ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2022 March 21; 28(11): 1088-1186

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Report® cites the 2020 impact factor (IF) for *WJG* as 5.742; Journal Citation Indicator: 0.79; IF without journal self cites: 5.590; 5-year IF: 5.044; Ranking: 28 among 92 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2020 is 6.9 and Scopus CiteScore rank 2020: Gastroenterology is 19/136.

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NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
March 21, 2022

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World J Gastroenterol 2022 March 21; 28(11): 1159-1171

DOI: 10.3748/wjg.v28.i11.1159

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Assessment of pathogens and risk factors associated with bloodstream infection in the year after pediatric liver transplantation

Yeong Eun Kim, Ho Jung Choi, Hye-Jin Lee, Hyun Ju Oh, Mi Kyoung Ahn, Seak Hee Oh, Jung-Man Namgoong, Dae Yeon Kim, Won Kyoung Jhang, Seong Jong Park, Dong-Hwan Jung, Deok Bog Moon, Gi-Won Song, Gil-Chun Park, Tae-Yong Ha, Chul-Soo Ahn, Ki-Hun Kim, Shin Hwang, Sung Gyu Lee, Kyung Mo Kim

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: El-Bendary M, Jiang M, Pop TL, Ullah K

Received: September 15, 2021
Peer-review started: September 15, 2021
First decision: November 7, 2021
Revised: November 20, 2021
Accepted: February 23, 2022
Article in press: February 23, 2022
Published online: March 21, 2022

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Abstract

BACKGROUND

Bloodstream infection (BSI) is one of the most significantly adverse events that can occur after liver transplantation (LT) in children.

AIM

To analyze the profile of BSI according to the postoperative periods and assess the risk factors after pediatric LT.

METHODS

Clinical data, collected from medical charts of children (n = 378) who underwent primary LT, were retrospectively reviewed. The primary outcome considered was BSI in the first year after LT. Univariate and multivariate analyses were performed to identify risk factors for BSI and respective odds ratios (ORs).

RESULTS

Of the examined patients, 106 (28%) experienced 162 episodes of pathogen-confirmed BSI during the first year after LT. There were 1.53 ± 0.95 episodes *per* children (mean ± SD) among BSI-complicated patients with a median onset of 0.4 mo post-LT. The most common pathogenic organisms identified were *Coagulase-negative staphylococci*, followed by *Enterococcus spp.* and *Streptococcus spp.* About half (53%) of the BSIs were of unknown origin. Multivariate analysis demonstrated that young age (≤ 1.3 year; OR = 2.1, P = 0.011), growth failure (OR = 2.1, P = 0.045), liver support system (OR = 4.2, P = 0.008), and hospital stay of > 44 d (OR = 2.3, P = 0.002) were independently associated with BSI in the year after LT.

CONCLUSION

BSI was frequently observed in patients after pediatric LT, affecting survival outcomes. The profile of BSI may inform clinical treatment and management in high-risk children after LT.

Key Words: Bloodstream infection; Liver transplantation; Children; Pathogens

Core Tip: Although bloodstream infection (BSI) is the most significant risk event after liver transplantation (LT) in children, few studies have indicated associated clinical profile and risks. In this study, BSI was frequently observed in the year after pediatric LT and common pathogens were analyzed. Young age, growth failure, use of liver support system, and long hospital stay were independent risk factors of BSI.

Citation: Kim YE, Choi HJ, Lee HJ, Oh HJ, Ahn MK, Oh SH, Namgoong JM, Kim DY, Jhang WK, Park SJ, Jung DH, Moon DB, Song GW, Park GC, Ha TY, Ahn CS, Kim KH, Hwang S, Lee SG, Kim KM. Assessment of pathogens and risk factors associated with bloodstream infection in the year after pediatric liver transplantation. *World J Gastroenterol* 2022; 28(11): 1159-1171

URL: https://www.wjgnet.com/1007-9327/full/v28/i11/1159.htm

DOI: https://dx.doi.org/10.3748/wjg.v28.i11.1159

INTRODUCTION

Pediatric liver transplantation (LT) is a successful state-of-the-art treatment option for children with end-stage liver disease[1,2]. Due to advances in both surgical and medical management, the survival rate after pediatric LT has increased in high-volume centers over time[3,4]. However, transplant patients are still exposed to risks of mortality and morbidity due to preexisting health conditions, the complex surgical procedures, and intense immunosuppression[5,6]. For example, post-LT bloodstream infection (BSI) is a major cause of death in both adult and pediatric LT patients[7-10]. BSI is infection present in the bloodstream, which is normally a sterile environment[8,11]. BSI is diagnosed when bacteria or fungi are detected in blood cultures, and sepsis is the common inflammatory immune response. Considering the perioperative complexity of LT, children may be exposed to the risk of BSI as a severe complication of localized infection in the abdomen, contamination during surgery, or from catheters or invasive procedures[7-10].

Approximately 20%-40% patients experience BSI after LT[8,12,13]. Risk factors of post-LT BSI in adult patients include age and transplant urgency, surgical options, graft types, and postoperative complications[6,8,13-15]. However, risk analysis of post-LT BSI is poorly studied in children[6,8,13,15]. Young age, operative blood loss, type of procedure, such as Roux-en Y method, biliary complications, and cytomegalovirus infection have been found to be risk factors for BSI. Unlike in adult studies, pediatric LT studies are conducted in highly selected cohorts. Notably, half of the indications for pediatric LT are biliary atresia[1,16], for which the Kasai procedure is conducted during the neonatal period. Hence, it is valuable to understand the unique characteristics of BSI in children after LT and to identify risk factors and preventative measures.

Recently, survival outcomes of pediatric LT have been gradually improving at experienced transplant centers[17-20]. Improved understanding of risks could lead to subtle but significant refinements in medical care for pediatric LT patients. In this context, we hypothesized that the characteristics and outcomes of BSI after LT have changed over time, as BSI was previously a highly recurrent problem in our pediatric LT program[13], likely due to catheter-related infection and biliary complications. In this study, we analyzed the profile of BSI according to the post-LT periods and retrospectively re-assessed the risk factors of BSI within the first year after LT in our center.

MATERIALS AND METHODS

Study subjects

Cases of pediatric LT at Asan Medical Center, Seoul, Republic of Korea from December 1994 to June 2020 were retrospectively reviewed. The pediatric group included patients ≤ 18 years of age on the day of transplant, as *per* the definition from the World Health Organization. We also included pediatric patients aged 17 years who were managed by the adult transplant program. A total of 378 cases were reviewed, including 287 (76%) living donor LTs and 91 (24%) deceased donor LTs. Among them, 27 patients required a second transplant. Medical records of the patients were reviewed for the period up to 36 mo after the transplant, or until death.

Definition of variables

Clinical data collection was conducted by retrospective review of medical charts. The primary outcome considered was BSI in the first year after transplant. BSI was defined based on conventional criteria from the Centers for Disease Control guidelines[11] with minor modifications. The clinical significance of BSI was classified according to the corresponding clinical and laboratory findings; skin contaminants, such as *coagulase-negative staphylococci*, *Micrococcus*, and *Propionibacterium* that were cautiously excluded when no signs of clinical sepsis were noted. Catheter-related BSI was reclassified based on the guidelines of the Infectious Diseases Society of America[21] with minor modifications. When no pathogen was found in the peripheral blood culture, catheter-related BSI was defined only if signs of clinical sepsis were present. Positive blood cultures on serial tests without negative conversion were considered the same infection. If the blood culture test returned negative and then positive again within a few days, it was considered a new infection. Secondary BSI was defined when a blood culture showed the same pathogen as a culture in a location other than the blood, such as abdominal drainage, sputum, or urine.

Perioperative variables including age, sex, pre-transplant anthropometry [weight, height, and body mass index (BMI) z-score; based on age-specific data of the World Health Organization[22]], etiology, Pediatric End-stage Liver Disease (PELD), or Model for End-stage Liver Disease (MELD) scores[23] at the time of transplant, donor type, donor age, sex, blood group and type, and BMI were collected. Clinical data including the following variables were also collected: Transplant number, graft type, post-operative surgical complications, operation time, graft weight, volume of red blood cell (RBC) transfusions during the operation, induction and maintenance immunosuppression, and the use of a ventilator, renal replacement therapy, or liver support system such as plasmapheresis. After LT, microbiology, laboratory tests, length of hospital stays, rejection in the first year after transplant, reoperation, cytomegalovirus infection, Epstein-Barr virus infection, post-transplant lymphoproliferative disorder, and recipient and graft survival information was collected. Growth failure was defined when the z-score of weight or height was less than -2.

Antimicrobial prophylaxis

The standard perioperative prophylaxis consisted of ampicillin plus sulbactam (150 mg/kg *per* day) and cefotaxime (100 mg/kg *per* day) administered intravenously within three hours before the operation, and it continued for about seven days or until there were no signs of clinical infection. For acute liver failure, cefotaxime (100 mg/kg *per* day) plus acyclovir (30 mg/kg *per* day) was administered at the time of diagnosis and then switched to the regular regimen after LT. When any signs of clinical sepsis or intraabdominal infections were noted, the antibiotics were promptly switched to vancomycin (50 mg/kg *per* day) plus meropenem (60 mg/kg *per* day) regardless of the documentation of pathogens. Vancomycin was selected based on the center's own experience with methicillin-resistant pathogens [13], while meropenem, assuming a severe intraabdominal infection, was chosen based on the 2010 Infectious Disease Society of America guideline[24]. Then, specific antibiotics were modulated according to the documented pathogen in the cultures. Sulfamethoxazole-trimethoprim (150 mg trimethoprim/m^2 *per* day) for *Pneumocystis jirovecii* prophylaxis and mycostatin (500000 U/day) for fungal infection prophylaxis were provided for six months or more.

Immunosuppression

For induction of immunosuppression, most recipients received oral tacrolimus (0.075 mg/kg) in addition to intravenous basiliximab (12 mg/m^2) and methylprednisolone (20 mg/kg), while cyclosporine-based induction was used in some patients from 1994 to 2001. For maintenance immunosuppression, oral tacrolimus was tapered to a dosage to maintain trough levels of < 5 ng/mL, according to the responses of the liver graft. The oral prednisolone (0.3 mg/kg) was also tapered and then stopped around 3-6 mo postoperatively.

Statistical analysis

In the univariate analysis, the differences of the variables between the groups were assessed using the Mann–Whitney *U* test for continuous parameters. For categorical variables, the χ^2 test or Fisher's exact test, as appropriate, were used. For the continuous variables, receiver-operating characteristic (ROC) curve analysis was performed to identify the optimal cutoff values based on the area under the ROC

curve (AUC). In multivariate analysis, variables with a P value of < 0.1 in the univariate analysis were included for logistic regression, and the odds ratio (OR) and 95% confidence intervals (CIs) were calculated. The sample size was evaluated for multivariate logistic regression[25], and ten variables were included in final analysis. The performance of a statistical model was evaluated in terms of goodness-of-fit, discriminatory ability, and calibration. The differences of cumulative survival rates according to BSI were compared by the Kaplan–Meier method with the log-rank test. The predictive performance of the model was also internally validated through a 10-fold cross-validation and bootstrap resampling method[26-28]. Based on the TRIPOD statement[29], the mean difference between the 200 bootstrapping re-samples was defined as the optimism. All statistical calculations were performed using IBM SPSS Statistics 27.0 (SPSS Inc., Armonk, NY, United States) and R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). A $P < 0.05$ was considered statistically significant.

RESULTS

Demographics of pediatric patients

The median recipient age of the 378 children was 1.58 years [interquartile range (IQR): 0.83-5.42 years], and the median weight was 10.9 kg (IQR: 8.5-18.3 kg). Biliary atresia (53%) and acute liver failure (23%) were the most common etiology for pediatric LTs. Other perioperative clinical characteristics are summarized in Table 1. Four patients (1.1%) had surgical complications involving a hepatic artery, 13% involving a portal vein, 10% a hepatic vein, and 5.6% a bile duct. Fifty (13%) children had a reoperation within 2 mo after the primary LT. Two hundred twenty-two (59%) children experienced cytomegalovirus viremia and 259 (69%) experienced Epstein-Barr virus viremia. Among them, fourteen (3.7%) suffered from post-transplant lymphoproliferative disorder. Acute cellular rejections were noted among 186 (49%) children.

Characteristics of BSI after pediatric LT

A total of 106 (28%) patients experienced 162 pathogen-confirmed BSIs during the first year after LT (Table 2). Among them, 67% (n = 71/106) had a single episode of BSI, while 33% (n = 35/106) had more than one. There were 1.53 ± 0.95 episodes (mean ± SD) *per* person observed among BSI-complicated patients. The median onset of the first BSI was 0.4 mo post-LT (IQR: 0.03-1.3 mo). Ninety-eight BSIs (60%) occurred within the first month after LT, 48 (30%) between one to six months, and 16 (10%) between six months and one year. Bacteria (99%) were the main pathogens of BSI in this cohort. The most common organisms identified were *coagulase-negative staphylococci*, followed by *Enterococcus spp.* and *Streptococcus spp.* (Table 2 and Figure 1). BSIs caused by Gram-negative bacteria were more prevalent in cases that occurred more than one month after LT. Half (53%) of the BSIs were of unknown origin, while catheter-related BSIs comprised 37% of cases and infections of intraabdominal origin 6%.

Clinical impact of BSI on post-LT outcome

The cumulative survival rates of grafts and patients with and without BSI were estimated using the Kaplan–Meier method (Figure 2). The survival rates of grafts that experienced BSI at 1 year, 5 years, and 10 years were 86%, 77%, and 76%, respectively, while the corresponding rates with no BSI were 95%, 92%, and 88%, respectively ($P < 0.001$ for the log-rank test). The survival rates of patients that experienced BSI at 1 year, 5 years, and 10 years were estimated to be 88%, 80%, and 80%, respectively. The corresponding rates for patients with no BSI were 97, 96%, and 95%, respectively ($P < 0.001$ for the log-rank test).

Risk factors for BSI in the first year after pediatric LT

To identify the risk factors of BSI during the first year after LT, the perioperative clinical variables were compared between the BSI (n = 106) group and the non-BSI (n = 272) group. In the univariate analyses, age, z-score of height, z-score of weight, the presence of growth failure, etiology biliary atresia, liver support system, total volume of RBC transfusion, post-LT hospital stay, portal vein complication, and reoperation were statistically different between the BSI and non-BSI groups (Supplementary Table 1). In the ROC curve analysis, cut-off values of the continuous variables were calculated as age ≤ 1.3 year (AUC = 0.599, P = 0.002), height z-score ≤ -1.22 (AUC = 0.594, P = 0.005), weight z-score ≤ -0.11 (AUC = 0.604, P = 0.002), volume of RBC transfusion > 21.51 cc/kg (AUC = 0.606, P = 0.002), and post LT hospital day > 44 d (AUC = 0.594, P = 0.004), respectively. These cut-off values were re-analyzed in the univariate logistic regression analysis.

In the multivariate analysis (Table 3), age of ≤ 1.3 years (OR = 2.1, P = 0.011), combined growth failure (OR = 2.1, P = 0.045), experience with a liver support system (OR = 4.2, P = 0.008), and longer hospital stay of > 44 d (OR = 2.3, P = 0.002) were independently associated with BSI in the first year after pediatric LT. This logistic regression model showed a Nagelkerke R^2 value of 0.201, and a goodness-of-fit of χ^2 = 8.262 based on the Hosmer–Lameshow test (P = 0.408). The model performance was evaluated

Table 1 Demographics and details of pediatric liver transplantation

Characteristics	Total *n* = 378, *n* (%) or median (IQR)
Primary LDLT: DDLT	287 (76): 91 (24)
Age, year	1.58 (0.83-5.42)
Male: Female	176 (47): 202 (53)
Height, z-score	-0.79 (-1.81-0.27)
Weight, z-score	-0.23 (-1.13-0.62)
Growth failure	94 (25)
Indications	
Biliary atresia	200 (53)
Acute liver failure	88 (23)
Metabolic liver	45 (12)
Malignancy	25 (6.6)
Other liver disease	20 (5.3)
Urgency of LT	
PELD	15.4 (10.6-23.2)
MELD	27.4 (23-29)
Ventilator	25 (6.6)
Renal replacement	19 (5)
Liver support system	20 (5.3)
Graft type	
LDLT, including dual LT	287 (76)
DDLT split	54 (14)
DDLT whole liver	37 (10)
ABO incompatible	11 (3)
Graft-recipient weight ratio, %	2.5 (1.69-3.22)
Total operation time, hours	6.9 (5.9-8.8)
Volume of RBC transfusion, cc/kg	19.2 (7.7-33.3)
Post-LT hospital stay, days	36 (26-51)
Surgical complication	
Hepatic artery	4 (1.1)
Portal vein	51 (13)
Hepatic vein	39 (10)
Bile duct	21 (5.6)
Re-operation	50 (13)
Cytomegalovirus infection	222 (59)
Epstein–Barr virus infection	259 (69)
Post-transplant lymphoproliferative disorder	14 (3.7)
Acute cellular rejection	186 (49)
Chronic rejection	19 (5)
Patients with ≥ 1 BSI episode	106 (28)
Total BSI cases	162 (1.5 times *per* patient)
Graft loss	58 (15)

Patient loss	34 (9)

BSI: Blood stream infection; DDLT: Deceased donor liver transplantation; IQR: Interquartile range; LDLT: Living donor liver transplantation; MELD: Model for End-Stage Liver Disease; PELD: Pediatric End-Stage Liver Disease.

by the discriminatory ability of AUC = 0.744 (95%CI: 0.689-0.80) and the calibration slope of 1.02 (95%CI: 0.721-1.319) (Supplementary Figure 1). The predictive performance of the model was internally validated through 10-fold cross-validation (Supplementary Table 2), and the average validation-corrected AUC was 0.701 (95%CI: 0.641-0.762). Bootstrap-corrected AUC was 0.71 and bootstrap-corrected calibration slope was decreased to 0.8 (Supplementary Figure 2).

DISCUSSION

This large-scale retrospective study aimed to assess prevalence and risk factors of pediatric post-LT BSI based on extensive statistical analysis. We observed that 28% of pediatric LT recipients had BSI episodes in the first year after LT. In previous studies, BSI was noted in 20%-40% of post-LT adults[9,12] and in 20%-45% of post-LT children (Supplementary Table 3)[8,13,15,30,31]. A prior study by Duncan *et al*[15] showed that 28% of pediatric transplant procedures were complicated by BSI in the first year[15], which is consistent with our data. Most of the first episodes of BSI in our cohort occurred in the early phase after LT; about 60% of BSI episodes within a year after LT developed in the first month after surgery (Supplementary Figure 3). A pediatric study in Denmark reported the overall incidence ratio of first BSI in the first year after LT was 1.91 *per* 100 recipients per month, and the incidence was highest in the first month after LT, with an incidence of 6.47 *per* 100 recipients per month[30]. In a study of adult solid organ transplantation, the incidence of BSI was also highest in the early stage after transplantation, and then it gradually decreased[32]. This indicates that more attention should be paid to prevention of BSI in first months after pediatric LT.

Post-LT BSI can be a fatal complication in children and was associated with both graft loss and mortality in this cohort (Figure 2). BSI is associated with 10%-52% of mortality in adults[14,33] and 10%-70% in children[6-8,20]. Our data showed a similar unfavorable impact of BSI on the outcome of LT survival. Shoji *et al*[8] also reported that the one-year mortality rate after LT was higher in patients with BSI compared with those without BSI (28.3% *vs* 3.2%)[8]. Therefore, it is important to prevent BSI after pediatric LT.

Coagulase-negative staphylococcus was the most common pathogen causing BSIs in our study. Gram-positive bacteria predominated as pathogens in the first month, but after that, the proportion of Gram-negative bacteria increased (Supplementary Figure 3). In general, Gram-negative bacteria dominate in pediatric infections after LT (Supplementary Table 4)[8,15,31]. In the study by Duncan, in which *coagulase-negative staphylococci* were defined as skin contaminants and excluded, Gram-negative bacteria were identified in 76% of BSI cases, and *Enterococcus faecium* was the only Gram-positive pathogen isolated[15]. In other studies, *coagulase-negative staphylococcus* was also considered a pathogen if the patient had clinical manifestations of infection, as in our study. These differences might be derived from variations in regional pathogen epidemiology, prophylactic antibiotics protocols, definitions of BSI, surgical techniques, use of intravenous catheters, and immunosuppressive regimens among centers[30,34]. We believe that based on the diversity of the LT program, each hospital should have its own pathogen profile and modified strategy.

The origin of BSI is generally unknown in half of pediatric post-LT cases (Supplementary Table 4)[8,13,30], as also noted in our study (53%). In adult LT, the proportion of BSI cases with an unknown cause has been shown to be lower than that among children[35]. The rationale to explain these differences is not clear; however, the unique preoperative and operative factors of pediatric LT are probably reflected in the onset of BSI after transplant. For example, unlike in adults, pediatric LT patients represent a highly selected cohort; biliary atresia is behind 35%-60% of cases in pediatric LT programs[1,16]. Most pediatric patients undergo a Kasai procedure during the neonatal period, and Roux-en-Y biliary anastomosis is also commonly performed, predisposing the bile duct to enteral bacterial infection. In addition, pediatric groups, especially infants, are not cooperative in maintaining the sanitation of catheter lines. Indeed, their rates of central line-associated BSI are higher than those of adults[36].

Young age, growth failure, liver support, and longer hospital stays were independent risk factors for BSI in multivariate analysis (Table 3). Age under 1 year was a significant risk factor of early BSI and, was explained by the difficulty of keeping peripheral intravenous lines in place and maintaining the central line aseptic[13]. In addition, younger patients have an immature innate immune system, probably resulting in increased risks of general infection, including BSI. Immune cells involved in innate immunity, such as natural killer cells and phagocytes, increase gradually in number after birth[37]. The adaptive immune system also matures as the child grows. The fact that older children were vaccinated prior to LT and thus had immunity to some pathogens may also have had an impact[38].

Table 2 Characteristics of blood stream infection in the first year after liver transplantation

Characteristics	*n* (%)
Number of patients complicated by BSI	106/378 (28)
Number of BSI episodes	162
Number of BSI episodes *per* patient	
0	272 (72)
1	71 (19)
2	24 (6)
3	4 (1.1)
≥ 4	7 (1.9)
Organisms (% of all organisms)	176 (100)
Gram-positive bacteria	133 (76)
Coagulase-negative staphylococci	67 (38)
Enterococcus spp.	21 (12)
Streptococci	17 (10)
Staphylococcus aureus	5 (2.8)
Other gram-positive pathogens	23 (13)
Gram-negative bacteria	41 (23)
Klebsiella spp.	11 (6.3)
Enterobacter spp.	9 (5.1)
Escherichia coli	6 (3.4)
Pseudomonas aeruginosa	3 (1.7)
Other gram-negative pathogens	12 (6.8)
Fungus	2 (1.1)
Candida albicans	2 (1.1)
Time of onset after LT (% of all BSI)	
0-30 d	98 (60)
31 d-6 mo	48 (30)
6 mo-1 yr	16 (10)
Origin (focus) of BSI (% of all organisms)	
Unknown	94 (53)
Catheter-related infection	65 (37)
Intraabdominal infection	11 (6.2)
Urinary tract infection	3 (1.7)
Respiratory infection	3 (1.7)

BSI: Blood stream infection; LT: Liver transplantation.

This is the first study to reveal growth failure as an independent risk factor of BSI, suggesting the clinical importance of nutritional care before LT. Growth failure may reflect a poor general condition or malnutrition, which may render the patient vulnerable to infection. In malnourished children, immunological alterations have been observed, including impaired gut-barrier function, decreased level of complements, and atrophied lymphatic tissue[39]. Adipose tissue has the ability to store cytokines and hormones involved in immune activity, but is decreased in malnourished children, affecting the immune response[40]. Vitamin A and D deficiency have also been reported to be associated with infectious diseases[40]. In the PELD score system, the index growth failure is used as one of the poor prognostic factors for 3-mo mortality in the waiting list for a LT[23].

Table 3 Multivariate analyses of risk factors for blood stream infection after liver transplantation

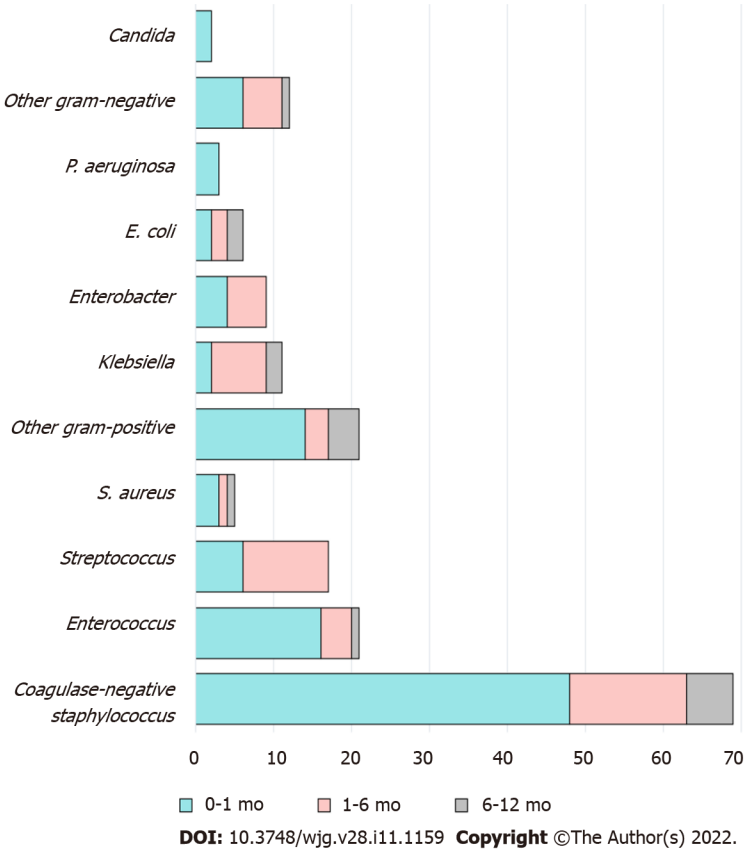
Variables	Non-BSI, *n* = 272		BSI, *n* = 106			Multivariate analysis		
	Median or *n*	(IQR) or (%)	Median or *n*	(IQR) or (%)	*P* value[1]	ORs	95%CI	*P* value
Age	1.83	(0.86-6.0)	1.17	(0.75-3.08)	0.005	2.1	(1.18-3.77)	0.011
Sex, male	124	(45.6)	52	(49)	0.544			
Height, z-score	-0.66	(-1.60-0.34)	-1.23	(-2.17-0.0)	0.005	1.1	(0.54-2.37)	0.722
Weight, z-score	-0.07	(-1.04-0.71)	-0.53	(-1.7-0.4)	0.002	1.2	(0.70-2.25)	0.438
Growth failure	52	(19)	42	(40)	< 0.001	2.1	(1.01-4.47)	0.045
Diagnosis: Biliary atresia	134	(49)	66	(62)	0.023	1.2	(0.66-2.15)	0.546
Ventilator	14	(5.1)	11	(10)	0.066			
Renal replacement	11	(4.0)	8	(7.5)	0.161			
Liver support system	10	(3.7)	10	(9.4)	0.025	4.2	(1.45-12.09)	0.008
PELD	16.2	(6.40-23.7)	15.5	(10.6-24.3)	0.209			
MELD	27.1	(11.3-32.3)	29	(27.8-29.7)	0.746			
LT, DDLT	71	(26)	20	(19)	0.139			
ABO mismatch	8	(2.9)	3	(2.8)	0.954			
Operation time, min	417	(357-536)	411	(350-507)	0.408			
RBC transfusion, cc/kg	17.4	(7.6-29.5)	25.7	(9.8-42.1)	0.003	1.5	(0.87-2.50)	0.146
Post-LT hospital stay	36	(26-50)	41	(28-67)	0.002	2.3	(1.35-3.91)	0.002
Donor, male	128	(47)	44	(42)	0.33			
Donor, body mass index	22.3	(20.3-24.4)	22.7	(21.1-24.5)	0.267			
Reoperation	29	(11)	21	(20)	0.018	1.30	(0.64-2.61)	0.470
Hepatic artery complication	2	(0.7)	2	(2.0)	0.326			
Hepatic vein complication	24	(8.8)	15	(14)	0.126			
Portal vein complication	27	(9.9)	24	(23)	0.001	1.85	(0.95-3.59)	0.070
Bile duct complication	16	(5.9)	5	(4.7)	0.657			
Cytomegalovirus infection	161	(59)	61	(58)	0.771			
Epstein–Barr virus infection	187	(69)	72	(68)	0.839			
Acute cellular rejection	127	(47)	59	(56)	0.117			

[1]Mann–Whitney *U* test, χ^2 test, or Fisher's exact test.

BSI: Blood stream infection; DDLT: Deceased donor liver transplantation; IQR: Interquartile range; MELD: Model for End-Stage Liver Disease; OR: Odds ration; PELD: Pediatric End-Stage Liver Disease; LT: Liver transplantation.

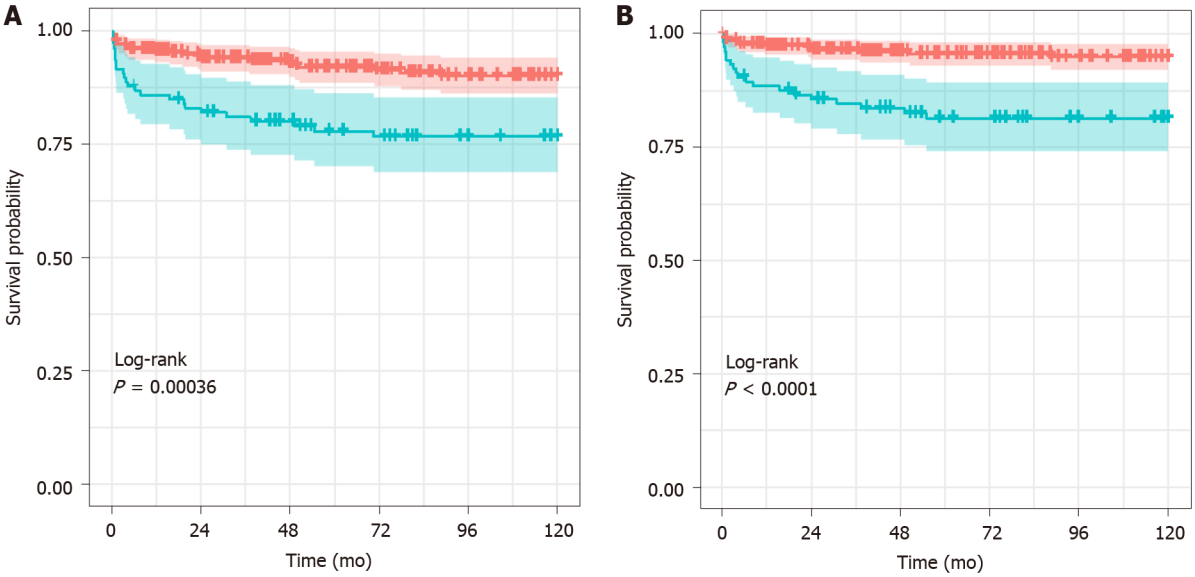
Longer hospital stay was also associated with an increase in BSI, which was confirmed by previous studies[31,34]. However, this should be interpreted with caution, because a longer hospital stay can also be a consequence of BSI. Liver support systems, such as plasma exchange, have been recently adopted as bridging therapies for patients with severe acute liver failure to remove circulating toxic substances [41]. Such treatment may pose a potential risk of infection in that immunoglobulins and complements can be also removed, resulting in immunodeficiency[42]. However, a clear plausible mechanism is not available currently; invasive procedures such as a liver support system or catheterization are risks of BSI from a commonsense standpoint. Blood loss during LT and subsequent massive transfusion are also known risk factors of BSI[8,43,44]. In our study, the total amount of RBC transfusion had a significant correlation with BSI only in the univariate analysis.

A recent meta-analysis suggested that the risk factors of post-LT BSI could be noted among the pre-existing conditions (sex, ascites, and urgency scores for waiting), LT options (ABO incompatibility, operation time, and operative blood loss), and post-LT issues (biliary complication, rejection, hemodialysis, and re-transplantation due to graft failure), for which the OR ranged from 1.28 to 3.37



DOI: 10.3748/wjg.v28.i11.1159

Figure 1 Profile of blood stream infection pathogens according to time after liver transplantation.



DOI: 10.3748/wjg.v28.i11.1159

Figure 2 Survival outcomes of grafts and patients with primary liver transplantation according to blood stream infection. A: Survival rates of grafts with blood stream infection (BSI) (green line) was lower than those without BSI (red line) ($P < 0.05$ in log-rank test); B: Survival rates of patients with BSI were lower than those without BSI ($P < 0.05$ in log-rank test).

[14]. In children, young age, high operative blood loss, type of procedure (such as the Roux-en Y method), biliary complications, and cytomegalovirus infection were risk factors of BSI (Supplementary Table 3)[8,13,15,30,34]. Presumably, the risks of BSI in children are also different from those in adults with regards to several unique issues such as immunity and LT indication[45,46]. Notably, cytomegalovirus infection, surgical complications of the bile duct, surgical techniques, and blood transfusion were not risk factors for BSI in this analysis. In general, biliary complications are related to

an increased risk of BSI after LT[13,15,31,43]. In our previous report of early BSI, age of < 1 year and bile duct complication were risk factors for BSI[13]. The rationale for the change in the risk factors over time is not clear, and the authors speculate that the refinement and intervention of post-LT care could probably alter the natural history of BSI in transplant children with high risks. For example, there was a remarkable difference in the prevalence of BSI among patients with bile duct complications over the last 10 years (2011-2020, 0%) and before that time (1994-2010, 45.5%) in our study. This improvement may be reflected in the change of the BSI rate and its risk factors according to the transplant era. In the SPLIT data, the rate of BSI significantly decreased with time[6]; our cohort demonstrated similar results.

The present study is limited by several factors. First, this study is a retrospective analysis. In addition, because it is a single-center study, all known risk factors of clinical importance were not included in the analysis to satisfy the minimum events *per* variable for reliable logistic regression analysis[25]. Additionally, the performance of this prediction model was characterized by acceptable goodness-of-fit and fair discriminatory ability. However, prognostic models usually only have an R^2 around 0.2-0.3[47] because substantial future uncertainty after LT is variable at the individual level in reality. In addition, internal validation showed optimism about the apparent performance. To develop a solid prediction model, multi-center studies are needed.

CONCLUSION

Our retrospective study of pediatric patients of LT revealed that BSI was frequently observed and affected the survival outcomes. The profile of the pathogens, onset, and origin site of BSI may be informative to establish individual policy in each surgery center against BSI after the transplant. As clinical practices in pediatric LTs continue to advance, further investigation is necessary to identify how risk factors have been altered by the dynamic nature of early post-LT care and to seek actionable changes in LT care.

ARTICLE HIGHLIGHTS

Research background

Bloodstream infection (BSI) is one of the most significantly adverse events that can occur after liver transplantation (LT) in children. However, risk analysis of post-LT BSI is poorly studied in children.

Research motivation

Our findings are an important step in improving hospital policies for pediatric LT patients and reducing incidence of BSI.

Research objectives

To analyze the profile of post-LT BSIs in children and their risk factor.

Research methods

Clinical data, collected from medical charts of children (n = 378) who underwent primary LT, were retrospectively reviewed.

Research results

BSI was observed in 28% of patients after pediatric LT and affecting survival outcomes. The most common pathogenic organisms identified were *Coagulase-negative staphylococci*. About half of the BSIs were of unknown origin. Young age (≤ 1.3 year), growth failure, liver support system, and hospital stay of > 44 d were independently associated with BSI in the year after LT.

Research conclusions

Our retrospective study of pediatric patients of LT revealed that BSI was frequently observed and affected the survival outcomes. The profile of the pathogens, onset, and origin site of BSI may be informative to establish individual policy in each surgery center against BSI after the transplant.

Research perspectives

The profile of BSI may inform clinical treatment and management in high-risk children after LT.

FOOTNOTES

Author contributions: Oh SH, Namgoong JM, and Kim KM designed the study; Kim YE and Oh SH wrote the manuscript and interpreted the data; Kim YE, Choi HJ, Lee HJ, Oh HJ, and Ahn MK collected patient data; Jhang WK and Park SJ were responsible for patient care and data collection during the intensive care unit stay; Namgoong JM, Kim DY, Jung DH, Moon DB, Song GW, Park GC, Ha TY, Ahn CS, Kim KH, Hwang S, and Lee SG participated in surgery and contributed to the treatment of complications related to surgery and the development of surgical technology; all authors have read and approve the final manuscript.

Supported by Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI); Ministry of Health & Welfare, Republic of Korea, No. HR21C0198.

Institutional review board statement: This study was approved by the Institutional Review Board of the Asan Medical Center, No. S2021-1917-0001.

Informed consent statement: Patients were not required to give informed consent to the study because this retrospective analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

Country/Territory of origin: South Korea

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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