



Duration of operation and diagnosis of hepatitis B (HBV) is an independent risk factor for surgical site infections after liver transplantation

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ABSTRACT

Objective: Surgical site infections (SSI) are the most common complications after liver transplantation (LT). Although there are some risk factors known in the literature after LT, the available data is insufficient for routine use. In the present study, it was aimed to define the parameters that may be used to clearly determine the risk of SSI after LT in our clinic.

Material and Methods: In the present study, we evaluated 329 patients who underwent liver transplantation with regard to risk factors for surgical site infections. The relation between demographic data and SSI was evaluated using SPSS, Graphpad, and Medcalc statistical programs.

Results: In a total of 329 patients, SSIs were determined in 37 (11.24%). Among the 37 patients, 24 were classified as organ space (64.9%) and 13 as deep SSI (35.1%). None of these patients developed superficial incisional infection. SSI showed statistically significant relation with operation time ($p=0.008$), diabetes ($p=0.004$), and cirrhosis due to hepatitis B ($p<0.001$).

Conclusion: As a result, deep and organ space infections are much more observed in patients undergoing liver transplantation with hepatitis B, diabetes mellitus and prolonged surgery. This is thought to have developed because of chronic irritation and increased inflammation. Since data on hepatitis B and duration of surgery are limited in the literature, this study is considered to be a contribution to the literature.

Keywords: Surgical site infection, liver transplantation, operation time

INTRODUCTION

Liver transplantation (LT) is one of the most effective therapeutic options for patients with liver diseases. However, complications constitute most of the previously reported causes of death in these patients. Postoperative infections are the most common complications after LT (1-8). Hospital infections, which occur as a result of invasive procedures and applications in the hospital, lead to prolonged hospital stay and cause significant morbidity and mortality. Surgical site infections (SSIs) constitute a significant part of hospital infections (2). SSIs are divided into three distinct types as superficial incisional, deep incisional and organ space. Although advances have been made in infection control practices, including improved operating room ventilation, sterilization methods, surgical technique, and availability of antimicrobial prophylaxis, SSIs remain a substantial cause of morbidity, prolonged hospitalization, and mortality (3).

Previous studies have documented increased risk for SSI based on patient and operative characteristics (3-5). Studies have shown that MELD score, diabetes, hyperglycemia, age, operation time, high volumes of blood transfusion are risk factors for SSI (5-7). The aim of this study was to determine and understand the risk factors of SSI in patients undergoing LT in our general surgery department.

MATERIAL and METHODS

Patients who underwent transplantation for chronic liver disease at Bursa Uludağ University from January 2007 and August 2020 were included in the current study. Ethics approval of the study was obtained from the local institutional ethics committee (No: 2011-KAEK-26/413, Date: 20.07.2020).

The same immunosuppression regimen was applied to all patients included in the study, which consisted of tacrolimus, steroid and mycophenolate mofetil (MMF).

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Standard dose steroid and MMF were used, and tacrolimus doses were checked daily to keep them within a certain range. Perioperative antibacterial prophylaxis consisted of ampicillin and sulbactam for the first 48 hours after transplantation. Anti-fungal and anti-viral prophylaxis included a combination of nystatin swish-and-swallow, micafungin, fluconazole, ganciclovir and valganciclovir for 3-6 months, depending on the risk profile. Post-transplantation antimicrobial therapy was changed on an individual basis considering clinical factors and specification of microbiology results.

Surgical site infections were classified according the centers for disease control and prevention classification system as follows:

- (a) superficial incisional involving only the skin or subcutaneous tissue of the incision;
- (b) deep incisional involving the fascia and/or muscular layers in the primary incision (deep incision primary) in a patient who had an operation involving one or more incisions and an SSI identified in the secondary incision (deep incision secondary) in an operation with more than one incision; and
- (c) organ-space involving any part of the body opened or manipulated during the procedure excluding the skin incision, fascia, or muscle layers. In the presence of more than one SSI type, the more complex SSI type was selected. Patients' demographic information, operative details, post-operative outcomes and infection outcomes were collected from the archive of the department of general surgery. SSIs were defined by using standardized Centers for Disease Control and Prevention's National Healthcare Safety Network.

The relation between demographic data and SSI was analyzed using SPSS, Graphpad, Medcalc statistical programs. Chi-square test was used between types of organism and source of infection. Overall survival details were presented for each of the three different SSI groups. The Kaplan Meier method was used to determine the effect of SSI on survival. Multivariate analyses were performed using a Cox proportional hazards regression model to investigate associations of patients features, operative information and postoperative complications within 30 days of liver transplantation with development of SSI after liver transplantation. Logistic regression analysis was performed to ana-

Table 1. Patient demographics

Features	Number
Sodium MELD score	18 (15-30)
Age (years, median)	51.4 (5-76)
BMI	27 (18-33)
Sex	
Male	215 (89.9)
Female	114 (34.7)
SSI	
None	292 (88.7)
Organ Space	24 (7.3)
Deep	13 (4.0)
Underlying Diseases	
HBV	126 (38.3)
HCV	21 (6.4)
NASH	24 (7.3)
PBC	16 (4.9)
Cryptogenic	43 (13.1)
Wilson	24 (7.3)
Others	75 (22.8)

lyze the risk factors. Student's t-test was used for comparison of quantitative outcome parameters.

RESULTS

The present study included 329 unrelated patients who had undergone LT. Of these patients, 215 were males and 114 were females, with a median age of 51.4 years (range 5-76 years). Median body mass index was 27 (Range 18-33), and median model for end-stage liver disease (MELD) score was 18 (range 15-30). The most common principal liver disease diagnosis was chronic hepatitis B (n= 126, 38.3%). Median operative time was 238 min (range 100-747 min). SSIs were determined in 37 (11.3%) patients. Among the 37 patients, 24 was classified as organ space (64.9%) and 13 (35.1%) as deep (Table 1). None of these patients developed superficial incisional infection. As reported in Table 2, the highest SSI incidence rates were observed in HBV-infected

Table 2. Diagnosis and SSI

Diagnosis	None (n= 292)	Organ Space (n= 24)	Deep (n= 13)	Total (n= 329)
HBV	105 (83.3%)	16 (12.7%)	5 (4.0%)	126
HCV	17 (81.0%)	1 (4.8%)	3 (14.2%)	21
NASH	24 (100%)	0 (0.0%)	0 (0.0%)	24
PBC	16 (100%)	0 (0.0%)	0 (0.0%)	16
Cryptogenic	42 (97.6%)	0 (0.0%)	1 (2.4%)	43
Wilson	24 (100%)	0 (0.0%)	0 (0.0%)	24
Others	40 (85.4%)	7 (9.3%)	4 (5.3%)	75

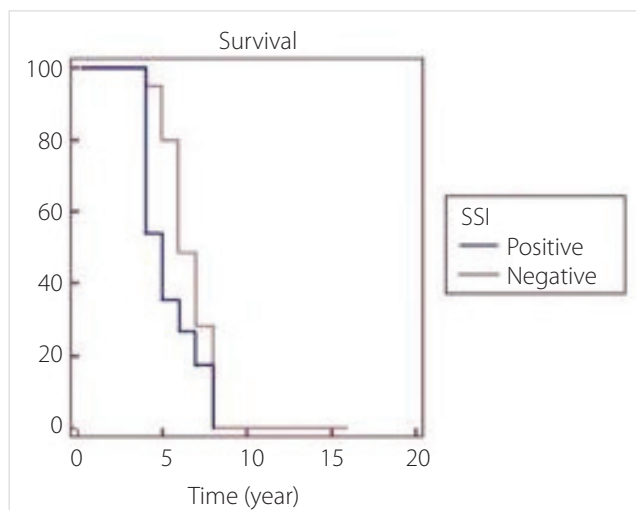


Figure 1. The effect of SSI on overall survival.

patients (56.8%; 95% CI 4.5-9.2). The growth of various bacterial pathogen was determined in 29 patients, and fungal pathogen was determined in eight. The most common micro-organisms isolated was *Escherichia coli* in 20 of 37 (54.0%) patients.

First, the relation between SSI and prognosis was investigated by Kaplan Meier analysis, and the effect of SSI development on short overall survival was determined (Log-rank, $p=0.003$, HR= 4.614, Figure 1).

In our study, SSI was 22 in males and 15 in females, and no statistically significant relation was found ($p>0.05$). In single variable analysis, there was an association between HBV-infection and SSI ($p=0.001$). SSI, which was associated with poor prognosis, showed a statistically significant relation with operation time ($p=0.008$), diabetes ($p=0.004$), HBV-infection $p<0.001$).

In our study, the operative time lasted longer than two hours, which resulted in an increase in the risk of SSI (Table 3). In the study, 21 of the 94 patients with diabetes mellitus developed

SSI. In the modeling based on logistic regression analysis with all parameters showing significance, operative time and HBV diagnosis were determined as independent risk factors for SSI (Table 4).

DISCUSSION

SSI is an important cause of morbidity in the early post-transplant period due to the complexity of the surgery, immunosuppression and patient comorbidities (8). Although progress has been made in infection control practices, SSI remains one of the most common health-related infections (8).

The incidence of SSI following liver transplantation ranges between 8.8% and 37.6%, depending on the definition of SSI and the differences in follow-up times (5,8-11). Softness et al., in their single center experience with 252 patients, have found SSI rate to be 9.5% (9). RA Oliveira et al. have determined an SSI rate of 26.9% in their study (10). In the study of Freire MP et al. in 2021, SSI rate was 30.1% (11). In our retrospective study, the incidence of SSI was 11.24% (37/329) and was consistent with the literature.

We observed solid evidence of a strong association between diagnosis, operative time and SSI, and these relationships were independent of other variables. As stated in many studies in the literature, operative time is closely related with surgical site infection. In the results of our study, operative time was found to be an independent risk factor in terms of surgical site infection, which was consistent with the literature (8-11).

In our study, the relation of SSI with diabetes mellitus was not statistically significant. According to a meta-analysis published by Martin et al in 2016, surgical site infections were found to be closely related to diabetes mellitus. According to this analysis, pre and post hyperglycemia and a history of diabetes mellitus were found to be risk factors for the development of surgical site infection, and our study is consistent with this result (12).

Table 3. Operative time and SSI

Operative Time (hour)	95% CI	p	Total (n= 329)
<2	0.93 to 1.56	0.956	24
2-4	1.23 to 2.01	0.025	47
4-5	0.88 to 1.77	<0.001	100
>6	1.25 to 2.20	<0.001	16

Table 4. Risk factors for SSI using logistic regression analysis

Features	OR	95%	p
Operation Time (>2 vs <2)	2.5	2.01-5.43	0.022
Diabetes (Yes vs. No)	-	-	0.066
HBV-mediated (Yes vs. No)	2.01	1.02-7.23	0.002

In our patient group who developed surgical site infection, the duration of intensive care and hospital stay increased in the postoperative period, but this result was not statistically significant.

Sangrasi et al. have shown the duration of postoperative stay as a risk factor for SSI, and hospitalization of the group with SSI was 16.2 days while the hospitalization period of the group without SSI was 6.3 days. In this study, it was shown that hospitalization time increased more than two times in patients who developed infection (13).

According to a study conducted by Işık et al. in 2015, operation time exceeding four hours was found to be a risk factor for the development of SSI (14). Our study was consistent with the results of this study. In our study, the operative time lasted longer than two hours and resulted in an increase in the risk of SSI. Malone et al. have compared patients with a duration of operation <2 hours, 2-4 hours, and >4 hours and found that as duration increased, so did the rates of SSI (2.1%-3.3%-6.4%, respectively) (15).

There is no reported relation between surgical site infection and hepatitis B in the literature. Although mechanisms that trigger the development of cirrhosis in the liver are thought to be induced by chronic inflammation, the current literature on the mechanisms of surgical site infection is insufficient, and more studies are needed. According to the findings of our study, the development of surgical site infection was found to be significantly higher in patients who had undergone liver transplantation due to hepatitis B cirrhosis compared to the other groups. According to this result, the determination of hepatitis B as an independent risk factor for the development of surgical site infection is a significant contribution to the literature.

Risk factors for the development of SSI have been determined in previous studies. In our study, risk factors of the patient were associated with increased operative time and hepatitis B. As a result of our work with this data, it can be changed to prevent the development of SSI, and intervention of predictable factors can be evaluated. However, studies that evaluate risk factors and have more patients are needed.

Our study has several limitations. As our study was a cohort study, we did not check the interventions that could have affected the results. Clinical parameters in the study are few.

In conclusion, we found that HBV-infection and operative time were associated with an increased risk of SSI. In order to reduce the rate of SSI in patients with LT, studies should be increased.

Ethics Committee Approval: The approval for this study was obtained from Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 2020-12/17, Date: 08.07.2020).

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ORJİNAL ÇALIŞMA-ÖZET

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Hepatit B (HBV) tanısı ve operasyon süresi karaciğer transplantasyonu sonrası cerrahi alan enfeksiyonları için bağımsız bir risk faktörüdür

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ÖZET

Giriş ve Amaç: Cerrahi alan enfeksiyonları (CAE), karaciğer nakli (KN) sonra en sık görülen komplikasyonlardan biridir. Literatürde KN sonrası bilinen bazı risk faktörleri olmasına rağmen, mevcut veriler rutin kullanım için yetersizdir. Bu çalışmada, kliniğimizde KN sonrası CAE riskini açıkça belirlemek için kullanılacak parametrelerin tanımlanması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada, KN uygulanan 232 hastayı değerlendirdik. Demografik veriler ve CAE arasındaki ilişki SPSS, Graphpad, Medcalc istatistik programları kullanılarak analiz edilmiştir.

Bulgular: Toplam 232 hastada 26 (%11,26) CAE saptandı. 26 hastanın 16'sı organ boşluk 16 (61,5) ve 10'u (39,5) derin CAE olarak sınıflandırıldı. Bu hastaların hiçbirinde yüzeysel cerrahi alan enfeksiyonu gelişmedi. Derin ve organ boşluk SS, operasyon süresi ($p=0,01$), diyabet ($p=0,004$), HBV enfeksiyonu ($p=0,001$) arasında istatistiksel olarak anlamlı ilişki saptandı.

Sonuç: Sonuç olarak, karaciğer nakli uygulanan hepatit B tanısı olan, diyabetik ve ameliyat süresi uzayan hastalarda daha fazla derin ve organ boşluk enfeksiyonu geliştiği görülmektedir. Bunun da kronik irritasyon ve artmış enflamasyon sonucunda geliştiği düşünülmüştür. Literatürde hepatit B ve ameliyat süresi ile ilgili veriler kısıtlı olduğundan bu çalışmanın literatüre katkı sağlayabileceği düşünülmüştür.

Anahtar Kelimeler: Cerrahi alan enfeksiyonu, karaciğer nakli, operasyon süresi

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