ORIGINAL ARTICLE

Clinical and economic burden of infections in hospitalized solid organ transplant recipients compared with the general population in Canada – a retrospective cohort study

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SUMMARY

Infections continue to be a major cause of post-transplant morbidity and mortality, requiring increased health services utilization. Estimates on the magnitude of this impact are relatively unknown. Using national administrative databases, we compared mortality, acute care health services utilization, and costs in solid organ transplant (SOT) recipients to nontransplant patients using a retrospective cohort of hospitalizations in Canada (excluding Manitoba/Quebec) between April-2009 and March-2014, with a diagnosis of pneumonia, urinary tract infection (UTI), or sepsis. Costs were analyzed using multivariable linear regression. We examined 816 324 admissions in total: 408 352 pneumonia; 328 066 UTI's; and 128 275 sepsis. Unadjusted mean costs were greater in SOT compared to non-SOT patients with pneumonia [(C$14 923 ± C$29 147) vs. (C$11 274 ± C$18 284)] and sepsis [(C$23 434 ± C$39 685) vs. (C$20 849 ± C$36 257)]. Mortality (7.6% vs. 12.5%; $P < 0.001$), long-term care transfer (5.3% vs. 16.5%; $P < 0.001$), and mean length of stay (11.0 ± 17.7 days vs. 13.1 ± 24.9 days; $P < 0.001$) were lower in SOT. More SOT patients could be discharged home (63.2% vs. 44.3%; $P < 0.001$), but required more specialized care (23.5% vs. 16.1%; $P < 0.001$). Adjusting for age and comorbidities, hospitalization costs for SOT patients were 10% (95% CI: 8–12%) lower compared to non-SOT patients. Increased absolute hospitalization costs for these infections are tempered by lower adjusted costs and favorable clinical outcomes.

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Introduction

Organ transplantation is one of the great advances in modern medicine and often the only treatment for end-stage organ failure. It has been shown to improve quality of life and is associated with lower health care costs than some traditional treatments for chronic organ diseases, such as dialysis for patients with end-stage renal disease [1–3]. However, even with these benefits, organ transplantation is an enormously expensive procedure. To evaluate the overall costs of transplantation, the Milliman Research Report analyzed several costs including the 30-day pretransplant period, organ procurement, the hospital transplant admission, physician

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charges during transplant, the 180-day post-transplant discharge period, and outpatient immunosuppressants as well as other medications. The report estimated that in 2014, the average billed charges in the United States per organ, ranged from $317 500 (USD) for a pancreas transplant at the least expensive end of the spectrum, to an intestine transplant at $1 546 200 (USD) [4]. In 2011, The United Network for Organ Sharing (UNOS) stated the average cost billed for pre- and up to 6 months post-transplant was as follows: for heart transplant $997 700 (USD), for a double lung transplant $561 200 (USD), for kidney $262 900 (USD), and intestine $1 206 800 (USD) [5]. In a Canadian study authored by Levy *et al*. [6], the mean costs of transplantation varied from $27 695 (CAD) for kidney recipients to $89 942 (CAD) for lung recipients. The majority of the cost was accrued from inpatient hospital stays [6]. In the second year of transplantation, immunosuppressant medications constitute two-thirds, to three-fourths of overall costs [6]. Both public and private third-party payers bear these high transplant costs [7].

Given the high costs of transplantation, it is important to ensure successful procedures, with the objective of improving graft and patient survival. Improvements in surgical techniques and immunosuppressive medications have enhanced both graft and patient survival rates, however, infection continues to be a major cause of morbidity and mortality among solid organ transplant (SOT) recipients [8–14]. A study by Dharnidharka, *et al*. using the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) dataset found that the causes of hospitalization over the years have shifted. Historically, the primary cause was acute rejection, whereas more recently post-transplant infections have become the principal reason for hospitalization [15]. Infections clearly contribute to post-transplant morbidity, mortality, and costs, but estimates on the magnitude of this impact in contemporary national samples are lacking [16]. In addition to their impact on survival, infections also increase the intensity and costs of post-transplant care [16]. In the first and second years after kidney transplantation, urinary tract infections (UTI), respiratory tract infections, and sepsis rank among the top five most common causes of re-hospitalization [17]. In a prior study of kidney transplant recipients, Medicare costs in the first-year post-transplant increased by $29 787 (USD) in those who developed sepsis and $18 107 (USD) in those with pneumonia [18]. It was noted to cost an additional $10 964 (USD) in patients who had evidence of both infections [18].

The cost of infections in transplant patients is considerable from hospital and societal perspectives, and in countries with a public health care system, these costs can be prohibitive. It is important to gauge costs associated with transplant infections and their determinants, in order to devise strategies that are more cost effective in managing these patients. Previous economic studies have focused on a single center or on only one type of transplant [16,19]. The objective of this study was to compare the clinical outcomes and direct medical costs associated with hospitalization for specific infections such as pneumonia, UTI, and sepsis in a national cohort of SOT recipients to nontransplant patients in Canada.

Materials and methods

Study design, population, and data sources

We performed a national administrative database analysis with data obtained from the Canadian Institute for Health Information (CIHI) using validated ICD-10-CA codes. We included all Canadian SOT recipients who were discharged from a hospital between April 1, 2009 and March 31, 2014, with the diagnosis of pneumonia, UTI, or sepsis (Tables S1–S3). We excluded the provinces of Manitoba and Quebec, and all territories since their data were not available in the dataset CIHI provided (this represented about 27% of the Canadian population [20]. The dataset provided included data from the Canadian Organ Replacement Register (CORR) and Discharge Abstract Database (DAD). CORR provides in-depth reports and analyses of all Canadian organ transplant recipients that are collected from transplant programs across Canada. The data includes information from the first treatment for end-stage organ failure until the patient's death. DAD captures administrative, clinical, and demographic information on hospital discharges such as, deaths, sign-outs, and transfers with the exception of the provinces of Manitoba and Quebec. DAD also provided data elements about use of specialized care units. Specialized care units were defined as inpatient units specifically designed, staffed and equipped for the continuous observation and treatment of critically ill patients, including all types of intensive care units, as well as intermediate care or step-down units" (Table S4) [21].

A subset database of DAD known as the Hospital Morbidity Database (HMDB) provided data on patient morbidity. Charlson comorbidities were analyzed as indicators of health status [22]. We collected and analyzed data when pneumonia, UTI, and sepsis were coded

as diagnosis type (M), as well as when it was not. Diagnosis type (M) is the one diagnosis or condition that can be described as being most responsible diagnosis (MRD) for the patient's stay in hospital. If there is more than one such condition, the one held most responsible for the greatest portion of the length of stay or greatest use of resources (e.g., operating room time, investigative technology) is selected [23]. The study was approved by the University of Toronto/University Health Network Institutional Review Boards (14-8718-AE).

Measuring costs

In the Canadian health care system, provincial governments are the sole funders of hospital and physician services for hospitalized patients. All costs were calculated in 2014 Canadian dollars, using Statistics Canada's consumer price index for health and personal care [24,25]. CIHI provided the resource intensity weight (RIW), which is the relative cost weight value assigned to each patient care episode [26]. RIW reflected the resource intensity of each patient care episode and is adjusted for a number of factors (including age, comorbidity level and selected interventions). The cost per weighted case (CPWC) was also provided by CIHI [26]. CPWC is the average cost of one patient receiving service in a hospital that was calculated using the total costs provided by the hospitals. The cost estimate is the estimated full cost of hospital services for the selected patient care episode. The estimates include the costs incurred by the hospitals in providing services and exclude physician costs, since physicians are normally paid directly by the jurisdiction. The hospital costs include labor, nursing and allied health professional, pharmacy (drugs), supply, medical imaging, laboratory, as well as overhead costs.

Statistical analysis

Values were expressed as the mean (standard deviation) or median (interquartile range) for continuous variables depending on the distribution or as a count (percent) for categorical variables. We compared groups using the Student *t* test, chi-squared test, or Wilcoxon rank sum test as appropriate. The criterion for statistical significance was set *a priori* at $\alpha = 0.05$, with all tests of significance being two-tailed. To estimate the effect of transplantation and other predictors on costs, we first transformed the outcome variable of costs using the natural logarithm, and generated a linear regression model with robust standard error corrections. Models were adjusted for age (continuous 10-year increments); gender (male/female); fiscal year (2009–2013); and Charlson comorbidity index (transformed into groups: 0, 1–2, 3–4, >4). All data were analyzed using STATAMP 12® (StataCorp LP, College Station, TX, USA).

Results

Demographics

From 2009 until 2013, 809 849 non-SOT and 6475 SOT patients were hospitalized with diagnoses of pneumonia, UTI, or sepsis. There were 408 352-recorded hospitalizations with the diagnosis of pneumonia, 328 066 for UTIs, and 128 275 for sepsis (Table 1). The median age for SOT patients with pneumonia, UTI, and sepsis was 60, 58, and 59 years, respectively. Males made up the majority in nontransplant and SOT populations except in the cohort diagnosed with UTIs (Table 1). The distribution of coded diagnoses associated with Charlson comorbidities was statistically significant between SOT and non-SOT groups in all three of the infection groups, with the exception of peripheral vascular disease (Table 1). Kidney recipients with any of the three infectious diagnoses followed by lung transplant recipients with pneumonia were the most frequently admitted patients (Fig. 1). For the SOT group, the median time post-transplant was 11 months (IQR: 4–22 months).

Clinical and economic characteristics

The use of infectious disease consultation was more common in the SOT cohort across all three infectious diagnoses (Pneumonia as MRD: Non-SOT 3.3% vs. SOT 19%; $P < 0.001$, Pneumonia for all diagnosis: Non-SOT 3.8% vs. SOT = 20.4%; $P < 0.001$, UTI as MRD: Non-SOT 3.9% vs. SOT 17% $P < 0.001$, UTI as all diagnosis: Non- SOT 4.5% vs. SOT 17.1%, $P < 0.001$. Sepsis as MRD: Non-SOT 12.4%, SOT 22.7%, $P < 0.001$; Sepsis as all diagnosis: Non-SOT 14% vs. SOT 25%, $P < 0.001$). This also varied by province, with Ontario having the highest rates of infectious disease consultation (22.8%), and Prince Edward Island the lowest (0%). Of the patients admitted with sepsis as the most responsible diagnosis, 45% were assigned at least one other infectious-related diagnostic code. These included urinary tract infections (22%), pneumonia (20%), abdominal (7%), and skin/soft tissue (1%). The proportion of patients that required transfer to a long-term care (LTC) facility were noted to be less in SOT groups (Tables 2 and S5). Specialized care units (SCUs) were utilized more often by the SOT group, however, for the diagnosis of

Table 1. Characteristics of nontransplant and transplant patients among those diagnosed with pneumonia, urinary tract infection, and sepsis.

	Pneumonia (*n* = 408 352)		Urinary tract infection (*n* = 328 066)		Sepsis (*n* = 128 275)	
Patient demographic	Non-SOT (% or range) (*n* = 405 617)	SOT (% or range) (*n* = 2735)	Non-SOT (% or range) (*N* = 325 385)	SOT (% or range) (*n* = 2681)	Non-SOT (% or range) (*n* = 126 841)	SOT (% or range) (*n* = 1434)
Age (years), mean (SD)	72.2 (16.3)	56.3 (15.6)	75.2 (15.6)	54.6 (16.3)	68.1 (16.7)	56.6 (14.1)*
Male gender	207 801 (51%)	1733 (63%)	113 844 (35%)	1079 (40%)*	68 418 (54%)	884 (62%)*
Fiscal year						
2009	76 806 (19%)	492 (18%)	57 031 (18%)	411 (15%)	20 732 (16%)	251 (18%)
2010	79 175 (20%)	527 (19%)	61 421 (19%)	503 (19%)	23 305 (18%)	252 (18%)
2011	80 575 (20%)	587 (21%)	66 045 (20%)	552 (21%)	25 190 (20%)	298 (21%)
2012	86 717 (21%)	550 (20%)	70 648 (22%)	604 (23%)	28 581 (23%)	286 (20%)
2013	82 344 (20%)	579 (21%)	70 240 (22%)	611 (23%	29 033 (23%)	347 (24%)
Charlson comorbidity index						
Mean (SD)	1.8 (1.8)	2.6 (1.9)*	1.6 (1.8)	3.0 (1.4)*	1.9 (1.9)	3.1 (1.8)*
Median (IQR)	1 (0, 3)	2 (1, 4)*	1 (0, 2)	2 (2, 4)*	2 (0, 3)	3 (2, 4)*
Comorbidities						
Acute myocardial infarction	23 713 (5.9%)	102 (3.7%)*	15 473 (5%)	98 (4%)*	8849 (7%)	93 (6%)
CHF	81 874 (20%)	341 (13%)*	37 988 (12%)	142 (5%)*	16 070 (13%)	114 (8%)*
PVD	6107 (2%)	47 (2%)	5341 (2%)	47 (2%)	4410 (3%)	49 (3%)
Cerebrovascular accidents	10 999 (3%)	47 (2%)*	18 162 (6%)	47 (2%)*	4715 (4%)	41 (3%)
Dementia	29 972 (7%)	31 (1%)*	48 374 (15%)	38 (1%)*	9228 (7%)	11 (1%)*
COPD	147 468 (36%)	386 (14%)*	30 828 (9%)	99 (4%)*	14 892 (12%)	82 (6%)*
Rheumatoid disease	5695 (1%)	53 (2%)*	4207 (1%)	63 (2%)*	2081 (2%)	24 (2%)
PUD	2265 (1%)	17 (1%)	2758 (1%)	12 (1%)*	1933 (2%)	12 (1%)*
Mild liver disease	4821 (1%)	364 (13%)*	3902 (1%)	245 (9%)*	3790 (3%)	313 (22%)*
Moderate liver disease	2264 (1%)	26 (1%)*	3241 (1%)	35 (1%)	3549 (3%)	55 (4%)*
Diabetes + complications	64 137 (16%)	789 (29%)*	57 462 (18%)	859 (32%)*	27 314 (22%)	481 (34%)*
Diabetes	40 388 (10%)	306 (11%)*	39 008 (12%)	251 (9%)*	13 539 (11%)	128 (9%)*
Renal disease	24 525 (6%)	1575 (58%)*	21 987 (7%)	2362 (88%)*	10 951 (9%)	1021 (71%)*
Hemiplegia or paraplegia	3499 (1%)	16 (1%)	8291 (3%)	16 (1%)*	2510 (2%)	8 (1%)*
Cancer	30 987 (8%)	114 (4%)*	18 789 (6%)	75 (3%)*	12 406 (10%)	62 (4%)*
Metastatic cancer	17 651 (4%)	56 (2%)*	13 041 (4%)	22 (1%)*	7150 (6%)	35 (2%)
AIDS	1783 (0.44%)	0 (0)*	311 (0.1%)	4 (0.2%)	571 (0.5%)	0

AIDS, acquired immunodeficiency syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease, PVD, peripheral vascular disease; PUD, peptic ulcer disease.

**P*-value < 0.05 for comparison between non-SOT and SOT groups.

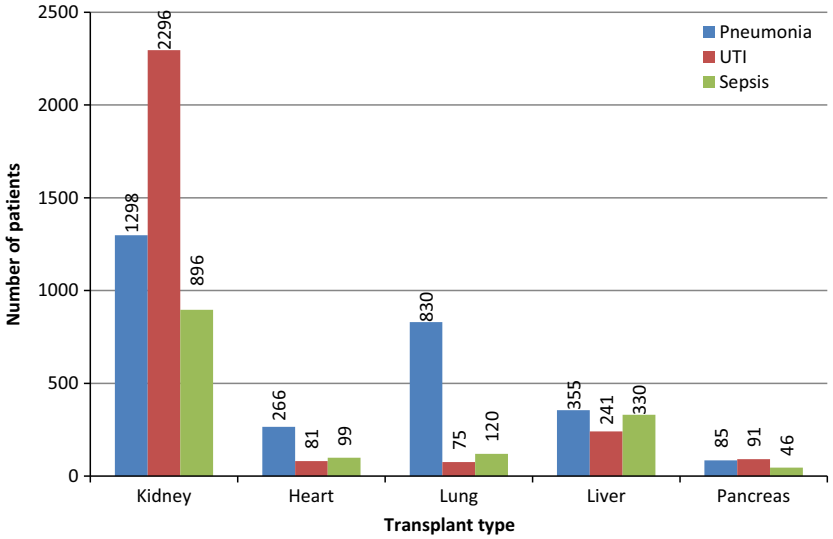

Figure 1 Allograft types among solid organ transplant patients for each diagnoses. Bar chart showing the numbers of transplant admissions reviewed in this study, for pneumonia, urinary tract infection and sepsis. UTI, urinary tract infection.

pneumonia and UTI the time spent in these units was less than the non-SOT group (Table 2). The SOT group was found to have decreased total lengths of stay (LOS) compared to the non-SOT group across all three infectious diagnoses (Table 2).

Overall, the unadjusted mean cost of each admission was greater among SOT ($14 613, SD = $29 177) patients compared to non-SOT ($12 879, SD = $22 000) patients ($P < 0.001$). The mean cost of each admission was greater when an SOT patient was diagnosed with pneumonia [Non-SOT group mean = $11 274 (SD = $18 284) vs. SOT group mean = $14 923 (SD = $29 147)] and sepsis [Non-SOT mean = $20 849 (SD = $36 257) vs. SOT group mean = $23 434 (SD = $39 685)] (Fig. 2). This was reversed for those diagnosed with UTI, with the mean cost of a non-SOT patient admission being greater compared to non-SOT [Non-SOT group mean = $12 407 (SD = $19 143) vs. SOT group mean = $10 590 (SD = $21 884)]. Additionally, hospitalization costs varied across provinces, with New Brunswick ($11 568, SD = $21 007), Ontario ($11 913, SD = $20 551), and Prince Edward Island ($12 049, SD = $17 806) having the lowest mean costs, and Nova Scotia ($13 408, SD = $23 591), Newfoundland and Labrador ($13 418, SD = $23 339) and Alberta ($17 287, SD = $28 399) having the highest mean costs. When compared among SOT patients, lung ($21 553, SD = $42 282) and liver ($17 119, SD = $33 566) allograft recipients had the highest associated costs, followed by heart ($15 864, SD = $37 968), kidney ($12 406, SD = $22 372), and pancreas ($11 268, SD = $22 372) recipients. Mortality at discharge was lower in the SOT compared to non-SOT groups, with a higher proportion of patients discharged home alive (Table 2).

Multivariable linear regression analysis

In the multivariable linear regression analysis for each diagnosis, hospitalization costs increased as the number of Charlson comorbidities increased. In the cost analysis, we found that the overall hospitalization costs to the Canadian healthcare system was lower for SOT patients compared to the non-SOT group. After adjusting for age, gender, fiscal year, and Charlson comorbidity index, costs were lower by 10% [exp (coefficient) = 0.90, CI = 0.88–0.92] when coded as any type of diagnosis, and 7% less [exp(coefficient) = 0.93, CI = 0.91–0.96] when these infections were coded as the most responsible diagnosis (Tables 3 and S6). These lower costs were driven by decreased costs of UTI and sepsis, whereas costs associated with pneumonia were actually increased.

Discussion

In this national Canadian administrative database analysis, we report that hospitalizations for pneumonia, UTI, and sepsis cost 7–10% less for SOT compared to non-SOT patients when controlling for age, gender, and comorbidities. To our knowledge, this study is the largest national study published comparing nontransplant patients to SOT recipient's clinical outcomes and healthcare costs of hospitalized patients for three infectious syndromes: pneumonia, UTI, and sepsis. It is the only study available that has investigated the cost impact of these diagnoses among different solid organ transplants. We also report that actual unadjusted mean hospitalization costs were greater for SOT compared to non-SOT patients treated for pneumonia and sepsis.

Table 2. Clinical outcomes and resource utilization for pneumonia, urinary tract infection, and sepsis when coded as any type of diagnosis.

	Pneumonia – all diagnoses			UTI – all diagnoses			Sepsis – all diagnoses			Combined – all diagnoses		
	Non-SOT (n = 405 617)	SOT (n = 2735)	P-value	Non-SOT (n = 325 385)	SOT (n = 459)	P-value	Non-SOT (n = 126 841)	SOT (n = 1434)	P-value	Non-SOT (n = 809 849)	SOT (n = 6475)	P-value
Transfer LTC, n (%)	53 272 (13.1)	118 (4.3)	<0.001	75 396 (23.2)	174 (6.5)	<0.001	17 013 (13%)	90 (6%)	<0.001	133 471 (16.5)	342 (5.3)	<0.001
Death at discharge, n (%)	50 628 (12.5)	205 (7.5)	<0.001	26 429 (8.1)	71 (2.7)	<0.001	32 841 (26)	244 (17)	<0.001	101 427 (12.5)	489 (7.6)	<0.001
Discharged to home, n (%)	202 131 (49.8)	1747 (63.9)	<0.001	129 928 (39.9)	1860 (69.4)	<0.001	41 057 (32)	681 (47)	<0.001	358 681 (44.3)	4089 (63.2)	<0.001
Need for SCU, n (%)	60 300 (14.9)	683 (25)	<0.001	30 712 (9.4)	315 (11.8)	<0.001	49 325 (39)	640 (45)	<0.001	130 050 (16.1)	1519 (23.5)	<0.001
Time spent in SCU (h)												
Mean (SD)	179.4 (331.8)	221.5 (326.1)	0.001	158.3 (335.8)	145.1 (223.3)	0.48	209.7 (392)	213.7 (287.3)	0.79	182.8 (347.7)	202.2 (296)	0.030
Median (IQR)	102 (50, 196)	119 (54, 242)	<0.001	87 (45, 164)	80 (43, 139)	0.14	109 (48, 233)	116 (51, 247)	0.12	98 (48, 198)	108 (49, 227)	0.005
Length of stay (days)												
Mean (SD)	11.2 (21.2)	11.7 (17.1)	0.25	14.8 (28.4)	8.9 (16)	<0.001	15.9 (29)	14.6 (21.5)	0.33	13.1 (24.9)	11 (17.7)	<0.001
Median (IQR)	6 (3, 12)	7 (4, 12)	<0.001	7 (4, 15)	5 (3,9)	<0.001	8 (4, 17)	7 (4, 16)	0.003	7 (3, 14)	6 (3, 11)	<0.001

IQR, interquartile range; LTC, long-term care; SCU, specialized care unit; SD, standard deviation; SOT, solid organ transplant; UTI, urinary tract infection.

However, clinical outcomes such as length of stay, rates of discharge directly to home, and mortality were all more favorable in SOT recipients. Although non-SOT patients were found to have overall increased lengths of stay for these three infections, this difference seems to be driven by those admitted for UTIs. However, since hospitalization costs for UTIs were lower compared to the other two infectious complications, this had a relatively mild impact on overall costs. The main driver of costs seemed to be a result of the increased use of specialized care units and increased costs associated with pneumonia and sepsis diagnosis.

Advances in transplantation, such as the development of new immunosuppressive strategies and new surgical techniques, have improved the long-term survival rates of both the graft and the patient, while decreasing the rates of rejection [27,28]. However, even with these successful interventions, infections remain a major complication of transplantation and are large contributors to mortality rates in SOT recipients [29–32]. Organ transplantation and its complications prove to be a costly investment that can significantly influence the socioeconomic status of healthcare systems. Current literature has produced a number of studies that have investigated the cost of infections, especially healthcare-associated infections and antibiotic usage, in nontransplant populations [33–37]. The cost to treat pneumonia has been studied in the nontransplant population with one study reporting the costs of community-acquired pneumonia treatment to be mostly attributable to unwarranted hospital admission (or unnecessarily long hospital stays) in cases of mild pneumonia, as well as over prescription of antibiotics [37]. Another study reported that hospital admissions for sepsis were more costly compared with other admissions including chronic obstructive pulmonary disease, heart failure, acute myocardial infarction, and pneumonia [38].

Costing literature in the SOT population revolves around cost-effectiveness and quality of life of transplantation, versus traditional care for patients with end-stage organ failure. The majority only report data on one type of organ transplantation or one infectious syndrome [18,39–44]. Naik *et al.* [16], used the United States Renal Data System for Medicare insured kidney transplant recipients from 2000 to 2011 to study the clinical cost and impact of UTI, pneumonia, and sepsis in kidney transplant recipients. Their results showed that a diagnosis for any of these three infections significantly increases first-year Medicare billing claims. Clinical and economic impacts also persisted in years 2 and 3 post-transplant. However, this study only included one organ transplant type, did not compare cohorts against the general

population, and did not control for comorbidities. Our results were different in comparison to Naik *et al.* [16], in that our incremental marginal costs for pneumonia and sepsis compared to UTI were about one-third of that reported by Naik *et al.*, perhaps reflecting a difference in efficiencies between Canadian and US public payers [45,46]. In addition, we report variability across different provinces within Canada, which may require further investigation as to whether this is a result of more efficient healthcare provision or other patient factors.

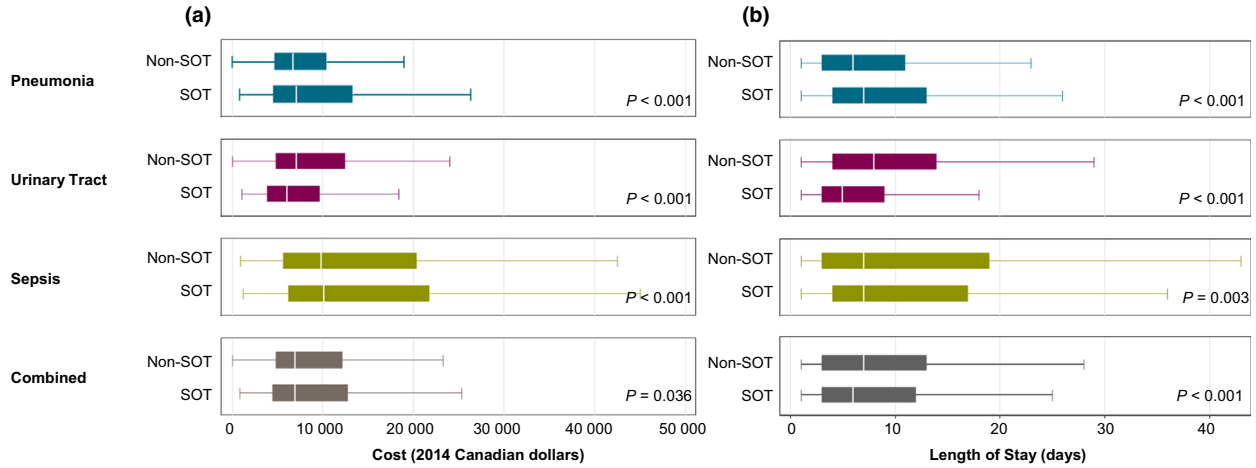

Figure 2 Cost analysis. Box-plot showing the (a) costs in 2014 Canadian Dollars, and (b) length of stay in days, for pneumonia, urinary tract infection, sepsis and combined cases in solid organ transplant compared to nonsolid organ transplant patients. Groups are compared using the Wilcoxon rank sum test. SOT, solid organ transplant.

Table 3. Multivariable linear regression analysis for hospitalization costs associated with pneumonia, urinary tract infection and sepsis when coded as any type of diagnosis.

	Pneumonia – all diagnoses		UTI – all diagnoses		Sepsis – all diagnoses		Combined – all diagnoses	
Variable*	Exp (β)	95% CI	Exp (β)	95% CI	Exp (β)	95% CI	Exp (β)	95% CI
Transplantation								
Non-SOT	Reference							
SOT	1.06	1.02–1.09	0.76	0.74–0.79	0.89	0.84–0.94	0.90	0.88–0.92
Age (continuous 10-year increments)	1.00	1.00–1.001	1.003	1.0029–1.0032	0.99	0.99–0.99	1.00	0.9995–0.9998
Gender								
Female	Reference							
Male	1.01	1.00–1.01	0.966	0.96–0.97	1.04	1.03–1.05	0.996	0.992–0.999
Fiscal year								
F2009	Reference							
F2010	0.98	0.97–0.99	0.98	0.97–0.99	0.95	0.93–0.96	0.976	0.970–0.981
F2011	0.99	0.98–0.99	0.981	0.97–0.99	0.96	0.94–0.98	0.986	0.980–0.992
F2012	1.01	1.01–1.02	1.002	0.99–1.01	0.97	0.96–0.99	1.012	1.006–1.018
F2013	1.02	1.01–1.03	0.992	0.98–1.001	0.96	0.94–0.97	1.012	1.007–1.018
Charlson comorbidity index								
0	Reference							
1–2	1.31	1.30–1.31	1.294	1.29–1.3	1.28	1.26–1.30	1.283	1.278–1.288
3–4	1.65	1.64–1.67	1.645	1.63–1.66	1.67	1.64–1.7	1.644	1.635–1.653
>4	1.75	1.73–1.76	1.833	1.81–1.85	1.56	1.53–1.60	1.747	1.734–1.761

SOT, solid organ transplant; UTI, urinary tract infection.

*Models adjusted for age (continuous 10-year increments); gender (male/female); fiscal year (2009–2013); and Charlson comorbidity index (transformed into groups: 0, 1–2, 3–4, >4).

The reasons of lower overall adjusted costs of caring for SOT patients were not specifically assessed in our study, however, possible reasons could include closer outpatient follow-up, a well-established relationship with a multi-disciplinary team, and lower threshold for specialized care admissions. SOT patients also have depressed or absent inflammatory responses and therefore, may lack expected clinical and radiographic signs and symptoms of infection during initial evaluation [47]. This population is known to have atypical presentations caused by opportunistic organisms and can suffer from a more diverse range of pathogens. The atypical presentations, broader list of possible pathogens, coupled with the high potential for rapid deterioration without appropriate therapy favors a prompt and aggressive approach. This can lead to more laboratory testing and imaging, use of extended spectrum medications, and pursuit of monitoring in specialized care units which creates an environment of expeditious diagnosis and treatment [47]. All of these reasons may lead to more timely medical intervention compared to non-SOT patients who may lack close access to a long-lasting relationship to a medical network [48].

Use of infectious diseases consultation may have also contributed towards lower adjusted overall costs. The use of infectious disease consultations has been shown to positively impact the quality of care of patients with various infectious syndromes [49–53]. This study reported that transplant patients were 2–5 times more likely to utilize infectious diseases consultations. Similar to other studies, our data showed improved outcomes such as decreased mortality and reduced transfer to an LTC facility, as more transplant recipients were able to be transferred to home compared to nontransplant patients [54,55]. Poor outcomes such as loss of life and productivity, or reduced quality of life also incur additional economic costs [56]. Our SOT cohort was noted to have decreased mortality, and decreased number of transfers to LTC, as more patients could be discharged directly home. Although more SOT patients were seen to require transfer to an SCU, the time actually spent in the SCU was less compared to nontransplant patients treated for all three infections (Tables S7–S9). The use of specialized care units could have played a role in the decreased adjusted costs of the SOT cohorts [57–59]. Prompt and appropriate medical attention may have optimized patient care, since lengths of stay were seen to be shorter in the all three infectious diagnosis SOT groups.

Our observation of lower mortality among SOT recipients has been demonstrated previously, at least for those diagnosed with sepsis. In a matched, propensity score–adjusted analysis of bacteremic sepsis patients, presenting to a tertiary care academic medical center in the United States, Kalil *et al*. [60] reported that SOT recipients had lower mortality following sepsis. In another study, SOT recipients hospitalized with sepsis exhibited lower mortality overall compared with the non-SOT population, however, patients with kidney, liver transplants, or co-transplants experienced lower sepsis mortality, whereas lung transplant recipients demonstrated increased mortality [61]. For sepsis, the authors of these studies have suggested that immunosuppression may actually provide a survival advantage through attenuation of the inflammatory response [60,61]. Better outcomes associated with the SOT population may also be related to extra vigilance due to their immunocompromised status, lower threshold for hospital admission and perhaps early detection of the infectious disease due to increased surveillance, especially for UTI in kidney transplant recipients and pneumonia in lung transplant recipients. However, based on the higher Charlson comorbidity index scores and higher proportion of comorbidities overall in the SOT patients, they were clearly sicker than the nontransplant patients at hospital admission, thus, faster healthcare access alone may not explain the better survival outcomes. This is an area where further research specific to solid organ transplant recipients should be investigated. Clinical pathways or guidelines based on these results can further cut down the costs without compromising the safety of the patients.

The limitations of this study include the use of a Canadian administrative data set. As with all administrative data set studies, the results are dependent on the coding and data entry techniques at each institution, systematic biases may be introduced due to differences in data input methods. Our study relied on the use of administrative coding as a substitute for diagnoses. Coding errors are possible in this scenario and it was not possible to access individual patient records to confirm the accuracy of submitted data. Furthermore, the results may have limited external validity in jurisdictions that do not possess a universal healthcare system such as the one found in Canada. Data related to a number of potentially relevant confounding variables such as medication/immunosuppression use, microbiological data, laboratory results, and radiologic information were not available. Use of these databases also did not provide any additional procedural or surgical information, such as placement of stents, drains, tubes, or catheters, to help us assess relevant triggers for infection risk. However, the intention of our study was to assess the cost associated with treatment of these specific infectious syndromes rather than the risk factors associated with the development of infections. Despite the limitation stated, administrative database studies have been routinely performed for cost analysis [62]. Moreover, we chose only three

infectious syndromes and did not assess the outpatient costs associated with them. We would argue that these three diagnoses will constitute the majority of infectious syndromes as reported previously [63,64], and that inpatients costs exceed the out patients costs [36,65,66]. Additionally, our analysis excluded the provinces of Manitoba and Quebec, and all Canadian territories since their data were not available to us, representing about 27% of the Canadian population. Although this analysis may not represent the overall true costs associated with the treatment of these infectious syndromes, it provides a good approximation of the cost incurred by these patients while admitted in the hospital.

In summary, this study shows hospitalizations cost more in SOT patients treated for pneumonia, UTI, and sepsis. However, the clinical outcomes, such as discharge to home, decreased mortality, and length of stay are all more favorable in transplant patients. When controlling for age and comorbidities, this study reports that the overall healthcare costs for transplant recipients is 10% less than nontransplant patients who are diagnosed with these clinical syndromes. Future research needs to focus on the use of overall health care resources utilized by these patients both while admitted, and not admitted to hospital. The high utilization of SCUs by transplant recipients suffering from these clinical syndromes provides us the opportunity to optimize the overutilization, by developing clinical care pathways identifying transplant recipients with pneumonia, UTI, or sepsis who will benefit most from admission to a specialized ICU.

Authorship

All authors contributed to the work presented in this paper. BH: study design, data collection, data analysis, data quality assurance, writing and critical review of manuscript. NL: study design, data collection, data analysis, data quality assurance, writing and critical review of manuscript. AA: data collection and critical review. EAP: critical review, acquisition of data, conceptualization of concept. I was responsible for the study design, data collection, data analysis, writing, and critical review of the manuscript.

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Conflicts of interest

The authors have the following relevant disclosures: Shahid Husain has received grant funding from Merck and Astellas, and consultancy fees from Cidara. Emmanuel A. Papadimitropoulos is an employee of Eli Lilly and Company.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. ICD-10-CA discharge diagnosis codes identifying pneumonia infections.

Table S2. ICD-10-CA discharge diagnosis codes identifying urinary tract infections.

Table S3. ICD-10-CA discharge diagnosis codes identifying sepsis.

Table S4. Canadian Institute for Health Information special care unit codes.

Table S5. Clinical outcomes and resource utilization for pneumonia, UTI and sepsis when coded as most responsible diagnosis.

Table S6. Multivariable linear regression analysis for hospitalization costs associated with pneumonia, UTI and sepsis when coded as most responsible diagnosis.

Table S7. Use of specialized care units – number and percent of total admissions by province.

Table S8. Time spent in specialized care units (h).

Table S9. Proportion of patients discharged directly home by province.

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