for non-normally distributed continuous variables, the Mann–Whitney test was used. The chi-square test or Fishers' exact test was used, as appropriate, to compare categorical variables. Univariable and backward-stepwise multivariable analysis of the predictors of AKI and mortality were performed using logistic regression models that were built with severity of liver dysfunction, gender, total maintenance daily dose of vancomycin, age, BMI, CCI, Child–Pugh score, CrCl, albumin level, concomitant use of nephrotoxins, mean vancomycin trough level. The findings of the logistic regression were presented using odds ratios (ORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs).

In a secondary analysis, Scr, CrCl, and BUN outcomes were measured daily and analyzed using longitudinal Bayesian proportional odds models with first-order Markov state transitions. The goal of this model is to understand the effect of liver disease severity on patients receiving vancomycin for these variables. Such models can capture the transition of outcomes over days as they model the previous readings of the outcomes. This is useful for serial time trends and serial correlation patterns as it accounts for the correlation structure [20]. Among many reasons, the model was chosen over the regular ANOVA for repeated measures because the distributional assumptions were not met in our case due to the small sample size, the nature of the variable, and existence of outliers. Markov state transition models and proportional odds models are robust to the distributional shape of outcomes, making them more appealing and flexible for analysis. Covariates in the model included previous outcome values, Child–Pugh score categories (A, B, and C), mean vancomycin trough levels, age, nephrotoxic drug exposure, CCI, and the number of follow-up days. Eight days of follow-up data on Scr, CrCl, and BUN were included as the dependent outcome variables. An interaction term between the number of days and the Child–Pugh score categories was included to assess temporal effects. The rmsb package in R was used to fit all models [21]. Restricted cubic splines with three knots were applied to model continuous variables flexibly. Default priors were used. Diagnostic evaluations, including trace plots and summaries of the Markov chain Monte Carlo (MCMC) sampling of the posterior

distribution, were conducted. The interpretation of the individual parameters from such models can be challenging, therefore visualization of the estimates is necessary [20]. In each model, we presented the partial effects plots and the relative explained variation (REV), which is defined as the proportion of variance in outcome (Y) that can explained by a subset of covariate (X). In Bayesian models, P-values are not calculated; instead, estimates are derived from the posterior distribution, and uncertainties are expressed with 95% credible intervals (CIs). Data were analyzed using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software (R Foundation for Statistical Computing, Version 4.0.1, Vienna, Austria).

Results

A total of 1,322 patients were screened for the study, of whom 110 met the inclusion criteria (Figure S1). Among these, 82 patients had MSLD, while 28 had MLD. The mean age was 59.5 ± 17.4 years in the MLD group and 64.7 ± 17.8 years in the MSLD group. The mean CCI was higher in the MSLD group than the MLD group (6.0 ± 2.4 vs. 4.4 ± 2.7, respectively). The most common primary etiology of liver disease in the MLD group was hepatitis C virus (39.3%), whereas fatty liver disease and non-alcoholic steatohepatitis (NASH) were predominant in the MSLD group (24.4%). Bacteremia was the most prevalent infection type in both groups affecting 37.3% of patients. Most patients received at least one concomitant nephrotoxic medication with vancomycin (96.4% in the MLD group and 86.6% in the MSLD group). The mean baseline CrCl was comparable between the groups (82.7 ± 33.0 in MLD vs. 81.3 ± 48.7 ml/min in MSLD) while the albumin levels were lower in the MSLD group than the MLD group (25.9 ± 5.3 g/L vs. 36.9 ± 10.0 g/L, respectively). Baseline characteristics, stratified by liver disease severity, are detailed in Table 1.

Although the incidence of AKI was numerically higher in the MSLD group compared to the MLD group (28.0% vs. 14.3%), this difference did not reach statistical significance ($p = 0.1440$). Mortality was significantly higher in the MSLD group compared to the MLD group (23.2% vs. 3.6%; $p = 0.0203$). The mean vancomycin trough level was significantly elevated in the MSLD group than in the MLD group (12.9 ± 5.2 vs. 10.2 ± 4.7 µmol/L, $p = 0.0143$). Additionally, a higher proportion of MSLD patients had a mean vancomycin trough level of > 13.8 µmol/L compared to the MLD group (35.4% vs. 10.7%, $p = 0.0131$) (Table 2).

Logistic regression analysis was conducted to assess predictors of AKI development. In the univariable model, Child–Pugh category C (OR 4.00; 95%CI 1.06–15.08), vancomycin mean trough level > 13.8 µmol/L (OR 4.85; 95%CI 1.92–12.27), baseline CrCl between 30 and 59.9 ml/min (OR 4.06, 95%CI 1.14–14.48) and baseline CrCl between 15.1 and 29.9 ml/min (OR 19.4, 95% CI 2.78 – 135.2) were associated with a higher risk of developing AKI. However, in the multivariable logistic regression model, only a baseline CrCl between 15.1 to 29.9 ml/min (aOR 45.5; 95%CI 4.99–414.8) and vancomycin mean trough level > 13.8 µmol/L (aOR 7.67; 95%CI 2.49–23.63) remained statistically significant (Table 3).

Predictors of mortality were also assessed in univariable and multivariable logistic regression analyses. In the multivariable model, patients with a BMI between 25 and 29.9 kg/m^2 had a higher mortality rate (aOR 6.69; 95%CI 1.73–25.8) compared to those with a BMI less than 25 kg/m^2. An albumin level of < 25 g/L was significantly associated with a higher risk of mortality (aOR 4.33; 95%CI 1.36–13.8). Lastly, a mean vancomycin trough level > 13.8 µmol/L was significantly associated with increased mortality (aOR 6.13; 95% CI 1.82–20.6) (Table 4).

In the secondary analysis, patients were further stratified according to their Child–Pugh scores: 28 patients were classified in Child–Pugh A (mild), 57 in Child–Pugh B (moderate), and 25 in Child–Pugh C (severe). The interaction of Child–Pugh score categories with time for the Scr outcome was shown in Fig. 1A. The credible intervals overlapped. The figure depicts a non-linear relationship between the Scr outcome and the liver disease categories. Patients in category C had higher log odds of the outcome in the first two days indicating potentially higher Scr levels. Compared to Child–Pugh category A (mild liver disease), the mean Scr β coefficient for Child–Pugh category B (moderate liver disease) increased by 1.6% (95% CI -0.65 – 3.89). Similarly, the mean Scr β coefficient for the Child–Pugh category C (severe liver disease) increased by 3.7% (95% CI 0.81 – 6.6). The estimated differences in mean Scr over time for category A vs. B, A vs. C, and B vs. C were illustrated in Fig. 2 (Panels A to D). The coefficient for the Scr outcome from the Bayesian proportional odds model were presented in Table S1 of the supplementary material. The relative explained variation (REV) for the model revealed that the variable that explained most of the variations in the outcome was previous Scr readings, followed by day number, mean trough level, and Child–Pugh score (Figure S2). Partial plots of the linear predictors in the log odds scale depicted the model estimates more efficiently. Most of the linear predictors were flat in their relationship with the outcome except for the previous Scr readings indicating little evidence of effects over time for the other variables (Figure S3).

For the CrCl outcome, the interaction of Child–Pugh score categories with time was shown in Fig. 1B. Patients in category C had lower log odds of the

Table 1 Baseline characteristics based on level of liver dysfunction

Variables	Severity of the liver disease	
	Mild	Moderate to severe
Number of patients	28	82
Age (years)	59.5 ± 17.4	64.7 ± 17.8
Female	13 (46.4)	39 (47.6)
Body Mass Index (kg/m^2)	28.7 ± 10.0	26.6 ± 7.9
Charlson Comorbidity Index	4.4 ± 2.7	6.0 ± 2.4
Child–Pugh Score	5.5 ± 0.5	9.1 ± 1.8
Comorbid conditions		
Diabetes	13 (46.4)	41 (50)
Hypertension	18 (64.3)	38 (46.3)
Cancer	6 (21.4)	17 (20.7)
Solid tumor	1 (3.6)	11 (13.4)
Localized	1 (3.6)	6 (7.3)
Metastasized	0 (0.0)	5 (6.1)
Hematologic	5 (17.8)	6 (7.4)
Leukemia	2 (7.1)	3 (3.7)
Lymphoma	3 (10.7)	3 (3.7)
Cerebrovascular accident or transient ischemic attacks	1 (3.6)	6 (7.3)
Asthma	4 (14.3)	5 (6.1)
Dementia	1 (3.6)	5 (6.1)
Myocardial infarction	3 (10.7)	4 (4.9)
Congestive heart failure	3 (10.7)	3 (3.7)
Chronic Obstructive pulmonary disease	0 (0.0)	2 (2.4)
Rheumatic or connective tissue disease	0 (0.0)	2 (2.4)
Ulcer disease	0 (0.0)	2 (2.4)
Chronic kidney disease (moderate to severe)	2 (7.1)	1 (1.2)
Peripheral vascular disease	1 (3.6)	1 (1.2)
Documented etiology for liver disease		
Fatty Liver and NASH	4 (14.3)	20 (24.4)
Hepatitis C Virus	11 (39.3)	13 (15.9)
Hepatocellular carcinoma	2 (7.1)	11 (13.4)
Hepatitis B Virus	5 (17.9)	7 (8.5)
Portal Vein Thrombosis	2 (7.1)	6 (7.3)
Autoimmune hepatitis	0 (0.0)	4 (4.9)
Alcoholic liver disease	0 (0.0)	2 (2.4)
Budd-Chiari Syndrome	0 (0.0)	2 (2.4)
Primary sclerosing cholangitis	0 (0.0)	2 (2.4)
Drug Induced Liver Disease	0 (0.0)	1 (1.2)
Hemochromatosis	0 (0.0)	1 (1.2)
Schistosomiasis	0 (0.0)	1 (1.2)
Others	4 (14.3)	12 (14.6)
Type of infection		
Bacteremia	9 (32.1)	32 (39.0)
Urinary	6 (21.4)	19 (23.2)
Respiratory	4 (14.3)	15 (18.3)
Skin or soft tissue	7 (25.0)	10 (12.2)
Intra-abdominal	1 (3.6)	10 (12.2)
Skeletal	0 (0.0)	2 (2.4)
Central nervous system	1 (3.6)	1 (1.2)

Table 1 (continued)

Variables	Severity of the liver disease	
	Mild	Moderate to severe
Concomitant nephrotoxins	27 (96.4)	71 (86.6)
Beta-lactam	21 (75.0)	58 (70.7)
Loop diuretic	5 (17.9)	30 (36.6)
NSAID	3 (10.7)	3 (3.7)
ARB	2 (7.1)	4 (4.9)
Quinolone	1 (3.6)	4 (4.9)
Acyclovir	1 (3.6)	4 (4.9)
Aminoglycoside	1 (3.6)	3 (3.7)
Radiocontrast agent	1 (3.6)	3 (3.7)
ACEI	2 (7.1)	1 (1.2)
Amphotericin B	0 (0.0)	2 (2.4)
Sulfonamide	0 (0.0)	2 (2.4)
Tenofovir	1 (3.6)	1 (1.2)
Valganciclovir	0 (0.0)	1 (1.2)
Cisplatin	0 (0.0)	1 (1.2)
Laboratory values at baseline		
Scr (μmol/L)	78.5 ± 45.6	80.2 ± 82.7
CrCl (ml/min)	82.7 ± 33.0	81.3 ± 48.7
BUN, mean ± SD (mmol/L)	4.8 ± 2.2	7.3 ± 4.8
Albumin (g/L)	36.9 ± 10.0	25.9 ± 5.3
Albumin level (g/L)		
> 35	14 (50.0)	3 (3.7)
28–35	14 (50.0)	27 (32.9)
< 28	0 (0.0)	52 (63.4)
Vancomycin dosing		
Loading dose given	0 (0.0)	4 (4.9)
Loading dose (mg)	––	1687.5 ± 688.4
Total maintenance daily dose (mg)		
500 to 1000	5 (17.9)	19 (23.2)
1001 to 2000	20 (71.4)	53 (64.6)
2001 to 3000	3 (10.7)	10 (12.2)
Dosing frequency		
Every 8 h	4 (14.3)	3 (3.7)
Every 12 h	18 (64.3)	70 (85.4)
Every 24 h	6 (21.4)	9 (11.0)

Numbers are presented as frequency with (%) or mean ± Standard deviation

Abbreviations: *SD* standard deviation, *NASH* nonalcoholic steatohepatitis, *CrCl* creatinine clearance, *Scr* serum creatinine, *BUN* blood urea nitrogen, *NSAID* nonsteroidal anti-inflammatory drug, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

Table 2 Clinical outcomes by level of liver dysfunction

Variables	Severity of the liver disease		*p*-value
	Mild (*n* = 28)	Moderate to severe (*n* = 82)	
Acute kidney injury	4 (14.3)	23 (28.0)	0.1440
Mortality	1 (3.6)	19 (23.2)	**0.0203**
Vancomycin mean trough level (μmol/L)	10.2 ± 4.7	12.9 ± 5.2	**0.0143**
Vancomycin mean trough level > 13.8 μmol/L	3 (10.7)	29 (35.4)	**0.0131**

Numbers are presented as frequency with (%) or mean ± Standard deviation

Table 3 Univariable and multivariable logistic regression model to assess factors associated with acute kidney injury

Variable	Acute kidney injury	OR (95% CI)[a]	aOR (95% CI)[b]
Liver dysfunction			
Mild	4 (14.3)	Reference	Reference
Moderate to severe	23 (28.0)	2.34 (0.73 – 7.48)	
Gender			
Male	14 (24.1)	Reference	Reference
Female	13 (25.0)	1.05 (0.44 – 2.50)	0.41 (0.13 – 1.28)
Total maintenance daily dose of vancomycin			
500 to 1000 mg	6 (25.0)	Reference	Reference
1001 to 2000 mg	17 (23.3)	0.91 (0.31 – 2.66)	---
2001 to 3000 mg	4 (30.8)	1.33 (0.30 – 5.96)	---
Age, years			
18 – 64 years	10 (18.9)	Reference	Reference
≥ 65	17 (29.8)	1.82 (0.75 – 4.46)	---
Body mass index, kg/m^2			
< 25	11 (21.2)	Reference	Reference
25 – 29.9	5 (18.5)	0.85 (0.26 – 2.75)	---
≥ 30	11 (35.5)	2.05 (0.76 – 5.53)	---
Charlson comorbidity index			
< 4	5 (19.2)	Reference	Reference
≥ 4	22 (26.2)	1.49 (0.50 – 4.43)	---
Child–Pugh Score			
Mild (A): ≤ 6	4 (14.3)	Reference	Reference
Moderate (B): 7 – 9	13 (22.8)	1.77 (0.52 – 6.04)	---
Severe (C): 10 – 15	10 (40.0)	**4.00 (1.06 – 15.08)**	---
CrCl, ml/min			
≥ 90	4 (11.4)	Reference	Reference
60 – 89.9	7 (19.4)	1.87 (0.50 – 7.06)	1.32 (0.31 – 5.64)
30 – 59.9	11 (34.4)	**4.06 (1.14 – 14.48)**	2.97 (0.73 – 12.09)
15.1 – 29.9	5 (71.4)	**19.4 (2.78 – 135.2)**	**45.5 (4.99 – 414.8)**
Albumin level, g/L			
≥ 25	9 (27.3)	Reference	Reference
< 25	18 (23.4)	1.23 (0.49 – 3.12)	---
Concomitant use of nephrotoxins			
No concomitant nephrotoxins	2 (16.7)	Reference	Reference
Use of concomitant nephrotoxins	25 (25.5)	1.71 (0.35 – 8.35)	7.80 (0.82 – 74.5)
Vancomycin mean trough level, µmol/L			
≤ 13.8	12 (15.4)	Reference	Reference
> 13.8	15 (46.9)	**4.85 (1.92 – 12.27)**	**7.67 (2.49 – 23.63)**

Abbreviations: *95%CI* 95% confidence interval, *CrCl* creatinine clearance

[a] The OR is from the univariate logistic regression

[b] The aORs are the adjusted odds ratio from the backward-stepwise multivariable logistic regression model including patient characteristics in the table

outcome in the first two days indicating potentially lower CrCl; however, all the credible intervals crossed the 0 log odds. Compared to Child–Pugh category A (mild liver disease), the mean CrCl β coefficient for Child–Pugh category B (moderate liver disease) decreased by -0.67% (95% CI -2.90 – 1.5). Similarly, the mean CrCl β coefficients for the Child–Pugh category C (severe liver disease) decreased by -2.5% (95% CI -5.5 – 0.4). Figure 3 (Panel A to D) presented estimates for the differences in CrCl means for category A vs. B, A vs. C, and B vs. C. The coefficients from the Bayesian proportional odds model were presented in Table S2 of the supplementary material. The REV for the model revealed the variable explaining most of the

Table 4 Univariate and multivariable logistic regression model to assess factors associated with mortality

Variable	Mortaltiy	OR* (95% CI)	aOR** (95% CI)
Liver dysfunction			
Mild	1 (3.6)	Reference	Reference
Moderate to severe	19 (23.2)	**8.14 (1.04 – 63.91)**	---
Gender			
Male	13 (22.4)	Reference	Reference
Female	7 (13.5)	0.54 (0.20 – 1.48)	---
Total maintenance daily dose of vancomycin			
500 to 1000 mg	4 (16.7)	Reference	Reference
1001 to 2000 mg	14 (19.2)	1.19 (0.35 – 4.03)	---
2001 to 3000 mg	2 (15.4)	0.91 (0.14 – 5.78)	---
Age, years			
18—64 years	8 (15.1)	Reference	Reference
≥ 65	12 (21.1)	1.50 (0.56 – 4.02)	---
Body mass index, kg/m^2			
< 25	7 (13.5)	Reference	Reference
25 – 29.9	10 (37.0)	**3.78 (1.24 – 11.54)**	**6.69 (1.73 – 25.8)**
≥ 30	3 (9.7)	0.69 (0.16 – 2.89)	0.75 (0.16 – 3.52)
Charlson comorbidity index			
< 4	3 (11.5)	Reference	Reference
≥ 4	17 (20.2)	1.94 (0.52 – 7.25)	---
Child–Pugh Score			
Mild (A): < 6	1 (3.6)	Reference	Reference
Moderate (B): 7 – 9	11 (19.3)	6.46 (0.79 – 52.78)	---
Severe (C): 10 – 15	8 (32.0)	**12.70 (1.46 – 110.7)**	---
CrCl, ml/min			
≥ 90	5 (14.3)	Reference	Reference
60 – 89.9	4 (11.1)	0.75 (0.18 – 3.06)	---
30 – 59.9	10 (31.3)	2.73 (0.82 – 9.11)	---
15.1 – 29.9	1 (14.3)	1.00 (0.10 – 10.17)	---
Albumin level, g/L			
≥ 25	11 (33.3)	Reference	Reference
< 25	9 (11.7)	**3.78 (1.39 – 10.3)**	**4.33 (1.36 – 13.8)**
Concomitant use of nephrotoxins			
No concomitant nephrotoxins	3 (25.0)	Reference	Reference
Use of concomitant nephrotoxins	17 (17.3)	0.63 (0.15 – 2.57)	---
Vancomycin mean trough level, µmol/L			
≤ 13.8	9 (11.5)	Reference	Reference
> 13.8	11 (34.4)	**4.02 (1.47 – 11.0)**	**6.13 (1.82 – 20.6)**

Abbreviations: *95%CI* 95% confidence interval, *CrCl* creatinine clearance

* The OR is from the univariate logistic regression

** The aORs are the adjusted odds ratio from the backward-stepwise multivariable logistic regression model including patient characteristics in the table

variations in the outcome was previous CrCl readings, followed by mean trough levels, age, number of days, and Child–Pugh score category (Figure S4). The partial effects plots for linear predictors in the log odds scale depicted the model estimates more efficiently (Figure S5). Most of the linear predictors were flat in predicting the outcome results except for previous CrCl readings.

For the BUN outcome, the interaction of Child–Pugh score categories with time were shown in Fig. 1C. Compared to Child–Pugh category A (mild liver disease), the mean BUN β coefficient or Child–Pugh category B

(moderate liver disease) increased by 0.05% (95% CI -2.19 – 2.41). Similarly, the mean BUN β coefficient for the Child–Pugh category C (severe liver disease) increased by 0.96% (95%CI -1.80 – 4.1). Figure 4 (Panel A to D) presented estimates for the differences in BUN means for category A vs. B, A vs. C, and B vs. C.. The coefficients from the Bayesian proportional odds model were presented in Table S3 of the supplementary material. The REV for the model revealed that that the variable explaining most of the variations in the outcome was previous BUN readings, followed by day number, trough levels, and Child–Pugh score category (Figure S6). Figure S7 showed the linear predictors in the log odds scale; many of these relationships were flat and the impact of previous BUN results was the strongest predictor for the next BUN.

Discussion

The study highlights the relationship between liver dysfunction and the risk of AKI in patients on vancomycin. The incidence of AKI was numerically higher in patients with MSLD than in those with MLD. Even though this increase in AKI did not reach statistical significance, similar to a previous study, this difference warrants attention as it suggests a possible connection to vancomycin-induced nephrotoxicity in patients with compromised liver function [11, 13]. On the other hand, there was a statistically significant increase in mean vancomycin trough levels in the MSLD group than the MLD group. In addition, there was a significant increase in the number of patients with vancomycin mean trough level > 13.8 µmol/L in the MSLD group than in the MLD group. These two findings might explain the increased incidence of AKI in the patients with MSLD.

Our study highlights several factors that contribute to the higher incidence of AKI. These factors, derived from the main multivariable regression models, include lower baseline CrCl (baseline CrCl between 15.1 and 29.9 ml/min) and mean vancomycin trough level above 13.8 µmol/L. Furthermore, the Bayesian proportional odds model analysis provided additional insights, revealing an association between liver disease severity and renal outcomes over time. Patients with severe liver disease (Child–Pugh C) exhibited a notable increase in Scr compared to those with mild disease (Child–Pugh A) in the first two days. This suggests that severe liver disease is strongly linked to impaired renal function. However, the contrast between the two means followed a non-linear trend with a small bump in Scr for the mild group in days 4 and 5. The relative explained variation (REV) indicated that previous Scr readings were the primary driver of the outcome, underscoring the importance of baseline renal function. Additionally, the model showed a decline in Scr and BUN clearance as liver disease progressed, particularly in the severe category (Child–Pugh C). This reinforces the understanding that worsening liver function is associated with reduced renal filtration capacity.

Another key factor affecting vancomycin pharmacokinetics in patients with liver dysfunction is hypoalbuminemia, which is commonly associated with advanced liver disease. Albumin binds to drugs and regulates the amount of free drug available for action. Hypoalbuminemia can increase the free fraction of vancomycin in the blood, leading to higher levels of active drug, which increases the risk of nephrotoxicity. Mizuno et al. demonstrated that severe hypoalbuminemia in elderly patients significantly prolonged vancomycin's half-life, thereby increasing the likelihood of its nephrotoxicity [12]. In our cohort with liver disease, we found comparable results as hypoalbuminemia was more prevalent among patients with MSLD. An albumin level below 25 g/L was associated with higher AKI incidence compared to patients with higher albumin levels.

In addition to pharmacokinetic considerations, the pathophysiology of liver dysfunction may also directly increase the risk of AKI. Hepatorenal syndrome (HRS), a condition characterized by the development of renal failure in patients with severe liver disease, is a well-recognized complication that may exacerbate the nephrotoxic effects of vancomycin [22]. Although our study did not specifically investigate HRS, its presence in patients with advanced liver disease could

(See figure on next page.)

Fig. 1 Child Pugh Score Categories Across Time for Scr, CrCl and BUN Outcomes. **A** Child Pugh score categories across time for the Scr outcome. Patients in the category C had higher log odds of the outcomes in the first 2 days. Category A had lower log odds of the outcomes; however, there was a non-linear relationship as patients progressing over time. Estimates were derived from longitudinal Bayesian proportional odds models with first order Markov state transitions to capture the correlation structure. **B** Child Pugh score categories across time for the CrCl outcome. Patients in the category C had lower log odds of the outcomes in the first 2 days. Category A had higher log odds of the outcomes; however, there was a non-linear relationship as patients progressing over time. Estimates were derived from longitudinal Bayesian proportional odds models with first order Markov state transitions to capture the correlation structure. **C** Child Pugh score categories across time for the BUN outcome. Patients in the category B had lower log odds of the outcomes in the first 2 days. Category C had higher log odds of the outcomes; however, these relationships were non-linear. Estimates were derived from longitudinal Bayesian proportional odds models with first order Markov state transitions to capture the correlation structure

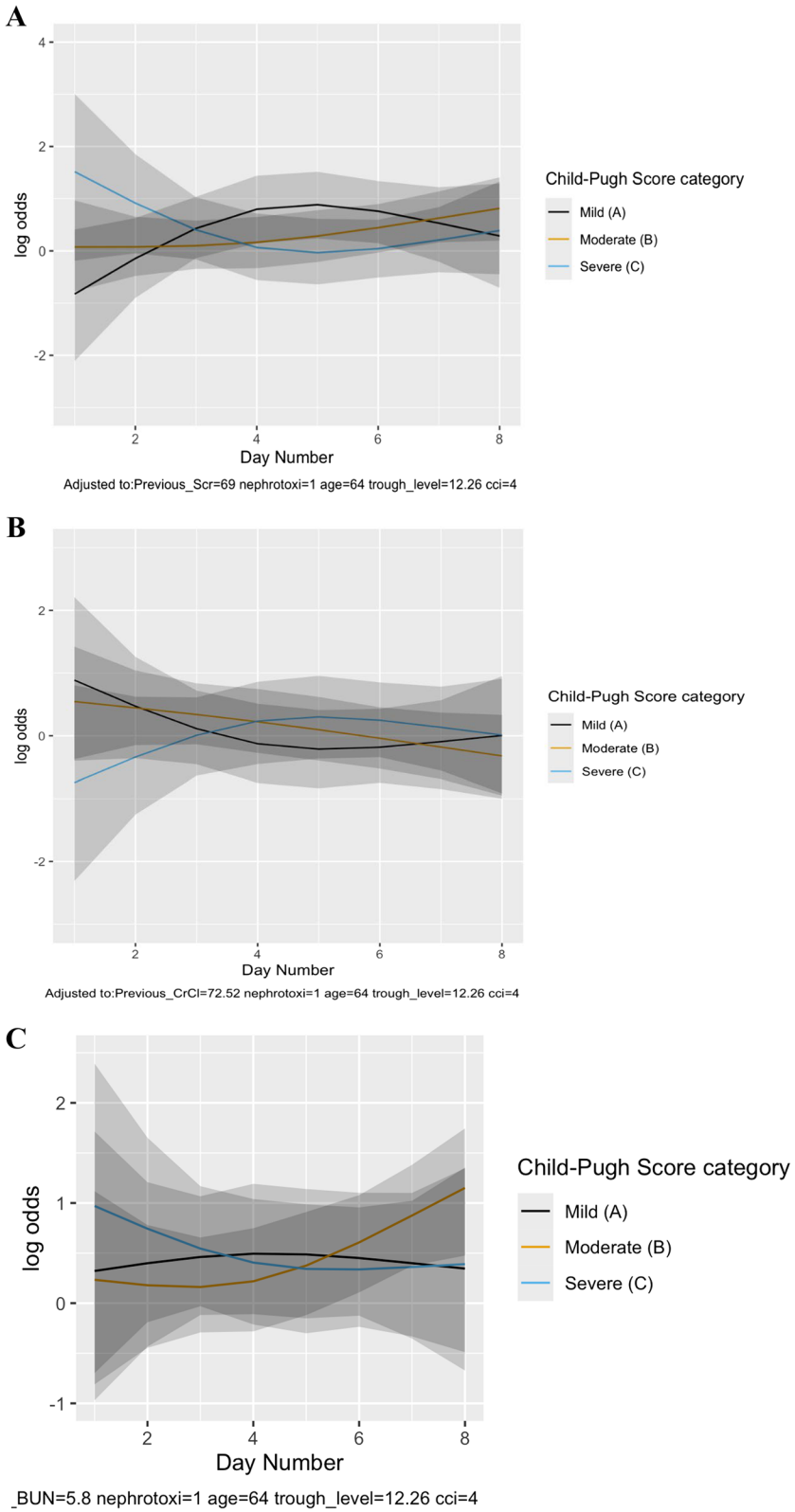
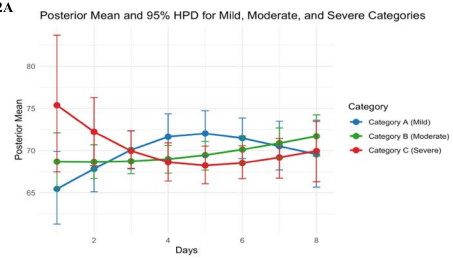
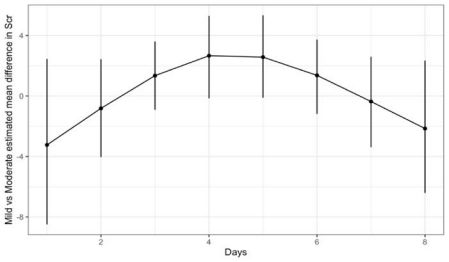


Fig. 1 (See legend on previous page.)

Panel 2A

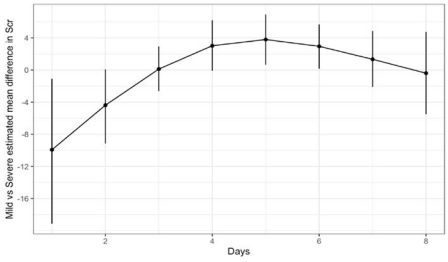


Panel 2B



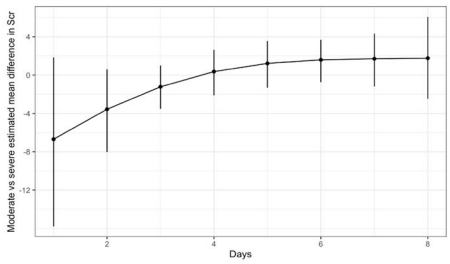
Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Mild vs Moderate	1	-0.90	-2.43 – 0.58	0.1288	-3.24	-8.49 – 2.45
Mild vs Moderate	2	-0.22	-1.13 – 0.58	0.3042	-0.82	-4.04 – 2.43
Mild vs Moderate	3	0.33	-0.22 – 0.89	0.8852	1.35	-0.91 – 3.60
Mild vs Moderate	4	0.63	0.01 – 1.27	0.9768	2.66	-0.16 – 5.30
Mild vs Moderate	5	0.60	-0.02 – 1.22	0.9695	2.57	-0.12 – 5.34
Mild vs Moderate	6	0.32	-0.27 – 0.86	0.8625	1.36	-1.19 – 3.73
Mild vs Moderate	7	-0.10	-0.85 – 0.58	0.4035	-0.37	-3.39 – 2.60
Mild vs Moderate	8	-0.53	-1.56 – 0.53	0.1710	-2.15	-6.41 – 2.34

Panel 2C



Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Mild vs Severe	1	-2.34	-4.31 – -0.42	0.0095	-9.93	-19.12 – -1.11
Mild vs Severe	2	-1.06	-2.17 – 0.00	0.0293	-4.38	-9.14 – 0.08
Mild vs Severe	3	0.03	-0.63 – 0.72	0.5352	0.12	-2.64 – 2.93
Mild vs Severe	4	0.73	0.02 – 1.52	0.9708	3.02	-0.09 – 6.19
Mild vs Severe	5	0.92	0.15 – 1.64	0.9915	3.79	0.65 – 6.91
Mild vs Severe	6	0.72	0.03 – 1.34	0.9830	2.95	0.16 – 5.67
Mild vs Severe	7	0.32	-0.46 – 1.22	0.7740	1.33	-2.09 – 4.86
Mild vs Severe	8	-0.10	-1.29 – 1.20	0.4305	-0.40	-5.5 – 4.75

Panel 2D



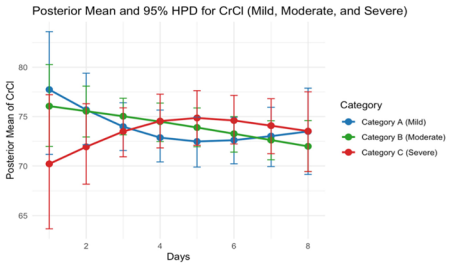
Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Moderate vs Severe	1	-1.44	-3.27 – 0.24	0.0535	-6.69	-15.8 – 1.84
Moderate vs Severe	2	-0.84	-1.81 – 0.13	0.0458	-3.57	-8.03 – 0.59
Moderate vs Severe	3	-0.30	-0.87 – 0.24	0.1430	-1.23	-3.52 – 1.00
Moderate vs Severe	4	0.10	-0.52 – 0.69	0.6162	0.36	-2.11 – 2.64
Moderate vs Severe	5	0.32	-0.30 – 0.95	0.8390	1.22	-1.31 – 3.55
Moderate vs Severe	6	0.40	-0.17 – 0.95	0.9150	1.58	-0.74 – 3.67
Moderate vs Severe	7	0.42	-0.27 – 1.09	0.8840	1.70	-1.20 – 4.33
Moderate vs Severe	8	0.43	-0.60 – 1.42	0.7998	1.76	-2.47 – 6.06

Fig. 2 Estimated Differences Serum Creatinine Differences Between Groups Over Time. **Panel A** Estimated Differences Serum Creatinine Means of Mild and Severe Groups Over Time. **Panel B** The Estimated Differences Serum Creatinine Means of Mild and Moderate Groups Over Time. **Panel 2C** The Estimated Differences Serum Creatinine Means of Mild and Severe Groups Over Time. **Panel D** The Estimated Differences Serum Creatinine Means of Moderate and Severe Groups Over Time. Estimates were derived from longitudinal Bayesian proportional odds models with first order Markov state transitions to capture the correlation structure. The probability of the contrast (i.e. difference) > 0 was presented as Pr(contrast > 0). HPD: Highest posterior distribution. CI: Credible interval

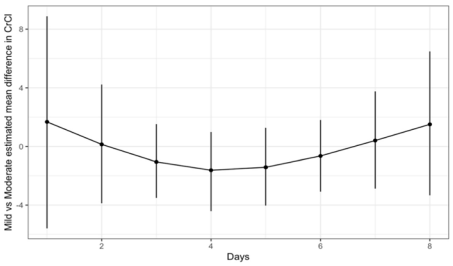
have contributed to the observed trend of higher AKI incidence in the MSLD group. The potential relationship between liver dysfunction and renal vulnerability emphasizes the importance of closely monitoring renal function and vancomycin levels in this population while receiving vancomycin.

The mortality observed in our study might be linked to advanced liver disease. Patients who are overweight

Panel 3A

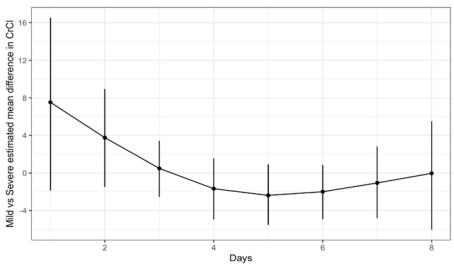


Panel 3B



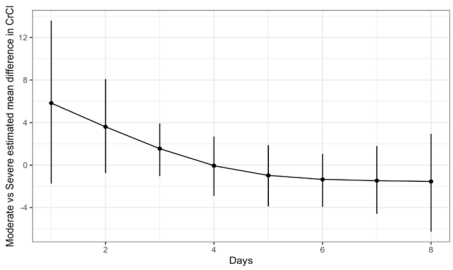
Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Mild vs Moderate	1	0.34	-1.14 – 1.81	0.6770	1.67	-5.59 – 8.88
Mild vs Moderate	2	0.03	-0.78 – 0.89	0.5240	0.14	-3.87 – 4.23
Mild vs Moderate	3	-0.22	-0.73 – 0.33	0.2018	-1.05	-3.51 – 1.52
Mild vs Moderate	4	-0.35	-0.92 – 0.25	0.1215	-1.62	-4.41 – 0.98
Mild vs Moderate	5	-0.31	-0.90 – 0.25	0.1508	-1.42	-4.03 – 1.27
Mild vs Moderate	6	-0.14	-0.68 – 0.39	0.3068	-0.65	-3.08 – 1.80
Mild vs Moderate	7	0.09	-0.65 – 0.79	0.5938	0.4	-2.88 – 3.76
Mild vs Moderate	8	0.33	-0.75 – 1.39	0.7302	1.51	-3.33 – 6.48

Panel 3C



Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Mild vs Severe	1	1.63	-0.48 – 3.54	0.9455	7.52	-1.88 – 16.53
Mild vs Severe	2	0.81	-0.33 – 1.93	0.9210	3.75	-1.50 – 8.94
Mild vs Severe	3	0.11	-0.55 – 0.72	0.6272	0.49	-2.56 – 3.43
Mild vs Severe	4	-0.36	-1.05 – 0.35	0.1622	-1.68	-4.96 – 1.57
Mild vs Severe	5	-0.51	-1.21 – 0.18	0.0732	-2.38	-5.52 – 0.92
Mild vs Severe	6	-0.43	-1.05 – 0.19	0.0952	-2.00	-4.92 – 0.86
Mild vs Severe	7	-0.23	-1.04 – 0.60	0.2932	-1.06	-4.82 – 2.82
Mild vs Severe	8	-0.01	-1.26 – 1.24	0.4928	-0.03	-6.05 – 5.51

Panel 3D

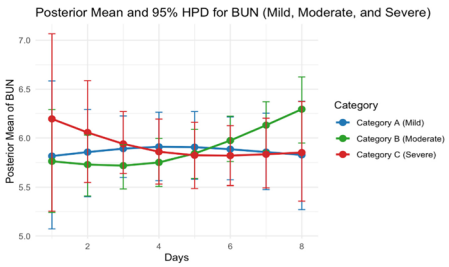


Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Moderate vs Severe	1	1.29	-0.35 – 3.04	0.9325	5.85	-1.74 – 13.59
Moderate vs Severe	2	0.78	-0.16 – 1.75	0.9472	3.61	-0.75 – 8.09
Moderate vs Severe	3	0.33	-0.16 – 0.88	0.8808	1.55	-1.03 – 3.92
Moderate vs Severe	4	-0.01	-0.62 – 0.55	0.4878	-0.06	-2.89 – 2.69
Moderate vs Severe	5	-0.20	-0.80 – 0.42	0.2578	-0.97	-3.90 – 1.87
Moderate vs Severe	6	-0.29	-0.83 – 0.24	0.1467	-1.34	-3.94 – 1.06
Moderate vs Severe	7	-0.31	-1.03 – 0.33	0.1640	-1.46	-4.60 – 1.79
Moderate vs Severe	8	-0.33	-1.33 – 0.69	0.2405	-1.54	-6.28 – 2.96

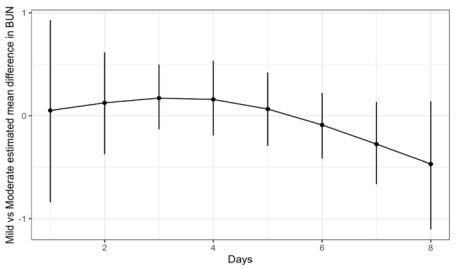
Fig. 3 Estimated Differences Creatine Clearance (CrCl) Means Between Groups Over Time. **Panel A** Estimated Differences Creatine Clearance (CrCl) Means of Mild and Severe Groups Over Time. **Panel B** The Estimated Differences Creatine Clearance (CrCl) Means of Mild and Moderate Groups Over Time. **Panel C** The Estimated Differences Creatine Clearance (CrCl) Means of Mild and Severe Groups Over Time. **Panel D** The Estimated Differences Creatine Clearance (CrCl) Means of Moderate and Severe Groups Over Time. Estimates were derived from longitudinal Bayesian proportional odds models with first order Markov state transitions to capture the correlation structure. The probability of the contrast (i.e. difference) > 0 was presented as Pr(contrast > 0). HPD: Highest posterior distribution. CI: Credible interval

(BMI 25–29.9 kg/m^2) exhibited significantly higher mortality rates than those with a BMI below 25 kg/m^2. Severe liver disease (Child–Pugh C) was associated with an elevated mortality risk compared to mild liver disease (Child–Pugh A). This could mean that these patients were in critical condition at baseline; however, the increased risk of AKI in patients with MSLD could have contributed to their higher mortality risk. In addition, elevated mean vancomycin trough levels (> 13.8

Panel 4A

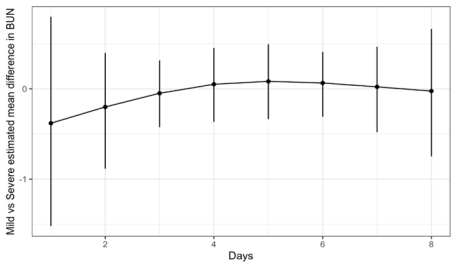


Panel 4B



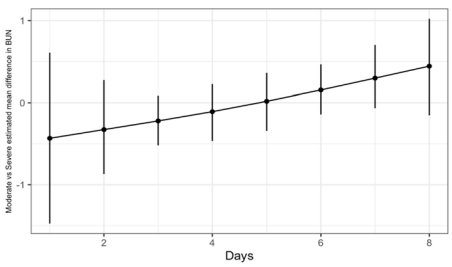
Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Mild vs Moderate	1	0.09	-1.49 – 1.59	0.5410	0.05	-0.84 – 0.93
Mild vs Moderate	2	0.22	-0.65 – 1.07	0.6788	0.13	-0.37 – 0.62
Mild vs Moderate	3	0.3	-0.22 – 0.86	0.8535	0.17	-0.13 – 0.5
Mild vs Moderate	4	0.28	-0.37 – 0.87	0.7935	0.16	-0.19 – 0.54
Mild vs Moderate	5	0.11	-0.5 – 0.74	0.6352	0.07	-0.29 – 0.42
Mild vs Moderate	6	-0.16	-0.68 – 0.43	0.2932	-0.09	-0.42 – 0.22
Mild vs Moderate	7	-0.48	-1.15 – 0.22	0.0965	-0.28	-0.67 – 0.14
Mild vs Moderate	8	-0.81	-1.95 – 0.19	0.0693	-0.47	-1.11 – 0.14

Panel 4C



Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Mild vs Severe	1	-0.65	-2.63 – 1.32	0.2575	-0.38	-1.52 – 0.80
Mild vs Severe	2	-0.34	-1.43 – 0.76	0.2695	-0.20	-0.88 – 0.40
Mild vs Severe	3	-0.08	-0.73 – 0.55	0.4005	-0.05	-0.42 – 0.32
Mild vs Severe	4	0.09	-0.66 – 0.75	0.6035	0.05	-0.37 – 0.45
Mild vs Severe	5	0.14	-0.63 – 0.81	0.6615	0.08	-0.34 – 0.49
Mild vs Severe	6	0.11	-0.51 – 0.73	0.6388	0.07	-0.31 – 0.41
Mild vs Severe	7	0.04	-0.81 – 0.82	0.5370	0.02	-0.48 – 0.47
Mild vs Severe	8	-0.04	-1.25 – 1.17	0.4670	-0.02	-0.75 – 0.66

Panel 4D



Comparison	Day	Log odds Contrast	95%CI for log odds of Contrast	Pr (Contrast>0)	Posterior Mean Difference	95%CI for Posterior Mean Difference
Moderate vs Severe	1	-0.74	-2.41 – 1.14	0.2032	-0.43	-1.48 – 0.61
Moderate vs Severe	2	-0.56	-1.55 – 0.41	0.1282	-0.33	-0.87 – 0.28
Moderate vs Severe	3	-0.38	-0.89 – 0.15	0.0782	-0.22	-0.52 – 0.09
Moderate vs Severe	4	-0.19	-0.79 – 0.39	0.2628	-0.11	-0.47 – 0.23
Moderate vs Severe	5	0.03	-0.60 – 0.62	0.5480	0.02	-0.34 – 0.36
Moderate vs Severe	6	0.27	-0.25 – 0.81	0.8468	0.15	-0.14 – 0.47
Moderate vs Severe	7	0.51	-0.12 – 1.19	0.9350	0.3	-0.07 – 0.70
Moderate vs Severe	8	0.76	-0.26 – 1.74	0.9255	0.44	-0.15 – 1.02

Fig. 4 Estimated Differences Blood Urea Nitrogen (BUN) Means Between Groups Over Time. **Panel A** Estimated Differences Blood Urea Nitrogen (BUN) Means of Mild and Severe Groups Over Time. **Panel B** The Estimated Blood Urea Nitrogen (BUN) Means of Mild and Moderate Groups Over Time. **Panel C** The Estimated Differences Blood Urea Nitrogen (BUN) Means of Mild and Severe Groups Over Time. **Panel D** The Estimated Differences Blood Urea Nitrogen (BUN) Means of Moderate and Severe Groups Over Time. Estimates were derived from longitudinal Bayesian proportional odds models with first order Markov state transitions to capture the correlation structure. The probability of the contrast (i.e. difference) > 0 was presented as Pr(contrast > 0). HPD: Highest posterior distribution. CI: Credible interval

μmol/L) and albumin levels below 25 g/L were also significantly associated with increased mortality risk.

Our findings should be interpreted considering several limitations. This was an observational study, which may have included unmeasured confounding factors that could not be accounted for. Prospective studies investigating the impact of different degrees of liver dysfunction on vancomycin-induced nephrotoxicity are needed to establish safer and more precise dosing recommendations. Our small sample size limited the

power of our study, potentially preventing the detection of statistically significant differences between groups in certain outcomes. Our use of vancomycin trough concentrations for vancomycin monitoring is not the currently advised method to monitor vancomycin as compared to using AUC: MIC ratio [4]. However, we could not calculate AUC in our population as this monitoring method is not currently practiced in the included institutions. Lastly, assessing renal function using alternative modalities, such as cystatin C, which may be less influenced by liver function [23], could provide more accurate assessments of renal function in these patients and improve dosing precision.

Conclusion

While renal function remains a critical factor in vancomycin dosing, our study adds to the growing evidence that liver dysfunction should also be carefully considered in patients receiving vancomycin. Although not statistically significant, the higher incidence of AKI observed in patients with MSLD suggests a trend that could lead to serious adverse outcomes, including mortality. Tailoring vancomycin dosing to account for both hepatic and renal function could potentially reduce the risk of nephrotoxicity and mortality in this vulnerable population, ultimately improving patient outcomes. Further research is needed to validate these findings and guide the development of more comprehensive vancomycin dosing recommendations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10763-3.

Supplementary Material 1.

Acknowledgements
The authors would like to extend their appreciation to King Saud University for funding this work through the Researcher Supporting Project (RSP2024R77), King Saud University, Riyadh, Saudi Arabia.

Authors' contributions
Reem F. Bamogaddam: Conceptualization, Methodology, Validation, Data Curation, Writing-review & editing. Ahmad Alamer: Formal analysis, Methodology, Writing—Review & Editing, Visualization, Resources. Shatha Alqarni: Investigation, Writing—Original Draft, Project administration. Mohammed M. Almotairi: Investigation, Resources, Writing—Original Draft, Project administration. Ali A. Almakrami:: Investigation, Writing—Original Draft. Alwaleed M. Alharbi: Investigation, Writing—Original Draft. Raghad Alamri: Investigation, Writing—Original Draft. Manar Altamimi: Investigation, Writing—Original Draft. Amal Alkhulaif: Investigation, Writing—Original Draft. Raghad Alanazi: Investigation, Writing—Original Draft. Omar A. Almohammed: Methodology, Formal analysis, Writing—Review & Editing, Visualization, Supervision. Majed S. Alyami: Resources, Writing-review & editing, Project administration.

Funding
The author (OAA) received funding from the Research Supporting Project (RSP2024R77), King Saud University, Riyadh, Saudi Arabia to support the publication of this article. The funding agency played no role in designing the study, analyzing and interpreting the data, or writing the manuscript.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
The study was carried out according to the principles of the Declaration of Helsinki, and approval was granted by the Institutional Review Boards at KAMC (IRB: 1755/23) and KFMC (IRB: 24–015). Due to the retrospective nature of the study, the need to obtain informed consent was waived by Institutional Review Boards at KAMC (IRB: 1755/23) and KFMC (IRB: 24–015).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Clinical Pharmacy Department, King Saud Medical City, Riyadh, Saudi Arabia. [2]Department of Clinical Pharmacy, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia. [3]Department of Pharmacy Practice, College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, P.O. Box 3660, Riyadh 11481, Kingdom of Saudi Arabia. [4]Pharmaceutical Care Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia. [5]Clinical Pharmacy Department, King Fahad Medical City, Riyadh, Saudi Arabia. [6]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. [7]Pharmacoeconomics Research Unit, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. [8]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.

Received: 29 October 2024 Accepted: 7 March 2025
Published online: 18 March 2025

References

1. Luque Y, Mesnard L. Vancomycin nephrotoxicity: frequency and mechanistic aspects. Nephrol Ther. 2018;14(Suppl 1):S133–8. https://doi.org/10.1016/j.nephro.2018.02.009.
2. Shenoy B, Joshi DN, Doddikoppad P. Vancomycin therapeutic drug monitoring. Pediatr Infect Dis. 2023;5(1):17–9. https://doi.org/10.5005/jp-journals-10081-1387.
3. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother. 2013;57(2):734–44. https://doi.org/10.1128/AAC.01568-12.
4. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835–64. https://doi.org/10.1093/ajhp/zxaa036.
5. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147–61. https://doi.org/10.1007/s00228-008-0553-z.
6. Weersink RA, Bouma M, Burger DM, Drenth JP, Hunfeld NG, Kranenborg M, et al. Evaluating the safety and dosing of drugs in patients with liver cirrhosis by literature review and expert opinion. BMJ Open. 2016;6(10):e012991. https://doi.org/10.1136/bmjopen-2016-012991.
7. Regal RE, Ren SP, Paige G, Alaniz C. Evaluation of vancomycin dosing in patients with cirrhosis: beginning de-liver-ations about a new nomogram. Hosp Pharm. 2019;54(2):125–9. https://doi.org/10.1177/0018578718772266.

8. Bauer LA. Applied Clinical Pharmacokinetics. Second edi. New York, USA: McGraw-Hill Professional Publishing; 2008.
9. Sharma A, Nagalli S. Chronic Liver Disease. [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554597/.
10. Bucsics T, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. Gastroenterol Rep (Oxf). 2017;5(2):127–37. https://doi.org/10.1093/gastro/gox009.
11. Brown N, Ho DHW, Fong KLL, Bogerd L, Maksymiuk A, Bolivar R, et al. Effects of hepatic function on vancomycin clinical pharmacology. Antimicrob Agents Chemother. 1983;23(4):603–9. https://doi.org/10.1128/AAC.23.4.603.
12. Mizuno T, Mizokami F, Fukami K, Ito K, Shibasaki M, Nagamatsu T, Furuta K. The influence of severe hypoalbuminemia on the half-life of vancomycin in elderly patients with methicillin-resistant Staphylococcus aureus hospital-acquired pneumonia. Clin Interv Aging. 2013;8:1323–8. https://doi.org/10.2147/CIA.S52259.
13. Brunetti L, Song JH, Suh D, Kim HJ, Seong YH, Lee DS, Lee SM, Suh DC. The risk of vancomycin toxicity in patients with liver impairment. Ann Clin Microbiol Antimicrob. 2020;19(1):13. https://doi.org/10.1186/s12941-020-00354-2.
14. Aldaz A, Ortega A, Idoate A, Giráldez J, Brugarolas A. Effects of hepatic function on vancomycin pharmacokinetics in patients with cancer. Ther Drug Monit. 2000;22(3):250–7. https://doi.org/10.1097/00007691-200006000-00004.
15. Harada H, Miyagawa S, Kawasaki S, Hayashi K, Kitamura H, Katsuyama Y, Atobe O, Tada A, Zenda H, Oguma T. Study of the pharmacokinetics of vancomycin in patients with impaired liver function. J Infect Chemother. 1999;5(2):104–7. https://doi.org/10.1007/s101560050018.
16. Martí R, Rosell M, Pou L, García L, Pascual C. Influence of biochemical parameters of liver function on vancomycin pharmacokinetics. Pharmacol Toxicol. 1996;79(2):55–9. https://doi.org/10.1111/j.1600-0773.1996.tb00242.x.
17. Vancocin Powder for Solution. Summary of Product Characteristics. Medicines.org.uk; [cited 2025 Feb 6]. Available from: https://www.medicines.org.uk/emc/product/6407/smpc.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83. https://doi.org/10.1016/0021-9681(87)90171-8.
19. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Disease: Improving Global Outcomes (KDIGO); [cited 2025 Feb 6]. Available from: https://kdigo.org/guidelines/acute-kidney-injury/.
20. Rohde MD, French B, Stewart TG, Harrell FE. Bayesian transition models for ordinal longitudinal outcomes. Stat Med. 2024;43(18):3539–61. https://doi.org/10.1002/sim.10133.
21. Harrell F. Bayesian Regression Modeling Strategies [R package rmsb version 1.1-1]. 2024 [cited 2025 Feb 6]. Available from: https://cran.r-project.org/web/packages/rmsb/index.html.
22. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med. 2009;361(13):1279–90. https://doi.org/10.1056/NEJMra0809139.
23. Randers E, Ivarsen P, Erlandsen EJ, Hansen EF, Aagaard NK, Bendtsen F, Vilstrup H. Plasma cystatin C as a marker of renal function in patients with liver cirrhosis. Scand J Clin Lab Invest. 2002;62(2):129–34. https://doi.org/10.1080/003655102753611753.

Publisher's Note