The Thesis Committee for You-Li Ling
Certifies that this is the approved version of the following thesis:

Outcomes and Expenditures of Clostridium Difficile Infection in Pediatric Solid Organ Transplant Recipients

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor: _____
Karen L. Rascati

_____
James P. Wilson

_____
Jamie C. Barner

Outcomes and Expenditures of Clostridium Difficile Infection in Pediatric Solid Organ Transplant Recipients

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You-Li Ling, B. S.

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Abstract

Outcomes and Expenditures of Clostridium Difficile Infection in Pediatric Solid Organ Transplant Recipients

You-Li Ling, M.S. Phr.

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Supervisor: Karen L. Rascati

The main purpose of this study was to assess outcomes (i.e., inpatient mortality, transplant failure or rejection, colectomy, and hospital length of stay) of clostridium difficile infection (CDI) and the association of expenditures (i.e., charges and costs) and CDI in pediatric solid organ transplant (SOT) recipients. Data from the 2000, 2003, 2006, and 2009 Kids' Inpatient Database (KID) files were used to identify events with SOT- related ICD-9-CM diagnosis codes.

Logistic regression was used to assess the association of CDI and dichotomous outcome variables, while log-linked gamma regression models were used to assess the association of CDI and continuous outcome variables. Methods accounting for the complex survey sample design of the KID were used when performing all statistical analyses.

The total number of pediatric SOT hospital events was 48,286. The overall prevalence of CDI for pediatric SOT hospitalizations was 1.76%. For SOT hospitalizations with CDI, inpatient mortality was 1.63%; the prevalence of transplant

failure or rejection events was 27.71%; the prevalence of a colectomy was 4.86%. The median hospital length of stay was seven days; the median charge and cost for each hospitalization was $48,409 and $17,412, respectively. The results showed that CDI was not significantly associated with inpatient mortality or transplant failure/ rejection in pediatric SOT hospitalizations. SOT patients with CDI were 2.6 times more likely to have a colectomy than SOT patient without CDI. The mean hospital length of stay (LOS) for a SOT admission with CDI was approximately 2 times the mean LOS for a SOT admission without CDI. The mean charges and the mean costs for a SOT admission with CDI was approximately 2 times that for a SOT admission without CDI.

In conclusion, CDI diagnoses were not significantly associated with higher inpatient mortality or transplant failure/ rejection for pediatric SOT hospitalizations. But CDI was significantly associated with a higher prevalence of a colectomy, longer hospital LOS, higher charges, and higher costs (all $p<0.05$). To avoid substantially higher expenditures and health care utilization, CDI in pediatric SOT recipients should be prevented when possible and promptly diagnosed and treated when it occurs.

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Chapter 1: Literature Review

1.1 Introduction

Diarrhea is a frequent complication following solid organ transplant (SOT) and can cause dehydration, malnutrition, skin breakdown, or even graft loss and death. Clostridium difficilie is one of the most concerning bacterial etiologies of diarrhea among SOT recipients because SOT recipients are antibiotic users, have vulnerable defense mechanisms, and have prolonged hospital stays. The increasing incidence of clostridium difficile infection (CDI) in the pediatric population has been reported recently. However, little has been reported in the literature regarding costs and outcomes in pediatric SOT recipients with CDI. The purpose of this proposed study is to evaluate the charges, costs and outcomes of hospitalized pediatric SOT recipients with CDI and determine whether CDI is significantly associated with higher charges, costs, and worse outcomes using the Kids' Inpatient Database (KID) from the Healthcare Cost and Utilization Project (HCUP).

1.2 Clostridium difficile infections

Clostridium difficile infection (CDI) accounts for the most common cause of antibiotic-associated diarrhea and colitis and annual costs are estimated to be between 1.1 and 3.2 billion dollars in the United States health care system.[1,2] Clostridium difficile is a gram-positive, spore-forming anaerobic bacillus and is acquired from the environment and spread via the fecal-oral route.[3] The process of CDI includes a disturbance of the normal gut flora, colonization of a exotoxin-producing strain of clostridium difficile, and mucosal damage due to toxin A and toxin B released by these bacillus.[4] The administration of broad-spectrum antibiotics, such as fluoroquinolones, cephalosporins, clindamycin, sulfonamides, tetracyclines, and

penicillins, can alter the normal colonic microflora and lead to CDI. CDI commonly occurs in hospitals and long-term care facilities.[5,6]

1.2.1 Clinical Presentation

The clinical presentation of clostridium difficile infections (CDIs) varies widely from asymptomatic intestinal colonization to diarrhea, pseudomembranous colitis, colonic perforation, toxic megacolon and death.[6,7] Symptoms include diarrhea, low abdominal pain and distention, fever, nausea, and dehydration. [7]

1.2.2 Treatment

According to the guidelines for diagnosis, treatment, and prevention of clostridium difficile infection, CDI severity is categorized into following four categories:

1. Mild disease: CDI with diarrhea as the only symptom;
2. Moderate disease: CDI with diarrhea with other moderate symptoms that are not included in the severe or the complicated disease;
3. Severe disease: CDI with serum albumin < 3 g/dl and either of the followings: 1) a white blood cell (WBC) count ≧15,000 cells/mm^3 or 2) abdominal tenderness without criteria of complicated disease;
4. Complicated disease: CDI with at least one of the following signs of symptoms: admission to intensive care unit, hypotension with or without required use of vasopressors, fever ≥ 38.5 °C, ileus, or significant abdominal distention, mental status changes, WBC ≥ 35,000 cells/mm^3 or <2,000 cells/mm^3, serum lactate levels >2.2 mmol/l, or any evidence of end organ failure.

Discontinuing the antibiotic that caused the CDI is the first step of treatment. Depending on the severity of the CDI, the second step of treatment may include medication and/or surgery.[8]

Medications:

Antibiotics used to treat C. difficile include metronidazole, fidaxomicin, and vancomycin. Metronidazole is usually used in patients with mild to moderate CDI. Fidaxomicin serves as an alternate antibiotic for mild to moderate CDI. For moderate to severe CDI and complicated CDI, vancomycin is recommended.[8]

Surgery:

CDI may progress despite appropriate medication therapy. If patients have severe pain, organ failure or inflammation of the lining of the abdominal wall, the performance of surgery to remove a diseased portion of the intestine may improve the outcome.[8]

Treatment of recurrent CDI:

To treat the first recurrence of CDI, the same regimen as that of the initial episode may be prescribed. For the second recurrence, a pulsed vancomycin regimen is recommended. A fecal microbiota transplant should be considered if the patient has more than three recurrences of CDI.

1.2.3 Incidence, prevalence, morbidity, and mortality of CDI

The epidemiological data have shown a marked increase in the incidence of CDI across North America over the past decade.[9-13] The rate of hospital discharge cases with CDI-associated diseases more than doubled (from about 150,000 to about 300,000 cases) during the period from 2001 to 2005.[14] Moreover, Miller et al. found that CDI has replaced methicillin-resistant *Staphylococcus aureus* as the leading

etiology of healthcare facility-associated infections in the southeastern United States in 2008.[15] In addition, the rate of CDI-related mortality increased from 5.7 per million population in 1999 to 23.7 per million in 2004 in the United States.[16] Coincidently, the recent emergence of a hypervirulent toxigenic bacterial strain of C. difficile—designated North American pulsed-field gel electrophoresis type 1 (BI/NAP1/027)—has caused increases in both hospitalizations and mortality rates since 2000.[13,17,18] Special features of this strain include: 16 times more production of toxins A and 23 times more production of toxin B than other strains, fluoroquinolone resistance, and the production of a binary toxin.[17,19]

1.2.4 Risk factors for Clostridium difficile infections

Antibiotic use was established as the main factor associated with clostridium difficile infections.[20,21] Studies have shown that broad-spectrum antimicrobial agents are most likely to lead to CDI.[22,23] But several studies also indicated that the use of fluoroquinolones is a predominant risk factor for CDI.[13,24] The risk of CDI also increases for patients receiving multiple antibiotic treatments.[20] Other risk factors for CDI include admission to an intensive care unit, age greater than 65 years, immunosuppression, multiple and severe underlying illnesses, placement of a nasogastric tube, prolonged hospitalization, a recent surgical procedure, residing in a nursing home, sharing a hospital room with a patient having CDI, and gastric acid suppression.[6,25-28]

1.3 Clostridium difficile infections in pediatric populations

1.3.1 Prevalence

Several studies have demonstrated an increasing CDI trend in pediatric

populations in the last decade. [29-32] In recent surveillance, Clostridium difficile has also been recognized as an important prevalent diarrheal pathogen in children.[29-33] Two studies conducted retrospective analyses using national-level databases. The study conducted by Kim et al. used the Pediatric Health Information System (PHIS), which contains inpatient data from more than 40 not-for-profit, freestanding, tertiary care children's hospitals in the United States.[30] A total of 4,895 children with CDI from 22 tertiary care pediatric hospitals were included. The study showed a 53% increase in the annual incidence of CDI from 2.6 cases/1,000 admissions in 2001 to 4.0 cases /1,000 admissions in 2006. Zilberberg et al. also revealed a crude 9.0% annual increased rate of pediatric CDI-related hospitalization from 7.2 to 12.8 per 10,000 hospital admissions by exploring the Kids' Inpatient Database (KID), which included data from more than 2,500 hospitals from 22 states in 1997 and from more than 3,700 hospitals from 38 states in 2006.[29]

Younger age groups tend to have a higher incidence rate of CDI.[29] Zilberberg et al. evaluated data from KID and detected that age groups 1-4 years and 5-9 years had the highest and second highest prevalence of CDI-related hospitalizations (approximately 45 and 35 hospitalizations per 10,000 admissions, respectively) compared to age groups <1 year, 10-14 years, and 15-17 years (approximately 32, 27, and 19 hospitalizations per 10,000 admissions, respectively). Younger age groups also have had higher increasing rates in CDI over time.[30] Kim et al. stratified their results according to age and found the rates of hospital admissions due to CDI increased 85% in children 1-5 years of age, while the group of children aged 15-17 increased 50% during the same time period, 2001-2006.

As for the neonates and infants younger than 1 year, the trend of CDI is unclear. In the PHIS study from 2001 to 2006, Kim et al. found no increasing trend in

CDI rates among hospitalized infants.[30] In contrast, by evaluating data from the National Inpatient Sample database, an increasing trend in infant CDI hospitalization prevalence (from 2.8 to 5.1 cases per 10,000 hospitalizations between 2000 and 2005) was demonstrated by Zilberberg et al.[34] However, since previous research indicated that C. difficile was normal common flora and nonpathogenic among infants younger than 1 year, true morbidity or asymptomatic carriage cannot be determined.[35-43]

The number of community-acquired pediatric CDI cases also increased in the past years. Many of these cases were not exposed to the traditional risk factor of recent antimicrobial drugs use.[32,44,45] Benson et al. conducted a retrospective cohort study at the Children's National Medical Center in Washington, D.C. and revealed a significant increase of pediatric community-acquired CDI cases in the outpatient setting. The incidence rate of community-acquired CDI increased by 2.5 fold (from 1.2 cases per 1,000 visits in 2001 to 2.5 cases per 1,000 visits in 2006); 43% of these children with CDI lacked a history of recent antibiotic use. A retrospective cohort study conducted by Sandora et al. also showed that 25% of 151 CDI episodes among the 199 positive tests in patients with diarrhea were community-acquired and 65% of patients with community-acquired CDI did not receive any antibiotics.[32] Khanna et al. reported that 75% of the CDI cases in their population-based cohort study from 1991 to 2009 were community-acquired; and 16.3% of these cases had no preceding antibiotic exposure.

The emergence of a more-virulent epidemic strain known as North American Pulsed Field type 1 (BI/NAP1/027) is likely associated with the increasing CDI prevalence in the pediatric population. Studies have revealed a 19.4% prevalence of the BI/NAP1/027 strain in pediatric patients with CDI, and this strain resulted in severe outcomes.[46,47]

1.3.2 Risk factors for CDI in children

The use of antibiotics, exposure to C. difficile in healthcare settings, and certain co-morbid conditions were associated with CDI in pediatric populations. Alteration of intestinal microflora due to antibiotics has been established as an important risk factor in adult populations. Similar results have been found in pediatric populations. Sandora et al. reported 61% and 15% incidence rates of CDI when children received non-quinolone and quinolone antibiotics in the previous 4 weeks, respectively. Co-morbid conditions significantly associated with CDI include: immunosuppression, inflammatory bowel disease, solid tumors, solid organ transplantation, cystic fibrosis, and the presence of a gastrostomy or jejunostomy tube.[32,48-50] By using national-level data, Kim et al. also detected 67% of patients in their study had underlying neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic, immunologic, metabolic, malignancy, or congenital disorders.[30]

1.4 Clostridium difficile infections in solid organ transplant (SOT) recipients

1.4.1 Prevalence in SOT Patients

Diarrhea is a frequently observed complication following solid organ transplant (SOT).[51-54] This complication can lead to dehydration, malnutrition, skin breakdown, alterations in immunosuppressant levels, or even graft loss and death.[53,55-57] The most common causes of diarrhea among SOT recipients include gastrointestinal infections and adverse effects due to immunosuppressant medications.[58,59] In SOT recipients, one of the most concerning bacterial etiologies of diarrhea is Clostridium difficile.[54,60,61] Several studies also revealed a higher incidence of CDI in SOT

recipients than in the general population of hospitalized patients.[57,62,63] Riddle and Dubberke summarized the reported incidence of CDI among different organ recipient populations. These included an incidence of 3-7% CDI in liver, 3.5-16% in kidney, 1.5-7.8% in pancreas-kidney, 9% in intestinal, 15% in heart, and 7-31% in lung recipients.[62] Studies indicated that the highest incidence of CDI in SOT recipients occurs within 3 months after transplantation, but that late-onset CDI could be detected from months to years after transplantation.[57,64,65]

The most common clinical manifestation of CDI in SOT recipients is diarrhea, which occurs in 86-97% of these patients. Other symptoms such as fever (11-67%), abdominal pain (7-50%), and intestinal obstruction (up to 23%), had been reported as well.[65-68]

1.4.2 Risk factors for CDI in SOT recipients

Several studies have established risk factors for CDI in SOT recipients. These included advanced age, underlying severe co-morbidities, and immune system dysfunction due to receiving monoclonal antibody therapy to prevent chronic rejection and hypogammaglobulinemia (low levels of serum immunoglobulin).[65,66,68] The prevalence of hypogammaglobulinemia in lung, heart, and liver transplantation is common.[69-71] Studies also indicated that the incidence of CDI was five times higher in SOT recipients with hypogammaglobulinemia.[68] In addition, SOT recipients are at higher risk for CDI because of perioperative antibiotic use and prolonged hospital stays, which are common risk factors in general populations for CDI.

1.4.3 Outcomes of SOT recipients with CDI

For SOT patients with CDI, worse outcomes, increased morbidity and more

complications were supported by several studies. By using a nationwide database, Pant et al. demonstrated that SOT recipients with CDI had significantly higher rates of in-hospital mortality (7.4% vs. 2.4%), length of stay in hospital (median 9 days vs. 4 days), charges (median $53,808 vs. $31,488), and organ complications (38.1% vs. 33.9%), compared to those SOT recipients without CDI.[72] Dallal et al. reviewed 2,334 hospitalized patients with C. difficile colitis from January 1989 to December 2000 and found that 13% of SOT recipients with CDI and 8% of immunocompetent patients developed fulminant colitis (a severe form of uncomplicated acute colitis). Among those patients who received a colectomy, 31% of them were SOT recipients. Their study also indicated that lung transplant patients were 46 times more likely to have C. difficile colitis than general hospitalized patients.[6] Boutros et al. evaluated 1,331 SOT recipients in one institution. Their research showed that 165 patients out of 1,331 SOT recipients developed Clostridium difficile-associated diarrhea. Of these 165 patients, a 15.8% incidence of complicated clostridium difficile colitis was found. Compared with previous studies, the rate of complicated clostridium difficile colitis in SOT recipients was 2 times higher than the general population.[73] However, Gellad et al. found no association with worse outcomes (mortality, intensive care unit admission, or urgent colectomy) in patients with CDI who had a SOT (N=80) versus patients with CDI but did not have a SOT (N=86).[74]

1.5 Clostridium difficile infections in pediatric solid organ transplant recipients

The increased trend of CDI prevalence among pediatric populations is relatively recent; thus, there are only a few studies that report relative incidence and outcomes in pediatric SOT recipients with CDI. One study performed a retrospective chart

review of a children's hospital and demonstrated a clostridium difficile colitis incidence of 5.4% in pediatric patients with lung transplantation. The overall survival rate was 75% among pediatric SOT recipients with CDI.[75] Blanche et al. studied pediatric renal transplant recipients' complications, and found that bacterial infection is one of the major causes of post-transplant morbidity and CDI was the major bacterial infection in pediatric renal transplant recipients≦5 years.[76]

1.6 Use of the Kids' Inpatient Database (KID) in Health Outcomes Studies

The Kids' Inpatient Database (KID) is part of the Healthcare Cost and Utilization Project (HCUP) and the data have been collected every three years since 1997. The KID contains information about hospital utilization, outcomes, and charges for the hospitalized pediatric population. Several studies have used the KID to analyze economic burden of disease, resource utilization patterns, and health outcomes.

Hasegawa et al. used the KID to examine trends in pediatric asthma hospitalizations, in-hospital mortality, mechanical ventilation use, and hospital charges between 2000 and 2009.[77] Kourtis et al. described hospital use patterns of an HIV-infected pediatric population using the KID in 2000.[78] A study regarding epidemiology, outcomes, and costs of invasive aspergillosis in immunocompromised children conducted by Zaoutis et al. used the KID in 2000 as well.[79]

Several studies have demonstrated that the large sample size from the KID is a good resource for making nationwide estimations. Researchers can use this database to describe hospitalization use patterns, health outcomes, charges, and cost attributable to a particular disease.

One limitation to the use of this database is that for patients with multiple admissions per year, patient-level analysis is not possible because there is no uniform

patient identifier. The KID only provides discharge-level records. This means that individual patients with multiple hospitalizations in a single year may have multiple records in the KID, each under a different ID. Readmissions for individual patients cannot be identified.

1.7 Study rationale

SOT recipients are at higher risk of getting CDI because they have impaired defense mechanisms, are antibiotic users, and have prolonged hospital stays. Although several studies have shown an increasing CDI prevalence in pediatric populations recently, based on our literature search, few studies reported the costs and outcomes in pediatric SOT recipients with CDI. There were several studies that reported worse outcomes, higher costs, and more severe complications because of CDI in adult SOT recipients.[6,72,80] However, studies of outcomes in pediatric populations were scarce. Since pediatric and adult SOT recipients differ in many aspects— etiology of organ failure, complexities of surgery, perioperative antibiotic use, immunologic maturation, response to immunosuppressive medications, comorbid conditions, and post-transplant complications and infections—these factors may result in different outcomes, severity in complications, and costs in pediatric SOT recipients with CDI as compared to their adult counterparts.[81-87] The findings of this study will contribute to the literature by providing information on the evaluation of utilization, costs, and outcomes in pediatric SOT recipients with CDI. By using the nationwide Kids' Inpatient Database (KID), we can reduce the limitations (e.g., regarding certain types of immunosuppression regimens, and reduced generalizability) of using data from a single center. This study will also help to identify factors associated with worse outcomes, complications, mortality, and higher costs.

1.8 Objectives and hypotheses

The objectives and related hypotheses of this study are:

1. To describe the demographic characteristics based on hospital admissions of pediatric SOT recipients with respect to age, gender, race, median household income for patient's ZIP code, payer type, and comorbid condition.
2. To describe the hospital-related characteristics of pediatric SOT admissions with respect to hospital size, geographic regions, teaching status, and type (e.g. children's general or specialty hospital).
3. To describe CDI prevalence based on hospital admissions among pediatric patient with SOT.
4. To describe the outcomes regarding transplant failure or rejection events, hospital mortality, colectomies, and hospital length of stay among pediatric SOT patients.
5. To estimate the charges (the amount that hospitals billed for services) and costs (charges multiplied by cost-to-charge ratios) of hospitalizations for pediatric patients with SOT.
6. To determine if the presence of CDI is significantly associated with hospital mortality while controlling for other covariates (i.e., demographic characteristics, comorbid condition, type of organ transplant, and hospital-related characteristics).

    H_1: There is a significant difference in the likelihood of inpatient mortality between pediatric SOT patient with CDI and pediatric SOT patients without CDI while controlling for other covariates (i.e.,

demographic characteristics, comorbid condition, type of organ transplant, and hospital-related characteristics).

7. To determine if the presence of CDI is significantly associated with transplant failures or rejections while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

   H_2: There is a significant difference in the likelihood of having a transplant failure or rejection event during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

8. To determine if the presence of CDI is significantly associated with having a colectomy while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

   H_3: There is a significant difference in the likelihood of having a colectomy during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

9. To determine if the presence of CDI is significantly associated with hospital length of stay (LOS) for pediatric SOT patients while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of

organ transplant, and hospital-related characteristics).

H_4: There is a significant difference in hospital length of stay (LOS) between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

10. To determine if the presence of CDI is significantly associated with charges (the amount that hospitals billed for services) for SOT hospitalizations while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

    H_5: There is a significant difference in hospital charges between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

11. To determine if the presence of CDI is significantly associated with costs (charges multiplied by cost-to-charge ratios) for SOT hospitalizations while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

    H_6: There is a significant difference in hospital costs between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).

Chapter 2: Methods

2.1 Study design and data source

This study was a retrospective database analysis. Discharge-level data was extracted from the Kids Inpatient Database (KID) for the years 2000, 2003, 2006, and 2009. The KID is within the Healthcare Cost and Utilization Project (HCUP), which is administered by the Agency for Healthcare Research and Quality (Rockville, MD, USA)[88]. The KID was specifically designed to enable analyses of healthcare utilization, access to services, charge information, and outcomes for the inpatient pediatric population across the United States. Pediatric discharges are stratified by uncomplicated in-hospital birth, complicated in-hospital birth, and all other pediatric cases. The discharges are sorted by state, hospital, diagnostic-related group (DRG), and a random number within each DRG in order to obtain an accurate representation of each hospital's pediatric admissions. By using systematic random sampling, 80% of pediatric hospital admissions and complicated in-hospital births and 10% of uncomplicated in-hospital births were selected. The KID contains data from 2,500 to 4,100 hospitals, and 2 to 3 million pediatric inpatient discharge records per year. Data sources were derived from 27 states in 2000, 36 states in 2003, 38 states in 2006, and 44 states in 2009. Discharge weights were developed using stratum in proportion to the number of American Hospital Association (AHA) newborns for newborn discharges and in proportion to the total number of non-newborn AHA discharges for non-newborn discharges. In order to get accurate national estimates, these discharge weights must be used.

2.2 Institutional Review Board Approval

An Institutional Review Board (IRB) application was submitted to the

University of Texas at Austin IRB Board (IRB protocol number: 2013-09-0045). A waiver was obtained from the University of Texas at Austin IRB Board because all data used in this study from the KID data set were de-identified.

2.3 Data Set

Three types of data files were used in this research. Two were from data files in the KID: Inpatient Core File and Hospital File. The third data file was the Hospital-specific Cost-to-Charge Ratio Files, which was from The HCUP Supplemental Files.

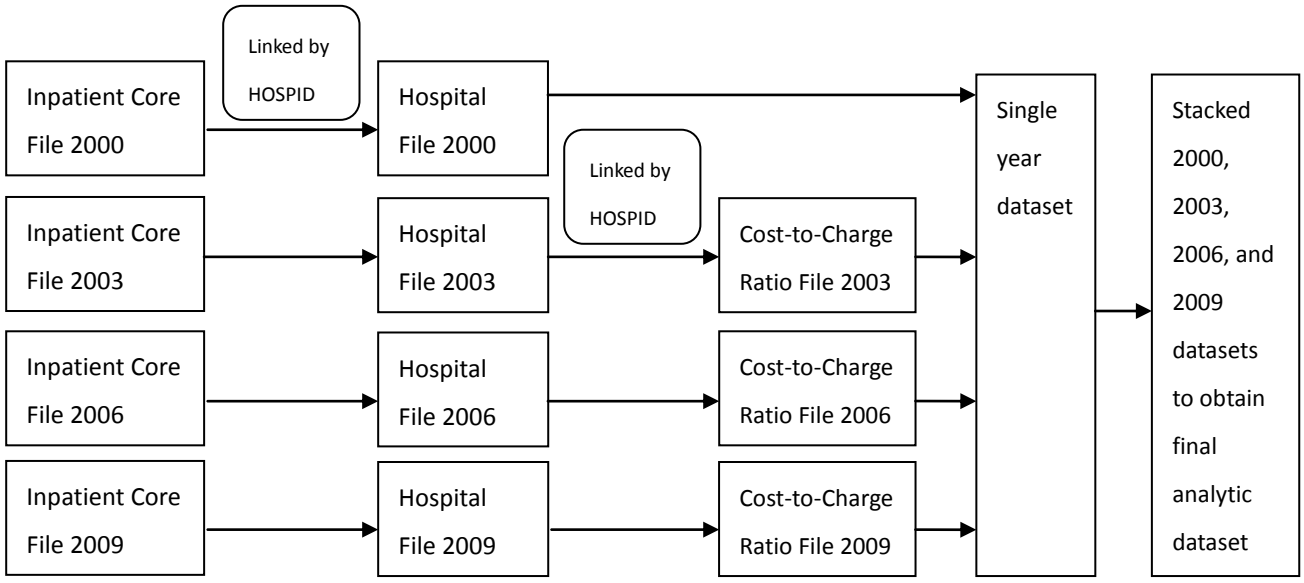
(1) Inpatient Core File: This file contains patient demographics, diagnosis and procedure information, hospital length of stay, median household income for the patient's zip code, payment information, and discharge weight;

(2) Hospital File: This file contains hospital characteristics such as teaching status, location, size, children's general or specialty hospital. The classification of the hospital's teaching status, size, and location are based on the American Hospital Association (AHA) Annual Survey of Hospitals. Children's general or specialty hospital is designated according to the information from the National Association of Children's Hospitals and Related Institutions (NACHRI) with the following categories: 1) not identified as a children's hospital, 2) children's general hospital, 3) children's specialty hospital, and 4) children's unit in a general hospital;

(3) Cost-to-Charge Ratio Files: These files are from the HCUP Supplemental Files. From charge information, we can get the amount that hospitals billed for services. However, charges may differ from actual costs of hospital services or the specific amounts that hospital received in payment. In order to convert hospital charges to estimated actual costs, the HCUP *hospital-specific* Cost-to-Charge Ratio Files can be used for its corresponding databases.

Because the variables required for this study were contained in the three different data files above, these various files were combined to get the analytical dataset. Data on hospitalization events for pediatric solid organ transplantation patients were extracted in the full year Inpatient Core Files. The HCUP hospital identifier (HOSPID) was used to link the Inpatient Core Files to the full-year corresponding Hospital File. The combination of the Inpatient Core File and the Hospital Files was linked to the corresponding full-year Cost-to-Charge Ratio File by using the HCUP hospital identifier (HOSPID) again. The combination of the Inpatient Core File, Hospital File, and Cost-to-Charge Ratio File formed a single year dataset. The combination of these 3 files was performed for the 2003, 2006, and 2009 files. However, since the corresponding Cost-to-Charge Ratio Files for the KID database were not available in 2000, the combination data file for 2000 was a link of 2 files – the Inpatient Core File and Hospital File. Therefore, we only included cost data in 2003, 2006, and 2009. The datasets in 2000, 2003, 2006, and 2009 were stacked to obtain the final analytical dataset. The linkage process for various datasets is shown in Figure 1.

Figure 1.1: Linkage method to create final analytic dataset



2.4 Study population

All entries with SOT diagnoses or procedures codes were extracted using International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) codes. These included patients with heart (diagnosis codes: V42.1, 996.83; procedure codes: 37.5, 37.51), liver (diagnosis codes:V42.7, 996.82; procedure codes: 50.5, 50.59), lung (diagnosis codes:V42.6, 996.84; procedure codes: 33.5, 33.50, 33.51, 33.52), kidney (diagnosis codes:V42.0, 996.81; procedure codes: 55.6, 55.69), pancreas (diagnosis codes:V42.83, 996.86; procedure codes: 52.8, 52.80-52.86), and intestine (diagnosis codes:V42.84, 996.87; procedure codes: 46.97) transplantation. Hospitalization events for children between 1 to 17 years old with an SOT diagnosis were eligible for this study. Although some previous studies revealed high rate of CDI-related hospitalization with infants younger than 1 year old[29,89], several studies also reported that clostridium difficile was a normal common flora and nonpathogenic among this population and true morbidity or asymptomatic carriage cannot be determined. [13,35-43,90,91] Therefore, we excluded the events with infants younger than 1 year old in our study.

2.5 Study variables

2.5.1 Outcomes of Interest

(1) In-hospital mortality was a dichotomous categorical variable with "did not die during hospitalization (coded 0)" versus "died during hospitalization (coded 1)." This value was obtained from Inpatient Core Files in the KID.

(2) Hospital length of stay (LOS) was a continuous variable, which indicated length of days of hospitalization. This information was obtained from Inpatient Core Files in the KID.

(3) Hospitalization charge was a continuous variable, which was the amount that a hospital billed for services. This information was obtained from Inpatient Core Files in the KID. All hospitalization charges were adjusted to 2009 dollars based on the Medical Care Consumer Price Index.[92]

(4) Hospitalization cost was a continuous variable and was generated from the corresponding KID Cost-to-Charge Ratio Files in the HCUP Supplemental Files. All hospitalization costs were adjusted to 2009 dollars based on the Medical Care Consumer Price Index.[92]

(5) Transplant failure or rejection was operationalized as having a transplant failure or rejection event during the hospitalization with any of the following ICD-9-CM diagnoses codes: 996.81-996.84, 996.86, and 996.87. This dependent variable was a dichotomous categorical variable with "no transplant failure or rejection (coded 0)" versus "a transplant failure or rejection event (coded 1)." This value was generated from Inpatient Core Files in the KID.

(6) Colectomy was operationalized as having any of the following colectomy ICD-9-CM procedure codes: 45.7, 45.71-45.76, 45.79, and 45.8 during hospitalization.

This dependent variable was a dichotomous categorical variable with "no colectomy (coded 0)" versus "having a colectomy (coded 1)." This value was generated from Inpatient Core Files in the KID.

2.5.2 Independent variables

Presence of CDI was the primary independent variable in this study. It was a dichotomous variable and its operational definition was the occurrence of a diagnosis of CDI (ICD-9-CM code 008.45) in any listed hospital diagnosis (Maximum diagnoses allowed per hospitalization: 15 diagnoses for 2000, 2003, and 2006 data; 25 diagnoses for 2009 data). This variable was dichotomous with no diagnosis of CDI (coded 0) versus a diagnosis of CDI (coded 1).

2.5.3 Covariates

2.5.3.1 Patient Characteristics

(1) Demographic variables: The demographic variables identified in the KID data set were: age, gender, race, region, payer type, and median household income for the patient's zip code.

Age was assigned at the time of admission and was treated as ordinal variable with four categories: 1-4 (coded 1), 5-9 (coded 2), 10-14 (coded 3), and 15-17 (coded 4) because a previous study reported that age groups 1-4 years and 5-9 years had the highest and second highest prevalence of CDI-related hospitalizations (approximately 45 and 35 hospitalizations per 10,000 admissions, respectively) compared to age groups <1 year, 10-14 years, and 15-17 years (approximately 32, 27, and 19 hospitalizations per 10,000 admissions, respectively).[29]

Gender was a dichotomous categorical variable with male (coded 0) versus female

(coded 1).

Race was a categorical variable with following categories: white (coded 1), black (coded 2), Hispanic (coded 3), Asian or Pacific Islander, Native American, and other (coded 4).

Payer type was a categorical variable which provided information about the expected primary payer. This variable had six categories: Medicare (coded 1), Medicaid (coded 2), private insurance—includes Blue Cross, commercial carriers, and private HMOs and PPOs (coded 3), self-pay (coded 4), and other (coded 5; includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs).

Household income was an ordinal variable which will provide a quartile classification of the estimated median household income for the patient's ZIP code. The 4 categories that indicated ordinal levels of household income were: from the poorest (Quartile 1) to the wealthiest (Quartile 4). The classification ranges of these quartile values varied by years. Table 2.1 describes the dollar ranges among each category by different years.

Table 2.1 The dollar ranges represented by each categories in each year

Year	Quartile 1	Quartile 2	Quartile 3	Quartile 4
2000	1 - 24,999	25,000 - 34,999	35,000 - 44,999	45,000+
2003	1 - 35,999	36,000 - 44,999	45,000 - 59,999	60,000+
2006	1 - 37,999	38,000 - 46,999	47,000 - 61,999	62,000+
2009	1 - 39,999	40,000 - 49,999	50,000 - 65,999	66,000+

(2) Comorbid conditions:

Previous studies have shown that additional medical comorbidities were associated with CDI in pediatric population.[30-32] The comorbid conditions might lead to worse outcomes in SOT recipients.[72,93-95] Studies have also shown that comorbid conditions could serve as a predictor of healthcare costs.[96,97] To determine the association between additional comorbid conditions and outcomes of pediatric SOT recipients, common infections in pediatric SOT recipients: urinary tract infection (UTI), pneumonia, and cytomegalovirus (CMV) were identified.[98-106] Since post-transplant lymphoproliferative disease (PTLD) has been recognized as a common post-transplant malignancy, the presence of having PTLD was treated as a covariate as well.[83] The Charlson Comorbidity Index (Deyo modification) was used as the tool to quantify the impact of different comorbidities on overall outcomes, charges, and costs. CCI is a common comorbidity adjustment measure based on clinical diagnoses.[107,108] The index includes 19 comorbid conditions with assigned weighted scores.[108] Table 2.3 describes the Charlson comorbidity conditions, the ICD-9-CM codes categorized in those comorbid conditions, and the corresponding weights. The validation of its use in administrative claims databases to predict health outcomes and control for confounding factors has been established.[97,107,108] Rhee et al. developed and validated a multispecialty risk index for pediatric surgical patients to adjust comorbidities.[109] This comorbidity index had superior mortality prediction than the CCI because it was developed specifically for pediatric surgical patients. However, since this pediatric surgery-specific index has not been fully tested, further external validation is required. Therefore, CCI was selected as the measure to adjust for additional comorbid conditions in this study. The followings are the operational definitions of specific comorbid condition variables of interest in this study:

Urinary tract infection (UTI) was operationalized as the occurrence of a hospitalization with a diagnosis of UTI (ICD-9-CM code 590.X) in any listed diagnosis. This variable was dichotomous with no diagnosis of UTI (coded 0) versus a diagnosis of UTI (coded 1).

Pneumonia was operationalized as the occurrence of a hospitalization with a diagnosis of pneumonia (ICD-9-CM code 480-487) in any listed diagnosis. This variable was dichotomous with no diagnosis of pneumonia (coded 0) versus a diagnosis of pneumonia (coded 1).

Cytomegalovirus (CMV) was operationalized as the occurrence of the hospitalization with a diagnosis of CMV infection (ICD-9-CM code 078.5) in any listed diagnosis. This variable was dichotomous with no diagnosis of CMV infection (coded 0) versus a diagnosis of CMV infection (coded 1).

Post-transplant lymphoproliferative disease (PTLD) was operationalized as pediatric SOT recipients who had the occurrence of hospitalization with a probable diagnosis of PTLD in any listed diagnosis. Since ICD-9-CM codes of PTLD (238.77) was implemented in 2009, we used PTLD ICD-9-CM codes based on the classification from the Kasiske et al. study and identification of PTLD from WHO in 2000, 2003, 2006, and 2009 dataset and ICD-9-CM code of PTLD (238.77) in 2009 dataset.[110,111] All ICD-9-CM codes used to identify PTLD are listed in Table 2.2 This variable was dichotomous with no diagnosis of PTLD (coded 0) versus a diagnosis of PTLD (coded 1).

Table 2.2 International Classification of Diseases 9th Revision, Clinical Modification (ICD-9-CM) codes used to identify post-transplant lymphoproliferative disorders (PTLD)

Diagnosis	ICD-9 CM Codes
Malignant neoplasm associated with transplanted organ	199.2
Reticulosarcoma	200.0X
Lymphosarcoma	200.1X
Burkitt's tumor or lymphoma	200.2X
Primary central nervous system lymphoma	200.5X
Anaplastic large cell lymphoma	200.6X
Large cell lymphoma	200.7X
Other named lymphoma variants	200.8X
Hodgkin's paragranuloma	201.0X
Hodgkin's granuloma	201.1X
Hodgkin's sarcoma	201.2X
Lymphocytic-histiocytic predominance	201.4X
Nodular sclerosis	201.5X
Mixed cellularity	201.6X
Lymphocytic depletion	201.7X
Hodgkin's disease, unspecified	201.9X
Nodular lymphoma	202.0X
Peripheral T-cell lymphoma	202.7X
Other lymphomas	202.8X
Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue	202.9X

Charlson comorbidity index score (CCI) was treated as a ordinal variable with an index score of 0 (coded 1), 1 (coded 2), and ≧2 (coded 3) instead of using CCI as a continuous variable because a previous study demonstrated that the majority of pediatric patients had a CCI score of between 0 and 2, while only a small portion had CCI scores ≧3.[112]

Table 2.3 Charlson Comorbidity Index (Deyo modification) with corresponding ICD-9-CM codes and weighted scores

Comorbid Condition	ICD-9 CM Codes	Charlson Score
Myocardial Infarction	410 – 410.9	1
Congestive Heart Failure	428 – 428.9	1
Peripheral Vascular Disease	433.9, 441 – 441.9, 785.4, V43.4	1
Cerebrovascular Disease	430 – 438	1
Dementia	290 – 290.9	1
Chronic Pulmonary Disease	490 – 496, 500 – 505, 506.4	1
Rheumatologic Disease	710.0, 710.1, 710.4, 714.0 – 714.2, 714.81, 725	1
Peptic Ulcer Disease	531 – 534.9	1
Mild Liver Disease	571.2, 571.5, 571.6, 571.4 – 571.49	1
Diabetes	250 – 250.3, 250.7	1
Diabetes with Chronic Complications	250.4 – 250.6	2
Hemiplegia or Paraplegia	344.1, 342 – 342.9	2
Renal Disease	582 – 582.9, 583 – 583.7, 585, 586, 588 – 588.9	2
Moderate or Severe Liver Disease	572.2 – 572.8	3
AIDS	042 – 044.9	6

(3) Type of organ transplantation

Type of organ transplantation was treated as a categorical variable with the following categories: heart (ICD-9-CM codes: V42.1, 996.83, 37.5, and 37.51), liver (V42.7, 996.82, 50.5, and 50.59), lung (V42.6, 996.84, 33.5, 33.50, 33.51, and 33.52), kidney (V42.0, 996.81, 55.6, and 55.69), pancreas (V42.83, 996.86, 52.8, and 52.80-52.86), intestine (V42.84, 996.87, and 46.97) transplantation.

2.5.3.2 Hospital Characteristics

Hospital size was an ordinal variable and was assigned to 3 categories: small, medium, and large based on the American Hospital Association (AHA) Annual Survey of Hospitals (Small—under 100 beds, medium—100-399 beds, and large—400+ beds).

Hospital geographic region was a categorical variable and was assigned to the following categories based on the AHA Annual Survey of Hospitals: Northeast, Midwest, South, and West.

Teaching Status was a dichotomous variable and was assigned to non-teaching hospital (coded 0) and teaching hospital (coded 1) based on the AHA Annual Survey of Hospitals.

Children's general or specialty hospital was a categorical variable and was assigned to the following categories based on the National Association of Children's Hospitals and Related Institutions (NACHRI): 1) not identified as a children's hospital, 2) children's general or specialty hospital, and 3) children's unit in a general hospital.

2.6 Statistical analyses

Descriptive statistics were used to summarize patient and hospital characteristics of pediatric solid organ transplant admissions, charges, costs, and outcomes. Medians, means and standard errors were used to describe continuous variables while frequencies and percentages were used to describe categorical variables. Logistic regressions were performed to examine factors statistically significantly associated with the following dichotomous variables: in-hospital mortality, transplantation failure/rejection, and colectomy while controlling for other covariates of interest. Gamma regressions with log link were used to determine whether having a diagnosis of CDI was statistically significantly related to LOS, hospitalization charges, and hospitalization costs while controlling for other covariates of interest. Data management was conducted using SAS version 9.3 (SAS Institute Inc, Cary, North Carolina). Statistical analyses for the complex sampling design were conducted using Stata version 12 (StataCorp LP, College Station, Texas). The priori alpha level of statistical significance was set at $p<0.05$ for all statistical analyses. A summary of the statistical tests that were performed to address the objectives and hypotheses is presented in Table 2.5.

2.7 Sample Size Calculations and Test Assumptions

Sample size calculations and test assumptions are listed for each type of test.

2.7.1 Logistic regressions

To address objectives 6, 7, 8, logistic regressions were performed. The following assumptions were assessed before conducting the analysis: 1) the dependent variable should be a binary variable; 2) independence of observations; 3) adequate responses in every given category to avoid unstable parameter estimates and standard errors.[113,114]

Figure 2.1 Logistic regression model

$\text{logit}[\Theta(x)] = \log[\Theta(x) / 1-\Theta(x)] = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots\ldots + \beta_{18} x_{18}$

$\Theta(x)$ = Probability of worse outcomes

(When addressing objective 6, $\Theta(x)$ = Probability of mortality; when addressing objective 7, $\Theta(x)$ = Probability of having transplant failure or rejection; when addressing objective 8, $\Theta(x)$ = Probability of colectomy)

$1-\Theta(x)$ = Probability of no worse outcomes

α = Constant of equation

β = Regression coefficient of the predictor variables

X_1= Presence of CDI

X_2= Age

X_3= Gender

X_4= Race

X_5= Payer type

X_6= Household income

X_7= UTI

X_8= Pneumonia

X_9= CMV

X_{10}= PTLD

X_{11}= CCI

X_{12}= Transplant type

X_{13}= Hospital size

X_{14}= Hospital geographic region

X_{15}= Teaching status

X_{16}= Children's general or specialty hospital

For the sample size calculations of logistic regressions, an alpha level of 0.05, power of 0.80, and a medium value of the expected squared multiple correlation coefficient between independent variable of interest and all other covariates (R^2 other $X=0.03^2$) were assumed.[115] The literature has limited information regarding the odds ratio and probability of event among mortality, transplant failure or rejection, and colectomy in pediatric SOT recipients. However, the research conducted by Pant et al. provided these parameters in adult SOT recipients. Therefore, we used these parameters to make our sample size estimation. G*Power 3.1.5 software was used to calculate sample size.

For logistic regression with in-hospital mortality as the dependent variable, an odds ratio of 2.48 and a probability of mortality for the SOT recipient=0.024 were used. Therefore, the minimum total sample size of 7,760 was required.

For the logistic regression assessing having a transplant failure or rejection as the dependent variable, the odds ratio of 1.36 and the probability of having a transplant failure or rejection for a SOT recipient=0.339 were used. Therefore, the minimum total sample size of 11,567 was required.

For the logistic regression regarding the presence of a colectomy as the

dependent variable, an odds ratio of 3.10 and a probability of colectomy for SOT recipient=0.003 were used. Therefore, the minimum total sample size of 33,263 was required.

2.7.2 Generalized linear model (GLM)—gamma regression with log link

The distributions among data with continuous values—hospital length of stay (LOS), charges, and costs— were highly positive skewed and violated normality assumption. GLM with gamma distribution is recommended when dealing with heavy-tailed, positive, and continuous data.[116] To address objectives 9, 10, and 11, gamma regressions with log link were performed. A small portion (2%) of hospital length of stay values were zero indicating a length of stay of less than one full day. These were recoded as 1 day so that logarithmic calculations could be conducted. The following assumptions were assessed before conducting the analysis: 1) independence of each observation in dependent variable; 2) correct specification of the variance function; 3) correct specification of the dispersion effect; 4) correct specification of the link function; 5) correct form for the explanatory variables; and 6) lack of undue influence of individual observations.[117] The first assumption of GLM- independence of each observation in dependent variable- was violated because we used discharge level data and a recurrence of CDI of the same patient could not be identified. However, since one previous study has shown that recurrence rate for CDI in hospitalized pediatric patients was 7.5%, we assumed that our data will be close to patient-level data and thus meet the first assumption.[118]

Figure 2.2 Generalized linear model (GLM)—gamma regression with log link

$\log E(Y|X) = a + b_1X_1 + b_2X_2 + \ldots\ldots + b_{18}X_{18}$

$E(Y|X)$ is the expected predicted value

(When addressing objective 9, Y = LOS; when addressing objective 10, Y =Charges; when addressing objective 11, Y = Costs)

a = constant of the equation

b = regression coefficient of the predictor variables

X_1= Presence of CDI

X_2= Age

X_3= Gender

X_4= Race

X_5= Payer type

X_6= Household income

X_7= UTI

X_8= Pneumonia

X_9= CMV

X_{10}= PTLD

X_{11}= CCI

X_{12}= Transplant type

X_{13}= Hospital size

X_{14}= Hospital geographic region

X_{15}= Teaching status

X_{16}= Children's general or specialty hospital

To confirm the correct link function, the Box-Cox tests were conducted. The Box-Cox test can be used to find the appropriate transformation.[119] The Box-Cox transformation is defined by:

$$y(\lambda)=\begin{cases} \frac{y^{\lambda}-1}{\lambda}, \text{if } \lambda \neq 0 \\ \log(y), \text{if } \lambda = 0 \end{cases}$$

For a log link to be appropriate, the value of λ should be approximate zero. The λ

values we obtained were -0.21, -0.14, and -0.14 for length of stay in hospital, charges, and costs, respectively.

In order to confirm the appropriate family of GLM, the modified Park Tests were conducted. This test assesses the distribution by doing regression of the raw-scale squared residuals from the log link on the log of linear predictors while using GLM with a log link and gamma distribution.[120]

$$\log((y-\hat{y})^2) = \gamma_0 + \gamma_1\left(\log(\hat{y})\right) + \varepsilon$$

y=outcome variable

$\hat{y}$=predicted value of outcome variable

γ_0=constant of the equation

γ_1=coefficient

ε=error term

The coefficient (γ_1) approximate 2 indicates gamma distribution is recommended. The coefficient (γ_1) were 2.38, 2.25, and 2.31 for length of stay in hospital, charges, and costs, respectively.

Little information regarding sample size calculation for gamma regression with log link has been reported. However, the results from Jin and Zhao's study indicates that the required sample size for a gamma distribution with a logarithmic transformation will not exceed the required sample size for a normal distribution while given a certain power level.[121] Therefore, the required sample size for linear multiple regression was used to estimate sample size. For the sample size calculation of linear multiple regression, a small effect size (f^2=0.02) based on conventional value, an alpha level of 0.05, and power of 0.80 were assumed.[115] G*Power 3.1.5 software was used to estimate sample size. With 16 independent variables, the minimum total sample size of 1,000 was required.

The sample sizes required for each statistical analysis are summarized in Table 2.4. Based on these values, the minimum total sample size for this study was 33,263.

Table 2.4 Summary of sample sizes for the statistical analyses

Statistical analysis	Dependent variable	Required sample size
Logistic regression	Mortality	7,760
Logistic regression	Transplant failure or rejection	11,567
Logistic regression	Colectomy	33,263
Gamma regression with log link	Length of stay (LOS)	1,000
Gamma regression with log link	Charges	1,000
Gamma regression with log link	Costs	1,000

2.8 Post-hoc power analyses

Before conducting this study, the minimum required sample sizes to reach a power of 0.8 were estimated based on the results from adult population because limited information for pediatric population has been reported. Therefore, post-hoc power analyses were performed in order to determine the power with actual sample sizes, standard deviations, and odds ratios. Statistical power was calculated using the "powercal" procedure designed for power calculations in generalized linear models from Stata version 12 packages (StataCorp LP, College Station, Texas).

Table 2.5 Summary of the study objectives, hypotheses, variables, and statistical tests

Objectives	Hypothesis	Dependent variable	Independent variable	Statistical test
1. To describe the demographic characteristics based on hospital admissions of the pediatric SOT recipients with respect to age, gender, race, median household income for patient's ZIP code, payer type, and comorbid condition.	N/A	N/A	N/A	Descriptive statistics
2. To describe the hospital-related characteristics of pediatric SOT admissions with respect to hospital size, geographic regions, teaching status, and whether it is a children's general or specialty hospital or children's unit in a general hospital based on the National Association of Children's Hospital and Related Institutions (NACHRI).	N/A	N/A	N/A	Descriptive statistics
3. To describe CDI prevalence based on hospital admissions among pediatric patient with SOT.	N/A	N/A	N/A	Descriptive statistics
4. To describe the outcomes regarding transplant failure or rejection events, hospital mortality, colectomies, and hospital length of stay among pediatric SOT patients.	N/A	N/A	N/A	Descriptive statistics
5. To estimate the charges (the amount that hospitals billed for services) and costs (charges multiply cost-to-charge ratios) of hospitalizations	N/A	N/A	N/A	Descriptive statistics

Table 2.5 Summary of the study objectives, hypotheses, variables, and statistical tests (cont'd)

for pediatric patients with SOT.				
6. To determine if the presence of CDI is significantly associated with hospital mortality while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	*H_1: There is a significant difference in the likelihood of inpatient mortality between pediatric SOT patient with CDI and pediatric SOT patients without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).*	Hospital mortality (categorical)	Presence of CDI, age, gender, race, payer type, household income, UTI, pneumonia, CMV, CCI, type of organ transplantation, hospital size, hospital geographic region, teaching status, children's general or special hospital (categorical)	Logistic regression
7. To determine if the presence of CDI is significantly associated with transplant failures or rejections while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	*H_2: There is a significant difference in the likelihood of having a transplant failure or rejection event during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).*	Having a transplant failure or rejection event (categorical)	Presence of CDI, age, gender, race, payer type, household income, UTI, pneumonia, CMV, CCI, type of organ transplantation, hospital size, hospital geographic region, teaching status, children's general or	Logistic regression

Table 2.5 Summary of the study objectives, hypotheses, variables, and statistical tests (cont'd)

			special hospital (categorical)	
8. To determine if the presence of CDI is significantly associated with having a colectomy while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	*H_3: There is a significant difference in the likelihood of having a colectomy during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).*	Having a colectomy (categorical)	Presence of CDI, age, gender, race, payer type, household income, UTI, pneumonia, CMV, CCI, type of organ transplantation, hospital size, hospital geographic region, teaching status, children's general or special hospital (categorical)	Logistic regression
9. To determine if the presence of CDI is significantly associated with hospital length of stay (LOS) for pediatric SOT patients while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	*H_4: There is a significant difference in hospital length of stay (LOS) between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).*	Hospital LOS (continuous)	Presence of CDI, age, gender, race, payer type, household income, UTI, pneumonia, CMV, CCI, type of organ transplantation, hospital size, hospital geographic region, teaching status,	Gamma regression with log link

Table 2.5 Summary of the study objectives, hypotheses, variables, and statistical tests (cont'd)

			children's general or special hospital (categorical)	
10. To determine if the presence of CDI is significantly associated with charges (the amount that hospitals billed for services) for SOT hospitalizations while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	*H_5: There is a significant difference in hospital charges between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).*	Hospital charges (continuous)	Presence of CDI, age, gender, race, payer type, household income, UTI, pneumonia, CMV, CCI, type of organ transplantation, hospital size, hospital geographic region, teaching status, children's general or special hospital (categorical)	Gamma regression with log link
11. To determine if the presence of CDI is significantly associated with costs (charges multiply cost-to-charge ratios) for SOT hospitalizations while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	*H_6: There is a significant difference in hospital costs between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).*	Hospital costs (continuous)	Presence of CDI, age, gender, race, payer type, household income, UTI, pneumonia, CMV, CCI, type of organ transplantation, hospital size, hospital geographic region,	Gamma regression with log link

Table 2.5 Summary of the study objectives, hypotheses, variables, and statistical tests (cont'd)

			teaching status, children's general or special hospital (categorical)	

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **LOS**= length of stay; **UTI**= Urinary tract infaction; **CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

Chapter 3: Results

3.1 Chapter overview

This chapter provides the study results. All results are organized by study objectives and associated statistical analyses. Since the weight for each hospital discharge is needed to be applied for generating national-level estimates, we used weighted data for descriptive and inferential statements unless results from unweighted data were specified.

3.2 Case identification

From 2000 to 2009, the total numbers for unweighted and weighted pediatric discharges in KID were 12,039,432 and 29,629,209, respectively. All entries aged between 1 to 17 years old with ICD-9-CM diagnoses or procedures codes for SOT were identified. The total unweighted sample size was 28,185. The total weighted sample size was 48,286.

3.3 Study objectives

3.3.1 Objective 1

Objective 1 was to describe the demographic characteristics based on hospital admissions of the pediatric SOT recipients with respect to age, gender, race, median household income for patient's ZIP code, payer type, and comorbid condition. A description of unweighted and weighted demographic characteristics is presented in Table 3.1.

Among admissions with SOT, around 52% were for male patients and 48% were for female patients. The proportions for all age groups (1~4, 5~9, 10~14, and 15~17

year old) ranged from approximately 22% to 27%. Patients with SOT were mainly whites (44.2%) and the majority of them had private insurance (40.82%). For income quartiles, patients fell nearly evenly in the first, second, third, and fourth quartiles (23.32%, 25.56%, 25.12%, and 23.44%, respectively). For comorbid condition among patients with SOT, nine percent of them had pneumonia during their hospitalization and around two percent had CMV, UTI, and PTLD; over 60 percent of the sample had a Charlson Comorbidity Index (CCI) score of zero (CCI=0: 62.29%, CCI=1: 11.69%, CCI≥2: 26.03%).

Among admissions with both SOT and CDI, around 54% were male patients and 47% were female patients. Almost half (46.24%) of the patients were 1~4 years old. Patients with both SOT and CDI were mainly whites (45.89%). Medicaid was the expected primary payer for approximately 43% of the admissions for patients with both SOT and CDI, followed by the private insurance (42.14%). For income quartiles, the proportions among patients with both SOT and CDI were as follows: 24.77% in 0^{th}~25^{th} percentile, 23.36% in 26^{th}~50^{th} percentile, 30.16% in 51^{th}~75^{th} percentile, and 19.48% in 76^{th}~100^{th} percentile. For comorbid conditions among events for patients with both SOT and CDI, 13.26% included pneumonia and around three percent of events included a diagnosis for CMV and PTLD; over 65 percent of the sample had CCI score zero (CCI=0: 67.37%, CCI=1: 12.32%, CCI≥2: 20.31%).

Table 3.1 Demographic characteristics of patients with SOT and CDI (cont'd)

Table 3.1 Demographic characteristics of patients with SOT and CDI

Variable		Unweighted				Weighted			
		SOT only		SOT+CDI		SOT only		SOT+CDI	
Total events, n (%)		27,670	(100.00)	515	(100.00)	47,434	(100.00)	852	(100.00)
Gender	Male	14,464	(52.27)	275	(53.40)	24,724	(52.12)	463	(54.34)
	Female	13,127	(47.44)	240	(46.60)	22,590	(47.62)	389	(45.66)
Age	1~4 Years old	7,509	(27.14)	240	(46.60)	12,970	(27.34)	394	(46.24)
	5~9 Years old	6,211	(22.45)	111	(21.55)	10,639	(22.43)	183	(21.48)
	10~14 Years old	7,136	(25.79)	94	(18.25)	12,235	(25.79)	158	(18.54)
	15~17 Years old	6,814	(24.63)	70	(13.59)	11,590	(24.43)	117	(13.73)
Race	White	11,842	(42.80)	234	(45.44)	20,964	(44.20)	391	(45.89)
	Black	3,851	(13.92)	56	(10.87)	6,563	(13.84)	90	(10.56)
	Hispanic	5,335	(19.28)	110	(21.36)	8,833	(18.62)	179	(21.01)
	Other†	1,885	(6.81)	30	(5.83)	3,082	(6.50)	48	(5.63)
Payer type									
	Medicare	4,183	(15.12)	40	(7.77)	7,111	(14.99)	67	(7.86)
	Medicaid	10,644	(38.47)	223	(43.30)	17,931	(37.80)	365	(42.84)
	Private	11,063	(39.98)	214	(41.55)	19,364	(40.82)	359	(42.14)
	Self-pay	276	(1.00)	8	(1.55)	483	(1.02)	13	(1.53)
	Other‡	1,405	(5.07)	30	(5.83)	2,346	(4.95)	48	(5.63)
Income quartiles for ZIP code									
	0^{th}~25^{th} percentile	6,678	(24.13)	130	(25.24)	11,062	(23.32)	211	(24.77)
	26^{th}~50^{th} percentile	7,083	(25.60)	119	(23.11)	12,126	(25.56)	199	(23.36)
	51^{th}~75^{th} percentile	6,814	(24.63)	158	(30.68)	11,914	(25.12)	257	(30.16)
	76^{th}~100^{th} percentile	6,378	(23.05)	96	(18.64)	11,119	(23.44)	166	(19.48)
Comorbid condition									
	Pneumonia	2,504	(9.05)	70	(13.59)	4,267	(9.00)	113	(13.26)
	CMV	517	(1.87)	15	(2.91)	904	(1.91)	24	(2.82)
	UTI	672	(2.43)	10	(1.94)	1,132	(2.39)	16	(1.88)
	PTLD	398	(1.44)	15	(2.91)	711	(1.50)	25	(2.93)
	CCI 0	17,069	(61.69)	348	(67.57)	29,545	(62.29)	574	(67.37)
	1	3,274	(11.83)	64	(12.43)	5,543	(11.69)	105	(12.32)
	≥2	7,327	(26.48)	103	(20.00)	12,346	(26.03)	173	(20.31)

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), tribal, and other government programs

3.3.2 Objective 2

Objective 2 was to describe the hospital-related characteristics of pediatric SOT admissions with respect to hospital size, geographic region, teaching status, and children's general or specialty hospital. A description of unweighted and weighted demographic hospital-related characteristics is presented in Table 3.2.

Among the weighted discharges with SOT, most of the admissions were at large size hospitals (53.88%). Around 19% of the admissions with SOT were in hospitals located in the Northeast USA, 22% in the Midwest, 33% in the South, and 26% in the West. The proportion of pediatric SOT hospitalizations was highest in teaching hospitals (89%).

Among the weighted discharges with both SOT and CDI diagnoses, most of the inpatient admissions were at large (48.4%) and teaching (89.8%) hospitals. Around 15% of the SOT with CDI admissions occurred in hospitals located in the Northeast USA, 22% in the Midwest, 30% in the South, and 32% in the West.

Table 3.2 Hospital characteristics of SOT admissions and SOT admissions with CDI

	Unweighted		Weighted	
Variable	SOT only	SOT+CDI	SOT only	SOT+CDI
Total admissions, n (%)	27,670(100.00)	515(100.00)	47,434(100.00)	852(100.00)
Hospital size, n (%)				
Small	3,167 (11.45)	56 (10.87)	6,156 (12.98)	105 (12.31)
Medium	6,929 (25.04)	154 (29.90)	12,711 (26.80)	275 (32.33)
Large	15,751 (56.92)	268 (52.04)	25,558 (53.88)	412 (48.38)
Hospital region, n (%)				
Northeast	5,229 (18.90)	74 (14.37)	8,995 (18.96)	128 (15.02)
Midwest	5,604 (20.25)	119 (23.11)	10,243 (21.59)	191 (22.41)
South	9,175 (33.16)	154 (29.90)	15,707 (33.11)	259 (30.45)
West	7,662 (27.69)	168 (32.62)	12,489 (26.33)	274 (32.11)
Teaching hospital, n (%)	24,649 (89.08)	464 (90.10)	42,418 (89.43)	766 (89.85)
Children's general or specialty hospital, n (%)				
Not identified as children's hospital	2,424 (8.76)	28 (5.44)	3,959 (8.35)	48 (5.62)
Children's general or specialty hospital	9,822 (35.50)	217 (42.14)	18,480 (38.96)	391 (45.92)
Children's unit in a general hospital	13,157 (47.55)	228 (44.27)	21,269 (44.84)	345 (40.51)

CDI= clostridium difficile infection; **SOT**= solid organ transplant

3.3.3 Objective 3

Objective 3 was to describe CDI prevalence of admissions among pediatric SOT patients. The number of SOT admissions and the corresponding prevalence of CDI were categorized by types of organ transplant in Table 3.3. For weighted admissions, the largest proportion of SOT events was associated with kidney transplants (41.5%), and the second largest proportion was liver transplants (36.0%).

Overall, the prevalence of CDI in weighted SOT admissions was 1.76%. Admissions with intestine transplant had the highest CDI prevalence (2.90%), followed by lung (2.54%) and liver (2.43%) transplant. Among all type of organ transplant, kidney transplant admissions had the lowest CDI prevalence (1.14%).

Table 3.3 Number of SOT admissions and the corresponding prevalence of CDI

	Unweighted			Weighted		
Organ transplanted	Number of admissions, n (%)		CDI prevalence, %	Number of admissions, n (%)		CDI prevalence, %
Any organ	28185	(100.00)	1.83	48286	(100.00)	1.76
Heart	4544	(16.12)	1.61	7868	(16.30)	1.57
Liver	10103	(35.85)	2.56	17376	(35.99)	2.43
Lung	1091	(3.87)	2.57	1927	(3.99)	2.54
Kidney	11784	(41.81)	1.16	20035	(41.49)	1.14
Pancreas	72	(0.26)	1.39	119	(0.25)	1.26
Intestine	591	(2.10)	2.88	961	(1.99)	2.90

CDI= clostridium difficile infection; **SOT**= solid organ transplant

3.3.4 Objective 4

Objective 4 was to describe the outcomes regarding transplant failure or rejections, hospital mortality, colectomies, and hospital length of stay for admissions of pediatric SOT patients. Descriptive statistics for these outcome variables are shown in Table 3.4.

Hospitalizations for SOT patients with CDI had higher mortality and colectomy rates than SOT hospitalizations without CDI (1.63% vs. 1.14% for mortality; 4.86% vs. 2.52% for colectomy), while the rate of transplant failure/rejections was lower (34.17% vs. 27.71%). The hospital length of stay (LOS) for patients with both SOT and CDI was more than twice as long as the LOS with SOT only (median: 7 days vs. 3 days; mean (SE): 17 days (1.32) vs. 8 days (0.28)).

Table 3.4 Outcomes of SOT admissions and SOT admissions with CDI

	Unweighted		Weighted	
Variable	SOT only	SOT+CDI	SOT only	SOT+CDI
Mortality, %	1.11	1.55	1.14	1.63
Transplant failure or rejection, %	34.59	27.96	34.17	27.71
Colectomy, %	2.58	4.85	2.52	4.86
LOS, days				
Median	3	7	3	7
Mean (SE)	8 (0.28)	17 (1.33)	8 (0.28)	17 (1.32)

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **LOS**= length of stay; **SE**= standard error

3.3.5 Objective 5

Objective 5 was to estimate the hospital charges and hospital costs of pediatric SOT admissions. All charges and costs are reported in 2009 US dollars. Estimations of charges and corresponding costs for SOT admissions and SOT admissions with CDI are shown in Table 3.5.

SOT admissions with CDI had higher median charges and median costs than SOT admissions without CDI (charges: $48,409 vs. $21,022; costs: $17,412 vs. $8,662). The mean charge per SOT admission was $67,629 (SE=$3,838) while the mean charge per SOT admission with CDI was $137,874 (SE=$12,338). The mean cost per SOT admission was $26,652 (SE=$1,510) while the mean cost per SOT admission with CDI was $49,471 (SE=$5,261).

Table 3.5 Charges and costs of SOT admissions and SOT admissions with CDI

	Unweighted		Weighted	
Variable	SOT only	SOT+CDI	SOT only	SOT+CDI
Charges, $				
Median*	21,750	48,633	21,022	48,409
Mean* (SE)	68,716 (3,664)	138,208 (12,649)	67,629 (3,838)	137,874 (12,338)
Costs, $				
Median*	8,686	17,631	8,662	17,412
Mean* (SE)	26,559 (1,425)	49,919 (5,242)	26,652 (1,510)	49,471 (5,261)

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **SE**= standard error
*rounded to the nearest dollar

3.3.6 Objective 6

Objective 6 was to determine if the presence of CDI was significantly associated with hospital mortality in pediatric SOT patients while controlling for other covariates. A logistic regression with hospital mortality as the dependent variable and presence of CDI as the independent variables was employed while controlling for the following covariates: age, gender, race, payer type, household income, UTI, pneumonia, CMV, PTLD, CCI, organ transplant type, hospital size, hospital geographic region, teaching status, and children's general or specialty hospital. The category—pancreas—in variable of transplant type was excluded from the regression model because no event occurred under this category. Table 3.6 provides the odds ratios, standard errors, t values, and 95% confidence intervals for the independent variable and all covariates.

The overall regression model was statistically significant ($F=23.12$, $p<0.001$). There was no significant difference in hospital mortality between patients with SOT admissions with CDI and patients with SOT admissions without CDI while controlling for other covariates (OR=1.41, 95% CI= [0.63, 3.13], p=0.40).

Regarding the covariates, admissions that were "self-pay" had more than 3 times the likelihood of hospital mortality compared to admissions with "private insurance" as the primary payer (OR=3.27, 95% CI= [1.30, 8.24], p=0.01). Admissions with a co-morbidity of pneumonia had double the likelihood of hospital mortality than those without this diagnosis (OR=2.14, 95% CI= [1.52, 3.00], $p<0.001$). Pediatric SOT admissions with greater comorbid burdens (CCI=1 and CCI=2) had higher likelihoods of hospital mortality than pediatric SOT admissions with no comorbid burden (CCI=0) while controlling for other covariates (For CCI=1: OR=2.67, 95% CI= [1.98, 3.61], $p<0.001$; For CCI=2: OR=5.12, 95% CI= [3.34, 7.86], $p<0.001$). Compared to admissions for kidney transplant patients, heart, liver,

lung, and intestine transplant admissions had higher rates of hospital mortality (Heart: OR=12.31, 95% CI= [5.78, 26.21], p<0.001; Liver: OR=6.33, 95% CI= [3.59, 11.16], p<0.001; Lung: OR=19.22, 95% CI= [9.35, 39.51], p<0.001; Intestine: OR=9.50, 95% CI= [3.81, 23.69], p<0.001;). Admission to a teaching hospital was also significantly associated with a higher mortality rate. Patients with SOT events in teaching hospitals were approximately 7 times more likely to die during hospitalization compared to patients in non-teaching hospitals while controlling for the other factors (OR=6.79, 95% CI= [1.49, 30.90], p=0.01).

H_1: *There is a significant difference in the likelihood of inpatient **mortality** between pediatric SOT patient with CDI and pediatric SOT patients without CDI while controlling for other covariates.* **[Rejected]**

Table 3.6 Logistic regression analysis for hospital mortality of SOT admissions

Variable	Odds Ratio	SE	t	95% CI		p-value
Presence of CDI (ref=without CDI)	1.41	0.57	0.84	0.63	3.13	0.40
Age (ref=1~4 Years old)						
5~9 Years old	0.63	0.14	-2.04	0.40	0.98	0.04*
10~14 Years old	0.73	0.15	-1.55	0.50	1.08	0.12
15~17 Years old	0.75	0.15	-1.41	0.50	1.12	0.16
Gender (ref=male)						
Female	0.96	0.12	-0.34	0.75	1.23	0.74
Race (ref=White)						
Black	1.41	0.34	1.40	0.87	2.28	0.16
Hispanic	0.94	0.17	-0.32	0.66	1.35	0.75
Other†	0.99	0.24	-0.04	0.61	1.60	0.97
Payer (ref=Private insurance)						
Medicare	0.83	0.28	-0.55	0.42	1.63	0.58
Medicaid	0.87	0.16	-0.72	0.61	1.26	0.48
Self-pay	3.27	1.54	2.52	1.30	8.24	0.01*
Other‡	1.27	0.31	1.00	0.79	2.04	0.32
Income quartiles for ZIP code (ref=0th~25th percentile)						
26^{th}~50^{th} percentile	1.09	0.14	0.69	0.85	1.41	0.49
51^{th}~75^{th} percentile	0.82	0.18	-0.91	0.53	1.26	0.36
76^{th}~100^{th} percentile	0.73	0.15	-1.48	0.49	1.11	0.14
Comorbid condition (ref=without specific infection)						
UTI	1.17	0.82	0.23	0.30	4.62	0.82
Pneumonia	2.14	0.37	4.40	1.52	3.00	<0.001*
CMV	1.80	0.52	2.03	1.02	3.18	0.04*
PTLD	0.45	0.20	-1.81	0.19	1.07	0.07
Charlson Comorbidity Index (ref= CCI=0)						
CCI=1	2.67	0.41	6.39	1.98	3.61	<0.001*
CCI≥2	5.12	1.12	7.49	3.34	7.86	<0.001*
Transplant organ (ref=kidney)						
Heart	12.31	4.74	6.52	5.78	26.21	<0.001*
Liver	6.33	1.83	6.39	3.59	11.16	<0.001*
Lung	19.22	7.05	8.06	9.35	39.51	<0.001*
Intestine	9.50	4.42	4.84	3.81	23.69	<0.001*
Hospital size (ref=small)						
Medium	1.38	0.42	1.07	0.76	2.51	0.28
Large	1.46	0.57	0.97	0.68	3.13	0.33
Hospital geographic region (ref=Northeast)						
Midwest	1.18	0.39	0.50	0.61	2.28	0.62
South	0.95	0.22	-0.24	0.60	1.50	0.81
West	1.15	0.24	0.65	0.76	1.72	0.51
Teaching status (ref=non-teaching hospital)						
Teaching hospital	6.79	5.24	2.48	1.49	30.90	0.01*

Table 3.6 Logistic regression analysis for hospital mortality of SOT admissions (cont'd)

Children's general or specialty hospital (ref=not identified as children's hospital)						
Children's general or specialty hospital	0.89	0.32	-0.34	0.44	1.79	0.74
Children's unit in a general hospital	0.74	0.33	-0.68	0.31	1.78	0.50

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs

*significant at $p<0.05$

3.3.7 Objective 7

Objective 7 was to determine if the presence of CDI was significantly associated with transplant failure or rejection while controlling for other covariates. A logistic regression with having a transplant failure or rejection event as the dependent variable and presence of CDI as the independent variables was employed while controlling for the following covariates: age, gender, race, payer type, household income, UTI, pneumonia, CMV, PTLD, CCI, organ transplant type, hospital size, hospital geographic region, teaching status, and children's general or specialty hospital. Table 3.7 provides the odds ratios, standard errors, t values, and 95% confidence intervals for the independent variable and all covariates.

The overall regression model was statistically significant ($F=22.20$, $p<0.001$). There was no significant difference in transplant failure or rejection event between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates (OR=0.82, 95% CI= [0.63, 1.07], p=0.15).

Regarding the covariates, age was significantly associated with transplant failure or rejection in SOT admissions. Patients in older age groups had a higher likelihood of having transplant failure or rejection during SOT admissions while controlling for other factors. Patients aged 5~9 years old, 10~14 years old, and 15~17 years old were more likely to have transplant failure/rejection during SOT admissions compared to patients aged 1~4 years old (5~9 years old: OR=1.26, 95% CI= [1.10, 1.43], $p<0.001$; 10~14 years old: OR=1.56, 95% CI= [1.40, 1.74], $p<0.001$; 15~17 years old: OR=1.81, 95% CI= [1.58, 2.08], $p<0.001$). Compared to White SOT recipients, the odds of having transplant failure or rejection were 22% higher for Black SOT recipients while controlling for other factors (OR=1.22, 95% CI= [1.09, 1.38], $p<0.001$).

Pediatric SOT admissions with Medicare as the expected primary payer were 27% more likely to have transplant failure/rejection when compared to SOT admission with private insurance as the expected primary payer (OR=1.27, 95% CI= [1.12, 1.43], p<0.001). Pediatric SOT admissions with other primary payers (charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs) were 30% more likely to have transplant failure/rejection when compared to pediatric SOT admissions with private insurance as expected primary payer (OR=1.30, 95% CI= [1.06, 1.60], p=0.01).

For comorbid conditions, pediatric SOT admissions with UTI were 64% more likely to have transplant failure/rejection compared to pediatric SOT admissions without UTI while controlling for other factors (OR=1.64, 95% CI= [1.27, 2.11], p<0.001). Pediatric SOT admissions with CMV were 3 times more likely to have transplant failure/rejection compared to pediatric SOT admissions without CMV while controlling for other factors (OR=3.18, 95% CI= [2.44, 4.15], p<0.001). However, the results indicated that pediatric SOT admissions with pneumonia was less likely to have transplant failure/rejection when other factors were held constant (Pneumonia: OR=0.59, 95% CI= [0.50, 0.70], p<0.001).

Pediatric SOT admissions with greater comorbid burdens (CCI=1 and CCI=2) had higher likelihoods to have transplant failure/rejection than pediatric SOT admissions with no comorbid burden (CCI=0) while controlling for other covariates (For CCI=1: OR=1.21, 95% CI= [1.05, 1.39], p=0.01; For CCI=2: OR=1.39, 95% CI= [1.26, 1.53], p<0.001).

When holding other factors constant, lung transplant patients were about 3 times more likely to have a transplant failure/rejection compared to patients with kidney transplants (OR=3.05, 95% CI= [1.95, 4.78], p<0.001).

Patients with SOT admissions to teaching hospitals were 49% more likely to have transplant failure/rejection compared to patients in non-teaching hospitals while controlling for the other factors (OR=1.55, 95% CI= [1.15, 2.09], p=0.01), and those with admissions to children's general or specialty hospitals were 48% more likely to have a transplant failure or rejection compared to those not identified as children's hospitals (OR=1.48, 95% CI= [1.07, 2.04], p=0.02); patients in a children's unit in a general hospital were 2 times more likely to have a transplant failure/rejection compared to admissions to a hospital not identified as children's hospitals (OR=1.96, 95% CI= [1.52, 2.54], p<0.001).

H_2: There is a significant difference in the likelihood of having a ***transplant failure or rejection event*** *during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates.* **[Rejected]**

Table 3.7 Logistic regression for the prevalence of transplant failure/rejection in SOT admissions

Variable	Odds Ratio	SE	t	95% CI		p-value
Presence of CDI (ref=without CDI)	0.82	0.11	-1.45	0.63	1.07	0.15
Age (ref=1~4 Years old)						
5~9 Years old	1.26	0.08	3.46	1.10	1.43	<0.001*
10~14 Years old	1.56	0.09	8.19	1.40	1.74	<0.001*
15~17 Years old	1.81	0.13	8.46	1.58	2.08	<0.001*
Gender (ref=male)						
Female	1.04	0.03	1.06	0.97	1.11	0.29
Race (ref=White)						
Black	1.22	0.07	3.41	1.09	1.38	<0.001*
Hispanic	0.93	0.06	-1.02	0.82	1.06	0.31
Other†	0.94	0.08	-0.70	0.79	1.12	0.49
Payer (ref=Private insurance)						
Medicare	1.27	0.08	3.80	1.12	1.43	<0.001*
Medicaid	1.10	0.06	1.75	0.99	1.23	0.08
Self-pay	1.30	0.38	0.89	0.73	2.29	0.37
Other‡	1.30	0.14	2.48	1.06	1.60	0.01*
Income quartiles for ZIP code (ref=0th~25th percentile)						
26^{th}~50^{th} percentile	1.00	0.05	0.05	0.91	1.10	0.96
51^{th}~75^{th} percentile	0.94	0.06	-0.97	0.83	1.06	0.33
76^{th}~100^{th} percentile	0.90	0.07	-1.32	0.78	1.05	0.19
Comorbid condition (ref=without specific infection)						
UTI	1.64	0.21	3.82	1.27	2.11	<0.001*
Pneumonia	0.59	0.05	-6.00	0.50	0.70	<0.001*
CMV	3.18	0.43	8.59	2.44	4.15	<0.001*
PTLD	0.66	0.14	-1.91	0.43	1.01	0.06
Charlson Comorbidity Index (ref= CCI=0)						
CCI=1	1.21	0.09	2.58	1.05	1.39	0.01*
CCI≥2	1.39	0.07	6.73	1.26	1.53	<0.001*
Transplant organ (ref=kidney)						
Heart	0.94	0.08	-0.71	0.80	1.11	0.48
Liver	0.91	0.06	-1.42	0.80	1.04	0.16
Lung	3.05	0.70	4.87	1.95	4.78	<0.001*
Pancreas	0.88	0.34	-0.33	0.41	1.88	0.74
Intestine	1.04	0.15	0.25	0.78	1.37	0.80
Hospital size (ref=small)						
Medium	1.20	0.13	1.65	0.97	1.50	0.10
Large	1.18	0.21	0.97	0.84	1.67	0.33
Hospital geographic region (ref=Northeast)						
Midwest	1.00	0.15	0.00	0.74	1.34	1.00
South	1.03	0.12	0.23	0.81	1.30	0.82
West	1.05	0.12	0.47	0.84	1.32	0.64
Teaching status (ref=non-teaching hospital)						

Table 3.7 Logistic regression for the prevalence of transplant failure/rejection in SOT admissions (cont'd)

Teaching hospital	1.55	0.24	2.91	1.15	2.09	0.01*
Children's general or specialty hospital (ref=not identified as children's hospital)						
Children's general or specialty hospital	1.48	0.24	2.38	1.07	2.04	0.02*
Children's unit in a general hospital	1.96	0.26	5.12	1.52	2.54	<0.001*

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs

*significant at $p<0.05$

3.3.8 Objective 8

Objective 8 was to determine if the presence of CDI was significantly associated with a colectomy while controlling for other covariates. A logistic regression with having a colectomy event as the dependent variable and presence of CDI as the independent variable was employed while controlling for the following covariates: age, gender, race, payer type, household income, UTI, pneumonia, CMV, PTLD, CCI, organ transplant type, hospital size, hospital geographic region, teaching status, and children's general or specialty hospital. The category—pancreas—in variable of transplant type was excluded from the regression model because no event occurred under this category. Table 3.8 provides the odds ratios, standard errors, t values, and 95% confidence intervals for the independent variable and all covariates.

The overall regression model was statistically significant ($F=10.17$, $p<0.001$). The results showed that pediatric SOT admissions with CDI diagnosis were 2.6 times more likely to include colectomy than admission for SOT without CDI while controlling for other covariates (OR=2.624 95% CI= [1.64, 4.24], $p<0.001$).

Regarding the covariates, patients aged 15~17 years old were 46% more likely to have a colectomy compared to patients aged 1~4 years old (OR=1.46, 95% CI= [1.06, 2.00], $p=0.02$).

For comorbid conditions, pediatric SOT admissions with PTLD were 65% less likely to have colectomy compared to pediatric SOT admissions without PTLD while controlling for other factors (OR=0.35, 95% CI= [0.16, 0.81], $p=0.01$).

Pediatric SOT admissions with greater comorbid burdens (CCI=1 and CCI=2) had higher likelihoods to have colectomy than pediatric SOT admissions with no comorbid burden (CCI=0) while controlling for other covariates (For CCI=1: OR=1.69, 95% CI= [1.24, 2.30], $p<0.001$; For CCI=2: OR=2.24, 95% CI= [1.74,

2.89], p<0.001).

When holding other factors constant, patients with heart transplants were 89% more likely to have a colectomy compared to patients with kidney transplants (OR=1.89, 95% CI= [1.35, 2.64], p<0.001); patients with intestine transplants were 2 times more likely to have a colectomy compared to patients with kidney transplants (OR=2.09, 95% CI= [1.28, 3.44], p<0.001).

While holding other factors constant, admissions to children's general or specialty hospitals were 2 times more likely to include a colectomy compared to those not identified as children's hospitals (OR=1.97, 95% CI= [1.11, 3.50], p=0.02).

H_3: *There is a significant difference in the likelihood of having a **colectomy** during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates.* **[Not rejected]**

Table 3.8 Logistic regression for the prevalence of colectomy in SOT admissions

Variable	Odds Ratio	SE	t	95% CI		p-value
Presence of CDI (ref=without CDI)	2.64	0.64	4.01	1.64	4.24	<0.001*
Age (ref=1~4 Years old)						
5~9 Years old	1.08	0.16	0.53	0.81	1.44	0.60
10~14 Years old	1.20	0.17	1.30	0.91	1.59	0.19
15~17 Years old	1.46	0.24	2.32	1.06	2.00	0.02*
Gender (ref=male)						
Female	0.96	0.10	-0.40	0.79	1.17	0.69
Race (ref=White)						
Black	1.17	0.17	1.07	0.88	1.56	0.28
Hispanic	0.90	0.17	-0.56	0.62	1.30	0.58
Other†	1.30	0.20	1.69	0.96	1.77	0.09
Payer (ref=Private insurance)						
Medicare	0.99	0.18	-0.04	0.69	1.43	0.97
Medicaid	0.80	0.09	-2.01	0.64	0.99	0.05
Self-pay	0.74	0.43	-0.53	0.24	2.30	0.60
Other‡	1.07	0.19	0.37	0.75	1.53	0.72
Income quartiles for ZIP code (ref=0th~25th percentile)						
26^{th}~50^{th} percentile	0.91	0.11	-0.76	0.72	1.16	0.45
51^{th}~75^{th} percentile	0.96	0.12	-0.36	0.75	1.22	0.72
76^{th}~100^{th} percentile	0.80	0.11	-1.55	0.61	1.06	0.12
Comorbid condition (ref=without specific infection)						
UTI	1.25	0.37	0.76	0.70	2.23	0.45
Pneumonia	0.82	0.12	-1.31	0.61	1.10	0.19
CMV	1.43	0.36	1.40	0.87	2.35	0.16
PTLD	0.35	0.15	-2.46	0.16	0.81	0.01*
Charlson Comorbidity Index (ref= CCI=0)						
CCI=1	1.69	0.27	3.34	1.24	2.30	<0.001*
CCI≥2	2.24	0.29	6.28	1.74	2.89	<0.001*
Transplant organ (ref=kidney)						
Heart	1.89	0.32	3.71	1.35	2.64	<0.001*
Liver	0.86	0.12	-1.10	0.65	1.13	0.27
Lung	1.05	0.41	0.13	0.49	2.25	0.90
Intestine	2.09	0.53	2.93	1.28	3.44	<0.001*
Hospital size (ref=small)						
Medium	1.39	0.29	1.56	0.92	2.09	0.12
Large	1.32	0.32	1.16	0.82	2.12	0.25
Hospital geographic region (ref=Northeast)						
Midwest	1.19	0.33	0.64	0.70	2.04	0.52
South	1.14	0.23	0.66	0.77	1.70	0.51
West	1.20	0.23	0.95	0.83	1.73	0.34
Teaching status (ref=non-teaching hospital)						
Teaching hospital	0.93	0.34	-0.19	0.45	1.93	0.85

Table 3.8 Logistic regression for the prevalence of colectomy in SOT admissions (cont'd)

Children's general or specialty hospital (ref=not identified as children's hospital)						
Children's general or specialty hospital	1.97	0.58	2.31	1.11	3.50	0.02*
Children's unit in a general hospital	1.83	0.65	1.71	0.91	3.67	0.09

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs

*significant at $p<0.05$

3.3.9 Objective 9

Objective 9 was to determine if the presence of CDI was significantly associated with hospital length of stay (LOS) for SOT admissions while controlling for other covariates. A gamma regression with log link with LOS as the dependent variable and the presence of CDI as the independent variables was used while controlling for the following covariates: age, gender, race, payer type, household income, UTI, pneumonia, CMV, PTLD, CCI, organ transplant type, hospital size, hospital geographic region, teaching status, and children's general or specialty hospital. Table 3.9 provides the coefficients, standard errors, t values, and 95% confidence intervals for the independent variable and all covariates.

All coefficients in Table 3.9 are arithmetic mean ratios of hospital LOS (in number of days) for SOT admissions under that specific category versus hospital LOS (in number of days) for SOT admissions under the reference category. Therefore, the mean hospital LOS for a SOT admission with CDI was almost twice as long as the mean hospital LOS for a SOT admission without CDI (coefficient=1.92, 95% CI= [1.67, 2.20], $p<0.001$).

The following covariates were significantly associated with a longer length of stay (LOS) in the hospital among SOT admissions: expected primary payer category—Medicare and Medicaid versus private insurance; presence of pneumonia and CMV; CCI=1 and CCI≥2 versus CCI=0; organ transplant type categories—heart, liver, lung, pancreas, and intestine versus kidney; teaching hospital; hospital was identified as a children's general or specialty hospital versus hospital was not identified as a children's hospital; and hospital was identified as a children's unit in a general hospital versus hospital was not identified as a children's hospitals.

The covariates that were significantly associated with a shorter length of stay in

hospitals include: age groups—5~9 years old, 10~14 years old, 15~17 years old versus 1~4 years old, income quartiles categories—51th~75th percentile and 76th~100th percentile versus 0th~25th percentile, and the presence of PTLD.

H_4: *There is a significant difference in* ***hospital length of stay (LOS)*** *between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates.* **[Not rejected]**

Table 3.9 Log-linked gamma regression to assess hospital LOS for SOT admissions

Variable	Coefficient§	SE	t	95% CI		p-value
Presence of CDI (ref=without CDI)	1.92	0.13	9.29	1.67	2.20	<0.001*
Age (ref=1~4 Years old)						
5~9 Years old	0.87	0.03	-3.83	0.81	0.93	<0.001*
10~14 Years old	0.80	0.03	-6.03	0.75	0.86	<0.001*
15~17 Years old	0.84	0.03	-4.61	0.78	0.91	<0.001*
Gender (ref=male)						
Female	1.04	0.03	1.47	0.99	1.09	0.14
Race (ref=White)						
Black	1.05	0.04	1.09	0.97	1.13	0.28
Hispanic	1.02	0.04	0.52	0.95	1.10	0.60
Other†	1.05	0.04	1.22	0.97	1.14	0.22
Payer (ref=Private insurance)						
Medicare	1.13	0.04	3.71	1.06	1.20	<0.001*
Medicaid	1.09	0.04	2.57	1.02	1.16	0.01*
Self-pay	1.04	0.12	0.35	0.83	1.30	0.72
Other‡	1.05	0.07	0.83	0.93	1.19	0.41
Income quartiles for ZIP code (ref=0th~25th percentile)						
26^{th}~50^{th} percentile	0.97	0.03	-1.11	0.91	1.03	0.27
51^{th}~75^{th} percentile	0.92	0.03	-2.47	0.86	0.98	0.01*
76^{th}~100^{th} percentile	0.90	0.03	-2.80	0.84	0.97	0.01*
Comorbid condition (ref=without specific infection)						
UTI	1.05	0.05	0.99	0.96	1.14	0.32
Pneumonia	1.38	0.08	5.32	1.22	1.55	<0.001*
CMV	1.48	0.10	5.55	1.29	1.70	<0.001*
PTLD	0.73	0.07	-3.33	0.61	0.88	<0.001*
Charlson Comorbidity Index (ref= CCI=0)						
CCI=1	1.83	0.09	12.67	1.67	2.01	<0.001*
CCI≥2	2.01	0.07	19.06	1.87	2.16	<0.001*
Transplant organ (ref=kidney)						
Heart	1.71	0.11	8.65	1.51	1.93	<0.001*
Liver	1.44	0.07	7.86	1.31	1.58	<0.001*
Lung	1.98	0.19	7.04	1.64	2.40	<0.001*
Pancreas	3.04	0.76	4.47	1.87	4.95	<0.001*
Intestine	2.47	0.25	8.79	2.02	3.02	<0.001*
Hospital size (ref=small)						
Medium	1.02	0.08	0.19	0.87	1.19	0.85
Large	1.09	0.09	1.08	0.93	1.28	0.28
Hospital geographic region (ref=Northeast)						
Midwest	0.92	0.07	-1.15	0.80	1.06	0.25
South	0.98	0.05	-0.33	0.88	1.09	0.74
West	0.93	0.06	-1.03	0.82	1.06	0.30
Teaching status (ref=non-teaching hospital)						
Teaching hospital	1.27	0.13	2.41	1.05	1.54	0.02*

Table 3.9 Log-linked gamma regression to assess hospital LOS for SOT admissions (cont'd)

Children's general or specialty hospital (ref=not identified as children's hospital)						
Children's general or specialty hospital	1.56	0.11	6.52	1.36	1.78	<0.001*
Children's unit in a general hospital	1.40	0.09	5.33	1.23	1.58	<0.001*

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs

*significant at $p<0.05$

3.3.10 Objective 10

Objective 10 was to determine if the presence of CDI was significantly associated with hospital charges for SOT admissions while controlling for other covariates. A gamma regression with log link was used, with hospital charges as the dependent variable and the presence of CDI as the independent variables, while controlling for following covariates: age, gender, race, payer type, household income, UTI, pneumonia, CMV, PTLD, CCI, organ transplant type, hospital size, hospital geographic region, teaching status, and children's general or specialty hospital. Table 3.10 provides the coefficients, standard errors, t values, and 95% confidence intervals for the independent variable and all covariates.

All coefficients in Table 3.10 are arithmetic mean ratios of charges (in 2009 US dollars) for SOT admissions under that specific category versus charges (in 2009 US dollars) for SOT admissions under the reference category. Therefore, the mean hospital charges for a SOT admission with CDI was about 2 times the mean hospital charges for a SOT admission without CDI (coefficient=1.99, 95% CI= [1.62, 2.44], $p<0.001$).

The following covariates were significantly associated with **higher** charges among SOT admissions: presence of pneumonia and CMV; CCI=1 and CCI≥2 versus CCI=0; organ transplant type categories—heart, liver, lung, pancreas, and intestine versus kidney; teaching hospital; teaching hospital; hospital was identified as a children's general or specialty hospital versus hospital was not identified as a children's hospital; and hospital was identified as a children's unit in a general hospital versus hospital was not identified as a children's hospitals.

The covariates that were significantly associated with **lower** charges include: age group—5~9 years old and 10~14 years old versus 1~4 years old; and the presence of

UTI and PTLD; and hospital geographic region category—Midwest versus Northeast.

H_5: *There is a significant difference in hospital **charges** between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates.* **[Not rejected]**

Table 3.10 Log-linked gamma regression to assess hospital charges for SOT admissions

Variable	Coefficient[§]	SE	t	95% CI		p-value
Presence of CDI (ref=without CDI)	1.99	0.21	6.66	1.62	2.44	<0.001*
Age (ref=1~4 Years old)						
5~9 Years old	0.88	0.04	-2.55	0.80	0.97	0.01*
10~14 Years old	0.85	0.04	-3.63	0.78	0.93	<0.001*
15~17 Years old	0.97	0.04	-0.71	0.89	1.06	0.48
Gender (ref=male)						
Female	0.98	0.03	-0.47	0.92	1.05	0.64
Race (ref=White)						
Black	1.03	0.06	0.48	0.92	1.15	0.63
Hispanic	1.01	0.05	0.31	0.92	1.11	0.76
Other†	1.10	0.06	1.69	0.98	1.22	0.09
Payer (ref=Private insurance)						
Medicare	1.02	0.04	0.39	0.94	1.09	0.69
Medicaid	1.00	0.03	-0.15	0.94	1.05	0.88
Self-pay	1.12	0.16	0.80	0.85	1.49	0.42
Other‡	1.11	0.08	1.38	0.96	1.29	0.17
Income quartiles for ZIP code (ref=0th~25th percentile)						
26^{th}~50^{th} percentile	0.94	0.03	-1.73	0.88	1.01	0.08
51^{th}~75^{th} percentile	0.95	0.04	-1.34	0.88	1.02	0.18
76^{th}~100^{th} percentile	0.91	0.04	-1.96	0.83	1.00	0.05
Comorbid condition (ref=without specific infection)						
UTI	0.74	0.05	-4.23	0.65	0.85	<0.001*
Pneumonia	1.20	0.08	2.63	1.05	1.38	0.01*
CMV	1.37	0.10	4.18	1.18	1.59	<0.001*
PTLD	0.52	0.06	-5.61	0.41	0.65	<0.001*
Charlson Comorbidity Index (ref= CCI=0)						
CCI=1	2.09	0.14	11.34	1.84	2.38	<0.001*
CCI≥2	2.99	0.11	29.97	2.79	3.22	<0.001*
Transplant organ (ref=kidney)						
Heart	1.94	0.16	8.14	1.65	2.27	<0.001*
Liver	1.41	0.07	6.83	1.28	1.56	<0.001*
Lung	2.37	0.27	7.46	1.89	2.97	<0.001*
Pancreas	2.76	0.62	4.50	1.77	4.29	<0.001*
Intestine	2.52	0.26	8.94	2.05	3.08	<0.001*
Hospital size (ref=small)						
Medium	0.97	0.13	-0.24	0.74	1.26	0.81
Large	1.14	0.15	0.98	0.88	1.47	0.33
Hospital geographic region (ref=Northeast)						
Midwest	0.79	0.09	-2.21	0.64	0.97	0.03*
South	0.90	0.10	-0.98	0.73	1.11	0.33
West	1.18	0.13	1.51	0.95	1.48	0.13
Teaching status (ref=non-teaching hospital)						
Teaching hospital	1.73	0.22	4.40	1.35	2.21	<0.001*

Table 3.10 Log-linked gamma regression to assess hospital charges for SOT admissions (cont'd)

Children's general or specialty hospital (ref=not identified as children's hospital)						
Children's general or specialty hospital	1.98	0.24	5.60	1.56	2.51	<0.001*
Children's unit in a general hospital	1.44	0.14	3.70	1.19	1.74	<0.001*

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs

*significant at $p<0.05$

3.3.11 Objective 11

Objective 11 was to determine if the presence of CDI was significantly associated with hospital costs for SOT admissions while controlling for other covariates. A gamma regression with log link was used, with hospital costs as the dependent variable and the presence of CDI as the independent variables, while controlling for the following covariates: age, gender, race, payer type, household income, UTI, pneumonia, CMV, PTLD, CCI, organ transplant type, hospital size, hospital geographic region, teaching status, and children's general or specialty hospital. Table 3.11 provides the coefficients, standard errors, t values, and 95% confidence intervals for the independent variable and all covariates.

All coefficients in Table 3.11 are arithmetic mean ratios of costs (in 2009 US dollars) for SOT admissions under that specific category versus costs (in 2009 US dollars) for SOT admissions under the reference category. Therefore, the mean hospital costs for a SOT admission with CDI was about 2 times the mean hospital costs for a SOT admission without CDI (coefficient=1.96, 95% CI= [1.49, 2.57], $p<0.001$).

The following covariates were significantly associated with **higher** costs among SOT admissions: presence of pneumonia and CMV; CCI=1 and CCI≥2 versus CCI=0; organ transplant type categories—heart, liver, lung, pancreas, and intestine versus kidney; teaching hospital; hospital was identified as a children's general or specialty hospital versus hospital was not identified as a children's hospital; and hospital was identified as a children's unit in a general hospital versus hospital was not identified as a children's hospitals.

The covariates that were significantly associated with **lower** charges include: age group—5~9 years old and 10~14 years old versus 1~4 years old; income quartiles

categories—26th~50th percentile versus 0th~25th percentile; the presence of UTI and PTLD.

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H_6: *There is a significant difference in hospital **costs** between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates.* **[Not rejected]**

Table 3.11 Log-linked gamma regression to assess hospital costs for SOT admissions

Variable	Coefficient[§]	SE	t	95% CI		p-value
Presence of CDI (ref=without CDI)	1.96	0.27	4.88	1.49	2.57	<0.001*
Age (ref=1~4 Years old)						
5~9 Years old	0.89	0.05	-2.21	0.80	0.99	0.03*
10~14 Years old	0.91	0.04	-2.31	0.84	0.99	0.02*
15~17 Years old	0.97	0.04	-0.87	0.90	1.04	0.39
Gender (ref=male)						
Female	0.98	0.04	-0.40	0.91	1.07	0.69
Race (ref=White)						
Black	0.98	0.05	-0.44	0.87	1.09	0.66
Hispanic	0.95	0.05	-0.86	0.86	1.06	0.39
Other†	1.09	0.06	1.58	0.98	1.22	0.12
Payer (ref=Private insurance)						
Medicare	1.02	0.05	0.47	0.93	1.12	0.64
Medicaid	0.96	0.03	-1.12	0.89	1.03	0.26
Self-pay	0.92	0.23	-0.32	0.56	1.52	0.75
Other‡	1.16	0.09	1.84	0.99	1.36	0.07
Income quartiles for ZIP code (ref=0th~25th percentile)						
26^{th}~50^{th} percentile	0.92	0.03	-2.22	0.85	0.99	0.03*
51^{th}~75^{th} percentile	0.98	0.04	-0.55	0.90	1.06	0.58
76^{th}~100^{th} percentile	0.94	0.05	-1.12	0.86	1.04	0.26
Comorbid condition (ref=without specific infection)						
UTI	0.74	0.06	-4.02	0.64	0.86	<0.001*
Pneumonia	1.16	0.08	2.07	1.01	1.34	0.04*
CMV	1.62	0.16	5.00	1.34	1.95	<0.001*
PTLD	0.55	0.07	-4.44	0.42	0.72	<0.001*
Charlson Comorbidity Index (ref= CCI=0)						
CCI=1	2.12	0.14	11.65	1.87	2.41	<0.001*
CCI≥2	2.96	0.12	26.61	2.73	3.20	<0.001*
Transplant organ (ref=kidney)						
Heart	1.98	0.13	10.52	1.74	2.25	<0.001*
Liver	1.37	0.06	6.87	1.25	1.50	<0.001*
Lung	2.07	0.17	8.62	1.75	2.44	<0.001*
Pancreas	2.11	0.28	5.64	1.63	2.74	<0.001*
Intestine	2.50	0.34	6.75	1.91	3.26	<0.001*
Hospital size (ref=small)						
Medium	1.02	0.12	0.14	0.80	1.29	0.89
Large	1.16	0.15	1.14	0.90	1.49	0.25
Hospital geographic region (ref=Northeast)						
Midwest	1.01	0.09	0.06	0.84	1.21	0.96
South	0.83	0.08	-2.01	0.69	1.00	0.05
West	1.14	0.13	1.18	0.92	1.42	0.24
Teaching status (ref=non-teaching hospital)						
Teaching hospital	1.98	0.23	5.92	1.58	2.49	<0.001*

Table 3.11 Log-linked gamma regression to assess hospital costs for SOT admissions (cont'd)

Children's general or specialty hospital (ref=not identified as children's hospital)						
Children's general or specialty hospital	1.82	0.26	4.23	1.38	2.41	<0.001*
Children's unit in a general hospital	1.47	0.16	3.48	1.18	1.82	<0.001*

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **UTI**= Urinary tract infaction **; CMV**= cytomegalovirus; **PTLD**= post-transplant lymphoproliferative disease; **CCI**= Charlson comorbidity index

†includes Asian or Pacific Islander, Native American, and other

‡includes charity funding, treatment as part of special research, medically indigent patient, or free care, worker's Compensation, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS), Civilian Health and Medical Program of the Department of Veterans Affairs (CHAMPVA), Title V, and other government programs

*significant at $p<0.05$

A summary of all hypotheses tests results is presented in Table 3.12.

Table 3.12 Results of hypotheses testing

Objectives	Hypothesis	Statistical test	Result
1. To describe the demographic characteristics based on hospital admissions of the pediatric SOT recipients with respect to age, gender, race, median household income for patient's ZIP code, payer type, and comorbid condition.	N/A	Descriptive statistics	N/A
2. To describe the hospital-related characteristics of pediatric SOT admissions with respect to hospital size, location in rural or urban area, geographic regions, teaching status, and whether it is a children's general hospital, children's specialty hospital or children's unit in a general hospital based on the National Association of Children's Hospital and Related Institutions (NACHRI).	N/A	Descriptive statistics	N/A
3. To describe CDI prevalence based on hospital admissions among pediatric patient with SOT.	N/A	Descriptive statistics	N/A
4. To describe the outcomes regarding transplant failure or rejection events, hospital mortality, colectomies, and hospital length of stay among pediatric SOT patients.	N/A	Descriptive statistics	N/A
5. To estimate the charges (the amount that hospitals billed for services) and costs (charges multiply cost-to-charge ratios) of hospitalizations for pediatric	N/A	Descriptive statistics	N/A

Table 3.12 Results of hypotheses testing (cont'd)

patients with SOT.			
6. To determine if the presence of CDI is significantly associated with hospital mortality while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	H_1: There is a significant difference in the likelihood of inpatient mortality between pediatric SOT patient with CDI and pediatric SOT patients without CDI while controlling for other covariates.	Logistic regression	Rejected
7. To determine if the presence of CDI is significantly associated with transplant failures or rejections while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	H_2: There is a significant difference in the likelihood of having a transplant failure or rejection event during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates.	Logistic regression	Rejected
8. To determine if the presence of CDI is significantly associated with having a colectomy while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	H_3: There is a significant difference in the likelihood of having a colectomy during a hospitalization between pediatric SOT patients with CDI and pediatric SOT patients without CDI while controlling for other covariates.	Logistic regression	Not rejected

Table 3.12 Results of hypotheses testing (cont'd)

9. To determine if the presence of CDI is significantly associated with hospital length of stay (LOS) for pediatric SOT patients while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	H_4: There is a significant difference in hospital length of stay (LOS) between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates.	Gamma regression with log link	Not rejected
10. To determine if the presence of CDI is significantly associated with charges (the amount that hospitals	H_5: There is a significant difference in hospital charges between pediatric	Gamma regression	Not rejected

billed for services) for SOT hospitalizations while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates.	with log link	
11. To determine if the presence of CDI is significantly associated with costs (charges multiply cost-to-charge ratios) for SOT hospitalizations while controlling for other covariates (i.e., demographic characteristics, comorbid conditions, type of organ transplant, and hospital-related characteristics).	H_6: There is a significant difference in hospital costs between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI while controlling for other covariates.	Gamma regression with log link	Not rejected

CDI= clostridium difficile infection; **SOT**= solid organ transplant; **LOS**= length of stay

3.4 Post-hoc power analyses

This study employed logistic regression and gamma log link regression analyses. Post-hoc power analyses were conducted in order to determine whether adequate statistical power based on actual sample sizes, odds ratios, and standard deviations from our observational data. The results of the post-hoc power analyses for each statistical procedure and its hypothesis testing are presented in Table 3.13. The results showed a wide range in power—from 0.09 to 0.99. Powers for H_1, H_2, H_3, and H_6 were below the targeted power of 0.8.

Table 3.13 Post-hoc power analyses

Hypothesis	Dependent variable	Statistical analysis	Estimated power
H_1	Hospital mortality	Logistic regression	0.09
H_2	Transplant rejection/failure	Logistic regression	0.42
H_3	Colectomy	Logistic regression	0.33
H_4	Length of stay	Gamma regression with log link	0.99
H_5	Charges	Gamma regression with log link	0.92
H_6	Costs	Gamma regression with log link	0.70

Chapter 4: Discussion

4.1 Review of study purpose and results

The aim of the present study was to evaluate the outcomes and expenditures of clostridium difficile infection (CDI) in pediatric solid organ transplant (SOT) recipients. We used the KID database from HCUP to generate national-level estimation. The overall prevalence of CDI for pediatric SOT events was 1.76%. For SOT admissions with CDI, hospital mortality was 1.63%; the prevalence of transplant failure or rejection event was 27.71%; the prevalence of a colectomy was 4.86%; the median length of stay in the hospital was seven days; the median hospital charge was $48,409; and the median hospital cost was $17,412. We found CDI was not significantly associated with higher mortality and transplant failure or rejection for pediatric SOT admissions. But CDI was significantly associated with a higher prevalence of a colectomy, a longer length of stay (LOS), higher hospital charges, and higher hospital costs.

4.2 Demographic characteristics

In this study, almost half the SOT admissions with CDI were for patients in the age category—1~4 years old (46.24%), followed by 5~9 years old (21.48%), 10~14 years old (18.54%), and 15~17 years old (13.73%). This age distribution is consistent with the results of CDI among hospitalized children in a previous study.[29] For the comorbid conditions, the prevalence of UTI in pediatric SOT events was less than the prevalence of UTI in adult SOT events (1.88% vs. 26.80%). This result may reflect the difference in the prevalence of UTI between children and adults—the prevalence of children with at least one UTI event before 10 years old was around 2.00%[122,123];

while the prevalence of adults with UTI ranged from 2~50% depending on gender and the type of UTI.[124,125] The majority pediatric SOT admissions were for patients with a score of zero on the CCI (SOT only: 62.29%; SOT+CDI: 67.37%) while most of the adult SOT admissions in the Pant et al. study were for patients with a CCI≥3 (SOT only: 58.4%; SOT+CDI: 66.6%).[72] This may be due to the fact that the CCI was developed for adult patients, not for pediatric populations.[107,108]

4.3 CDI prevalence

Overall, the prevalence of CDI in weighted SOT admissions was 1.76%. Admissions for intestine transplants had the highest CDI prevalence (2.90%), followed by lung (2.54%) and liver (2.43%) transplants. Among all type of organ transplant admissions, kidney transplant events had the lowest CDI prevalence (1.14%). In the adult population, Riddle and Dubberke had proposed that the difference in prevalence among different types of organ transplant may partially because of hypogammaglobuilinemia (low levels of serum immunoglobulin) commonly associated with lung, liver, and heart transplants and this may increase the risk of infection after organ transplantation.[62] In the pediatric population, several studies have also reported that hypogammaglobulinemia was observed after intestine, lung, and liver transplantation.[126-128] The decrease of immunoglobulin level may make these children more susceptible to CDI.

4.4 Post-hoc power analysis and sample size

Logistic regression analyses showed that the presence of CDI was not significantly associated with hospital mortality and transplant failure or rejection. However, the powers regarding their corresponding hypothesis testing (H_1 and H_2)

were below our targeted power value—0.8 (Hospital mortality: power=0.09; transplant failure/rejection: power=0.42). The low powers could be due to a small difference between group means, large variability within study group, or inadequate sample sizes.[129] The results indicated that the estimated sample sizes generated from adult populations were inadequate because of the different odds ratios for the presence of CDI between children and adults (OR for hospital mortality—adults: 2.48, children: 1.41; OR for transplant failure/rejection—adults: 1.36, children: 0.82).[72] Since a null hypothesis fails to be rejected if 1) no difference exist between group means; or 2) the power to adequately detect the test hypothesis is insufficient,[129] the non-significance of the association between "CDI and hospital mortality (H_1)" and the association between "CDI and transplant failure/rejection (H_2)" may be because the power to detect a difference was low.

Logistic regression showed that the presence of CDI was significantly associated with having a colectomy. However, the power for the corresponding hypothesis testing (H_3: power=0.33) was relatively lower than our targeted power value—0.8. This indicated there was a great difference in having a colectomy between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI. Therefore, although we had a small sample size, the difference between groups was still detected.

Gamma regression with log link showed that the presence of CDI was significantly associated with hospital LOS. The power for the corresponding hypothesis testing (H_4: power=0.99) was higher than our targeted power value—0.8. This indicated that we had adequate power to detect the difference between groups. The gamma regression with log link showed that the presence of CDI was significantly associated with hospital charges. The power for the corresponding hypothesis testing (H_5: power=0.92) was higher than our targeted power value—0.8.

This indicated that we had adequate power to detect the difference between groups.

Gamma regression with log link showed that the presence of CDI was significantly associated with hospital costs. The power for the corresponding hypothesis testing (H_6: power=0.70) was relatively lower than our targeted power value—0.8. This indicated that the difference in hospital costs between pediatric SOT admissions with CDI and pediatric SOT admissions without CDI was relatively large. Therefore, although the power was slightly lower than our targeted value due to the sample size, the difference between groups was still detected.

4.5 Mortality

The mortality rate for pediatric SOT events with CDI was 1.63%. This is less than the mortality rate for adult SOT events with CDI—7.4% reported by Pant et al. in 2012.[72] Previous studies have reported that a greater comorbid burden was significantly associated with an increased risk of patient death in adult solid organ transplants.[72,130,131] Therefore, it is likely that this difference is due to the difference in comorbid conditions between pediatric and adult populations.

In this study, the logistic regression procedure indicated that the presence of CDI was not significantly associated with hospital mortality after controlling for other covariates. One possible explanation is that pediatric transplant recipients stay in the intensive care unit and receive more medical surveillance than non-SOT patients. A previous study of adult SOT patients highlighted that close follow-up after transplantation might contribute to better outcomes for SOT patients with CDI.[6]

4.6 Transplant failure or rejection

The prevalence of a transplant failure or rejection for pediatric SOT events with

CDI was 27.71%. This is less than the prevalence for their adult counterpart—38.1%.[72] We found that there was no significant association between the prevalence of transplant failure or rejection and CDI using logistic regression analysis. Pant et al. had reported that CDI was significantly related to a higher risk of transplant failure or rejection in the adult population.[72] The difference in transplant failure or rejection prevalence and its association with CDI may explained by the difference in age-related immune functions between children and adults. For example, levels of adhesion receptor expression are age-dependent for different T cell subpopulations;[87] natural killer cell activity, proliferative response of T cells, cytotoxic response, and cytokine production are different in pediatric and adult populations.[132] Therefore, children with less mature immune function may be more likely to get infection but they may be less likely to have strong adaptive immune responses to alloantigens on the graft and thus reduce the chance of having transplant failure or rejection.[133] Further investigation may be needed to elucidate the factors explaining the difference among the association of transplant failure or rejection and CDI for pediatric and adult populations.

4.7 Colectomy

The prevalence of a colectomy for pediatric SOT admission with CDI was 4.86%, which is 2.6 times higher than SOT admissions without CDI. The result is higher than the colectomy prevalence in general CDI patients—1.25%—reported in the Kim et al. study.[30] Keven et al. has proposed that the severity of CDI depends on the antibody-mediated response to clostridial toxins.[67] Since SOT recipients use immunosuppression or monoclonal antibodies to prevent rejection, these factors may cause them to be more vulnerable to CDI and develop severe CDI, which often leads

to surgery to remove the diseased portion of the colon. The prevalence of colectomies in adult SOT events with CDI reported by Pant et al. was 1.1%, which is lower than the result from our pediatric population. A possible explanation is the difference in immune functions between children and adults. Another possible factor to consider is that the response to immunosuppression and the metabolism of immunosuppressant medications vary with age (e.g., T cells in infants are more sensitive than adult T cells to dexamethasone; pharmacokinetics of cyclosporine is different in children and adults).[134,135] Further analysis may be required to explore the reason for the different prevalence of colectomies for SOT events with CDI in pediatric and adult populations.

As we expected, because of the nature of CDI, the presence of a colectomy was significantly associated with CDI for SOT events while controlling other covariates in our logistic regression analysis. This is consistent with the results from an adult population in the Pant et al. study.[72] A possible explanation for this association is that—hypogammaglobulinemia is common after pediatric organ transplantation.[126-128] The decrease in levels of immunoglobulin may weaken the immune system and lead to worse outcomes when the patient gets CDI. Another possible may be the emergence of the more-virulent clostridium difficile strain—BI/NAP1/027, which has been reported with severe outcomes in children.[46,47]

4.8 Length of stay in hospital

The median hospital length of stay (LOS) for pediatric SOT admissions with CDI was 7 days, which was 2 times longer than SOT admissions without CDI. The result is shorter than the LOS in adult SOT events with CDI, reported as —9 days in the Pant et al. study.[72] We found that CDI was significantly associated with a longer

hospital LOS while controlling for other covariates in the gamma regression with log link analysis. The association might be, in part, due to the vulnerability to CDI triggered by hyogammaglobulinemia after organ. This may develop into severe CDI. If patients have shown symptoms of CDI, further laboratory tests to detect clostridium difficile may be required.[62] Once a patient is diagnosed with CDI, medication treatment (e.g., 10-14 days for metronidazole or vancomycin) or surgery performance is essential.[8] All of these factors—testing for clostridium difficile toxin, medication treatment, and surgery— may increase the number of days in the hospital.

4.9 Hospital charges and costs

The median hospital charges and costs for pediatric SOT events with CDI were $48,409 and $17,412, respectively. Both charges and costs for pediatric SOT admissions with CDI were 2 times higher than SOT admissions without CDI. We found that CDI was significantly associated with higher hospital charges and hospital costs while controlling for other covariates in the gamma regression with log link analysis.

The median hospital charge was lower than the median hospital charge for adult SOT events with CDI—$53,808—reported by the Pant et al. study.[72] The difference may be because adult SOT recipients have greater comorbid burdens. Specifically for adult SOT admissions with CDI, the majority had a CCI≧3 (66.6%)[72] while the majority in our pediatric study had a CCI=0 (67.37%). When patients have more complex chronic comorbid conditions, this is likely to result in higher hospital charges and costs.

A possible reason for charges and costs being significantly higher in pediatric SOT admissions with CDI than SOT admissions without CDI is because the immune

functions among patients who undergo SOT are weakened. Therefore, once CDI is diagnosed, these patients have a higher chance of developing severe CDI. They might need medication or even a colectomy for the treatment of CDI.[8] These CDI treatments may increase the charges, costs, and LOS. Because children who undergo organ transplantation often suffer from complex diseases, medication for complex diseases they have already had, those follow-up expenditures after organ transplant—immunosuppressant, laboratory tests, etc—charges and costs might increase the total charges and costs substantially if patients have longer LOS.

4.10 Limitations

The following potential limitations should be considered while interpreting the results of this study:

First, SOT patient selection was only based on ICD-9-CM diagnosis codes. Miscoding of ICD-9-CM codes may occur and lead to exclusion of those patients with relevant diagnoses. Also, disease severity could not be assessed from ICD-9-CM codes.

Second, several covariates regarding comorbid conditions for solid organ transplant recipients, such as BK virus and Estein-Barr virus infections, were not available in this study due to the lack of specific ICD-9-CM codes. As for the comorbidity index, we used CCI in this study. Although CCI is commonly used to account for patient comorbidities, the sensitivity of the CCI in this study is unknown since CCI is not a specific comorbidity index for pediatric populations.

Third, since we used a retrospective database, a number of covariates that may have explained partially significant variance in the dependent variables (e.g., prior use of antibiotics, laboratory values, and patient vitals) were not included in this study.

Fourth, the Kids' Inpatient Database contains discharge-level rather than patient-level data. This means readmissions cannot be identified—a patient with multiple hospitalizations in one year may have multiple records under different identifiers. Since we used discharge-level data, if one admission was due to a recurrence of CDI, the estimation of outcomes and expenditures remained unbiased, but the variances would become unstable.[136] However, Kelsen et al. reported that the recurrence rate for CDI in hospitalized pediatric patients was 7.5%, which only accounts for a small portion in hospitalized pediatric patients with CDI.[118] Therefore, although we used event-level data to capture the outcomes and expenditures of CDI in pediatric SOT recipients, the results may not be far from the results that would have been obtained if patient-level data were available.

Finally, before conducting this study, we estimated our minimum total required sample sizes based on the data from adult populations. After conducting post-hoc analyses to calculate the actual power of our test, it was found that the power for some tests was relatively small.

4.11 Strengths

Since the KID was designed to collect data from US hospitalized pediatric populations, the samples represented our target population fairly well. Also, the dataset used for this study, the Kids' Inpatient Database (KID), is a nationally representative database. Thus, the generalizability of this study was more expansive than studies using a database from a single institution or single population.

4.12 Conclusions and suggestions for future research

The results of this study suggest that CDI is not significantly associated with higher hospital mortality and transplant failure or rejection. However, our results implicate CDI as a factor significantly related to a higher prevalence of colectomies, longer hospital LOS, higher charges, and higher costs.

In general, health care providers need to be aware of risk factors for CDI in pediatric SOT recipients. Patients with diarrhea after organ transplantation should be evaluated carefully. In order to avoid substantially higher expenditures and health care utilization, CDI in pediatric SOT recipients should be promptly diagnosed and treated.

Future research can use other data sources which include other important explanatory covariates (e.g., record of prior antibiotic use, laboratory data) and have more work on building and validating general comorbidity index for pediatric populations. Further investigation may focus on elucidating the factors that explain the difference of the association among outcomes, expenditures, and CDI between pediatric and adult populations.

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