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Impact of pre-transplant carbapenem-resistant *Enterobacterales* colonization and/or infection on solid organ transplant outcomes

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Abstract

The impact of pre-transplant (SOT) carbapenem-resistant *Enterobacterales* (CRE) colonization or infection on post-SOT outcomes is unclear. We conducted a multi-center, international, cohort study of SOT recipients, with microbiologically diagnosed CRE colonization and/or infection pre-SOT. Sixty adult SOT recipients were included (liver $n = 30$, hearts $n = 17$). *Klebsiella pneumoniae* ($n = 47$, 78%) was the most common pre-SOT CRE species. Median time from CRE detection to SOT was 2.32 months (IQR 0.33–10.13). Post-SOT CRE infection occurred in 40% ($n = 24/60$), at a median of 9 days (IQR 7–17), and most commonly due to *K pneumoniae* ($n = 20/24$, 83%). Of those infected, 62% had a surgical site infection, and 46% had bloodstream infection. Patients with post-SOT CRE infection more commonly had a liver transplant (16, 67% vs. 14, 39%; $p = .0350$) or pre-SOT CRE BSI (11, 46% vs. 7, 19%; $p = .03$). One-year post-SOT survival was 77%, and those with post-SOT CRE infection had a 50% less chance of survival vs. uninfected (0.86, 95% CI, 0.76–0.97 vs. 0.34, 95% CI 0.08–1.0, $p = .0204$). Pre-SOT CRE infection or colonization is not an absolute contraindication to SOT and is more common among abdominal SOT recipients, those with pre-SOT CRE BSI, and those with early post-SOT medical and surgical complications.

KEYWORDS

carbapenem-resistant enterobacterales, multidrug-resistant organisms, solid organ transplantation

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Data collected by SMP at Columbia University Medical Center and RPM at Montefiore Medical Center.

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1 | BACKGROUND

Infections due to carbapenem-resistant *Enterobacteriales* (CRE) are an evolving global public health threat and are associated with high mortality and healthcare costs.^{1,2} Therapeutic challenges associated with CRE infections are immense due to the ability of carbapenemases to hydrolyze almost all beta-lactams and frequent concomitant resistance to other classes of antibiotics such as aminoglycosides and fluoroquinolones.^{3,4} Emergence of resistance to CRE-active agents such as polymyxins, tigecycline, and ceftazidime-avibactam has also been reported, further limiting therapeutic options for patients with CRE infections.⁵⁻¹¹

Solid organ transplantation (SOT) is an independent risk factor for CRE infection.³ The rate of CRE infections in the SOT population varies by region and organ transplanted. Incidence rates of 3%–10% have been reported among SOT recipients in CRE-endemic areas,^{1,12} and CRE infections have been associated with mortality rates between 30% and 50%.^{2,12}

CRE colonization has been associated with post-SOT CRE infection¹³⁻¹⁶; however, most data are limited to single center studies and pertain to abdominal transplantation only. While CRE colonization or previous infection is not an established contraindication to transplantation,^{17,18} impact on post-SOT outcomes is not well understood, and there is little guidance on peri-operative antimicrobial management in this setting. Therefore, we conducted this study to evaluate the clinical outcomes of patients who underwent SOT with prior CRE infection and/or asymptomatic colonization.

2 | METHODS

2.1 | Settings and study population

This multi-center, retrospective, and international cohort study evaluated adults (≥ 18 years of age) who underwent SOT from January 1, 2007 to July 31, 2013 and who had confirmed pre-SOT CRE colonization and/or infection at any time prior to SOT. We recruited study sites via email notification using the American Society of Transplant Infectious Diseases Community of Practice (AST ID COP) hub. Each participating site obtained Institutional Review Board approval. Sites were asked to identify patients without specifying the procedure to do so. The Icahn School of Medicine at Mount Sinai in New York City served as the host study site, and each participating site submitted de-identified demographic, clinical, and microbiologic data to a centralized database at Mount Sinai for analysis. Each site co-investigator reviewed relevant patient medical records through date of patient death or last follow-up.

2.2 | Clinical data and definitions

The following variables were collected for each patient: gender; pre-SOT renal replacement therapy (kidney transplant recipients only), indication for liver transplantation; presence of ventricular assist device

or total artificial heart and device-related infection as applicable (heart transplant recipients only); cystic fibrosis (lung transplant recipients only); age at the time of SOT; pre-SOT CRE isolated with identified mechanism of resistance as available; source of pre-SOT CRE; organ transplanted; alteration of standard peri-operative prophylaxis based upon CRE history with alternate agent(s) used as applicable; induction and maintenance immunosuppressive regimens; post-SOT surgical complications (bleeding, anastomotic leak, thrombosis, and re-operation); post-SOT medical complications (renal replacement therapy, tracheobronchitis in lung transplant recipients only, early allograft rejection [rejection within 30 days of SOT], and delayed graft function); development of post-SOT CRE infection with time to infection, type of infection, and CRE organism isolated as applicable.

Source of pre-SOT CRE detection was classified based on type of specimen as *surveillance* cultures representing colonization, or *clinical* cultures representing colonization or infection.

CRE infection (pre- and post-SOT) was defined as the isolation of CRE in a clinical specimen in the presence of clinical signs and symptoms of infection. *CRE colonization* was defined as isolation of CRE in a surveillance specimen, or in a clinical specimen in the absence of clinical signs and symptoms of infection. Pre- and post-SOT CRE species were considered *concordant* whether the same species of CRE was detected microbiologically. Typing of bacterial strains was not performed.

2.3 | Microbiologic testing

The clinical microbiology laboratories at each participating site performed bacterial identification and antimicrobial susceptibility testing of bacterial isolates and applied the 2013 Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoints for diagnosis of carbapenem resistance.¹⁹ Additional testing for the presence of carbapenemases was not required for inclusion in the study but was performed at some sites using either traditional biochemical (Modified Hodge testing) or molecular methodology (polymerase chain reaction), depending on the laboratory protocol of participating center.²⁰

2.4 | Statistical analysis

Descriptive statistics were used to report key variables for the full cohort and for those with and without post-SOT CRE infection. Continuous variables were expressed as medians and interquartile ranges (IQRs) and were compared using the Mann-Whitney *U* test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square or Fisher's exact test as appropriate. As a post hoc analysis, we looked to see if there is a difference in outcomes for patients who had a SOT within 1 year of CRE diagnosis vs patients who had a SOT >1 year after CRE diagnosis. Due to the time-dependent nature of the patient developing a post-transplant CRE infection, overall survival was depicted using the method by Simon and Makuch.²¹ Comparisons of time to event distributions among those who developed a post-transplant infection were evaluated using the

time-dependent Cox regression model. A two-tailed p -value $<.05$ was considered statistically significant. All analyses were performed using SAS v.9.4 statistical software (SAS Institute).

3 | RESULTS

The study cohort consisted of 60 SOT recipients with CRE colonization and/or infection diagnosed at a median of 2.3 months (IQR 0.33–10.13) before transplantation. The most common type of organ transplant was liver (LT, $n = 30$; 50%) followed by heart (HT, $n = 17$; 28%) and kidney (KT, $n = 7$; 12%). A total of 30 patients received induction immunosuppression; 19 (63%) received IL-2 receptor antagonists; 10 (33%) received anti-thymocyte globulin; and 1 (3%) received alemtuzumab. Organ types that received induction immunosuppression included LT ($n = 11$), HT ($n = 9$), KT ($n = 7$) lung transplant ($n = 2$), and intestine (ITX, $n = 1$). Five patients in the cohort (8%) were re-transplant recipients (4 LT, 1 LT/KT; Table 1).

3.1 | Pre-transplant CRE infection and colonization

Pre-SOT CRE was isolated in 34 clinical and 26 surveillance specimens (Table 1). Among the clinical specimens with CRE, definitive distinction between colonization and infection could not be made for 16/60 isolates (4 from the respiratory tract, 12 from the urine). Thirty percent of the total cohort ($n = 18$) was diagnosed with pre-SOT CRE bloodstream infection at a median of 1.84 (0–29) months prior to SOT. The most common pre-SOT CRE species was *Klebsiella pneumoniae* ($n = 47$, 78%), followed by *Enterobacter cloacae* ($n = 4$, 7%). The mechanism of CRE resistance was known for 29 (48%) isolates, of which 21 were identified by modified Hodge testing and 8 by polymerase chain reaction (7 were positive for *Klebsiella pneumoniae* carbapenemases [KPC] and 1 isolate was positive for New-Delhi metallo-beta-lactamase [NDM-1]).

3.2 | Post-transplant CRE infection

Post-SOT infection occurred in 40% ($n = 24/60$) of the total cohort at a median of 9 (7–17) days after transplant and most commonly involved the surgical site (SSI) ($n = 15/24$, 62%), urinary tract (6/24, 25%), and lungs ($n = 3/24$, 12.5%). Majority of infections occurred in LT recipients ($n = 16/24$; 9 SSI, 2 pneumonia, 5 urinary tract infections), followed by HT ($n = 4/24$; 3 SSI, 1 urinary tract infection), LT/KT ($n = 2/24$; both SSI), LTX ($n = 1/24$; pneumonia) and ITX recipients ($n = 1/24$; 1 SSI). Secondary bloodstream infection (BSI) was seen in 46% of those infected ($n = 11/24$), and the majority of these were associated with surgical site infection [9/11, 82%]. Fourteen of 24 patients were in the ICU at the time of post-SOT infection diagnosis with a median ICU stay of 11 days (2–32), and 10 died within the transplant hospitalization.

Species concordance between pre- and post-SOT CRE species was observed most commonly for *Klebsiella pneumoniae*. Of the 20

patients with post-SOT CRE *K pneumoniae* infection, 19 had pre-SOT evidence of the same bacteria; detected in the bloodstream in 9 patients, and in other sites in 10 patients (Table 2). For the one remaining patient with post-SOT CRE *K pneumoniae* infection, *Klebsiella oxytoca* was diagnosed on culture of LVAD exit site pre-SOT. Among the three patients who had post-SOT CRE *Enterobacter cloacae* infection, the same was detected pre-SOT in two patients (1 BSI and rectal colonization, 1 respiratory and rectal colonization). The remaining one patient with post-SOT *E cloacae* infection had *K pneumoniae* rectal colonization and BSI diagnosed pre-SOT. There was only one patient with post-SOT CRE *Serratia marcescens* infection, who had rectal colonization due to the same detected pre-SOT.

We investigated potential association of key pre- and post-SOT variables with post-SOT CRE infection. The results of univariable analysis are outlined in Table 1. Due to small outcome size, a multivariable analysis was not performed. The distribution of organ types between those with post-SOT CRE infection and those without was significantly different, and those with post-SOT CRE infection were more likely to have undergone LT (16, 67% vs. 14, 39%; $p = .0350$). Those with post-SOT CRE infection were also more likely to have had pre-SOT CRE BSI than those without (11/24, 46% vs. 7/36, 19%, $p = .03$). Among those who developed post-SOT CRE infection, the median time from most recent pre-SOT CRE (detected closest to transplant) and transplant surgery, was significantly shorter versus those who did not develop infection post-SOT (0.9, 0.1–3.1 vs. 4.2, 0.5–13.6 months, $p = .0168$). When looked at in the sub-group of patients with pre-SOT BSI ($n = 18/60$), this difference was smaller but remained statistically significant [1.00, 0–23 vs. 11.8, 0.4–29 months, $p = .05$]. Peri-operative prophylaxis targeted to pre-SOT CRE species was more common among patients with post-SOT CRE infection than those without (13/24, 54% vs. 8/36, 22%, $p = .0145$). Of the 21 total patients who received targeted prophylaxis, 10 (48%) had a history of pre-SOT CRE bacteremia, and 11 (52%) patients had CRE detected in urine ($n = 5$), rectal surveillance swab ($n = 4$) and LVAD exit site ($n = 2$).

We also conducted a univariate analysis to see if there was a difference in patient characteristics and outcomes, when compared by time of CRE detection in relation with time of SOT. Using the time of CRE detection closest to SOT, there was no significance difference in patient characteristics except type of organ transplant (LT $n = 28$ vs. 2, KT 2 vs. 5, LT/KT 2 vs. 1, ITX 0 vs. 1, Lung 2 vs 0, HT 13 vs. 4, $p = .0014$), among those who had pre-SOT CRE detected ≤ 12 months and > 12 months from time of SOT. Similarly, there was no significant difference between the groups in post-SOT outcomes of CRE infection, re-transplantation, mortality within transplant hospitalization, and 1-year post-SOT mortality (data not shown).

3.3 | Post-transplant medical and surgical complication

Patients with post-transplant CRE infection more commonly had complications including post-transplant surgery (14/24, 58% vs. 3/36, 8%, $p < .0001$) and medical complications including renal

TABLE 1 Pre- and post-transplant characteristics by post-transplant infection outcome

Patient characteristic	Post-SOT CRE infection (n = 24)	No post-SOT CRE infection (n = 36)	p-value
Median age at transplant, years (IQR)	55 (48–61)	52 (45–61)	.6129
Male gender, n (%)	15 (62.5)	25 (69.4)	.5762
Organ transplant type, n (%)			
Liver	16 (66.7)	14 (38.9)	.0143
Heart	4 (16.7)	13 (36.1)	
Kidney	0 (0.0)	7 (19.4)	
Liver-kidney	2 (8.3)	1 (2.8)	
Intestine	1 (4.2)	0 (0.0)	
Lungs	1 (4.2)	1 (2.8)	
Re-transplantation, n (%)	3 (12.5)	2 (5.56)	.3803
Induction immunosuppression, n (%)	10 (41.67)	20 (55.56)	.2918
IL-2 Receptor antagonist	7 (70.0)	12 (60.0)	
Anti-thymocyte Globulin	3 (30.0)	7 (35.0)	
Alemtuzumab	0 (0.0)	1 (5.0)	
Pre-SOT CRE species, n (%)			
<i>K pneumoniae</i>	20 (83.3)	27 (75.0)	.6340
<i>K oxytoca</i>	1 (4.2)	1 (2.8)	
<i>C freundii</i>	0 (0.0)	1 (2.8)	
<i>E cloacae</i>	2 (8.3)	2 (5.6)	
<i>E coli</i>	0 (0.0)	4 (11.1)	
<i>S marcescens</i>	1 (4.2)	1 (2.8)	
Pre-transplant CRE bacteremia	11 (45.8)	7 (19.4)	.0289
Site of most recent pre-SOT CRE identification			
Surveillance specimens			
Rectal	4 (16.7)	13 (36.1)	.0524
Respiratory	0 (0.0)	3 (8.3)	
Urine	2 (8.3)	6 (16.7)	
Wound	0 (0.0)	1 (2.8)	
Clinical specimens			
Blood	9 (37.5)	4 (11.1)	
Surgical site	1 (4.2)	2 (5.6)	
Respiratory	4 (16.7)	1 (2.8)	
Urine Culture	4 (16.7)	6 (16.7)	
Receipt of CRE-active peri-operative prophylaxis, n (%)	13 (54.2)	8 (22.2)	.0145
Post-SOT surgical complications prior to CRE infection, n (%)			
Anastomotic leak	2 (8.3)	0 (0.0)	<.0001
Bleeding	1 (4.2)	3 (8.3)	
Reoperation	10 (41.7)	0 (0.0)	
Other	1 (4.2)	0 (0.0)	
None	10 (41.7)	33 (91.7)	
Post-SOT medical complications prior to CRE infection, n (%)			
Renal replacement therapy	8 (33.3)	3 (8.3)	.0186
Early rejection	2 (8.3)	1 (2.8)	
Other	1 (4.2)	1 (2.8)	
None	13 (54.2)	31 (86.1)	

(Continues)

TABLE 1 (Continued)

Patient characteristic	Post-SOT CRE infection (n = 24)	No post-SOT CRE infection (n = 36)	p-value
Median time from most recent pre-transplant CRE detection to transplant, months (IQR)	0.9 (0.1-3.1)	4.2 (0.5-13.6)	.0168
Mortality during SOT hospitalization, n (%)	6 (25.0)	3 (8.3)	.0859 ^b
1-year post-SOT mortality, n (%)	8 (33.3)	6 (16.7)	.1286 ^b

Abbreviation: IQR, Interquartile range.

^aMann-Whitney *U* test for continuous variables and chi-square/Fisher's exact test for categorical variables

^bTime to event outcomes compared using the log-rank test.

Bold p-values are explained in paragraph form where the table is referenced

replacement therapy prior to onset of post-SOT CRE infection (11/24, 46% vs. 5/36, 14%, $p = .0186$). One-year post-SOT survival for the entire cohort was 77%, and those with post-SOT CRE infection had a 50% less chance of survival than those without (0.86; 95% CI, 0.76-0.97 vs. 0.34; 95% CI 0.08-1.00; log rank $p = .0204$; Figure 1).

4 | DISCUSSION

This is the first international, multi-center investigation of outcomes in SOT recipients with pre-SOT CRE colonization and/or infection. Overall one-year survival for the cohort was 77%. This is an important finding as the significance of CRE colonization or

TABLE 2 Pre-transplant microbiology of patients with post-transplant infection (n = 24)

Pre-SOT CRE species	Site of Pre-SOT CRE	Targeted surgical prophylaxis	SOT type	Post-SOT CRE species.	Post-SOT infection site	Secondary BSI
<i>K pneumoniae</i>	Bld, Ur, rectum, resp	Yes	LT	<i>K pneumoniae</i>	Pna	No
<i>K pneumoniae</i>	Rectum	No	LT, KT	<i>K pneumoniae</i>	SSI	No
<i>K pneumoniae</i>	Bld, rectum	Yes	LT	<i>K pneumoniae</i>	SSI	Yes
<i>K pneumoniae</i>	Bld	Yes	LT	<i>K pneumoniae</i>	SSI	Yes
<i>K pneumoniae</i>	Resp, Ur	No	LT	<i>K pneumoniae</i>	Pna	Yes
<i>K pneumoniae</i>	Ur	Yes	LT	<i>K pneumoniae</i>	UTI	No
<i>K pneumoniae</i>	Ur	No	LT	<i>K pneumoniae</i>	UTI	No
<i>S marcescens</i>	Rectum	No	LT	<i>S marcescens</i>	SSI	Yes
<i>K pneumoniae</i>	Bld, rectum	No	LT	<i>K pneumoniae</i>	SSI	Yes
<i>K pneumoniae</i>	Bld	No	LT	<i>K pneumoniae</i>	SSI	Yes
<i>K pneumoniae</i>	Resp	No	LT	<i>K pneumoniae</i>	SSI	No
<i>K pneumoniae</i>	Bld	No	LT	<i>K pneumoniae</i>	UTI	No
<i>K pneumoniae</i>	Resp	Yes	HT	<i>K pneumoniae</i>	SSI	Yes
<i>K pneumoniae</i>	Ur	No	LT	<i>K pneumoniae</i>	UTI	No
<i>K oxytoca</i>	DLI	Yes	HT	<i>K pneumoniae</i>	UTI	Yes
<i>K pneumoniae</i>	Ur	Yes	LTX	<i>K pneumoniae</i>	Pna	No
<i>K pneumoniae</i>	Ur	Yes	LT, KT	<i>K pneumoniae</i>	SSI	No
<i>K pneumoniae</i>	Bld, rectum	Yes	ITX	<i>E cloacae</i>	SSI	Yes
<i>E cloacae</i>	Resp, rectum	Yes	HT	<i>E cloacae</i>	SSI	Yes
<i>E cloacae</i>	Bld, rectum	Yes	HT	<i>E cloacae</i>	SSI	No
<i>K pneumoniae</i>	Ur	Yes	LT	<i>K pneumoniae</i>	SSI	No
<i>K pneumoniae</i>	Bld, Ur	Yes	LT	<i>K pneumoniae</i>	SSI	Yes
<i>K pneumoniae</i>	Bld	No	LT	<i>K pneumoniae</i>	UTI	No
<i>K pneumoniae</i>	Bld, rectum	No	LT	<i>K pneumoniae</i>	SSI	No

Abbreviations: Bld, blood; BSI, bloodstream infection; DLI, LVAD driveline exit-site; *E cloacae*, *Enterobacter cloacae*; *K pneumoniae/oxytoca*, *Klebsiella pneumoniae/oxytoca*; Pna, pneumonia; Rectum, rectal surveillance specimen; Resp, respiratory; *S marcescens*, *Serratia marcescens*; SSI, surgical site infection; Ur, urine; UTI, urinary tract infection.

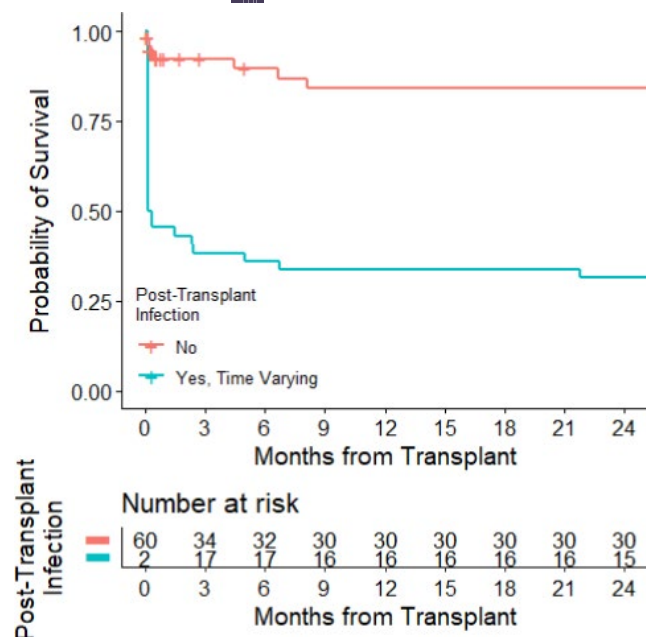


FIGURE 1 Time dependent one-year post-SOT survival estimate—post-SOT CRE infection vs. none: 0.338 (95% CI 0.080, 1.000) vs. 0.857 (95% CI 0.755–0.973), $p = .0204$

infection prior to SOT was unknown prior to this study. As the global multi-drug resistant organism (MDRO) epidemic grows, the CDC¹⁹ and WHO²² recommend that all healthcare institutions develop a multi-modal approach including surveillance to prevent CRE infections. Many transplant institutions are already conducting screening of SOT candidates for MDRO colonization to implement targeted infection prevention measures, and in future, these practices may become even more widespread if validated by studies. This study shows that pre-SOT CRE colonization or infection is not an absolute contraindication to SOT and is associated with favorable one-year post-SOT survival in nearly 80% of patients. Our findings also shed some light on the risk of post-SOT infection conferred by different sites of pre-SOT CRE detection, although we were not able to confirm these findings in an adjusted analysis. We found that pre-SOT CRE BSI was significantly more common among those who developed post-SOT CRE infection. There was otherwise no difference in the percent of patients with post-SOT infection by site of pre-SOT CRE detection in this cohort. This finding is a step toward the much-needed clarity about this commonly encountered issue, and informs us of the risk of post-transplant CRE infection in colonized and infected transplant candidates. We also found that in patients who developed post-SOT CRE infection, the time between the most recent pre-SOT CRE (any site) and transplantation was significantly shorter for those who than those did not develop infection following SOT, and this difference while smaller, remained significant for patients with pre-SOT BSI only. This finding suggests that detection of CRE infection or colonization closer to time of transplantation may carry greater risk of post-SOT infection, than CRE detected more remotely pre-SOT. However, in a separate analysis dividing the study cohort by time

of pre-SOT CRE detection closest to time of SOT, we were unable to detect any difference in post-SOT infection and mortality. Nonetheless, we feel this an important finding that warrants further investigation in future studies.

Peri-SOT prophylaxis targeted to CRE was given to 35% of patients in our cohort; however, details of the regimen used was not available for most. Of the cases where this information was available, targeted prophylaxis consisted primarily of a combination of 2 to 3 agents, most commonly carbapenems, polymyxins, and tigecycline. Data on antimicrobial dosing and duration of peri-operative prophylaxis were not collected. Interestingly, we found that patients who received targeted CRE prophylaxis more commonly developed post-transplant CRE infection than those who did not. Multiple factors likely account for this finding. Nearly 48% of patients who received targeted prophylaxis had pre-transplant CRE BSI (10/21) and were at greater risk of post-SOT infection despite targeted prophylaxis. Furthermore, the adequacy of targeted prophylaxis for this cohort is unknown, and type of antibiotic regimen may have contributed to the risk of infection. It is also important to note that novel and potentially more effective agents for treatment of CRE such as ceftazidime-avibactam²³ were not available in the timeframe of this study. Based on our data it is therefore unclear, if peri-operative prophylaxis targeted to pre-SOT CRE species is indicated. However, the presence of concordance between the most common pre- and post-CRE SOT species, speaks of the high risk of post-SOT infection due to pre-SOT colonizing and infecting pathogens, highlighting the importance of targeted empiric antibiotic therapy in patients who develop signs and symptoms of infection post-SOT. This study further reiterates the high risk of CRE infection among abdominal transplant recipients, those with post-transplant surgical complications and post-transplant renal failure requiring renal replacement therapy.

This study has several limitations including a retrospective design, and the lack of a multivariable analysis due the small number of patients with post-transplant infection. An adjusted analysis to ascertain independent infection predictors should be pursued in the future to confirm the findings of this study. Due to lack of clinical information, we were not able to discern pre-SOT CRE infection from colonization in 16 non-blood clinical specimens. While we were able to show the impact of pre-SOT CRE BSI, we are unable to provide the same clarity on the post-SOT infection risk conferred by pre-SOT CRE colonization versus active infection in other sites. We must also acknowledge that the CLSI MIC breakpoints for CRE were updated since this study. However, the clinical significance of these breakpoint changes and the percent change in species susceptibility does not appear to be universally significant.^{24,25} Hence, we feel this change does not influence the relevance of these findings.

5 | CONCLUSION

In our retrospective cohort study, 77% of SOT recipients with pre-CRE colonization or infection were alive one year after SOT, although

post-SOT CRE infection was associated with reduced survival. Post-transplant CRE infection occurred more commonly among abdominal transplant recipients, those with pre-SOT CRE BSI, and those with post-transplant surgical complications and renal replacement therapy.

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Original data available on request.

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