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Original Article

Liver Transplant Recipients Have Markedly Different Vancomycin Pharmacokinetics: A Pharmacokinetic Model-Based Analysis

Seyed Soroush Jalali[1,2†], Afsaneh Vazin[2†], Mahtabalsadat Mirjalili[3], Parisa Ghasemiyeh[2,4], Soliman Mohammadi-Samani[3], Hamed Nikoupour[1], Seyed Mohammad Firoozifar[1], Sara Arabsheybani[1], Mojtaba Shafiekhani[1,2,4*]

[1]Shiraz Transplant Center, Abu-Ali Sina Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Traditional Pharmacy and Pharmaceutical Sciences Research Center, and Department of Clinical Pharmacy, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[4]Department of Pharmaceutics, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background: Vancomycin is considered the antibiotic of choice for many gram-positive bacterial infections. Following the use of this medication, the risk of acute kidney injury (AKI) in patients increases significantly. Also, the kinetics of some medications, including vancomycin, differ between liver transplant recipients (LTRs) and the normal population.

Objective: The evaluation of the pharmacokinetics of vancomycin in LTRs and its association with the risk of AKI.

Methods: In this prospective study on 34 LTRs, blood samples were collected at specific time points from patients who had received vancomycin at 12-hour intervals, with a loading dose of 20–35 mg/kg and a maintenance dose of 15–20 mg/kg. The collected samples were analyzed using high-performance liquid chromatography (HPLC). Then, the area under the concentration-time curve (AUC) and other pharmacokinetic parameters were calculated. The occurrence of AKI and its related risk factors was also investigated.

Results: The mean observed values of Vd, Clvan, $t_{1/2}$, and Ke for vancomycin were 1.08±0.66 L/kg, 4.91±2.98 L/h, 12.15±6.63 h, and 0.08±0.045 h^{-1}, respectively. All these pharmacokinetic parameters were significantly different in LTRs compared to the normal population. The incidence of AKI was 44.1%, which was higher than in healthy individuals. Factors that influenced the incidence of AKI included trough and intermediate concentrations, urinary tract infection (UTI), elimination constant (Ke), half-life ($t_{1/2}$), AUC, length of hospital stay, serum albumin level, and baseline total and direct bilirubin concentrations.

Conclusion: Differences in pharmacokinetic parameters between LTRs and the general population underscore the need for vancomycin therapeutic drug monitoring (TDM) in all patients.

KEYWORDS: Therapeutic drug monitoring; Vancomycin; Acute kidney injury; Liver transplantation

INTRODUCTION

The liver plays a major role in the metabolism of most drugs. Therefore, hepatic dysfunction can significantly affect the pharmacokinetics of these medications. Liver transplantation (LT) is an important treatment option for patients with end-stage liver disease [1, 2].

Organ transplantation in Iran began in 1967 with the first successful live donor kidney transplant at Namazi Hospital in Shiraz. Progress was slow, and political upheavals such as the 1979 Revolution and the Iran-Iraq War further delayed development. In 1988, Tehran

†These authors share first authorship.
*Correspondence: Mojtaba Shafiekhani, PharmD, BCPS
Department of Clinical Pharmacy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
Tel/Fax: +98-7132424127
ORCID: 0000-0001-8661-1838
E-mail: mojtabashafiekhani@gmail.com

introduced a paid-donation model widely adopted nationwide, while Shiraz focused on establishing a deceased donor program despite significant challenges [3].

LT started over 20 years ago at the Shiraz Organ Transplantation Center (SOTC), now the nation's leading center with over 3,000 transplants. A decade later, the Imam Khomeini Hospital Complex in Tehran followed, and several other centers soon launched LT programs. Today, both adult and pediatric LTs are performed successfully across Iran [4].

Bacterial infections are common among liver transplant recipients (LTRs), with a prevalence of 53-70% [1, 2]. Their occurrence is highest during the first month following LT [5]. Staphylococcus aureus is considered one of the major causes of septicemia, pneumonia, wound infections, and intra-abdominal infections in LTRs, particularly during the first trimester post-transplantation [6]. The isolation rate of methicillin-resistant Staphylococcus aureus (MRSA) in LTRs varies across different medical centers and may account for up to 50% of bloodstream infections [7].

Vancomycin is among the most commonly prescribed antibiotics for liver transplant recipients (LTRs) to treat infections caused by Gram-positive microorganisms. It is a hydrophilic glycopeptide antibiotic with a narrow therapeutic index; therefore, therapeutic drug monitoring (TDM) and precise dose adjustment are necessary to achieve therapeutic goals and to prevent or minimize adverse drug reactions, including vancomycin-induced nephrotoxicity [8, 9].

A number of studies have shown that vancomycin TDM significantly reduces the incidence of nephrotoxicity [10, 11]. The ratio of the area under the 24-hour concentration-time curve to the minimum inhibitory concentration determined by broth microdilution (AUC24h/MICBMD) is the parameter that best correlates with vancomycin efficacy [8]. According to previous studies, this ratio should be maintained between 400 and 600 mg h/L to achieve optimal efficacy with minimal toxicities [12]. Studies have demonestrated that higher AUC24h and trough concentrations of vancomycin are associated with a greater risk of acute kidney injury (AKI) [8]. Furthermore, the pharmacokinetic parameters of vancomycin vary significantly among individual patients. Although vancomycin is eliminated almost entirely by glomerular filtration, several other factors may influence its pharmacokinetics and should be considered. Fluid overload (e.g., ascites or edema following liver transplantation) may increase the volume of distribution (V_d), thereby lowering plasma concentrations.

Additionally, hypoalbuminemia—which is common among liver transplant recipients in the early post-transplant period—can increase the free fraction of vancomycin, although the drug is only approximately 50% protein-bound. These considerations formed the basis for the assumptions underlying this study. Therefore, individualization of the treatment regimen and clinical pharmacokinetic studies are essential to optimize drug efficacy, minimize drug toxicity, and drug resistance.

Although LTRs are more prone to vancomycin-induced nephrotoxicity [13, 14], few studies have addressed this issue. Therefore, the main purpose of this study was to evaluate the pharmacokinetic parameters of vancomycin in LTRs individually to develop an optimized dosing regimen and reduce the risk of vancomycin-associated nephrotoxicity.

MATERIALS AND METHODS

Study Setting

This prospective study was conducted at Abu-Ali Sina Solid Organ Transplant Hospital in Shiraz, Iran—one of the largest solid organ transplant centers in the world—affiliated with Shiraz University of Medical Sciences, from February 2023 to January 2024.

Inclusion and Exclusion Criteria

All adult patients (above 18 years old) who had undergone liver transplantation and received at least four doses of vancomycin over a 48-

hour period were included in this study. Pregnant women, individuals with a documented history of hypersensitivity reactions to vancomycin, subjects receiving theophylline during vancomycin administration, and individuals with documented underlying AKI or CKD were excluded.

Dosing and Initiation of Vancomycin

"In this study, vancomycin was prescribed with a loading dose of 20–35 mg/kg and a maintenance dose of 15–20 mg/kg every 12 hours for at least four doses, either empirically or definitively by infectious disease specialists. Vancomycin was administered as a 60- to 90-minute intermittent intravenous infusion.

Sampling Method and TDM

After 48 hours of vancomycin initiation, four venous blood samples (4 mL) were taken from each patient at specific time intervals (Table 1). Blood samples were collected just before administration of the fifth dose (trough 1), immediately after the 1-hour infusion of the fifth dose (peak), 6 hours after administration of the fifth dose (intermediate), and 12 hours after the fifth dose or just before administration of the sixth dose (trough 2).

Samples were centrifuged at 5,000 rpm for approximately 5 minutes to obtain serum for further analysis using a validated high-performance liquid chromatography (HPLC) technique.

Samples were analyzed via a validated HPLC method (Knauer, Germany) using a C18 column (length 250 mm × width 4.6 mm, pore size 5 μm; Knauer, Germany). Standard vancomycin powder was donated by Dena Pharmaceutical Company (Tabriz, Iran), and standard theophylline powder was donated by Exir Pharmaceutical Company (Boroujerd, Iran).

A 950 μL aliquot of prepared patient serum was mixed with 50 μL of internal standard (theophylline) solution at a concentration of 0.8 mg/L, and vortexed for 1 minute. The mixture was then combined with 1,000 μL of methanol to precipitate plasma proteins. Following centrifugation at 12,000 rpm for 15 minutes, the supernatant was analyzed by HPLC in accordance with our previous study on vancomycin quantification using HPLC in human plasma [15].

Evaluation of Pharmacokinetic Parameters

Measured pharmacokinetic parameters of vancomycin were calculated for each patient individually based on Eq.1 to Eq.4.

Vancomycin clearance was calculated based on Eq. 1.

$$Cl_v = X_0/AUC\tau \quad (1)$$

where the unit of vancomycin clearance is L/h, X_0 is the dose administered (mg) in each interval and AUCτ is the interval AUC (mg h/L).

AUCτ of vancomycin was calculated using the trapezoidal rule from four samples obtained from each patient at various time points [16]. AUC_{24h} was calculated for these patients by doubling the AUCτ (τ= 12 hours).

The V_d was assessed using Eq. 2.

$$V_d = X_0/(C_{max} - C_{min}) \quad (2)$$

Where V_d is the volume of distribution (L), X_0 is the dose administered (mg) in each interval, and C_{max} and C_{min} are the peak and trough concentrations (mg/L), respectively.

The vancomycin elimination rate constant (h^{-1}) was estimated based on Eq. 3.

$$k_e = Cl_v/V_d \quad (3)$$

The vancomycin half-life (hr) was calculated using Eq. 4.

$$t_{1/2} = 0.693/k_e \quad (4)$$

Estimated pharmacokinetic parameters of vancomycin were calculated according to Winter's Clinical Pharmacokinetics, and are introduced in Eq.5 to Eq.11.

$$C_{min} = C_{max}\ (e^{-k\tau}) \quad (5)$$

Table 1: Specifications and timing of the four stages of blood sampling.

Concentration	Time	Details
C1	Immediately before the fifth dose	The required time to reach steady state was at least 48 hours, so the first sample was taken before the fifth dose.
C2	5 minutes after the end of vancomycin infusion	Immediately after the injection of vancomycin
C3	6 hours after the initia-tion of vancomycin infu-sion	This sample was needed to calculate the area under the curve (AUC)
C4	Immediately before the sixth dose	This sample was needed to calculate the AUC

In this regard, C_{min} and C_{max} are the trough and peak concentrations in terms of mg/L in steady state conditions, respectively.

$$C_{max} = (Dose/V_d)/(1-e^{-k\tau}) \quad (6)$$

$$AUC\tau = AUC_{24h}/(24/\tau) \quad (7)$$

$$AUC_{24h} = Dose_{24h}/Cl_v \quad (8)$$

$$V_d = \begin{cases} 0.90\ L/Kg, & \text{If } Cl_{Cr} < 60\ ml/min \\ 0.72\ L/Kg, & \text{If } Cl_{Cr} \geq 60\ ml/min \end{cases} \quad (9)$$

$$Cl_v = (Cl_{Cr} \times 0.689) + 3.66 \quad (10)$$

Where Cl_v is the clearance of vancomycin.

$$k = \ln(C_{max}/C_{min})/\tau \quad (11)$$

Where k is the elimination rate constant in terms of h^{-1}.

AKI Evaluation

According to the KDIGO 2012 guideline, AKI is diagnosed when a patient's serum creatinine increases by more than 0.3 mg/dL within a 48-hour period, or when it increases by more than 50% relative to baseline over seven consecutive daily readings. AKI is also diagnosed when urine output falls below 0.5 mL/kg/hour for a duration of six hours following vancomycin administration [17]. The lowest serum creatinine value recorded prior to vancomycin exposure during the current hospitalization was considered the baseline [18]. Additionally, serum creatinine and creatinine clearance were measured daily for each patient throughout the period of vancomycin administration until hospital discharge.

Clinical and Laboratory Outcomes

The clinical information of the patients—such as length of ICU and hospital stay, patient and graft status, type of isolated pathogen, site of infection, empiric or definitive vancomycin administration, and biochemical factors related to kidney function—was evaluated and recorded daily by a pharmacist during the hospital stay.

According to a previous study in the general population, for serious MRSA infections, the target AUC_{24h}/MIC should be 400–600 mg h/L (assuming an MIC ≤ 1 mg/L) [12].

This study aimed to report the rate of vancomycin-associated AKI, along with related risk factors and pharmacokinetic parameters in liver transplant recipients (LTRs).

Ethical Considerations

The guidelines outlined in the Declaration of Helsinki were followed throughout this research. Before enrollment, patients or their first-degree relatives were informed about the purpose of the study, and each participant was required to complete a written informed consent form. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1400.21).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 16). The correlation

Table 2: Demographic data of liver transplant patients receiving vancomycin (N = 34).

Parameters	Total (N=34)	Non-AKI (N=19)	AKI (N=15)	P-value
Demographic data				
Age (year)	43.26 ± 11.96	43.5 ± 12.7	42.9 ± 11.4	0.884
Gender				
Male, n (%)	21 (62)	13 (68.4)	8 (53.3)	0.371
Female, n (%)	13 (38)	6 (31.6)	7 (46.7)	
BMI (kg/m^2)	24.2 ± 3.8	23.6±3.8	24.9 ± 3.9	0.336
Time since liver trans-plantation (days)	5 ± 8	6 ± 14	5 ± 9	0.306
Previous ICU admission, n (%)	18 (53)	9 (47.4)	9 (60)	0.465
MELD Score	24.5 ± 11.5	22.8 ± 8.8	26.8 ± 6.6	0.153
Indication for transplantation (N)				
NASH + Cryptogenic	7	4	3	0.940
PSC+PBC	7	3	4	0.440
HBV+HCV	3	2	1	0.696
Wilson	1	1	0	1.000
AIH	12	8	4	0.353
Others	4	1	3	0.210
Comorbidities (N)				
Diabetes Mellitus	4	3	1	0.426
Hypertension	0	0	0	—
CVD	0	0	0	—
COPD + Asthma	0	0	0	—
Hypothyroidism	2	2	0	0.999
Dyslipidemia	5	2	3	0.445
Concomitant antibiotics (N)				
Aminoglycosides	5	2	3	0.445
Colistin	8	3	5	0.240
Carbapenems	10	5	5	0.656
Amphotericin B	3	2	1	0.696

Abbreviations: AKI (acute kidney injury), BMI (body mass index), ICU (intensive care unit), MELD (model for end-stage liver disease), NASH (non-alcoholic steatohepatitis); PSC (primary biliary cirrhosis) PBC (primary sclerosing cholangitis); HBV (hepatitis B virus), HCV (hepatitis C virus), AIH (Autoimmune hepatitis), CVD (cardiovascular disease), COPD (chronic obstructive pul-monary disease)

between observed and calculated pharmacokinetic parameters of vancomycin was assessed using Pearson's correlation test. Logistic regression was employed to evaluate the effects of demographic, clinical, laboratory, and pharmacokinetic variables on the occurrence of acute kidney injury (AKI), as well as the associations between each pharmacokinetic pa-

rameter and vancomycin-induced AKI. Additionally, the relationship between baseline kidney function indicators [including SCr(base) and ClCr(base)] and the incidence of AKI was examined using a nonparametric two-sample independent t-test.

AKI incidence was compared across patient groups stratified by vancomycin trough concentrations (<10, 10–15, 15–20, and ≥20 µg/mL) and AUC values (<400, 400–600, and >600 µg h/mL) using the Chi-square test. A p-value of <0.05 was considered statistically significant. Finally, receiver operating characteristic (ROC) curve analysis was used to determine cut-off values for trough concentrations, average trough concentrations, AUC, and elimination rate constant ($k_{1/2}$) predictive of AKI occurrence.

RESULTS

Demographic & Clinical Data

Thirty-four eligible adult patients were enrolled in this study. As shown in Table 2, the majority (61.8%) were male. Participants ranged in age from 21 to 66 years, with a mean ± SD of 43.26 ± 11.95 years. The most common indication for liver transplantation was autoimmune hepatitis, followed by viral hepatitis, primary sclerosing cholangitis (PSC), and non-alcoholic steatohepatitis (NASH). The mean ± SD maintenance and loading doses of vancomycin were 16.44 ± 2.09 mg/kg and 28.17 ± 2.21 mg/kg, respectively. The median duration of vancomycin administration was 5 ± 3 days. Vancomycin was empirically administered in most cases (18 patients), while other indications included surgical site infections (7 cases), bloodstream infections (4 cases), urinary tract infections (3 cases), and pneumonia (2 cases).

Laboratory Parameters

Baseline creatinine clearance did not differ significantly between patients with and without vancomycin-induced nephrotoxicity (98 ± 79.2 mL/min vs. 90.6 ± 57.2 mL/min, respectively). However, patients who developed nephrotoxicity had significantly higher total bilirubin (6.0 ± 6.5 mg/dL vs. 2.2 ± 3.6 mg/dL) and direct bilirubin (3.3 ± 2.7 mg/dL vs. 1.1 ± 1.8 mg/dL) levels compared to those without nephrotoxicity. These patients also had significantly lower serum albumin levels (2.8 ± 0.5 g/dL vs. 3.3 ± 0.7 g/dL; P= 0.040) as shown in Table Sup. I.

Clinical Outcomes

During vancomycin therapy, 15 patients (44.1%) developed AKI, with onset occurring within an average of 7 days from treatment initiation. According to Table 3, 10 patients (29.4%) died due to complications, including sepsis, liver transplant rejection, and COVID-19. Patients with vancomycin-induced nephrotoxicity had longer ICU and hospital stays and required mechanical ventilation more frequently than others, although only the difference in hospital stay reached statistical significance (P= 0.016). Furthermore, the incidence of vancomycin nephrotoxicity was significantly higher in patients with urinary tract infections (UTI) (81% vs. 19%).

AKI Occurrence in Different Groups of Trough Concentration and AUC

Fig. 1 shows the stratification of AKI occurrence by vancomycin trough concentrations. Among patients with a C1 <10 µg/mL, 27.8% developed AKI. This frequency was 20% for the C2 group. AUC_{24h} values were categorized into three ranges: <400, 400–600, and >600 µg h/mL. Of the patients within the therapeutic AUC range (400–600 µg h/mL), 62.5% developed AKI. Conversely, among patients with AUC_{24h} <400 µg h/mL (59% of the cohort), 30% developed AKI. These findings suggest a positive association between elevated AUC_{24h}/trough levels and the occurrence of AKI.

ROC Curves and Cut-off Point Calculation for AKI Occurrence

Fig. 2 presents ROC curves identifying cut-off thresholds predictive of vancomycin-induced AKI. The average threshold for trough concentration was approximately 10 mg/L; trough concentrations above this value were associated with increased AKI risk. For

Table 3: Clinical outcomes and pharmacokinetic parameters of LTRs that had been administered vancomycin (N = 34).

Variables	Total (N=34)	Non-AKI (N=19)	AKI (N=15)	P-value
Clinical Outcomes				
Vancomycin treatment type, n (%)				
Empirical	21 (62.0)	14 (73.7)	7 (46.7)	0.113
Definitive	13 (38.0)	5 (26.3)	8 (53.3)	
Days on vancomycin**	5 ± 3	5 ± 3	5 ± 4	0.852
Length of ICU stay, (days)*	17.1 ± 10.8	14.3 ± 8.7	20.5 ± 8.9	0.114
Length of hospital stay, (days)*	23.0 ± 11.0	18.6 ± 8.9	28.6 ± 11.1	0.016
Mechanical ventilation (days)*	2.6 ± 4.0	1.4 ± 1.5	4.2 ± 5.6	0.133
Septic shock, n (%)	17 (50)	7 (36.8)	10 (66.7)	0.089
Ascites post LT, n (%)	21 (62)	11 (57.9)	10 (66.7)	0.602
Death, n (%)	10 (29)	4 (21)	6 (40)	0.235
Dialysis or CRRT after vancomycin, n (%)	1 (3)	0 (0)	1 (6.7)	1
Encephalopathy post LT, n (%)	6 (18)	2 (10.5)	4 (26.7)	0.234
Graft dysfunction, n (%)	12 (35)	4 (21.1)	8 (53.3)	0.057
Re-transplantation, n (%)	2 (6.0)	1 (5.3)	1 (6.7)	0.863
Maximum level of tacrolimus during hospitalization (ng/dL)	6.24 ± 2.54	5.61 ± 3.20	6.15 ± 2.80	0.112
Isolated pathogen				
Enterococcus	13	5	8	0.113
MRCoNS	3	1	2	0.425
VRE	4	1	3	0.215
Psuedomunas	6	2	4	0.234
klebsiella	9	2	7	0.027
E. coli	5	4	1	0.264
Acintobacter	1	0	1	1.000
Candida	1	0	1	1.000
Mucormycosis	2	1	1	0.863
Type of infection (N)				
DSI***	16	9	7	0.968
UTI	11	2	9	0.005
Pneumonia****	10	3	7	0.059
Bacteremia	14	5	9	0.053
Concentration (mg/dL)				
C1 (Trough 1)	11.3 ± 6.3	9.1 ± 5.3	14.1 ± 6.4	0.026
C2 (peak)	24.4 ± 12.2	21.3 ± 9.3	28.4 ± 14.4	0.101
C3 (Intermediate)	14.3 ± 8.1	11.8 ± 7.9	17.5 ± 7.3	0.049
C4 (Trough 2)	11.8 ± 6.1	9.3 ± 4.9	15.0 ± 6.1	0.011

Table 3: Continued ...

Variables	Total (N=34)	Non-AKI (N=19)	AKI (N=15)	P-value
Pharmacokinetic variables				
K (1/h)	0.08 ± 0.04	0.08 ± 0.03	0.07 ± 0.06	0.287
$T_{1/2}$ (h)	12.2 ± 6.6	9.7 ± 4.2	15.3 ± 7.9	0.024
V_d (L)	76.2 ± 54.2	70.0 ± 28.4	84.2 ± 77.5	0.467
Vancomycin clearance (L/h)	4.9 ± 3.0	5.5 ± 2.4	4.2 ± 3.6	0.206
AUC_{24h} /MIC	383.3 ± 192.3	319.7 ± 167.9	463.9 ± 196.1	0.037

Abbreviations: CRRT (continuous renal replacement therapy), MRCoNS (methicillin-resistant coagulase-negative staphylococci), VRE (vancomycin resistant enterococci), *E. coli* (*Escherichia coli*), CMV (cytomegalovirus), UTI (urinary tract infection), DSI (deep and superficial infections)
* Mean ± SD
** Median ± IQR
*** Includes Abdominal fluid collections and wound cultures
**** VAP + HAP: VAP (Ventilator-associated pneumonia), HAP (Hospital-associated pneumonia)

individual time points, cut-off values were approximately 7.8 mg/L for C1 and 10.2 mg/L for C4 (Table Sup. II).

Correlation between Observed and Calculated Pharmacokinetic Parameters

As shown in Table Sup. III, no statistically significant correlation was found between the observed and calculated pharmacokinetic parameters (AUC_{12h}, AUC_{24h}, V_d, Cl_v, $k_{1/2}$, and $t_{1/2}$) within the studied population.

Trough Concentration Distribution within the Therapeutic AUC Range

Table 4 shows that among patients with therapeutic AUC values, 62.5% had C1 and C2 trough concentrations within the 15–20 µg/mL range. All measured trough concentrations were below 20 µg/mL.

DISCUSSION

One of the common adverse effects of vancomycin is nephrotoxicity. Therefore, vancomycin dosing adjustments based on TDM have been recommended in certain clinical conditions to maximize efficacy while minimizing nephrotoxicity. The results of our study, one of the few conducted on LTRs, revealed that 44% of patients developed vancomycin-induced nephrotoxicity. Various studies have reported a vancomycin-induced nephrotoxicity rate ranging from 5% to 59% [19, 20]. Various reasons have been proposed to explain the wide variation in the rate of vancomycin-induced nephrotoxicity, including differences in the prescribed loading dose, the clinical setting of the patients—such as whether they are critically ill—the criteria used to diagnose vancomycin-induced nephrotoxicity, the duration of vancomycin therapy, and the type of administration (intermittent or continuous). [21-24]. On the other hand, liver transplant recipients (LTRs) appear to be at a higher risk of developing drug-induced nephrotoxicity due to various factors, such as the presence of hepatorenal syndrome prior to transplantation, as well as third-spacing and ascites following transplantation, which may result from poor function of the transplanted liver [25].

Comparison and investigation of vancomycin pharmacokinetic factors in LTRs revealed that several of these parameters differ significantly from those observed in the general population. In our study, the mean ± SD V_d of vancomycin was 1.08 ± 0.66 L/kg, whereas the average in the normal population ranges from 0.4 to 1.0 L/kg. [10]. The following reasons can be mentioned to justify the large V_d in patients: First, in critically ill patients, capillary leakage caused by inflammatory cytokines released in SIRS conditions, as well as fluid retention due to organ dysfunction, can lead to a higher V_d for hydrophilic antibiotics such as vancomycin [26]. Additionally, due to the presence of ascites as third-space fluid and lower baseline

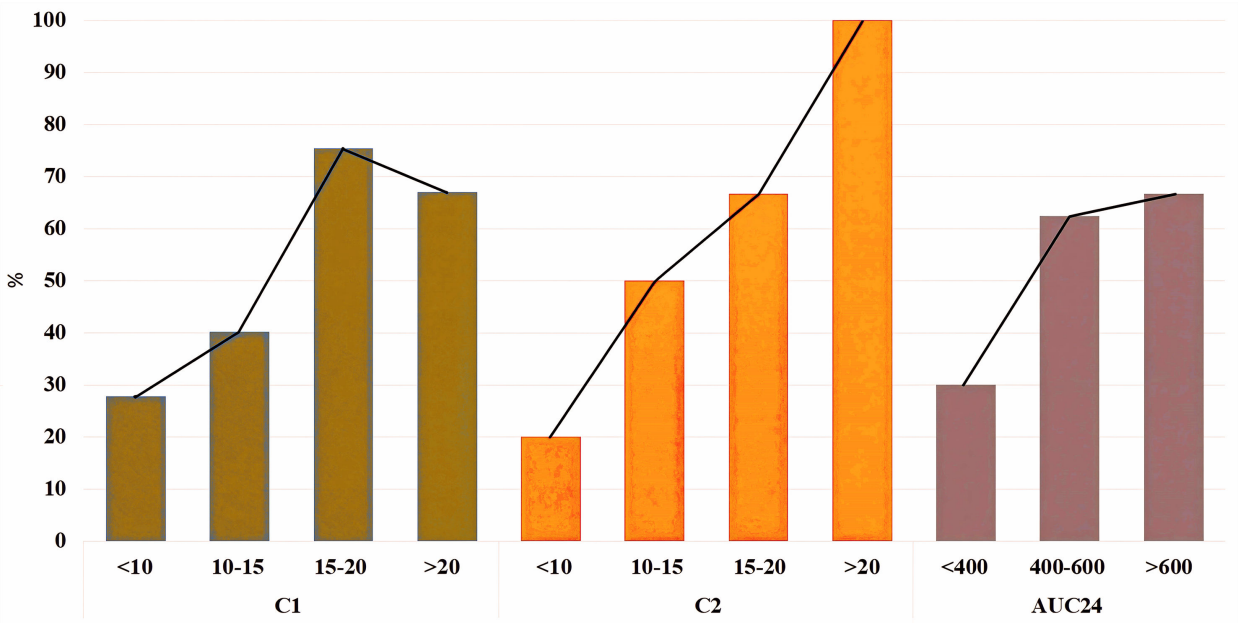

Figure 1: Acute kidney injury (AKI) Occurrence in different groups of trough concentration and area under the concentration-time curve (AUC) among liver transplant recipients (LTRs).

albumin levels in LTRs before normalization of transplanted liver function, an increase in vancomycin's V_d is expected [27].

Another pharmacokinetic factor investigated in our study was vancomycin clearance, which was 4.91 ± 3.00 L/h in LTRs, whereas the average value reported in the general population is approximately 2.6 L/h [28]. There are several reasons for the increased clearance of vancomycin in LTRs. First, as previously mentioned, these patients have lower albumin levels compared to the general population; therefore, the amount of unbound vancomycin increases, leading to a rise in total clearance—both renal and non-renal [27]. It has also been observed that the inflammatory process itself increases the clearance of antibiotics primarily excreted by the kidneys. Therefore, patients following liver transplantation—an extensive intra-abdominal surgery—and due to the presence of critical conditions, experience a state of inflammation, which supports the increased clearance of vancomycin in these patients.

The results of our study showed that ke in LTRs is lower than that in the healthy population (0.08 ± 0.045 vs. 0.11 to 0.17 h^{-1}). As mentioned in Equation 7 in the Methods section, ke is directly proportional to Cl_{van} and inversely proportional to its V_d. Considering the altered Cl_{van} and V_d values in LTRs, the observed lower ke in these patients is rational. Furthermore, given the decreased vancomycin elimination rate in LTRs, an increase in $t_{1/2}$ is expected. Harada *et al.* have reported that vancomycin $t_{1/2}$ is higher in patients with hepatic impairment [29].

Recent evidence supports the adoption of vancomycin AUC-guided dosing strategies to reduce nephrotoxicity while preserving clinical efficacy. Traditional trough-based monitoring often results in elevated drug exposure without additional therapeutic benefit, increasing the risk of AKI [30]. AUC thresholds exceeding 650–700 mg h/L have consistently been linked to higher AKI incidence across diverse patient populations, including those with hematologic malignancies, where an AUC_{24h} of 644 mg h/L was found predictive of nephrotoxicity [31]. Furthermore, AUC ≥700 mg h/L during both early and later phases of therapy was independently associated with AKI in enterococcal bloodstream infections,

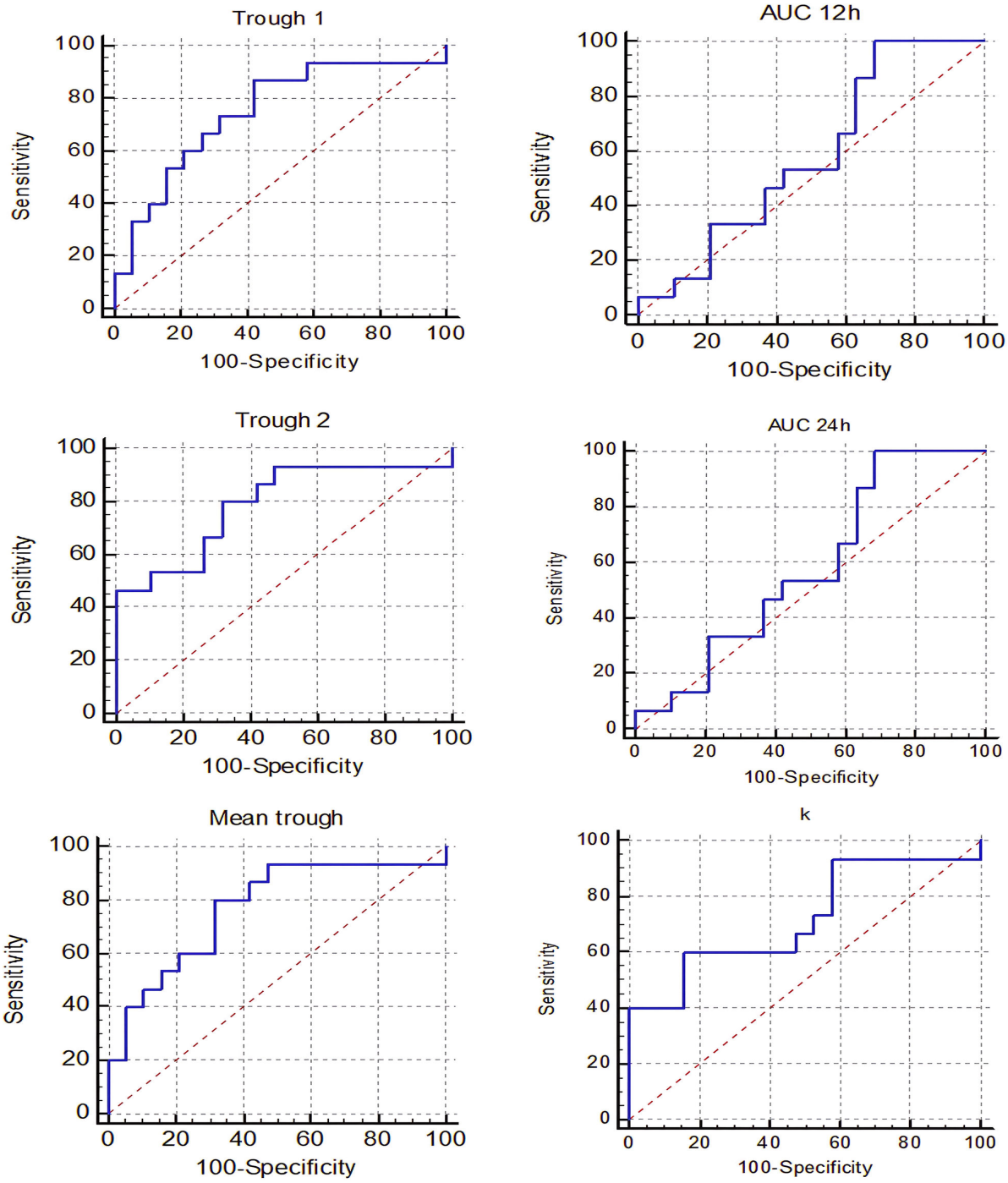

Figure 2: ROC curves of C1, C2, AUC_{12h}, AUC_{24h}, average trough concentrations and k_e.

particularly among patients receiving concomitant nephrotoxins [32]. These findings underscore the narrow therapeutic window of vancomycin and advocate for individualized AUC-based approaches to balance safety and efficacy.

The mean AUC_{24h} and AUC_{12h} in these 34 patients were 383.30 ± 32.98 mg h/L and 191.65 ± 16.49 mg h/L, respectively, which are lower than the therapeutic levels reported in previous studies [33]. In a study by Osvaldo *et al.* [34] on critically ill patients admitted to the ICU, those who received a loading dose exhibited an

Table 4: Distribution of trough concentrations in patients whose AUC was within the therapeutic range.

Targeted AUC values	Trough concentration	Categories (μg/ml)	Frequencies of patients, n (%)
$400 < AUC_{24h} < 600$ μg h/mL	C1	<10	1 (12.5)
		10-15	2 (25.0)
		15-20	5 (62.5)
		≥20	0 (0.0)
	C4	<10	0 (0.0)
		10-15	3 (37.5)
		15-20	5 (62.5)
		≥20	0 (0.0)

AUC ranging from 600 to 700 mg h/L. Additionally, in a study conducted by Shimamoto et al., the vancomycin AUC in the normal population was reported as 477 mg h/L, while in patients with systemic inflammatory response syndrome, it ranged from 308 to 466 mg h/L [35]. In another study by Natasha *et al.* [36] on patients with bacteremia caused by *S. aureus*, 54% of patients with liver dysfunction or receiving immunosuppressive therapy had an AUC greater than 400 mg h/L. Similarly, in a study by Brown *et al.* [37] on patients with infective endocarditis and complex bacteremia caused by MRSA, a significantly lower mortality rate was observed in those with AUC/MICs above 400 mg h/L, and 35% of patients achieved an AUC exceeding this threshold. In comparison, 41.2% of patients in the present study had an AUC above 400 mg h/L. Our findings indicated that mortality was higher among patients who did not reach the target AUC. Given the pharmacokinetic alterations of vancomycin in LTRs, a higher loading dose than currently recommended may be necessary to achieve therapeutic AUC levels. Moreover, our study observed that trough concentrations exceeding 10 mg/L were associated with an increased risk of AKI, whereas this AUC level poses minimal AKI risk in other patient populations. Therefore, given differences in vancomycin kinetic parameters between LTRs and the general population, further multicenter studies are warranted to determine the optimal loading dose and target AUC in LTRs.

The non-pharmacokinetic, independent risk factors for vancomycin-induced nephrotoxicity among LTRs in our study include elevated total direct bilirubin levels before transplantation, lower serum albumin prior to initiating vancomycin therapy, prolonged hospital stay, and UTI. Kovacevic *et al.* concluded that hypoalbuminemia increases vancomycin trough concentrations, thereby elevating the risk of nephrotoxicity [21]. Similarly, Mizuno *et al.* observed that vancomycin half-life and nephrotoxicity increase in elderly patients with hypoalbuminemia [38]. In alignment with our findings, several studies have identified hyperbilirubinemia as a risk factor for vancomycin-induced nephrotoxicity. However, two important considerations should be highlighted. First, elevated serum bilirubin may interfere with creatinine analysis, potentially leading to an underestimation of creatinine levels. Second, case reports have suggested that vancomycin hepatotoxicity may present as hyperbilirubinemia, indicating the possibility that elevated bilirubin levels could stem from vancomycin-induced liver injury. Although some studies have found no significant association between infection site and vancomycin-induced nephrotoxicity [23], both our study and the study by Altowayan *et al.* demonstrated that UTIs may increase the risk of nephrotoxicity in vancomycin-treated patients [24].

Selecting an appropriate analytical method for TDM of vancomycin is critically important in LTRs. Azadi *et al.* conducted a comparative

analysis of two analytical techniques, HPLC and chemiluminescent microparticle immunoassay (CMIA), to evaluate their suitability for this patient population. HPLC demonstrated superior sensitivity, specificity, and precision in quantifying vancomycin levels, particularly in patients with nephrotoxicity. It provided more accurate estimates of pharmacokinetic parameters, such as half-life and AUC, and detected significantly elevated drug concentrations in nephrotoxic cases ($p= 0.026$). These findings underscore HPLC's ability to uncover clinically relevant variations in vancomycin exposure.

In contrast, CMIA offered a faster, more convenient workflow for routine monitoring but was less effective at detecting subtle pharmacokinetic changes. It did not distinguish vancomycin levels between patients with and without nephrotoxicity, potentially underestimating drug accumulation in critical scenarios. Taken together, the evidence suggests that HPLC is the preferred method for vancomycin TDM in LTRs due to its analytical robustness and clinical relevance, while CMIA may serve as a supplementary tool when rapid turnaround is necessary [39].

This study has several limitations that should be acknowledged. The relatively small sample size may limit the generalizability of the findings and reduce the statistical power to detect significant differences. Additionally, the absence of data on the minimum inhibitory concentrations (MICs) of isolated pathogens, such as Staphylococcus aureus, restricts the ability to assess the appropriateness of vancomycin dosing and its clinical efficacy. Furthermore, the study did not include a comparative analysis of vancomycin pharmacokinetic parameters between patients with and without AKI, which could have provided valuable insights into dosing adjustments and toxicity risk in this vulnerable population. These limitations highlight the need for larger, more comprehensive studies to validate and expand upon the current findings [39].

In conclusion, based on the observed pharmacokinetic parameters, it is clear that vancomycin pharmacokinetics in LTRs were significantly altered compared to those in the general population. V_d, Cl_{van}, and $t_{1/2}$ were elevated, while ke was reduced relative to previously reported values in healthy individuals—none of the observed pharmacokinetic parameters correlated with the calculated ones. The AKI rate in our subjects was 44.1%, higher than in healthy individuals and other populations. Factors statistically associated with AKI included trough 1, trough 2, intermediate levels, UTI, k, $t_{1/2}$, AUC, hospital stay length, Alb_0, T. bil base, and D. bil base. The mean AUC in these patients was below the therapeutic range reported in previous studies. Given pharmacokinetic differences and the aim of achieving therapeutic AUC with minimal nephrotoxicity risk, precise vancomycin monitoring is recommended.

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