A Retrospective Cohort Study of Risk Factors for Surgical Site Infection Following Liver Transplantation

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Abstract

Background: Surgical site infection is an important complication in the postoperative period among liver transplant recipients. However, little is known about the risk factors in this patient group. Therefore, the objective of this study was to analyze the incidence and risk factors for surgical site infections among adult liver transplant recipients. **Methods:** Medical records of adult liver transplant recipients from January 1, 2009, to December 31, 2015, were analyzed in this retrospective cohort study. **Results:** We enrolled 156 recipients' medical records. Forty-two (26.9%) cases of surgical site infections were identified. The main isolated microorganisms were methicillin-resistant *Staphylococcus* species, extended spectrum β-lactamase-producing *Klebsiella* species, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and vancomycin-susceptible *Enterococcus faecalis*. We found that long operative times ($\geq$487 minutes) and differences in body mass index between donor and recipient ($\geq$1.3 kg/m^2) increased the risk for surgical site infections by approximately 5 times (odds ratio [OR], 5.5; 95% confidence interval [CI], 2.5-11.8), and capillary glycemia $\geq$175 mg/dL in the first 96 postoperative hours increased the risk by approximately 3 times (OR, 2.97; 95% CI, 1.43-6.17). **Conclusions:** There was a high incidence of surgical site infections among the studied population and that some risk factors identified differ from those reported in the scientific literature.

Keywords

health-care-associated infections, surgical wound infection, prevention and control, hepatic transplantation, immunocompromised host

Background

Surgical site infection (SSI) is among the leading health-care-associated infections (HCAIs), involving serious complications that contribute to an increase in morbidity and mortality in the postoperative period. In addition to the physical and emotional consequences of prolonged hospitalization, such as withdrawal from social, family, and work commitments, there are economic repercussions due to increased treatment costs.[1-4]

Among liver transplantation recipients, previous investigations have shown that SSI is the main complication in the postoperative period among HCAIs, responsible for prolonged hospitalization in intensive care units (ICUs), the use of mechanical ventilation, acute renal injury, multiple organ failures, allograft loss, septic shock, and death.[5-7]

Additionally, a recent review of the scientific literature noted that uncertainties remain about risk factors for SSI among liver transplant recipients, although the topic has been widely investigated.[8] Thus, this study aimed to analyze the incidence and risk factors for SSI among adult liver transplant recipients.

Patients and Methods

We conducted a retrospective cohort follow-up by analyzing the medical records of liver transplant recipient population in a large tertiary referral center in Brazil. After the study design was approved by the relevant institutional review board, the written informed consent was obtained from all patients. All liver transplant recipients or relatives were contacted by sending a free for charge answer envelope or through telephone. Medical records of recipients were included in the study if the recipient was older than 18 years; had received an allograft

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from a deceased donor from January 1, 2009, to December 31, 2015; and had survived the first 72 hours after the transplantation. If the recipient was subjected to any kind of surgical procedures in the 30 days prior to the transplantation or required retransplantation within 30 days of the initial transplant, the medical record was excluded from analysis. The facility involved with this research began performing liver transplants on January 1, 2009; therefore, all recipients of liver transplantation performed at that institution were investigated. Since the inception of the program, 176 liver transplants have been performed.

Routine measures for SSI prevention performed during the research period included antibiotic prophylaxis with intravenous ampicillin and cefotaxime for 48 hours. Despite this routine, if the recipient presented with infection, or in cases when infection was suspected in the donor, this antibiotic protocol was changed. In these circumstances, preventive antibiotic prophylaxis was administered using antibiotics selected for treating the known infection. An alcohol-based chlorhexidine gluconate solution was used for preparing the surgical site and iodine-impregnated incisive drapes were used for all patients. The choledocho–choledocho terminal anastomosis of donors and recipients was used in all transplant procedures.

Patients who had capillary glucose equal to or greater than 180 mg/dL were initiated on a glycemic control protocol, consisting of subcutaneous administration of regular insulin. Initially, all patients received a triple immunosuppression regimen comprising prednisone, tacrolimus, and mycophenolate mofetil.

Medical records were screened to identify SSI cases using the diagnostic criteria established by the Centers for Disease Control and Prevention and by reviewing microbiological examinations from the date of the transplant up to 30 days following the procedure.[9]

Data Analysis

Categorical variables were assessed using the Pearson χ^2 test or the Fisher exact test. Continuous variables and variables with a non-normal distribution were evaluated using the Mann-Whitney U test and the Wilcoxon-Mann-Whitney test, respectively. After bivariate analysis, we performed multivariate analyses to evaluate which clinical and surgical factors influenced the incidence of SSI. Thus, using the entire cohort, a form of recursive partitioning called classification and regression tree (CART) analyses was performed. Variables identified as risk factors for SSI in this patient population by a previous review of the literature[8] were used to build the CART model. The CART method was used to separate patients into different homogeneous risk groups and to determine risk of SSI. Moreover, the algorithm selects the predictor that provides the best split, such that each of the 2 subgroups has a more homogeneous outcome. Each subgroup is further dichotomized into smaller and more homogenous groups by choosing the variable that best splits the subgroup. To prune the tree and minimize the overfitting, we used the criteria of group homogenization,
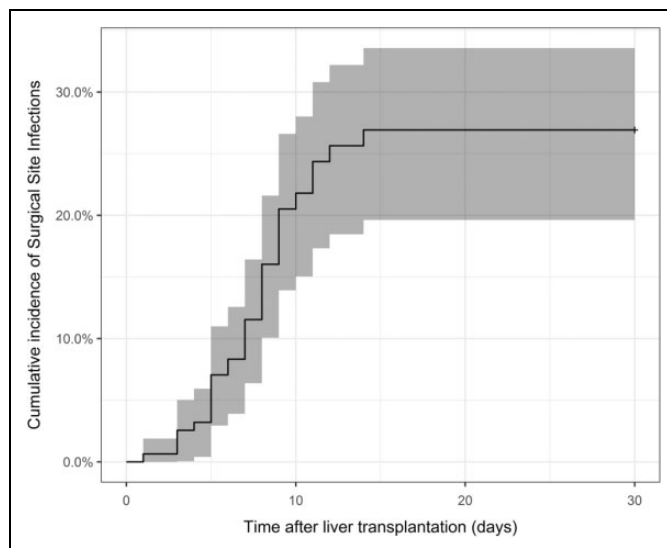

Figure 1. Estimated cumulative incidence of surgical site infections after liver transplantation.

Gini index, and cross-validation. The software SPSS IBM version 22.0 (IBM, Corp, Armonk, New York) was used for statistical analysis.

Results

A total of 176 eligible medical records were examined, 20 were excluded for the following reasons: 1 patient was younger than 18 years, 1 medical record could not be found for review after 3 attempts, 4 patients were submitted for retransplantation within 30 days, and 14 patients died within the first 72 hours of the postoperative period.

The incidence of SSI in the 156 recipients between the years 2009 and 2015 was 26.9% (n = 42). On average, diagnostic signs and symptoms of SSIs manifested 7.8 (standard deviation = 2.9) days following the transplant (median, 8.0; interquartile range [IQR], 5.2-9.0; Figure 1). Of the 42 cases of SSI, the most prominent topography was deep incisional SSI, in 23 (54.8%) cases, followed by superficial SSI (n = 10; 23.8%) and SSI in the organ/space (n = 9; 21.4%).

Clinical specimens were collected for culture analysis from 11 patients with SSIs (26.2%). One case of SSI (2.4%) was polymicrobial. Results of the culture analysis were as follows: 2 specimens of *Staphylococcus* species were isolated, with 1 (50.0%) resistant to methicillin; 4 specimens with Enterobacteriaceae, 2 (50.0%) were ESBL-producing *Klebsiella* species; 2 specimens with *Pseudomonas aeruginosa*, 1 (50.0%) of which was resistant to carbapenems; 2 specimens with *Acinetobacter baumannii*, of which 1 (50.0%) was resistant to carbapenems; 1 case of *Enterococcus faecalis* sensitive to vancomycin; and 1 SSI of fungal etiology caused by *Candida albicans*.

The difference between the body mass index (BMI) of donors and recipients, including the median difference in BMI for those with or without SSI, was calculated. The median difference for the SSI group was 5.7 kg/m^2 (IQR, 3.1-8.2) and 3.3 kg/m^2 for the

Table 1. Clinical Characteristics of Liver Transplant Recipients and Donors by the Occurrence of Surgical Site Infections.

Variables	SSI, n = 42	Non-SSI, n = 114	P Value
Characteristics of recipients			
Age, years, median (IQR)	56.5 (48.9-61.5)	56.1 (49.3-63.3)	.912
Weight, kg, median (IQR)	70.0 (67.2-88.7)	75.5 (66.0-87.4)	.460
BMI, kg/m^2, median (IQR)	27.9 (24.2-30.9)	26.3 (23.8-29.9)	.238
Male, n (%)	35 (83.3)	88 (77.2)	.405
History of tobacco use, n (%)	17 (40.5)	37 (32.4)	.247
History of alcohol use, n (%)	16 (38.1)	45 (39.5)	.770
Diabetes mellitus, n (%)	17 (40.5)	31 (27.2)	.111
Systemic arterial hypertension, n (%)	11 (26.2)	29 (25.4)	.924
Characteristics of donors			
Age, years, median (IQR)	32.1 (20.4-46.4)	39.7 (30.1-47.0)	.159
Weight, kg, median (IQR)	72.5 (65.0-78.0)	70.0 (65.0-80.0)	.181
BMI, kg/m^2, median (IQR)	24.3 (22.7-23.7)	24.8 (23.1-27.7)	.353
Male, n (%)	28 (66.7)	62 (58.8)	.186
Diabetes mellitus, n (%)	–	1 (0.88)	>.99
Systemic arterial hypertension, n (%)	12 (28.6)	45 (39.5)	.261
Causa mortis			
External causes, n (%)	23 (54.8)	57 (50.0)	.632
Cerebrovascular diseases, n (%)	16 (38.1)	45 (39.5)	.845
Diseases of the nervous system, n (%)	3 (7.1)	11 (26.2)	.760
Interrelationship between donor and recipient variables			
Differences between donor vs recipient's BMI average, median (IQR)	5.7 (3.1-8.2)	3.3 (1.3-6.2)	.006
Male donor/female recipient, n (%)	37 (34.4)	101 (88.6)	.778
Difference in age greater than 10 years, n (%)	30 (71.4)	74 (64.9)	.484

Abbreviations: BMI, body mass index; IQR, interquartile range.

group not affected by SSI (IQR, 1.3-6.2). There was a statistically significant difference between the donor–recipient BMI and the occurrence of SSI ($P = .006$; Table 1).

The median time of anesthesia was 590.0 (IQR, 542.5-630.0) minutes and 555.0 (IQR, 510.0-603.8) minutes for recipients who developed an SSI and those who did not develop an SSI, respectively ($P = .025$). The median operative time for patients who developed an SSI was 507.5 (IQR, 422.2-542.8) minutes and was 450.0 (IQR, 392.2-502.2) minutes in non-SSI ($P = .013$).

The cutoff point of 175 mg/dL for the average capillary glucose was computed, considering a sensitivity of 54.7 and a specificity of 71.0. Patients with an average glucose higher than 175 mg/dL in the first 96 hours after transplantation were approximately 3 times more likely to be affected by SSI compared to recipients with an average that remained below this value (odds ratio [OR], 2.97; 95% confidence interval [CI], 1.43-6.17; $P = .002$; Table 2).

The median postoperative hospitalization time was 19 days (IQR, 17.5-22.5) and 12 days (IQR, 10.0-18.0) for SSI and non-SSI recipients, respectively ($P = .001$). Readmission to the ICU was associated with the occurrence of SSI; 4 patients required readmission to the ICU with 3 (7.1%) in the SSI group and 1 (0.8%) in the non-SSI group ($P = .05$; Table 2).

Liver recipients with an operative time <487 minutes were less likely to be affected by SSI, as shown in the intermediate node of CART model. However, at the terminal node, we demonstrated that an operative time ≥487 minutes and differences in BMI ≥1.3 kg/m^2 between donors and recipients

predisposes patients to 5.5 times greater risk of developing an SSI compared to recipients without the combination of those 2 variables (OR, 5.5; 95% CI, 2.5-11.8). When evaluating the entire CART model using predictive parameters, the overall percentage of correct prediction was 54.8%, while the risk of misclassification was 45.2% (Figure 2). Hence, liver recipients exposed to both extended operative times and considerable differences in BMI between donors and recipients were more likely to develop SSI in contrast to recipients not exposed. This was based on the principle of CART by separating into homogenous groups of SSI and non-SSI patients.

Discussion

The SSI incidence observed in this study is higher than that previously documented in the literature, with reports indicating that the incidence of SSI in liver transplant recipients with allografts from deceased donors ranges from 9.6% to 18%.[5,10-13] It should be noted that a previous study had a higher frequency of SSI (37.8%), which could be explained by the adoption of a period of 1 year of surveillance.[14]

We found a high incidence of SSI among recipients in this study. Our results indicate that high glycemic levels in the postoperative period, longer surgical procedure duration, and differences between donor and recipient BMI are risk factors for SSI in this patient population. Among the effects of SSIs, this study showed that SSIs led to an increase in the average time of hospitalization in the postoperative period by

Table 2. Differences Between SSI and Non-SSI Groups for Waiting Time for Transplantation, Clinical, Surgical, Immunosuppressant Therapy Characteristics, and the Effects of Surgical Site Infections in Liver Transplant Recipients.

Variables	SSI, n = 42	Non-SSI, n = 114	P Value
Waiting time for transplantation, days, median (IQR)	133.0 (38.5-271.2)	114 (45.2-190.7)	.591[a]
Physical Status Classification System			
ASA III, n (%)	9 (21.4)	15 (13.1)	.405
ASA IV, n (%)	31 (73.8)	92 (80.7)	
ASA V, n (%)	2 (4.8)	7 (6.1)	
Preoperative preparation and origin			
Recipients at ICU before transplant, n (%)	3 (7.1)	8 (7.0)	>.99
Bath before transplant, n (%)	35 (83.3)	88 (77.2)	.626
No bath before transplant, n (%)	7 (16.7)	26 (22.8)	.405
Trichotomy, n (%)	30 (71.4)	90 (78.9)	.323
Interval between trichotomy and skin incision, minutes, median (IQR)	240.0 (174.8-329.2)	285.0 (210.0-360.0)	.845
Intraoperative characteristics			
MELD transplant indication score, median (IQR)	17.0 (14.0-20.7)	16.0 (12.2-20.7)	.485
MELD transplant performance score, median (IQR)	17.0 (12.2-23.7)	17.0 (14.0-24.0)	.543
Cold allograft ischemia time, minutes, median (IQR)	412.0 (360.0-464.0)	404.5 (50.0-445.0)	.248
Time of anesthesia, minutes, median (IQR)	590.0 (542.5-630.0)	555.0 (510.0-603.8)	.025
Operative time, minutes, median (IQR)	507.5 (422.2-542.8)	450.0 (397.2-502.2)	.013
Concentrated red blood cells, median (IQR)	2.0 (2.0-4.0)	3.0 (2.0-4.0)	.860
Use of vasopressor drug, n (%)	32 (76.2)	79 (62.3)	.399
Ascitic fluid flow above 1.0 mL, n (%)	15 (35.7)	40 (35.1)	.903
Immunosuppressant received			
Prednisone, n (%)	35 (83.3)	81 (71.0)	.119
Mycophenolic acid, n (%)	40 (95.2)	102 (89.5)	.355
Tacrolimus, n (%)	41 (97.6)	103 (90.3)	.183
Methylprednisolone, n (%)	37 (88.1)	107 (93.8)	.307
Capillary glucose in the first 96 hours after transplantation			
Capillary glucose ≥175 mg/dL, n (%)	23 (54.8)	33 (28.9)	.002
Capillary glucose <175 mg/dL, n (%)	19 (45.2)	81 (71.1)	
Effects of SSI			
Length of ICU stay, days, median (IQR)	8.0 (6.0-10.5)	6.0 (5.0-9.0)	.085[a]
Total postoperative time of hospitalization, days, median (IQR)	19.0 (17.5-22.5)	12.0 (10.0-18.0)	.001[a]
ICU readmission, n (%)	3 (7.1)	1 (0.8)	.050
Reoperation, n (%)	4 (9.5)	10 (8.7)	>.99

Abbreviations: ASA, American Society Anesthesiologists; ICU, intensive care unit; IQR, interquartile range; MELD, Model for End-Stage Liver Disease.
[a]Log rank (Mantel Cox).

approximately 5 days and an elevation in the frequency of readmission to the ICU.

Previous investigations of SSIs in liver recipients identified an increase of approximately 24 days in the postoperative period, a greater frequency of reoperations, medications, and laboratory tests, increasing the consumption of resources by up to US$160 000.[14] Further, when compared to those who did not develop SSIs, the risk of death in the first year after transplantation or allograft failure is approximately 2.5 times and 4 times higher with SSI, respectively.[5] Finally, the survival rate is 5% lower in recipients affected by SSI compared to those not affected.[6]

There are controversies in the scientific literature regarding the ideal glycemic maintenance for recipients. Some guidelines and studies recommend maintaining blood glucose below 200 mg/dL in the perioperative period between surgical procedures, including liver transplantation.[2,12] However, other targets for glucose maintenance have been suggested: 150 to 200 mg/dL by the World Health Organization,[15] 150 mg/dL by Paka et al,[16] and 140 to 180 mg/dL in the guideline proposed by the American Association of Clinical Endocrinologists and the American Diabetes Association.[17] A review of the literature, concurrent with the guidelines, suggests that further studies evaluating the optimal glycemic value that may act as a protective factor against SSI in liver transplant recipients in the perioperative period are required.[18]

The effect of operative time has been of concern among researchers; an investigation indicated that for every hour elapsed during surgery, there is a 14% increase in the risk of SSI.[13] In addition, studies have shown that among liver recipients exposed to long operative times, there is a 19% increase in the risk of SSI.[5,14]

Previous investigations have attempted to estimate liver weight in order to optimize the match between donors and recipients.[19,20] It is known that the available formula has an unavoidable margin of error of approximately 20% among 33% of the assessed grafts. However, it is also known that BMI predicts liver weight.[21] Furthermore, early studies involving human patients who underwent liver transplantation indicated
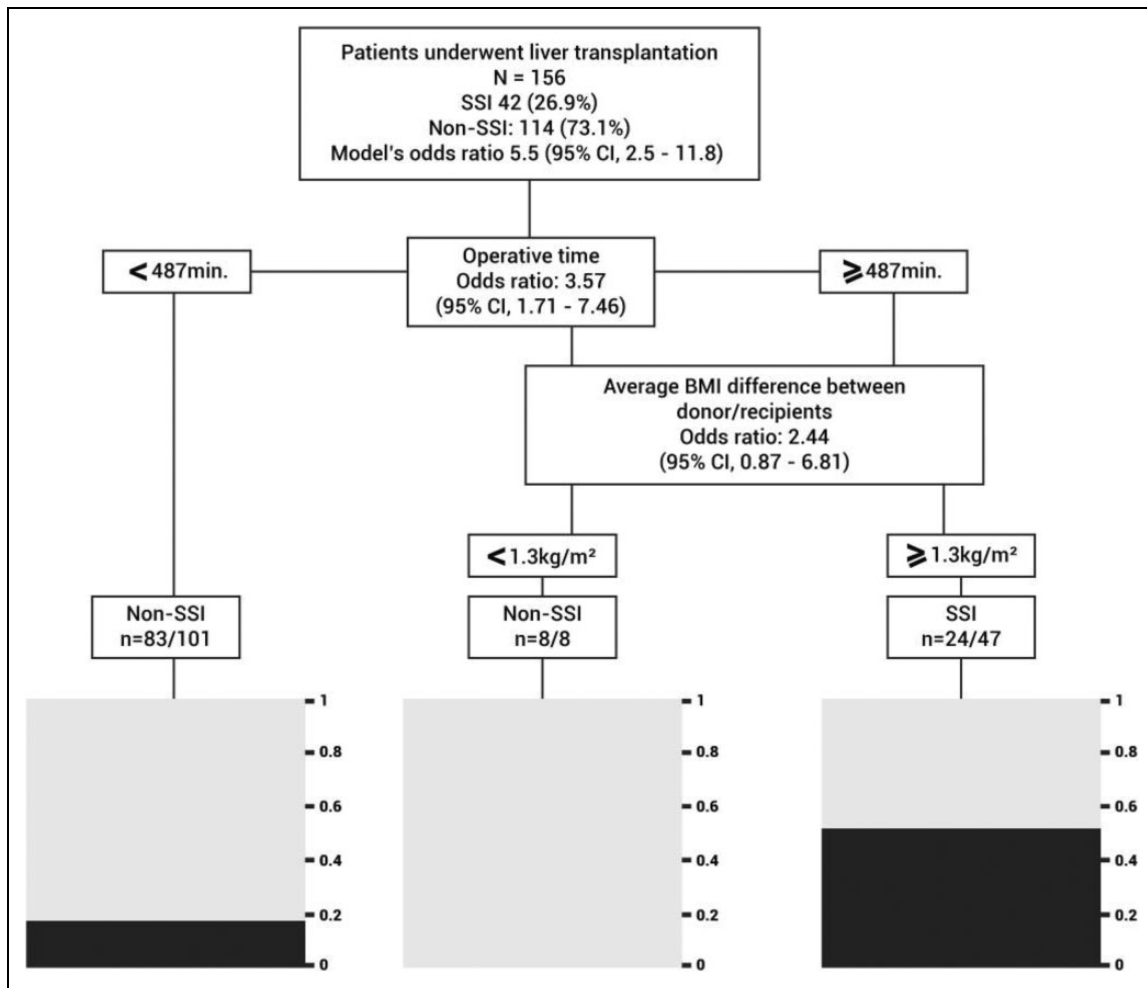
Figure 2. Classification and regression tree model for predicting surgical site infection between adults who underwent liver transplantation.

that a higher frequency of postoperative complications, such as primary allograft insufficiency, acute rejection, infections, higher frequency of acute respiratory failure, longer duration of mechanical ventilation, and consequent extension of ICU stay, were seen with large-for-size allografts.[22,23]

It has been suggested that allografts considered large for size have local and systemic deleterious effects. The local effects include technical difficulties in the intraoperative period, such as difficulties in performing the anastomosis, lower allograft oxygen perfusion, obstacles in the synthesis phase, allograft compression, and necrosis. The effects on microcirculation cause tissue hypoperfusion.[24,25] Furthermore, few studies have evaluated the association between allografts considered large for size and SSI among liver transplant recipients from a deceased donor. Studies investigating living donor liver transplantation and pediatric patients are more common.[23,26]

The main limitation of this study was the retrospective design. The investigation of the occurrence of large-for-size allografts was impaired, as complete data were unavailable in the medical records selected. Additionally, few microbial cultures were performed in the facility. In order to mitigate these limitations, we used several sources of information, such as reports from the Hospital Infection Control Service and multidisciplinary team records to obtain data on SSIs.

We suggest that further investigations are required to clarify the relationship between large-for-size allografts, the maintenance of strict glycemic control in the perioperative period, and the incidence of SSIs.

Conclusions

The risk factors for SSI among adult liver recipients are similar to those reported in the scientific literature; however, our results indicate that there is a relationship between long operative times and differences in donor–recipient BMI and that this increases the risk of SSI occurrence by up to 5.5 times, when compared to the risk of patients not exposed to this combination of variables. Furthermore, a mean capillary blood glucose ≥ 175 mg/dL in the first 96 postoperative hours increased the risk of SSI by approximately 3 times.

Declaration of Conflicting Interests

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