ORIGINAL ARTICLE

The Impact of *Clostridium difficile* Infection on Future Outcomes of Solid Organ Transplant Recipients

Ruihong Luo, MD, PhD;[1,2] Janice M. Weinberg, ScD;[3] Tamar F. Barlam, MD, MSc[2]

OBJECTIVE. *Clostridium difficile* infection (CDI) is common in solid organ transplant (SOT) recipients, but few studies have examined long-term outcomes. We studied the impact of CDI after SOT on mortality and transplant organ complication-related hospitalizations (TOH).

METHODS. SOT recipients ≥18 years of age with at least 1 year of posttransplant data were analyzed using the MarketScan database for 2007–2014. Patients who died within one year of transplant were followed until death. Patients were grouped as early CDI (ie, first occurrence ≤90 days posttransplant), late CDI (ie, first occurrence >90 days posttransplant) and controls (ie, no CDI occurrence during follow-up). The risk of mortality or TOH after CDI was evaluated using Cox and logistic regressions, respectively.

RESULTS. Overall, 96 patients had early CDI, 97 patients had late CDI, and 5,913 patients were used as controls. The risk for death was significantly higher in the early CDI group than the control group (hazard ratio [HR],1.92; 95% confidence interval [CI], 1.12–3.29; $P = .018$); there was no significant difference between the late CDI group and the control group (HR, 0.86; 95% CI, 0.38–1.94; $P = .717$). Both the early CDI group (odds ratio [OR], 2.19; 95% CI, 1.45–3.31; $P < .001$) and the late CDI group (OR, 4.36; 95% CI, 2.84–6.71; $P < .001$) had higher risk for TOH than the control group. For those patients who survived >90 days posttransplant, both the early CDI group (n = 89) and the late CDI group (n = 97) had increased risk for death or TOH during follow-up than the control group (n = 5,734).

CONCLUSION. Though our study could not prove causality, both early and late CDI occurrence in SOT recipients were associated with worse future outcomes than for SOT recipients without CDI.

Infect Control Hosp Epidemiol 2018;39:563–570

Clostridium difficile infection (CDI) is the leading cause of antibiotic-associated nosocomial diarrhea and colitis in the industrialized world. Solid organ transplant (SOT) recipients experience a period of generalized increased infection risk following transplantation due to the use of immunosuppressive agents, complications of surgery, and extended hospital stays, resulting in the need for antibiotic treatments.[1–3] In addition, SOT recipients are at increased risk for CDI because of posttransplant hypogammaglobulinemia, and the use of antibiotic prophylaxis and gastric suppressing agents.[4–6] *Clostridium difficile* infection has been investigated in different SOT recipients; incidence varies widely, from 1.5% to 31%.[1,7–11] Prior studies have shown that CDI greatly impacts the health of SOT recipients, causing increased mortality and graft loss as well as greater healthcare service utilization.[1,6,12,13] Severe complications related to CDI, such as fulminant colitis requiring colectomy and ICU admission, are also more common in SOT recipients than in the general hospitalized population.[1,14–16]

Few data on the long-term impact of CDI associated with SOT have been published. Although CDI can occur at any time after transplantation, it is most common within 1–3 months posttransplant.[9,10] Our objective was to evaluate the occurrence of CDI in SOT recipients for different posttransplant periods and to determine how CDI affects the future clinical course of SOT patients.

METHODS

Data Source and Study Cohort

We analyzed the Truven Health MarketScan Research Databases from 2007 to 2014. This database includes the MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database. It is composed of deidentified administrative claims from a sample of large employers and health plans throughout the United States. It captures patient-level utilization of medical services, payment, prescription drugs, and enrollment across inpatient and outpatient settings. It represents annually ~30–50 million covered lives for employed subscribers younger than 65 years and their dependents.[17] The

Affiliations: 1. Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine at University of California–Los Angeles, California; 2. Section of Infectious Diseases, Boston University School of Medicine, Boston, Massachusetts; 3. Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts.

Received September 7, 2017; accepted February 8, 2018; electronically published March 19, 2018

 0899-823X/2018/3905-0008. DOI: 10.1017/ice.2018.48

Institutional Review Board of Boston University Medical Campus approved this study.

Patients aged ≥18 years who underwent SOT from January 2008 to December 2013 were identified by *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure codes or current procedural terminology (CPT) codes, including kidney (55.6, 55.61, 55.69, 50360, 50365, 50380), liver (50.5, 50.51, 50.59, 47135, 47136), heart (37.5, 37.51, 00580) or lung transplant (33.5, 33.50, 33.51, 33.52, 50360, 50365, 50380). We included patients if they were continuously enrolled in healthcare plans captured by Marketscan from at least 1 calendar year before transplant until 1 calendar year after transplant. Patients who died within 1 year of transplant were followed until death. The occurrence of CDI was identified using ICD-9-CM diagnostic code 008.45. Patients with CDI occurrence within 1 year before transplant were excluded. Patients undergoing retransplant procedures were analyzed based on their first SOT claims.

Patients were divided into 3 groups based on the first occurrence of CDI. The early CDI group included patients with the first CDI occurrence ≤90 days posttransplant; the late CDI group comprised patients with a first CDI occurrence >90 days posttransplant; and the control group included patients who had no documentation of CDI during the posttransplant follow-up period.

Independent Variables

We examined the patient demographic characteristics including age, sex, Charlson comorbidity index (CCI) at the time of SOT,[18] the transplanted organ (kidney, liver, heart, lung and concurrent multiple organs transplant), the calendar year of SOT surgery (2008–2013) and CDI occurrence after transplant. We assessed the CCI by identifying comorbid conditions using their corresponding ICD-9-CM codes.[19] Stratifications of age (18–34, 35–44, 45–54, and 55–65 years) and CCI score (1–2, 3–4, and ≥5) were used for the comparison between groups and for multivariate analyses.

Outcomes of Interest

The outcomes of interest in our study included CDI incidence of SOT recipients, mortality, transplant organ complication–related hospitalizations (TOH), and readmissions during the posttransplant follow-up period in the CDI groups compared with the control group. We defined CDI incidence as the number of patients with the first occurrence of CDI for 3 periods: the full posttransplant follow-up, ≤90 days posttransplant, or >90 days posttransplant. Mortality was defined as a discharge outcome of death during the posttransplant follow-up. We identified TOH using ICD-9-CM code 996.8x. In addition, we examined the impact of CDI as a risk factor for the outcomes of mortality and TOH in the SOT recipients.

Statistical Analysis

We compared the independent variables and outcomes among groups using Pearson χ^2 test or the Fisher exact test for categorical variables and 1-way ANOVA for continuous variables. After adjustment for the independent variables, Cox regression was conducted for survival analysis of patient groups and for assessment of the risk factors for mortality during the posttransplant follow-up period; logistic regression was conducted to evaluate the risk factors for TOH. We performed 3 subgroup analyses. The first subgroup analysis was performed in patients who survived >90 days posttransplant. The second subgroup analysis of TOH was performed in patients who survived the entire follow-up period. The third subgroup analysis was performed after excluding the patients with recurrent CDI associated hospitalization. Recurrent CDI associated hospitalization was defined as a patient with a second CDI hospitalization at least 60 days after the first CDI hospitalization. A P value $< .05$ was considered statistically significant. All statistical analyses were performed using Statistical Analysis System (SAS) version 9.4 software (SAS Institute, Cary, NC) and Statistical Program for Social Sciences (SPSS) version 22.0 software (IBM, Armonk, NY).

RESULTS

A total of 6,106 patients underwent SOT from 2008 to 2013 and met our inclusion and exclusion criteria (Figure 1), including 3,862 patients who received kidney transplants (63%), 442 who received heart transplants (7.2%), 1,358 who received liver transplants (22.2%), 138 who received lung transplants (2.3%), and 306 concurrent multiple organs transplant recipients (5.0%). There were 96 patients in the early CDI group, 97 patients in the late CDI group, and 5,734 patients in the control group. The median posttransplant follow-up period for the full cohort of SOT patients was 534 days (interquartile range, 441–629 days).

During the posttransplant follow-up period, CDI occurred in 3.2% of the SOT recipients. The CDI incidence was highest in lung, liver, and concurrent multiple-organ transplant recipients (5.8%, 5.5%, and 5.6%, respectively), followed by heart transplant recipients (4.3%). The incidence was lowest in kidney transplant recipients (1.9%). Almost half of the first CDIs occurred within 90 days posttransplant, with an incidence of 1.6%.

The average age of SOT recipients in our study were 49.5 ± 10.5 years, and 63% of the patients were male. Compared to the control group, the early CDI group had more patients with CCI ≥3; fewer patients with kidney transplant; and more patients with heart, liver, lung, or concurrent multiple organs transplant (Table 1). For those patients who survived >90 days posttransplant, there was no significant difference in demographics, CCI, or transplanted organ between early and late CDI groups (data not shown).

The overall mortality of SOT recipients was 5.1%. Those with lung and concurrent multiple organs transplant had the highest mortality (15.9% and 16.0%, respectively), followed by

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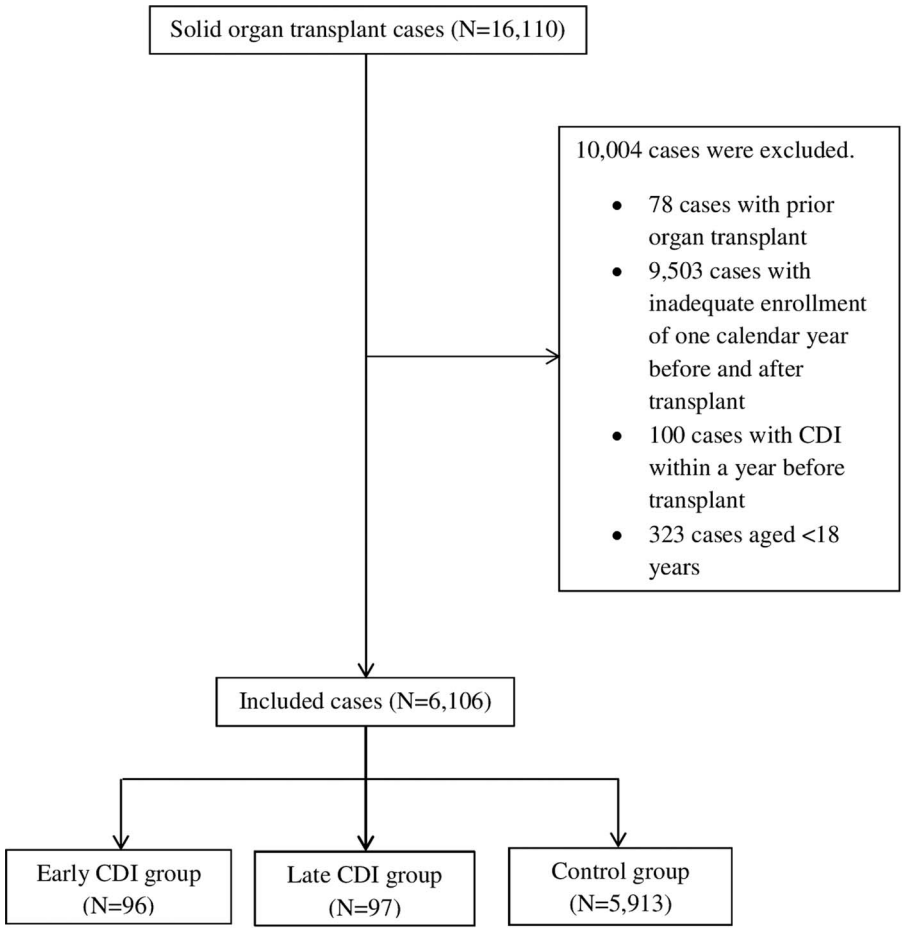

FIGURE 1. Flow sheet of case inclusion and exclusion.

liver transplant (10.8%) and heart transplant (9.5%). Patients who had a kidney transplant had the lowest overall mortality (1.4%). In univariate analysis, we analyzed mortality, readmissions and TOH for early CDI, late CDI, and control groups, as well as comparisons among groups (Table 2). Subgroup analyses for those patients who survived >90 days posttransplant and for those who survived the entire follow-up period are described in Supplementary Table 1. Mortality in the early CDI group (14.6%) was significantly higher than the late CDI group (6.3%) and control group (5.0%) ($P < .001$, respectively), while for those patients who survived >90 days posttransplant, the subsequent mortality was significantly higher in both the early CDI and late CDI groups than in the control group (7.9% and 6.3% vs 2.0%; $P < .001$, respectively). Readmissions and TOH were significantly higher for both early and late CDI groups compared with controls and did not change in subgroup analyses.

In multivariate analysis, the early CDI group had a lower cumulative survival than the control group on posttransplant day 90 (93% vs 97%), day 180 (91% vs 96%), and day 360 (86% vs 96%) (Figure 2). The patients in the early CDI group had almost twice the risk of death during follow-up (HR, 1.92; 95% CI, 1.12–3.29; $P = .018$) than controls. There was no significant difference in risk of death between the late CDI group and controls (HR, 0.86; 95% CI, 0.38–1.94; $P = .717$) (Table 3). We could not demonstrate a significantly different risk for mortality in the late CDI group compared with the early CDI group (HR, 0.45; 95% CI, 0.17–1.17; $P = .101$) (data not shown). Patients in both the early CDI group (OR, 2.19; 95% CI, 1.45–3.31; $P < .001$) and the late CDI group (OR, 4.36; 95% CI, 2.84–6.71; $P < .001$) had 2–4 times higher risk for TOH than those in the control group (Table 3). For patients who survived >90 days posttransplant, both the early CDI group (HR, 2.64; 95% CI, 1.22–5.71; $P = .014$) and the late CDI group (HR, 2.33; 95% CI, 1.02–5.33; $P = .045$) had higher risk for mortality than the control group (Figure 3, Table 4).

DISCUSSION

The SOT recipients represent a patient population with increased risk for infections including CDI, and CDI incidence is higher in SOT recipients than for the general hospitalized population.[10,11] Few longitudinal, long-term data on the

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TABLE 1. Comparison of Demographics, Charlson Comorbidity Index and Transplanted Organs Among Patients in Different Groups

	Early CDI, No. (%) (N = 96)	Late CDI, No. (%) (N = 97)	Controls, No. (%) (N = 5,913)
Age, mean y ± SD	51.5 ± 10.5	50.6 ± 10.2	49.5 ± 10.5
Age group, y			
18–34	8 (8.3)	11 (11.3)	617 (10.4)
35–44	11 (11.5)	9 (9.3)	1,000 (16.9)
45–54	27 (28.1)	34 (35.1)	1,926 (32.6)
55–64	50 (52.1)	43 (44.3)	2,370 (40.1)
Gender			
Male	58 (60.4)	59 (60.8)	3,729 (63.1)
Female	38 (39.6)	38 (39.2)	2,184 (36.9)
Charlson comorbidity index			
1–2	42 (43.8)[a,b]	37 (38.1)[b]	3,382 (57.2)
3–4	43 (44.8)[a,b]	48 (49.5)[b]	1,968 (33.3)
≥5	11 (11.5)[a,b]	12 (12.4)[b]	563 (9.5)
Transplant organ			
Kidney	34 (35.4)[a,b]	40 (41.2)[b]	3,788 (64.1)
Heart	12 (12.5)[a,b]	7 (7.2)[b]	423 (7.2)
Liver	36 (37.5)[a,b]	39 (40.2)[b]	1,283 (21.7)
Lung	5 (5.2)[a,b]	3 (3.1)[b]	130 (2.2)
Multiple-organ transplant	9 (9.4)[a,b]	8 (8.2)[b]	289 (4.9)

NOTE. CDI, *Clostridium difficile* infection; SD, standard deviation.
[a]Compared with the late CDI group, $P < .05$.
[b]Compared with the control group, $P < .05$.

TABLE 2. Comparison of Outcomes Among Patients in Different Groups

Characteristic	Early CDI, No. (%) (N = 96)	Late CDI, No. (%) (N = 97)	Controls, No. (%) (N = 5,913)
Readmission ≤1 year post-SOT			
Cases with ≥1 readmission	80 (83.3)[a,b]	93 (95.9)[b]	2,766 (46.8)
Cases with ≥2 readmissions	59 (61.5)[a,b]	77 (79.4)[b]	1,273 (21.5)
Cases with ≥3 readmissions	39 (40.6)[a,b]	60 (61.9)[b]	641 (10.8)
Mortality	14 (14.6)[a,b]	6 (6.2)	293 (5.0)
TOH	49 (51.0)[b]	64 (66.0)[b]	1,698 (28.7)

NOTE. CDI, *Clostridium difficile* infection; SOT, solid organ transplant; TOH, transplant organ complication-related hospitalization.
[a]Compared with the late CDI group, $P < .05$.
[b]Compared with the control group, $P < .05$.

impact of CDI on future outcomes of SOT recipients are available. Hsu et al[20] found a higher mortality rate among SOT recipients with CDI in the first year posttransplant, but the number of deaths was too small to do further analysis. We sought to evaluate outcomes of CDI in SOT recipients for up to 18 months of follow-up.

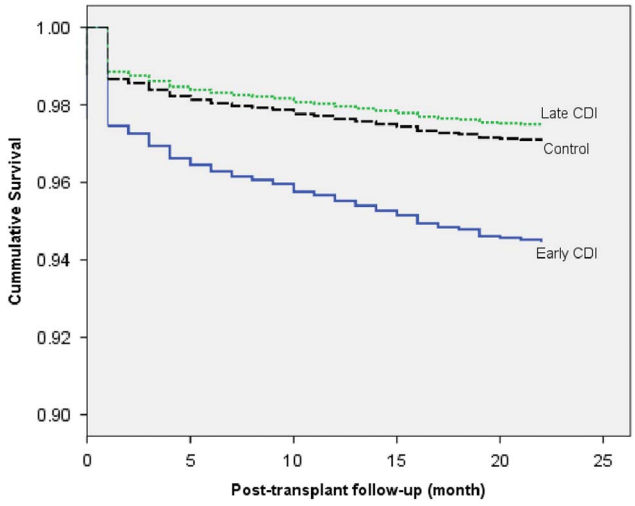

FIGURE 2. Survival curves of all solid organ transplant recipients in early *Clostridium difficile* infection (CDI), late CDI, and control groups by Cox regression.

Occurrence of CDI during the early posttransplant period is likely related to greater exposure to known risk factors for CDI, such as hospitalization, intense immunosuppression and antimicrobial treatments.[9,10] We estimate that ~32 cases per 1,000 SOT recipients experienced at least 1 CDI occurrence in the 18 months posttransplant, and nearly 50% of them had their first CDI occurrence ≤90 days posttransplant.

In SOT recipients, CDI incidence is known to vary according to the transplanted organ received.[9,21,22] Consistent with prior studies,[23,24] we found that CDI occurred more often in patients with lung, liver, heart and concurrent multiple organs transplant than in those with kidney transplant.

We defined early CDI as up to 90 days posttransplant to best link that episode to the initial surgical procedure and perioperative period, based on several prior studies. The CDI incidence in SOT recipients is highest within the first 3 months after the transplant.[9] Generally, the period of maximum risk for CDI related to antibiotic exposure, eg, from surgical prophylaxis, appears to be within 30 days after the start of antibiotic use. Although there is a significant decrease in CDI risk after 45 days, a continuous risk remains until nearly 80 days.[25] Late CDI occurred months to more than a year after transplant. Late CDI is unlikely to be related to the index surgery, although a small subset of patients (n = 73) had >1 transplantation procedure. Late CDI was more likely secondary to either antimicrobial exposure due to infection or intensified immunosuppression to treat graft rejection.[11]

We found higher mortality in SOT recipients with CDI than in those without CDI. This result could be multifactorial. It is

https://doi.org/10.1017/ice.2018.48 Published online by Cambridge University Press

TABLE 3. Risk Factors for Death and Transplant Organ Complication-Related Hospitalization (TOH) by Multivariate Analyses

	Risk for Death[a]		Risk for TOH[b]	
Characteristic	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age group, y	Reference: 18–34		Reference: 18–34	
35–44	1.28 (0.71–2.30)	.410	0.71 (0.57–0.88)	.002
45–54	1.12 (0.66–1.92)	.669	0.71 (0.59–0.89)	.001
55–64	1.91 (1.16–3.16)	.012	0.82 (0.68–1.00)	.049
Gender	Reference: Male		Reference: Male	
Female	0.93 (0.73–1.18)	.538	1.12 (1.00–1.26)	.061
Charlson comorbidity index	Reference: 1–2		Reference: 1–2	
3–4	1.84 (1.29–2.63)	.001	1.01 (0.86–1.18)	.923
≥5	1.95 (1.30–2.93)	.001	1.07 (0.86–1.32)	.553
Transplant organ	Reference: Kidney		Reference: Kidney	
Heart	7.62 (5.02–11.55)	<.001	1.74 (1.41–2.15)	<.001
Liver	4.87 (3.35–7.07)	<.001	1.44 (1.21–1.72)	<.001
Lung	13.01 (7.79–21.71)	<.001	3.19 (2.25–4.51)	<.001
Multiple organs	10.36 (6.98–15.39)	<.001	2.82 (2.22–3.58)	<.001
Transplant year	Reference: 2008		Reference: 2008	
2009	1.26 (0.87–1.82)	.222	0.89 (0.73–1.08)	.238
2010	1.01 (0.69–1.49)	.948	0.99 (0.82–1.21)	.938
2011	0.78 (0.52–1.15)	.202	0.98 (0.82–1.18)	.845
2012	1.12 (0.78–1.62)	.637	0.98 (0.82–1.18)	.830
2013	0.71 (0.46–1.08)	.708	0.83 (0.68–1.01)	.067
CDI occurrence	Reference: No CDI		Reference: No CDI	
Early CDI	1.92 (1.12–3.29)	.018	2.19 (1.45–3.31)	<.001
Late CDI	0.86 (0.38–1.94)	.717	4.36 (2.84–6.71)	<.001

NOTE. HR, hazard ratio; CI, confidence interval; OR, odds ratio; CDI, *Clostridium difficile* infection.
[a]By Cox regression.
[b]By logistic regression.

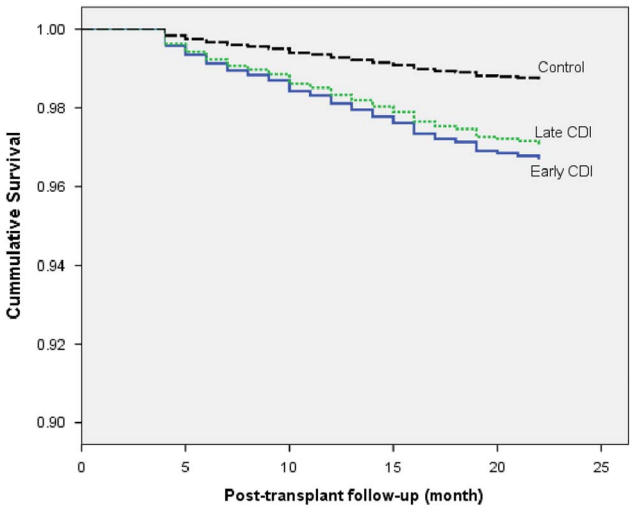

FIGURE 3. Survival curves of solid organ transplant recipients surviving posttransplant >90 days in early *Clostridium difficile* infection (CDI), late CDI, and control group by Cox regression.

known that severe complications are more common in SOT recipients with CDI.[1–3,24] Our study showed that the patients with CDI occurrence posttransplant had higher CCI scores. Although the predictive value of CCI for immediate and future mortality of SOT recipients differs in the literatures by transplanted organ received,[26–28] an increasing burden of comorbid conditions increases the risk for premature death or graft loss in SOT recipients.[28] In our study, kidney recipients composed fewer cases in the CDI groups than in the control group. Kidney recipients are known to have a lower mortality risk than other SOT recipients.[23]

Mortality was higher in patients with early CDI than in those with late CDI or in the control group, but it was not different between late CDI and controls. The perioperative period is of high risk for recipients.[1–3,11] During this period, CDI may be a marker of the severity of illness in the patients. Unmeasured confounding factors, rather than CDI, may be causing the increased mortality. When the patients survived >90 days posttransplant, the impact of late CDI on mortality was significant and was less likely due to perioperative complications. However, increased mortality might still be caused by confounding variables rather than CDI directly.

Our study demonstrated that SOT recipients with CDI had increased hospital utilization as measured by their readmissions and TOH. Donnelly et al[23] evaluated the health services utilization in 1,109 SOT recipients from the University HealthSystem Consortium clinical database. They found that CDI was

https://doi.org/10.1017/ice.2018.48 Published online by Cambridge University Press

TABLE 4. Impact of *Clostridium difficile* infection (CDI) on Mortality and Transplant Organ Complication-Related Hospitalization (TOH) in Solid Organ Transplant (SOT) Recipients Surviving >90 Days Posttransplant

	Risk for Death[a]		Risk for TOH[b]	
Characteristic	HR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age group, y	Reference: 18–34		Reference: 18–34	
35–44	1.77 (0.69–4.54)	.236	0.71 (0.57–0.89)	.003
45–54	1.09 (0.44–2.71)	.850	0.72 (0.59–0.88)	.001
55–64	2.53 (1.09–5.84)	.030	0.84 (0.69–1.02)	.077
Gender	Reference: Male		Reference: Male	
Female	0.74 (0.50–1.10)	.133	1.12 (0.99–1.26)	.067
Charlson comorbidity index	Reference: 1–2		Reference: 1–2	
3–4	1.59 (0.93–2.73)	.091	1.03 (0.87–1.21)	.752
≥5	1.27 (0.66–2.45)	.475	1.09 (0.88–1.35)	.429
Transplant organ	Reference: Kidney		Reference: Kidney	
Heart	3.45 (1.64–7.26)	.001	1.92 (1.55–2.38)	<.001
Liver	3.84 (2.16–6.82)	<.001	1.54 (1.29–1.83)	<.001
Lung	15.6 (7.91–30.6)	<.001	3.52 (2.46–5.04)	<.001
Multiple organs	11.3 (6.44–19.8)	<.001	3.10 (2.42–3.98)	<.001
Transplant year	Reference: 2008		Reference: 2008	
2009	0.95 (0.55–1.63)	.850	0.89 (0.73–1.09)	.245
2010	0.85 (0.49–1.48)	.555	1.01 (0.83–1.22)	.959
2011	0.52 (0.29–0.93)	.029	0.99 (0.82–1.20)	.931
2012	0.58 (0.32–1.05)	.073	1.01 (0.83–1.23)	.906
2013	0.59 (0.32–1.08)	.087	0.83 (0.68–1.02)	.070
CDI occurrence	Reference: No CDI		Reference: No CDI	
Early CDI	2.64 (1.22–5.71)	.014	2.24 (1.46–3.45)	<.001
Late CDI	2.33 (1.02–5.33)	.045	4.17 (2.71–6.42)	<.001

NOTE. HR, hazard ratio; CI, confidence interval; OR, odds ratio.
[a]By Cox regression.
[b]By logistic regression.

associated with increased 30-day readmissions, transplant organ complications, inpatient costs and length of stay.[23] A meta-analysis by Paudel et al[15] revealed a 19.7% CDI recurrence rate in SOT recipients. Several studies have reported that CDI increased the risk of transplant organ complications including graft failure.[1,14,29,30] Hence, our data are consistent with the observation that both the early and late CDI occurrence in SOT recipients can result in increased transplant organ complications and readmissions, leading to increased healthcare service utilization.

Our study has several limitations. First, our data include only individuals with employer-based insurance and their beneficiaries and may not be generalizable to the uninsured, underinsured, and those who rely solely on state and federal healthcare coverage like Medicaid. Second, all diagnoses were based on administrative claims data using ICD-9 codes. Coding errors leading to missed or erroneous diagnoses are possible. Similarly, CDI subjects were identified using administrative diagnostic codes not confirmed by laboratory data. Nevertheless, studies have shown good correlation between a *C. difficile* toxin assay and ICD-9-CM coding.[31,32] Third, the lack of laboratory and medication information in the inpatient MarketScan database prevented us from evaluating the role of improved diagnostic testing for *C. difficile* during the study or the use of antibiotics, gastric acid suppressants, or immunosuppressant agents on CDI occurrence. Fourth, the severity of comorbidities is associated with the outcomes of the SOT recipients. We were unable to analyze the severity of a disease because of the limitations of claims data. Our study might have underestimated the burden of comorbidities and therefore the impact on the outcomes of SOT recipients. Fifth, the organ donor information was unavailable from the database. Donor factors can significantly affect the outcomes of the grafts after transplant.[33,34] Finally, patients who died during follow-up had less opportunity to have CDI. We attempted to address this through our subset analyses.

Despite these limitations, our results suggest significant evidence that occurrence of CDI after SOT was associated with worse outcomes for at least 1 year posttransplant and with predicted higher mortality and healthcare service utilization for these patients. Further research to determine whether CDI is the direct cause of worse outcomes or a marker of other risk factors is needed. However, better CDI prevention and management strategies are important and could improve outcomes for SOT recipients.

https://doi.org/10.1017/ice.2018.48 Published online by Cambridge University Press

ACKNOWLEDGMENTS

We would like to acknowledge Truven Analytics for licensing the use of their MarketScan commercial claims and encounter data for this project. Additionally, we would like to thank Dr Benjamin Linas and Jake Roberts Morgan for their guidance regarding the use of the MarketScan database.

Financial support: No financial support was provided relevant to this article.

Potential conflicts of interest: All authors report no conflicts of interest relevant to this article.

Address correspondence to Ruihong Luo, 10833 Le Conte Ave, CHS 37-121, Los Angeles, California 90095 (RuihongLuo@mednet.ucla.edu).

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.48.

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https://doi.org/10.1017/ice.2018.48 Published online by Cambridge University Press