

Importance of daptomycin dosage on the clinical outcomes in early post-liver transplant recipients with vancomycin-resistant enterococci infection

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Abstract

Background: The prevalence of vancomycin-resistant enterococci (VRE) is increasing among liver transplant recipients. This study aimed to explore the clinical features of liver transplant recipients with VRE infection/colonization and to determine the impact of daptomycin dosage on the outcomes.

Methods: We retrospectively enrolled pre-transplant and post-transplant patients with VRE colonization/infection from 2016 to 2019.

Results: Altogether, 428 patients underwent liver transplantation. Among these, 22 (5.1%) patients developed VRE colonization/infection. All VRE isolates were *Enterococcus faecium*. Two (9%) patients acquired VRE in the pre-transplant period, 16 (3 colonizations and 13 infections) (72.7%) in the early post-liver transplant period (≤ 60 -day after transplantation), and 4 (2 colonization and 2 infections) (18.1%) in the late post-liver transplant period (> 6 -month after transplantation). Among 13 patients with early post-liver transplant VRE infection, 12 (92.3%) underwent living-donor liver transplantation and 1 underwent deceased donor liver transplantation. Among these 13 patients, the median time from transplant to emergence of VRE infection was 12 days. The median interval from VRE infection to death was 27 days and the 30-day mortality was 67%. Of these 13 patients, eleven patients (8 survived; 3 died) received daptomycin therapy for VRE. Among them, 4 (36.3%) received daptomycin doses < 8 mg/kg. Non-survivors ($n=3$) received significantly lower daptomycin dose than survivors ($n=8$) ($P=0.040$). Daptomycin doses < 8 mg/kg were more frequently associated with non-survivors ($n=3$) than with survivors ($n=8$) ($P=0.024$).

Conclusions: In summary, the suboptimal dosage of daptomycin may have contributed to a higher rate of in-hospital mortality. Doses ≥ 8 mg/kg may be needed to adequately treat VRE infection in early post-liver transplant recipients.

Level of evidence: Level III

Introduction

Although enterococci are constituents of the normal bacterial flora of the lower gastrointestinal tract in humans, they have become one of the most common causes of healthcare-associated infections in the intensive care unit setting and in immunocompromised patients [1,2]. *Enterococcus faecalis* and *Enterococcus faecium* contribute to most of the enterococcal infections. These species exhibit decreased susceptibility to ampicillin as well as resistance to vancomycin [2,3]. Vancomycin-resistant enterococci (VRE) were first described in 1986 [4] and their prevalence has rapidly increased globally over the past decades especially among *Enterococcus faecium*, in which 80%–95% of isolates are vancomycin-resistant [5,6].

VRE infection/colonization has been linked to prolonged length of hospitalization, higher costs of hospitalization, and increased mortality in hospitalized patients [7,8]. Notably, poor outcomes have been

reported among liver transplant recipients with VRE infection [9-12]. McNeil et al. revealed that the 90-day mortality was significantly higher among those who developed VRE infection after liver transplantation [9]. In addition, patients with VRE infection had worse graft survival than those without VRE infection [10-12]. Treatment options for VRE are limited. Linezolid or daptomycin is recommended for the treatment of VRE [13]. Myelosuppression is one of the major adverse events associated with linezolid [14]. Daptomycin is being used increasingly for the treatment of VRE, particularly in patients with cirrhosis [15,16]. However, data regarding the use of daptomycin for the treatment of VRE in liver transplant recipients is inadequate. Most of the previous studies have focused on the impact of daptomycin dosing for treatment of VRE infection in the general population and little is known regarding the optimal dosage of daptomycin for the treatment of VRE in liver transplant recipients. The aim of the present study was to explore the clinical features and outcomes in liver transplant recipients with VRE infection and to determine the effect of daptomycin dosage on the clinical outcomes.

Patients And Methods

Hospital setting and patients

This study was conducted at Kaohsiung Chang Gung Memorial Hospital, a 2700-bed primary care and tertiary referral medical center in Taiwan and a leading liver transplantation center in Asia [17]. We retrospectively enrolled pre-liver transplant and post-liver transplant patients admitted to liver transplant surgical intensive care unit with VRE colonization/infection from January 2016 to December 2019. If a patient had multiple episodes of VRE infection or colonization during the study period, only the first episode was included. A standardized form for clinical data collection was designed. Patients' electronic medical records were reviewed to verify the information regarding demographic characteristics, pre-transplant and post-transplant clinical characteristics, laboratory and microbiological tests, and outcomes. Patients who developed VRE infection/colonization during the first 60 days after liver transplantation were assigned to the early post-liver transplant colonization/infection group. Patients who acquired VRE infection/colonization at 6 months after liver transplantation was assigned to the late post-liver transplant colonization/infection group.

Antimicrobial susceptibility testing

Enterococcus spp. were identified using the Phoenix (BD Diagnostic Systems, Sparks, MD, USA) identification system in the clinical microbiology laboratory. Vancomycin resistance was defined as an enterococcus isolate with minimum inhibitory concentration of vancomycin ≥ 32 mg/L. The VRE isolates were considered daptomycin sensitive if they had a minimum inhibitory concentration ≤ 4 mg/L according to the Clinical and Laboratory Standards Institute [18]. The choice of antibiotic (daptomycin, linezolid, or tigecycline) for VRE infection was based on physicians' judgment. Daptomycin dose was selected by the attending physicians and the dose was calculated according to the actual body weight.

Statistical analysis

Patients were divided into three groups: the pre-liver transplant group, the early post-liver transplant group, and the late post-liver transplant group. Continuous variables were presented as median and range. Categorical variables were presented as percentages. To analyze the impact of VRE infection among patients in the early post-liver transplant group, we compared demographic, clinical, surgical, and laboratory characteristics as well as daptomycin dosage of survivors and non-survivors using Fisher's exact test for categorical variables and Mann-Whitney U test for numerical variables. The differences were considered statistically significant at $P < 0.05$. Data were analyzed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Patients characteristics

Altogether, 428 patients who underwent liver transplantation were identified during the study period. Among them, 22 (5.1%) patients (median age: 60.5 years [range: 1–67 years]) who developed VRE colonization/infection were included in the analysis. All patients with VRE colonization/infection had undergone transplant for the first time. Twenty patients underwent living-donor liver transplantation and 2 underwent transplantation from deceased donors. The three leading comorbidities were hepatocellular carcinoma (40.9%), hepatitis B infection (36.4%), and hepatitis C infection (36.4%). Among the 22 patients with VRE colonization/infection, 2 (9%) patients acquired VRE in the pre-transplant period, 16 (72.7%) in the early post-liver transplant period, and 4 (18.1%) in the late post-liver transplant period. VRE colonization was observed in 3 patients in the early post-liver transplant period and in 2 patients in the late post-liver transplant period. VRE bacteremia developed in 6 (27.3%) patients. Two patients acquired VRE infection while they were on the waiting list for a liver transplant. However, none of them developed VRE infection after transplantation. Four out of 22 patients died, including 3 deaths in the early post-liver transplant period and 1 death in the late post-liver transplant period, resulting in a mortality rate of 18.2% (Table 1).

Clinical characteristics of patients with VRE infection in the early post-liver transplant period

Thirteen (median age: 62 years [range: 1–67 years]) patients had VRE infection during the first 60 days following transplantation. All VRE isolates were *Enterococcus faecium*. Among these patients, 1 patient experienced vancomycin-susceptible *Enterococcus faecium* bacteremia before liver transplantation. Hepatocellular carcinoma (46.2%) and hepatitis B infection (46.2%) were the most common underlying liver conditions followed by hepatitis C infection (30.8%) and alcoholic liver cirrhosis (15.4%). Seven (53.8%) patients were categorized as Child-Pugh class C. The median Model for End-stage Liver Disease score at transplant was 15.5 (range: 9–32). Twelve (92.3%) patients underwent living-donor liver transplantation and 1 patient underwent deceased donor liver transplantation. Seven (61.5%) patients required surgical re-exploration due to biliary stricture (3 patients), bleeding (2 patients), wound dehiscence (1 patient), or portal vein thrombosis (1 patient). Primary graft failure was observed in 4 (30.8%) patients. Glycopeptides (vancomycin or teicoplanin) and third or fourth generation

cephalosporins were commonly used prior to the diagnosis of VRE infection. The median time from transplant to emergence of VRE infection was 12 (range: 1–59) days. Most of the VRE were isolated from abdominal (e.g., ascites, bile, and vein graft) (76.9%) and blood (30.8%) specimens. Coinfections with other bacteria in ascites were found in 6 (46%) patients, which included *Staphylococcus hemolyticus* in 4 (67%) patients and *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* in one patient each (16.6%). Delayed VRE treatment (≥ 48 hours after infection) was noted in 12 (92.3%) patients. The VRE isolates were universally susceptible to daptomycin, linezolid, and tigecycline. Eleven patients received daptomycin therapy for VRE. Among them, 4 (36.3%) received daptomycin doses < 8 mg/kg. Three patients died, accounting for 23% of overall in-hospital mortality. The characteristics of the 13 patients with VRE infection in the early post-liver transplant period are summarized in Tables 2 and 3.

Comparison between survivors and non-survivors with VRE infection in the early post-liver transplant period

In the 3 non-survivors, the median interval from VRE infection to death was 27 (range: 22–32) days and the 30-day mortality after VRE infection was 67%. Among 11 patients received daptomycin therapy for VRE, the non-survivors (n=3) received significantly lower daptomycin dosages than survivors (n=8) (median 7.8 mg/kg vs. 8.7 mg/kg, $P=0.040$). Daptomycin dosage < 8 mg/kg were associated more frequently with non-survivors (n=3) than with survivors (n=8) (100% vs. 12.5%, $P=0.024$). The frequency of VRE bacteremia and primary graft failure was higher in non-survivors (n=3) than in survivors (n=10) (67% vs. 20% and 67% vs. 10%, respectively). However, these differences were not statistically significant. There were no statistically significant differences between survivors (n=10) and non-survivors (n=3) in demographic characteristics, underlying conditions, pre-transplant factors, surgical factors, post-operative complications, and delayed antibiotic therapy for VRE (Tables 2 and 3).

Discussion

VRE have emerged as important nosocomial pathogens in bloodstream, urinary tract, and wound infections over the past 2 decades and will remain so for the foreseeable future [19]. Importantly, immunocompromised patients appear to be at high risk for VRE colonization or infection and show poor prognosis [20,21]. The present study described the clinical features and outcomes of liver transplant recipients with VRE infection in detail. Association of an inadequate dose of daptomycin with death was a key finding from the study. Our findings are consistent with those reported in previous series [9-12]. These findings may help solidify our understanding of the clinical features of VRE infection among liver transplant recipients.

Vancomycin resistance is independently associated with increased mortality among patients with enterococcal bloodstream infections [22]. Importantly, an overall in-hospital mortality rate of 18.2% was observed among all included liver transplant recipients with VRE colonization or infection in the present study. For subjects who developed VRE infection in the early post-liver transplant period, their in-hospital mortality rate increased to 23%. Moreover, 15% of these patients died within 30 days after development of

VRE infection. Previous studies have indicated that the crude mortality rate of VRE infection among liver transplant recipients ranged from 23% to 82% [9,10,12,22-24]. Excluding the data from an era before the availability of effective antibiotic treatment for VRE infection, the observed mortality rates for VRE bacteremia are still unacceptably high in this patient population (33% to 56%) [10,25]. Some previous studies and our report indicate that VRE infection in liver transplant recipients serves as an indicator for is associated with increased mortality. Thus, implementation of appropriate preventive strategies and timely identification of VRE infection in these patients is vital to avoid preventable mortality and morbidity.

Appropriate antimicrobial therapy is crucial in reducing the mortality in patients with VRE infection. Limited effective antimicrobial agents are available to treat VRE infection [26]. Linezolid and daptomycin as are the two most commonly used agents for treatment of VRE infection [13]. Linezolid is a bacteriostatic antibiotic that is approved for the use in VRE infection [13]. Safety concerns limit the use of linezolid, particularly in cirrhotic patients with thrombocytopenia [27]. Additionally, a study including 644 patients with VRE bacteremia noted that treatment with linezolid was associated with significantly higher treatment failure when compared with daptomycin [15]. Daptomycin is a concentration-dependent bactericidal agent. It has been shown to exert rapid bactericidal activity against enterococci [28]. Daptomycin dosage for staphylococcal bacteremia is 6 mg/kg intravenously once daily [29]. Many clinicians are using similar doses of daptomycin for treatment of VRE infection. In the setting of enterococcal bloodstream infections, Britt et al. revealed that high-dose daptomycin (≥ 10 mg/kg) was associated with reduced 30-day mortality when compared with the standard-dose (6 mg/kg) [16]. In a study involving 112 patients, Chuang et al. reported that daptomycin regimens with higher doses (≥ 9 mg/kg) were associated with lower mortality than those with standard (< 7 mg/kg) doses [30]. Nonetheless, most of these studies have presented data regarding daptomycin therapeutic dosages for VRE infection in the general patient population rather than in liver transplant patients. We found an association between higher daptomycin dose and survival in liver transplant recipients with VRE infection. Daptomycin dose ≥ 8 mg/kg was associated with significantly better patient survival than a dose < 8 mg/kg. Survivors received higher median daptomycin dose than non-survivors (8.7 mg/kg vs. 7.8 mg/kg). The present study expands the previous findings about the importance of daptomycin therapeutic dosage for the treatment of VRE infection in liver transplant patients. To the best of our knowledge, this is the first study that reported the impact of daptomycin dosage for treatment of VRE infection in liver transplant recipients. Our findings highlight the urgent need for clinicians' awareness regarding optimal daptomycin dosage for the treatment of VRE infection in liver transplant recipients.

Although enterococci are less virulent than many other bacteria, delayed antibiotic therapy for patients with VRE infection is associated with poor clinical outcomes [31]. In the present study, delays in initiating the antimicrobial therapy against VRE did not contribute significantly to increased mortality. Remarkably, only 1 patient in our study received effective antimicrobial therapy within 48 hours after the onset of VRE infection. This finding should be considered with caution while interpreting the data, as it may lead to bias in the results of the present study. Larger prospective studies are required to elucidate whether the delay in the treatment of VRE infection affects the outcome in liver transplant recipients.

Data regarding the influence of VRE infection on clinical endpoints other than mortality are lacking. We observed that two-thirds of the non-survivors in the early post-transplant period developed VRE bloodstream infection and primary graft failure. The association between VRE bacteremia and primary graft failure is unclear. Multiple factors have been studied as risk factors for graft failure including optimum donor selection; vascular, biliary, and immunological complications; and bacterial infection [32,33]. We agree with the suggestions from other studies that VRE infection may have contributed to graft failure in liver transplant recipients [10-12]. On the other hand, the greater number of graft failure in non-surviving patients in this study can be partly explained by the poor general condition including relatively higher Model for End-stage Liver Disease scores at the time of transplantation compared to survivors, although this difference did not reach statistical significance (Table 2).

Pre-transplant VRE colonization or infection could contribute to a higher incidence of VRE infection at the time of organ transplantation. In a prospective surveillance study involving 22 patients with VRE colonization before liver transplantation, 7 (32%) developed clinical VRE infection post-transplantation [9]. In a study of 61 patients who underwent pre-transplant VRE surveillance, 44% of the patients exhibited VRE colonization after liver transplantation [34]. In the present study, 2 patients experienced VRE infection prior to the transplantation. Notably, none of them had VRE colonization or infection after transplantation. Additionally, 13 patients developed VRE infection within 60 days after liver transplantation, but none of them had a history of VRE colonization prior to the transplantation. This finding is inconsistent with previously published findings that suggested that VRE colonization in patients was associated with post-transplant VRE infection. The possible explanation for this discrepancy could be that the number of events in our study were not high enough to detect the effect of pre-transplant colonization on post-transplant infection. Additionally, in the present study, the incidence of VRE colonization/infection was 5.1% among patients admitted to liver transplant surgical intensive care unit, which is lower compared to findings in earlier studies from other countries [23,34]. Although hospital-wide routine active surveillance for VRE was not performed at our institution, poorer outcomes associated with acquisition of VRE infection after transplantation in our study and in earlier reports highlight the importance of infection-control measures including contact precautions, usage of personal protective equipment, and appropriate disinfection strategies to prevent nosocomial acquisition of VRE, especially in the post-transplantation period.

The present study has several limitations. This was a retrospective study and suffered from the limitations of this design. The statistical power was quite low due to the small number of cases studied. Due to the limited sample size, we could not compare the treatment outcomes between daptomycin and linezolid in liver transplant recipients.

Conclusions

In this study, we observed that VRE infection in liver transplant recipients was associated with poor clinical outcomes. Suboptimal dosages of daptomycin may have contributed to the higher in-hospital mortality rate. Doses greater than or equal to 8 mg/kg may be needed to adequately treat VRE infection in

early post-liver transplant recipients. Although larger studies including controlled clinical trials are needed to ensure the efficacy and the safety of daptomycin dosages ≥ 8 mg/kg in liver transplant recipients, our study highlighted the importance of optimal daptomycin dosages for the treatment of VRE infection.

Abbreviation

VRE: vancomycin-resistant enterococci

Declarations

Acknowledgement

Not applicable.

Authors' contributions

CCW conceived of the study, and participated in its design and coordination. IKL interpretation of data, performed the statistical analysis, and draft the manuscript. YPS collect the data, assisted in the preparation of the manuscript, and reviewed the manuscript. WFL, CLC, CCL and ILC provided critical appraisal of the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

The Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital approved the study (document no.: 202000991B0). The committee waived the requirement for informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1 Characteristic of 22 liver transplantation patients with vancomycin-resistant enterococci infection

Variable	<i>N</i> = 22
Median age (range), years	60.5 (1-67)
Male	12 (54.5)
Underlying conditions	
Hepatitis B	8 (36.4)
Hepatitis C	8 (36.4)
Alcoholic liver cirrhosis	4 (18.2)
Primary biliary cirrhosis	2 (9.1)
Biliary atresia	2 (9.1)
Cryptogenic liver disease	1 (4.5)
Hepatocellular carcinoma	9 (40.9)
Diabetes mellitus	3 (13.6)
Hypertension	5 (22.7)
Chronic kidney disease	4 (18.2)
Child-Pugh class	
Class A	1 (4.5)
Class B	11 (50)
Class C	10 (45.5)
Acquisition of VRE colonization/infection	
Pre-liver transplant	2 (9.1)
Early post-liver transplant (<2 months)	16 [*] (72.7)
Late post-liver transplant (\geq 6 months)	4 [†] (18.2)
Site of VRE infection	
Blood	6 (27.3)
Bile	2 (9.1)
Ascites	8 (36.4)
Catheter	1 (4.5)
Vein graft	1 (4.5)
Urine	3 (13.6)

Mortality	
Overall in-hospital mortality	4 (18.2)

Data were no (%) unless otherwise indicated

VRE Vancomycin-resistant enterococci

* VRE colonization was found in 3 patients

† VRE colonization was found in 2 patients

Table 2 Demographic characteristics and comorbid conditions of 13 patients with vancomycin-resistant enterococcus infection in the early post-liver transplant period.

Variable	Total (N = 13)	Survivors (N = 10)	Non-survivors (N = 3)	P
<i>Demographic feature</i>				
Median age (range), years	62 (1-67)	63 (1-67)	62 (44-67)	0.865
Male	6 (46.2)	4 (40)	2 (67)	0.599
Underlying conditions				
Hepatitis B	6 (46.2)	4 (40)	2 (67)	0.599
Hepatitis C	4 (30.8)	3 (30)	1 (33)	>0.99
Alcoholic liver cirrhosis	2 (15.4)	2 (20)	0	>0.99
Primary biliary cirrhosis	1 (7.7)	1 (10)	0	>0.99
Biliary atresia	1 (7.7)	1 (10)	0	>0.99
Cryptogenic liver disease	1 (7.7)	1 (10)	0	>0.99
Hepatocellular carcinoma	6 (46.2)	4 (40)	2 (67)	0.599
Diabetes mellitus	1 (7.7)	1 (10)	0	>0.99
Hypertension	3 (23.1)	3 (30)	0	0.528
Chronic kidney disease	2 (15.4)	1 (10)	1 (33)	0.423
Median Child-Pugh scores (range)	10 (7-13)	9 (7-13)	10 (9-11)	0.488
Child-Pugh class C				
Class A	0	0	0	-
Class B	6 (46.1)	5 (50)	1 (33)	>0.99
Class C	7 (53.8)	5 (50)	2 (67)	>0.99
Median MELD score (range)	15.5 (9-32)	15 (9-32)	23.5 (19-28)	0.194
<i>Pre-transplant factor (6 months before liver transplantation)</i>				
Hospitalization history	9 (69.2)	7 (70)	2 (67)	>0.99
Stay in intensive care unit history	5 (38.5)	4 (40)	1 (33)	>0.99
Receipt of B-lactam antibiotics	2 (15.4)	2 (20)	0	>0.99
Receipt of 3-4th generation cephalosporins	12 (92.3)	9 (90)	3 (100)	>0.99
Receipt of quinolones	3 (23.1)	3 (30)	0	0.528
Receipt of carbapenems	4 (30.8)	4 (40)	0	0.497

Receipt of glycopeptides	3 (23)	3 (30)	0	0.528
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Data are no. (%) of patients, unless otherwise indicated

MELD Model for End-stage Liver Disease

Table 3 Surgical and clinical characteristics as well as outcomes of 13 patients with vancomycin-resistant enterococcus infection in the early post-liver transplant period.

Variable	Total (N= 13)	Survivors (N= 10)	Non- survivors (N= 3)	P
<i>Surgical factor</i>				
Median surgery time (range), min	574 (440-750)	577 (440-750)	522 (471-591)	0.459
Median anhepatic time (range), min	65.5 (33-180)	71 (41-180)	57 (33-63)	0.116
Median cold ischemic time (range), min	42 (24-345)	38 (24-70)	46 (37-345)	0.405
Living donor liver transplant	12 (92.3)	10 (100)	2 (67)	0.231
Cadaver donor liver transplant	1 (7.7)	0	1 (33)	0.231
Median intraoperative blood loss (range), ml	4650 (210-15000)	4675 (210-10200)	3250 (800-15000)	0.866
Median intraoperative transfusion (range), units				
Leukocyte-poor packed red cells	16 (1-34)	16 (1-32)	18 (6-34)	0.798
Fresh Frozen Plasma	12 (4-30), n = 12	10 (4-20), n = 9	16 (10-30)	0.190
Leukocyte-poor platelet concentrates	24 (12-60), n =11	18 (12-36), n = 8	24 (12-60)	0.442
Cryoprecipitate	12 (12-24), n = 8	12 (12-24), n = 5	12 (12-24)	0.860
<i>Postoperative factor</i>				
Re-exploration*	7 (53.8)	5 (50)	2 (67)	>0.99
Primary graft failure	3 (23.1)	1 (10)	2 (67)	0.108
Biliary stricture	5 (38.5)	5 (50)	0	0.231
Biliary leak	4 (30.8)	4 (40)	0	0.497
Venous thrombosis	1 (7.7)	1 (10)	0	>0.99
Graft rejection	4 (30.8)	3 (30)	1 (33)	>0.99
Received hemodialysis	2 (15.4)	1 (10)	1 (33)	0.423
Bacteremia before occurring VRE infection	5 (38.4)	4 (40)	1 (33)	>0.99
Antibiotics before occurring VRE infection				
Receipt of B-lactam antibiotics	1 (7.7)	1 (10)	0	>0.99
Receipt of 3-4th generation cephalosporins	11 (84.6)	8 (80)	3 (100)	>0.99

Receipt of quinolones	6 (46.2)	5 (50)	1 (33)	>0.99
Receipt of carbapenems	8 (61.5)	6 (60)	2 (67)	>0.99
Receipt of glycopeptides	11 (84.6)	9 (90)	3 (100)	>0.99
Receipt of tigecycline	2 (15.4)	1 (10)	1 (33)	0.423
Receipt of daptomycin	2 (15.4)	1 (10)	1 (33)	0.423
Median interval between liver transplant and development of VRE infection (range), day	12 (1-59)	10 (1-59)	18 (3-57)	0.735
VRE infection site [†]				
Intra-abdominal infection	10 (76.9)	8 (80)	2 (67)	>0.99
Bile	1 (7.7)	1 (10)	0	>0.99
Ascites	8 (61.5)	6 (60)	2 (67)	>0.99
Vein graft	1 (7.7)	1 (10)	0	>0.99
Blood	4 (30.8)	2 (20)	2 (67)	0.203
Catheter	1 (7.7)	0	1 (33)	0.231
Urine	1 (7.7)	1 (10)	0	>0.99
VRE species				
<i>Enterococcus faecium</i>	13 (100)	10 (100)	3 (100)	-
<i>Enterococcus faecalis</i>	0	0	0	-
Delayed VRE treatment (\geq 48h after infection)	12 (92.3)	10 (100)	2 (67)	0.231
VRE treatment				
Receipt of linezolid	1 (7.7)	1 (10)	0	>0.99
Receipt of daptomycin	11 (84.6)	8 (80)	3 (100)	>0.99
Receipt of tigecycline	1 (7.7)	1 (10)	0	>0.99
Median daptomycin dose (range), mg/kg	8.2 (3.5-9.6) (n = 11)	8.7 (4.5-9.6) (n = 8)	7.8 (3.5-7.8)	0.040
Daptomycin dose < 8mg/kg	4 (36.3) (n = 11)	1 (12.5) (n = 8)	3 (100)	0.024
Mixed VRE and other bacterial infection	6 (46)	5 (50)	1 (33)	>0.99
Laboratory data at the time of VRE infection				
Median white blood cell (range) (10^9 cells/L)	7.6 (2.8-	6.8 (2.8-	8.5 (4-9)	0.781

	10.6)	10.6)		
Median hemoglobin (range) (g/dL)	8.9 (6.6-10.6)	9.3 (7-10.6)	8.3 (6.6-9.3)	0.266
Median platelet (range) (10 ⁹ cells/L)	73 (20-343)	76 (20-343)	70 (33-110)	0.782
Median creatinine (range) (mg/dl)	1.0 (0.23-4.22)	1.0 (0.2-1.6)	2.3 (0.5-4.2)	0.221
Median total bilirubin (range) (mg/dL)	5.0 (0.7-66)	3.7 (0.74-66)	26.8 (1.8-35.4)	0.405
Median GOT (range) (U/L)	102 (27-2879)	84 (27-495)	133 (39-2879)	0.309
Median GPT (range) (U/L)	60 (33-1139)	56 (33-462)	64 (49-1139)	0.518
Median PT (range), INR	1.1 (1.0-2.3)	1.1 (1-1.7)	1.7 (1.1-2.3)	0.052
Median albumin (range) (g/dL)	3.7 (2.8-4.3)	3.7 (2.8-4.3)	3.8 (2.9-4.2)	0.926
Median length of hospital stay (range), day	100 (44-168)	118 (44-168)	80 (46-101)	0.310
Outcome				
Died	3 (23)	-	3 (100)	-
Median interval from VRE infection to death (range), day	-	-	27 (22-32)	-
Mortality at 30 days from VRE infection	2 (15.3)	-	2 (67)	-

Data are no. (%) of patients, unless otherwise indicated

AST Aspartate Aminotransferase, ALT Alanine aminotransferase, PT Prothrombin time, VRE vancomycin-resistant enterococci

*Biliary stricture in 3 patients, bleeding in 2, wound dehiscence in 1, and portal vein thrombosis in 1

†One patient might have more than one site of VRE infection