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Association between Gut Colonization of Vancomycin-resistant Enterococci and Liver Transplant Outcomes

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VRE colonization affected 20% of liver transplant candidates and 10% acquired it post-transplant, and was associated with post-transplant AKI, clinically significant infections and trend towards increased death

Running title:

VRE and liver transplant

Author contribution statement:

Drs. Walter, Abraldes and Cervera designed the study

Diana Chiang and Drs. Dingle, Belga and Bhanji collected data

Dr. Chiang wrote the manuscript

Drs. Abraldes and Cervera performed the statistical analysis

Drs. Kabbani, Walter, Abraldes and Cervera supervised data quality and manuscript draft

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ABBREVIATIONS:

AKI: Acute kidney injury

CMV: Cytomegalovirus

CNI: Calcineurin inhibitor

GPCR: G-protein coupled receptor

ICU: Intensive Care Unit

IQR: Inter-quartile range

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IRI: Ischemia reperfusion injury

KDIGO: Kidney Disease Improving Global Outcomes

MELD: Model for end-stage liver disease

SCFA: Short chain fatty acids

SD: Standard deviation

TMA: Trimethylamine

TMAO: Trimethylamine-N-Oxide

VRE: Vancomycin-resistant enterococci

ABSTRACT

Background: Vancomycin-resistant enterococci (VRE) colonization is common in liver transplant recipients and has been associated with worse post-transplant outcomes.

Methods: We conducted a retrospective cohort study at the University of Alberta Hospital including patients who underwent a liver transplant between September 2014 and December 2017.

Results: Of 343 patients, 68 (19.8%) had pre-transplant VRE colonization and 27 (27/275, 9.8%) acquired VRE post-transplant, 67% were males and the median age was 56.5 years. VRE colonized patients at baseline had higher MELD scores and required longer post-transplant hospitalization. VRE colonization was associated with increased risk of early acute kidney injury (AKI) (64% vs 52%, p = 0. 044), clinically significant bacterial/fungal infection (29% vs 17%, p = 0. 012) and invasive VRE infection (5% vs 1%, p = 0. 017). Mortality at 2-years was 13% in VRE-colonized versus 7% in non-colonized (p = 0.085). On multivariate analysis, VRE colonization increased the risk of post-transplant AKI (HR 1.504, 95% CI: 1.077-2.100, p = 0.017) and clinically significant bacterial or fungal infection at

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6 months (HR 2.038, 95%CI: 1.222-3.399, p = 0.006), and was associated with non-significant trend towards increased risk of mortality at 2-years post-transplant (HR 1.974 95% CI 0.890-4.378; p = 0.094).

Conclusions: VRE colonization in liver transplant patients is associated with increased risk of early AKI, clinically significant infections, and a trend towards increased mortality at 2-years.

Keywords: Vancomycin-resistant enterococci, liver transplantation, post-transplant outcomes, microbiota, VRE colonization, acute kidney injury, MELD, mortality.

1. INTRODUCTION

Vancomycin-resistant enterococci (VRE) is a prevalent antibiotic-resistant bacteria in patients undergoing liver transplantation. VRE has the ability to colonize the host and is often found in patients with chronic liver diseases.[1,2] The risk of VRE colonization increases post-transplant.[3-6] In a meta-analysis conducted by Ziakas, et al., the rates of pre- and post-liver transplant VRE colonization were 11.9% and 16%, respectively.[6] In addition, patients undergoing liver transplantation are admitted to intensive care units (ICUs), common hospital areas of reservoirs for VRE (VRE colonization rates of 9.7 compared to 51.9 in general wards versus ICUs, respectively), and other antibiotic resistant bacteria.[3,4] Progression from VRE colonization to infection is uncommon but is associated with a high mortality rate.[5]

VRE colonization can dominate the gut ecosystem and dramatically decrease the microbiota diversity.[7-9] VRE colonization, therefore, may represent a marker of microbiota dysbiosis.[8,10,11] In a mouse model of VRE colonization, recolonization of the gut with anaerobic bacteria from *Barnesiella* genus eradicated VRE from the gut microbiota.[12] Also, the presence of cephalosporinase-producing *Bacteroides* prevented expansion and colonization of VRE in the gut microbiota of mice.[13] Thus, microbiota dysbiosis, a common phenomenon in patients with liver cirrhosis,[14] may explain the increased VRE colonization seen in this patient population. Moreover, VRE gut colonization may lead

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to compromise innate immune defence that can lead to bacterial translocation.[15,16] This in turn triggers both, inflammation in the liver and systemic inflammatory responses causing progression of liver disease[17,18] hypothetically resulting in the development of graft rejection in the transplanted liver.

In a study by Russell and colleagues, VRE infection and colonization were both associated with a significantly increased hazard of death (HR of 1.78 and 2.12, respectively).[5] These findings are similar in other geographic areas including South Korea.[19]Acquisition of VRE following transplantation also has deleterious consequences with an increased risk in mortality at 90 days post-transplantation.[20] Likewise, VRE colonization impacts liver transplant patient morbidity, with longer preoperative hospital stay and higher model for end-stage liver disease (MELD) scores compared to non-colonized patients.[19] Despite this overall association, the specific mechanisms explaining the increased risk of mortality in VRE-colonized patients remain unknown.

In this study, we aimed to define the impact of VRE colonization on major outcome endpoints of liver transplantation.

2. MATERIALS AND METHODS

2.1 Study population

We performed a retrospective cohort analysis of all adult patients (≥18 years old) who underwent liver transplantation for chronic liver disease between 1st September 2014 and 31st December 2017 at the University of Alberta Hospital in Edmonton, Alberta, Canada. Data was collected from the Organ Transplant Tracking Record database (OTTR, HKS Medical Information Systems, and Omaha, Nebraska, USA). This database has been prospectively tracking and following solid organ transplant recipients since 1995 to support clinical management at the University of

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Alberta Hospital. This study was approved by the University of Alberta Health Research Ethics Board (HREB_Pro00082528).

2.2 Study design and definitions

Data gathered for this study included patients' age, gender, indications for liver transplantation, aspartate transaminase (AST) and serum creatinine levels, MELD score, Cytomegalovirus (CMV) donor-recipient status, infection complications, acute rejection, immunosuppression, follow-up, and survival status at the time of data collection.

A pre-transplant rectal swab to screen for VRE (culture in chromogenic agar) was collected on all liver transplant candidates. VRE colonization screening by rectal swabs was done weekly post-transplant for patients without VRE colonization pre-transplant. Pre-transplant VRE colonized patients were not screened for VRE post-transplant. Pre- and post-transplant VRE screen results were retrieved from the Alberta Precision Laboratories laboratory information system**.**

The initiation of tacrolimus was delayed until day-7 post-transplant to avoid nephrotoxicity. Surgical antibiotic prophylaxis consisted of imipenem or meropenem plus linezolid for 24 hours post-surgery. We used targeted antifungal prophylaxis with fluconazole 400 mg iv daily for liver transplant patients at higher risk of invasive fungal infection (transplant for acute liver failure, requirement of renal replacement therapy, reintervention for hemoperitoneum and intra-operative transfusion of ≥20 units of cellular blood products). For CMV seronegative recipients of a liver from a CMV seropositive donor (CMV D+/R-), three months valganciclovir prophylaxis (900 mg QD) was administered. CMV D+/R+ patients were managed by a pre-emptive strategy with weekly CMV viral load monitoring from weeks 2 to 8 and treatment with valganciclovir (900 mg bid) when the CMV viral load reached 5,000 IU/mL or higher. CMV D-/R+ and CMV D-/R- patients received no prophylaxis and were not monitored. All patients received *Pneumocystis* prophylaxis with sulfamethoxazole-trimethoprim for 6-months.

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MELD score was calculated by determining bilirubin (mg/dl), INR and serum creatinine (mg/dl) values pre-transplantation.[21,22] Acute kidney injury (AKI) was defined as an increase of 1.5 times the levels of baseline creatinine (lowest creatinine in the 30 days preceding liver transplantation) during the first 30 days post-transplantation. Severity of AKI was based on the increase in baseline creatinine and defined as stage 1 (1.5-1.9 times), stage 2 (2.0-2.9 times) and stage 3 (3.0 or higher times). Both definitions (AKI and severity) followed the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[23] Clinically significant infections were defined as microbiologically confirmed infections requiring systemic antimicrobials treatment or requiring hospital admission in the first 6-months after transplantation. Only biopsy-proven episodes of acute rejection according to Banff criteria were included in the first 6-months after transplantation. Ischemia reperfusion injury (IRI) was categorized using the levels of AST in the first 72 hours post-transplant, following previously published criteria[24-26] (Group 1: < 600 IU/L; Group 2: 601--2,500 IU/L; Group 3: 2,501-5,000 IU/L).

The primary outcome was mortality at 2-years post-transplant. Secondary endpoints included AKI in the first 30 days post-transplant, episodes of acute rejection and clinically significant infections at 6-months post-transplant. To assess kidney function, we used values of median creatinine 30 days pre-transplant and median peak of creatinine 30 days post-transplantation.

2.3 Statistical methods

Categorical variables were described as proportions and compared using Chi-square (or Fisher exact test, if necessary). Continuous variables were described as mean and standard deviation (SD) if normally distributed, or median and inter-quartile range (IQR), if non-normally distributed and compared by Student's T test or by Mann-Whitney U test, respectively. Multivariable analysis was performed by Cox-regression analysis, entering clinically relevant covariables and variables with a level of significance < 0.1 in the univariate analysis. For all performed tests, a two-sided p-value

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<0.05 was considered statistically significant. All statistics were calculated with IBM SPSS Statistics software (Chicago, IL) version 26.

3. RESULTS

3.1 Characteristics of the cohort

During the study period, we identified and retrospectively reviewed 351 adults who underwent liver transplantation at the University of Alberta Hospital. Of these, 8 patients had missing information on pre-transplant VRE colonization and were excluded from the study. The final cohort included 343 liver transplant recipients. Median age was 56.5 years (IQR 45.5-61.4) and 231 (67%) were male. Most common indications for liver transplantation included viral hepatitis (35%), alcohol related cirrhosis (15%), and primary sclerosing cholangitis (13%). The median MELD score was 18 (IQR 12--25). Median creatinine pre-transplantation was 75 μmol/l (IQR, 61--98). Prevalence of VRE colonization pre-liver transplant was 19.8 % (68/343).

Sixty-eight (68) patients were colonized pre-transplant with VRE and 275 non-VRE colonized. Twenty-seven (27) patients without VRE colonization at baseline acquired VRE post-transplant (27/275, 9.8%). Post-transplant VRE colonization in non-colonized patients at baseline occurred at a median of 8-days (IQR 4--44.5 days).

3.2 Liver transplant characteristics according to pre-transplant VRE colonization

The clinical characteristics of VRE colonized and non-colonized patients pre-transplant are summarized in Table 1. Median days of post-transplant admission was 21 days (IQR 16--49.5), being significantly higher in VRE pre-transplant colonized patients. Initial immunosuppressive therapy was based on calcineurin inhibitors in 320 (93%) and sirolimus in 23 (7%) patients. Median MELD score was higher for the VRE colonized at baseline (24, IQR 18--29) in comparison to the non-VRE

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colonized (17, IQR 12--24, P<0.001). Length of hospital admission was longer in pre-transplant VRE-colonized than non-colonized patients (21 [IQR 16--49.5] versus 19 [12-32] days respectively, p = 0.024).

3.3 Impact of VRE colonization on pre-defined endpoints

To analyze the impact of VRE colonization on pre-defined endpoints we included cases of VRE colonization post-transplant when VRE colonization occurred before the event of interest. Table 2 summarizes the primary and secondary endpoints of VRE colonized versus non-VRE colonized patients. Median creatinine pre-transplant was 85 (65-109.5) versus 74 (60-96) (p = 0.018) for VRE colonized versus non-VRE colonized, respectively. A higher median peak of creatinine was seen post-transplant for the VRE colonized in comparison to the non-VRE colonized individuals (158 [113-195.5] vs 121 [77-173.5], p<0.001). AKI in the first 30 days post-transplant was statistically more frequent in VRE-colonized patients (64% versus 52%; table 2). The severity of AKI was not significantly different between VRE and non-VRE colonized (stage 1: 45% vs 45%; stage 2: 39% vs 38%; and stage 3: 16% vs 17%; p = 0.992).

VRE colonized patients had increased risk of clinically significant bacterial or fungal infections (p = 0.003) and higher risk of invasive infections by VRE (p = 0.017). The risk of clinically significant bacterial or fungal infection in VRE colonized patients was similar at 3-months (HR 1.911, 95%CI 1.112-3.283) than at 6-months (HR 2.092, 95%CI 1.290-3.394). Excluding invasive VRE infections, VRE colonization increased the risk of non-VRE clinically significant infections (p = 0.010).

VRE colonization was not associated with increased risk of CMV infection or acute rejection of the liver allograft.

There was no difference in probability of survival at 2-years between patients with VRE colonization and non-colonized patients; p = 0.107.

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3.4 Multivariable analysis of the impact of VRE colonization on AKI, clinically significant bacterial or fungal infections and mortality

We performed a multivariate analysis to identify independent variables associated with mortality at 2-years (table 3), the development of AKI at 30 days (table 4), and the occurrence of clinically significant bacterial or fungal infections at 6 months post-transplant (table 5).

Of the 87 patients with VRE colonization pre-transplant or who acquired VRE in the first 30 days, 56 (64.4%) had AKI versus 133 (52.4%) of non-colonized patients. VRE colonization increased the risk for AKI at 30 days post-transplantation (HR 1.504, 95% CI: 1.077-2.100; p = 0.017).

A multivariate analysis to identify the risk factors for bacterial or fungal infections at 6 months showed that VRE colonized patients had 2-fold risk of this complication (HR 2.038, 95%CI: 1.222-3.399, p = 0.006).

Of 95 patients with pre- or post-transplant VRE colonization, 12 (12.6%) died at two years compared to 17 of 248 (6.9%) of non-colonized patients. Although there was no statistically significant difference in adjusted mortality at 2-years between VRE colonized and non-VRE colonized groups, there was a trend to increased mortality in VRE-colonized patients (HR 1.974, 95%CI 0.890-4.378, p = 0.094).

4. DISCUSSION

In our study, VRE colonization in liver transplant patients was associated with increased risk of AKI at 30 days post-transplantation, an increased risk of clinically significant bacterial or fungal infections, increased risk of invasive VRE infections and a non-statistically significant trend towards higher mortality than non-colonized patients. As the rate of VRE infection in our cohort was low (only 7 cases, 2% of the cohort), the more complicated post-transplant course and excess mortality

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may be explained by indirect effects. VRE colonized patients had longer hospitalization and higher rates of complications, that collectively may result in increased costs of transplant.[27]

VRE has been associated with higher mortality rate and complications following liver transplant.[6,18,25] This bacterium is a nosocomial pathogen and has the ability to colonize the gut during extensive hospitalization stays and ICU admissions. The risk for VRE colonization in liver transplant recipients is associated with the use of antibiotics and disruptions of the microbiota diversity (dysbiosis). In a study by Ubeda et al., mice treated with antibiotics developed VRE microbiota dominance.[9] In the same study, patients undergoing allogeneic hematopoietic stem cell transplantation developed bloodstream infection due to early post-transplant VRE colonization.[9] These patterns of microbiota disruption characterized by dominance of a single taxa and loss of diversity were significant predictors of mortality in allogeneic hematopoietic-cell transplantation.[26] Furthermore, gut dysbiosis may induce negative effects in the host's immunity and homeostasis, potentially compromising patients' outcomes.

An important finding is the increased risk of AKI in VRE colonized liver transplant patients. AKI is a common complication post-liver transplantation that can develop in upward of 50% of patients.[28] Major risks factors for AKI post-liver transplant include pre-transplant comorbidities (chronic kidney disease, hypertension, diabetes), donor and recipient factors (donor age > 60 years, deceased donor graft, donation after circulatory death graft), intraoperative factors (hypotension, post-perfusion syndrome, amount of blood loss) and post-transplant factors (calcineurin inhibitors use, other nephrotoxic medications).[29] In our cohort, VRE colonization was associated with higher pre-transplant levels of creatinine (and MELD scores) that may explain in part the higher risk of AKI post-transplant. VRE colonization-associated dysbiosis may also contribute to the increased risk of AKI.[30] Short-chain fatty acids (SCFA) produced by the digestion of dietary fiber in the gut microbiota, protect the development of AKI in mice.[31] The production of SCFA negatively correlates with microbiome diversity in patients with liver disease.[14] As VRE colonization is associated with

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dysbiosis,[8] it is reasonable to hypothesize that VRE colonization itself, may also decrease the production of SCFA.

Clinically significant bacterial/fungal infections were more frequent in VRE colonized patients, with a similar risk in the first 3-months than at 6-months. VRE bloodstream infection occurred in around 4% of colonized patients in a study done in hospitalized and long-term care facility patients.[32] In our study, immunosuppression was independently associated with this complication, with almost 13-fold increased risk.[32] A meta-analysis of studies in intensive care units found rates of VRE bacteremia varying from 2% to 16% in VRE colonized patients.[33] Interestingly, we also found a higher risk of non-VRE clinically significant infections in VRE colonized patients. This may in part be explained by sicker candidates (higher MELD scores) and prolonged hospital admission in VRE colonized patients. In addition, the increased risk of bacterial and fungal infections in colonized patients extended beyond 3-months post-transplantation, suggesting a potential indirect effect of VRE in the risk of infections. The risk for bacterial translocation may also be explained due to VRE affecting the mucosal innate immune defence,[16] although this association needs to be confirmed in larger studies.

Microbiome dysbiosis produces a series of alterations that may better explain other post-liver transplantation outcomes due to its role in triggering immunological cascades, inflammation, and metabolism. Although microbiome dysbiosis has been associated with rejection in transplantation,[37,38] and VRE is a cause of gut dysbiosis, we found no association between VRE colonization and acute liver rejection.

We did not find a significant difference in mortality, although there was a trend towards increased risk of death at 2-years in VRE colonized patients. Previous studies have shown an increased risk of death in VRE colonized liver transplant patients.[5,34] A previous large study found a 2-fold increased risk of death in colonized liver transplant patients.[5] Another study showed that the

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mortality is much higher when VRE is acquired post transplant (8.1%, 33.3% and 15.5% in pre-transplant colonized, post-transplant colonized and non colonized respectively, p = 0.04).[19] The development of AKI post-transplant is associated with higher risk of chronic kidney disease,[28] that may in part explain the increased mortality. Our findings suggest following thoroughly the suggested renal protective strategies for VRE colonized patients undergoing liver transplantation (maintenance of mean arterial pressure, intravascular volume, and avoiding resuscitating liver transplant recipients with hydroxyethyl starch and chloride-liberal fluids).[23,35]

Potential solutions to prevent VRE-related complications include VRE decolonization. Several research groups are exploring new strategies to treat and prevent colonization of resistant bacteria against healthcare associated infections,[36] currently approached through horizontal and vertical infection control strategies. Fecal microbiota transplant is a novel and promising therapy that has been suggested as a potential tool for VRE decolonization.[37] However, this topic is still in early research stages.[38-40]

Our study has some limitations. This is a single-center retrospective study using registry data and our findings should be confirmed in multicenter larger cohorts. We used broad-spectrum perioperative antibiotic prophylaxis as we had high rates of VRE invasive infection with fatal outcomes. Although it is uncertain if our antibiotic prophylaxis may have impacted our results, these associations may not be reproductible in other populations. As previously discussed, the causes for post-transplant AKI are numerous and most of them were not collected and analyzed in our study. Regarding impact on mortality, there were only 29 deaths at two years, therefore, our study may be underpowered to detect survival differences according to VRE colonization. Finally, as we did not analyze the stool microbiome composition in our cohort, the potential implications of VRE colonization on microbiota

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dysbiosis and worse outcomes is merely a hypothesis. Future research should address this association.

In conclusion, VRE colonization in liver transplant patients was associated with increased risk of AKI, clinically significant bacterial infections and VRE invasive infections, and a trend towards increased mortality. Larger cohort studies should confirm the stated associations.

Conflicts of interest: Dr. Abraldes reports grants and personal fees from Gilead, personal fees from Genfit, Intercept, Lupin and Gilead outside the submitted work. Dr. Cervera reports grants and personal fees from Merck, personal fees from AVIR pharma, Verity Pharma and Takeda, outside the submitted work. Dr Kabbani reports personal fees from AVIR pharma, and grant fees from Merck outside the submitted work. All other authors reported no conflicts. The authors received no funding for this work.

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Table 1. Cohort characteristics and demographics

Variables	VRE colonized N = 68	Non VRE colonized N = 275	p Value
Mean age (SD)	50.2 (13.5)	52.9 (11.7)	0.092
Male sex	40 (59)	191 (70)	0.094
Median MELD (IQR)	24 (18-29)	17 (12-24)	<0.001
Reason for transplant:			0.054
• Viral	14 (21)	107 (39)	
• NASH	8 (12)	24 (9)	
• Alcohol	12 (17)	41 (15)	
• Autoimmune	24 (35)	63 (23)	
• Other	10 (15)	40 (14)	
Fulminant liver failure	2 (3)	13 (5)	0.744
CMV serostatus			
• CMV D-/R-	10 (15)	51 (19)	
• CMV D-/R+	24 (35)	70 (25)	0.235
• CMV D+/R+	16 (23)	91 (33)	
• CMV D+/R-	18 (27)	63 (23)	

Data represent no. (%) of patients unless otherwise specified.

SD: Standard deviation; IQR: Interquartile-range; MELD: Model of End-Stage Liver Disease;

NASH: Non-alcoholic steatohepatitis, MMF: mycophenolate mofetil

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Table 2. Cohort Clinical Outcomes			
Variables	VRE colonized	Non VRE colonized	p Value*
Ischemia-reperfusion†			
• Median AST (72h) (IQR)	544 (296-1,041)	538 (282-1,020)	0.874
• Ischemia-reperfusion ≥ 3	6 (9)	21 (8)	0.801
Kidney function‡			
• Median creatinine pre-transplant (IQR)	85 (65-109.5)	74 (60-96)	0.018
• Acute kidney injury (30 days)	56 (64)	133 (52)	0.044
• Median peak creatinine post-transplant (IQR)	158 (113-195.5)	121 (77-173.5)	<0.001
CMV infection§			
• CMV infection	15 (16)	44 (18)	0.708
• Median peak CMV viral load (IU/mL) (IQR)	2580 (1192-6665)	1985 (1092-5050)	0.520
Bacterial/fungal infections¶			
• Clinically significant bacterial/fungal infection	27 (31)	42 (16)	0.003
• Bacteremia/fungemia	6 (7)	8 (3)	0.218
• Invasive VRE infection	5 (5)	2 (1)	0.017
Acute rejection††	12 (35)	83 (27)	0.297
Mortality	12 (13)	17 (7)	0.085

* p-values were calculated by chi-square test (or Fischer's exact test)

† Only pre-transplant VRE was considered

‡ 87 cases had VRE colonization at baseline or acquired VRE colonization in the first 30 post-transplant days

§ 94 cases had VRE colonization at baseline or acquired VRE colonization before the episode of CMV infection

¶ 86 cases had VRE colonization at baseline or acquired VRE colonization before clinically significant bacterial/fungal infection

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†† 95 cases had VRE colonization at baseline or acquired VRE colonization before acute rejection

Data represent no. (%) of patients unless otherwise specified.

IU/mL: International units per milliliter.

Table 3. Multivariate analysis assessing risk factors for mortality at 2-years.

Variable	Category	n	Dead at 2 years	aHR (95%CI)	p
Mean age at transplant	Death	29	52.08	1.012 (0.979-1.047)	0.470
	Alive	314	52.43		
Male sex	Male	231	18 (7.8%)	0.946 (0.417-2.143)	0.894
	Female	112	11 (9.8%)		
Mean MELD at transplant	Death	29	20.9	0.997 (0.960-1.036)	0.888
	Alive	314	19.63		
Reason for transplant:					
· **Viral**	Number	121	9 (7.4%)	1	-
· **NASH**		32	3 (9.4%)	1.162 (0.307-4.402)	0.825
· **Alcohol**		53	3 (5.7%)	0.726 (0.193-2.729)	0.636
· **Autoimmune**		87	4 (4.6%)	0.580 (0.161-2.089)	0.405
· **Other**		50	10 (20%)	3.216 (1.090-9.488)	0.034
VRE colonization*	Yes	95	12 (12.6%)	1.974 (0.890-4.378)	0.094
	No	248	17 (6.9%)		

* Includes 68 patients colonized at baseline and 27 patients that acquired VRE colonization post-transplant

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Table 4. Multivariate analysis assessing risk factors for acute kidney injury at 30 days

Variable	Category	n	Acute kidney injury (30 d)	aHR (95%CI)	p
Mean age at transplant	AKI	189	52.8	1.005 (0.991-1.019)	0.528
	No AKI	154	51.9		
Male sex	Male	231	131 (56.7%)	1.255 (0.897-1.757)	0.163
	Female	112	58 (51.8%)		
Mean MELD at transplant	AKI	189	20.18	1.015 (0.998-1.032)	0.092
	No AKI	154	19.2		
Reason for transplant:					
· **Viral**	Number	121	73 (60.3%)	1	-
· **NASH**		32	12 (37.5%)	0.432 (0.231-0.808)	0.009
· **Alcohol**		53	31 (58.5%)	0.814 (0.528-1.257)	0.354
· **Autoimmune**		87	50 (57.5%)	0.928 (0.609-1.413)	0.728
· **Other**		50	23 (46.0%)	0.722 (0.418-1.246)	0.241
Sirolimus-based immunosuppression	Yes	23	8 (9.2%)	1.358 (0.791-2.330)	0.267
	No	320	79 (24.7%)		
VRE colonization*	Yes	87	56 (64.4%)	1.504 (1.077-2.100)	0.017
	No	256	133 (52.0%)		

* 87 cases had VRE colonization at baseline or acquired VRE colonization in the first 30 post-transplant days

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Table 5. Multivariate analysis assessing risk factors for clinically significant bacterial infection (CSBI) at 6 months.

Variable	Category	n	CSBI at 6 months	aHR (95%CI)	p
Mean age at transplant	CSBI	69	50.93	0.993 (0.972-1.015)	0.528
	No CSBI	274	52.77		
Male sex	Male	231	40 (17.3%)	0.688 (0.409-1.156)	0.157
	Female	112	29 (25.9%)		
Mean MELD at transplant	CSBI	69	21.83	0.985 (0.958-1.013)	0.292
	No CSBI	270	21.82		
Reason for transplant:	Number				
· **Viral**		121	19 (15.7%)	1	-
· **NASH**		32	10 (31.3%)	1.866 (0.857-4.062)	0.116
· **Alcohol**		53	9 (17.0%)	1.132 (0.511-2.511)	0.760
· **Autoimmune**		87	19 (21.8%)	1.073 (0.516-2.229)	0.851
· **Other**		50	12 (24.0%)	1.400 (0.603-3.255)	0.434
VRE colonization*	Yes	86	42 (16.3%)	2.038 (1.222-3.399)	0.006
	No	257	27 (31.4%)		

* 86 cases had VRE colonization at baseline or acquired VRE colonization before clinically significant bacterial/fungal infection

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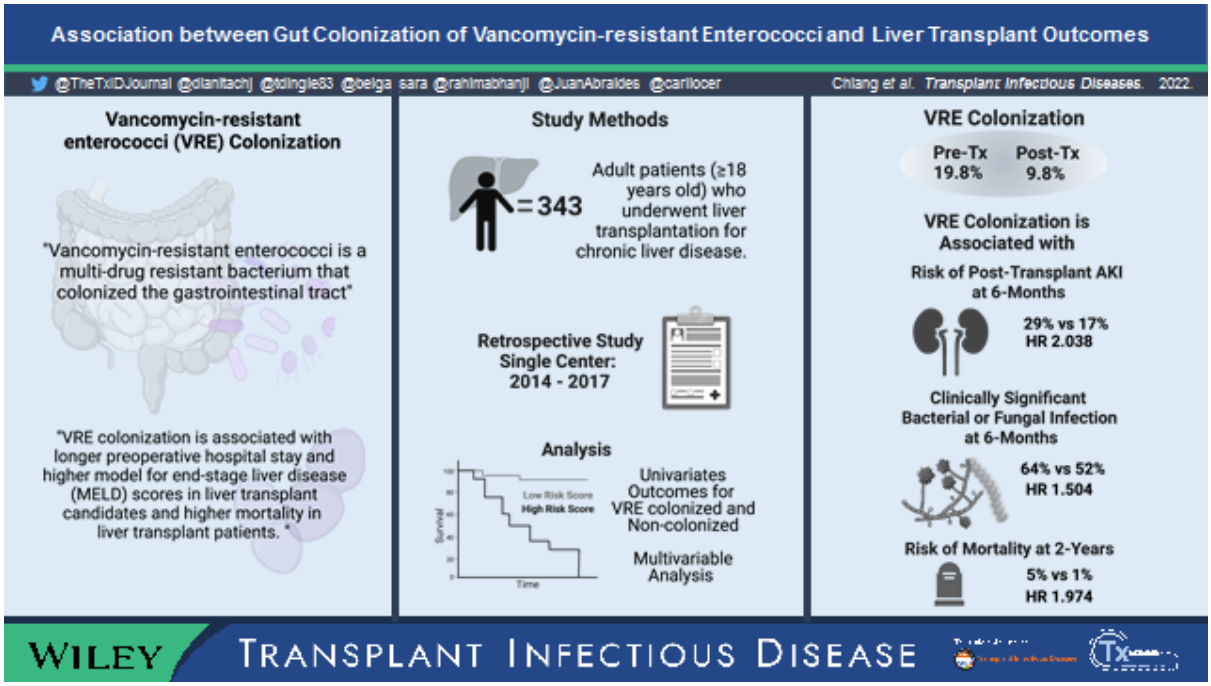
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