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Impact of Spontaneous Bacterial Peritonitis History on Liver Transplantation Outcomes: A Historical-Cohort Study

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1. Abstract

1.1. Introduction: Liver transplantation is a pivotal treatment modality for end-stage liver disease, offering a chance for extended survival and improved quality of life. However, the postoperative phase is fraught with potential short-term and long-term complications that can significantly affect patient outcomes. Among these, spontaneous bacterial peritonitis (SBP) has been hypothesized to play a critical role in influencing factors such as re-transplantation necessity, mortality rates, transplant rejection, and the duration of both hospital stays and the surgical procedure itself. Understanding the influence of SBP on post-transplant outcomes is essential for optimizing patient selection and management strategies.

1.2. Methods: This historical-cohort study aims to elucidate the impact of a pre-transplant history of SBP on the prognosis and mortality of liver transplant recipients. We retrospectively analyzed the medical records of 235 patients who underwent liver transplantation at Imam Khomeini Hospital between 2011 and 2018. Patients were categorized into two groups based on the presence (n=75) or absence (n=160) of a documented history of SBP, and demographic, clinical, and paraclinical data were thoroughly reviewed and recorded.

1.3. Results: The study cohort had an average age of 44.8 years (SD=±14.204), with a predominance of male patients (60.9%). Comparative analysis revealed no statistically significant differences in demographic characteristics between the groups. Moreover, the presence of SBP history did not exhibit a notable influence on post-transplant mortality, duration of hospital admission, or surgical operation time, indicating a lack of significant impact on these key outcomes.

1.4. Conclusion: Our findings suggest that the prognosis of liver transplant recipients, in terms of re-transplantation rates, mortality, graft rejection, length of hospital stay, and surgery duration, is not adversely affected by a history of SBP. These results underscore the complexity of post-transplant outcomes and highlight the need for further research to delineate the factors contributing to successful liver transplantation.

2. Introduction

Spontaneous bacterial peritonitis (SBP) is an infection frequently reported in adults with underlying liver disease and cirrhosis, signaling the need for liver transplantation in patients with end-stage liver disease [1, 2]. It predominantly affects individuals with alcoholic cirrhosis, post-necrotic cirrhosis, chronic hepatitis, viral hepatitis, metastatic malignancies, lupus, lymphedema, and congestive heart failure,

while it rarely occurs in patients without any underlying disease [3]. The prevalence of SBP in cirrhotic patients ranges from 10% to 30% [4], rendering it one of the most common bacterial infections. Approximately 9% of diagnoses are made at the time of hospitalization or during admission, particularly one year after the onset of the disease [5]. The mortality rate of SBP varies from 10% to 46% [6].

The liver plays a crucial role in regulating the inflammatory response for bacterial clearance, acute phase reaction, and metabolic compatibility with inflammation [7]. In cirrhotic patients, persistent immune system stimulation results in increased inflammatory cytokines, subsequently weakening the immune system. This weakening leads to higher sepsis rates, acute respiratory failure, and sepsis-related death [8-10]. The severity of these infections correlates with the severity of liver dysfunction [11, 12].

In cirrhosis patients diagnosed with SBP and receiving standard treatment, a Model for End-Stage Liver Disease (MELD) score of ≥22 and a peripheral blood leukocyte count of $\geq 11 \times 10^9$ cells/L are independent mortality factors. Mortality in patients lacking these factors is less than 10%, whereas it exceeds 50% in patients possessing both. Moreover, the mortality rate reaches 50% in untreated patients. About 30% of cirrhosis patients develop ascites during five years of follow-up, which leads to a poor prognosis. Hence, special consideration is essential when deciding on liver transplantation for these patients [5].

Bacterial infections in patients listed for liver transplantation have led to liver dysfunction and subsequent multi-organ involvement, thus increasing the mortality risk and potentially leading to removal from the transplant list [14, 15].

Studies on the prognosis of patients with SBP infection before liver transplantation are scarce and yield contradictory results. Some studies suggest that SBP occurrence one year before liver transplantation does not influence postoperative mortality [16–18], while another study indicates a poorer prognosis post-discharge for patients who had SBP before liver transplantation compared to those who did not [19]. Given the knowledge gap and contradictory findings, we designed a study to evaluate the impact of SBP before transplantation on post-liver transplantation prognosis.

3. Materials and Methods

This historical-cohort study was conducted on patients who underwent liver transplantation at the Imam Khomeini Hospital Complex in Tehran, Iran, the second-largest liver transplant center in the country, from March 2011 to August 2018. We reviewed the data of 719 liver transplant recipients. Among these, 75 patients with a history of SBP before liver transplantation were assigned to the case group, and 160 patients without a history of SBP before liver transplantation were included in the control group. A diagnosis of SBP was considered with a neutrophil count of more than 250 cells/mL of ascites fluid, with or without a positive culture. Exclusion criteria included death within the first 24 hours post-transplantation, combined liver-kidney or pancreas transplant, and administration of anti-thymocyte globulin (ATG) as induction therapy within the first week after liver transplantation.

Demographic and basic information before liver transplantation (age, sex, weight, height, blood group type, etiology of liver transplantation, severity of underlying liver disease based on MELD and CHILD scores), perioperative variables (duration of liver transplant surgery, units of blood transfused during surgery, duration of warm and cold ischemic times), and post-transplant data (length of hospital stay, transplant rejection, re-transplant or reoperation, and infection rate) were collected from various sources, including paper and electronic patient records and interviews with physicians and patients. Two authors independently verified data entry and subsequently analyzed the data using SPSS Version 21.0.

Data are presented as mean ± standard deviation (SD), median, or percentage (%), and all reported p-values are two-tailed. The Mann-Whitney U test was employed for comparing non-parametric variables, while categorical data were analyzed using Chi-square and Fisher's tests. Correlations between quantitative variables were assessed using Pearson and Spearman's rank correlation coefficients. Multivariable logistic regression analysis was utilized to adjust for confounding variables, with results reported as odds ratios (95% confidence interval).

Data collection commenced following approval from the Tehran University of Medical Sciences ethics committee. Patient information was kept confidential throughout the study, adhering to the principles of the Helsinki Declaration and the ethics guidelines of the Tehran University of Medical Sciences. Given the retrospective nature of the study and the absence of intervention in the diagnostic and treatment processes, written consent was not required from the patients.

4. Results

The demographics and clinical characteristics of the patients are summarized in Table 1. In total, 143 patients were male, with an average age of 44.8 years (SD = ±14.204). The leading causes of liver transplantation among our study participants were cryptogenic liver disease (20%, n = 47), hepatitis B and C (18.3%, n = 43), and nonalcoholic steatohepatitis (NASH) (8.9%, n = 21).

No significant statistical differences were observed in sex ($p = 0.371$), age ($p = 0.46$), or BMI ($p = 0.32$) between the two patient groups. Patients with SBP exhibited a greater severity of liver disease before liver transplantation (LT) compared to the control group, as determined by the CHILD score ($p = 0.001$). However, the MELD score did not show a significant difference ($p = 0.413$). Additionally, history of hospitalization and antibiotic use before transplantation were more frequent in the SBP group (18.7% vs. 3.1% and 18.7% vs. 1.3%, respectively) (Table 2).

Patients with a history of SBP prior to liver transplantation required more packed red blood transfusions (p = 0.001) and had longer total surgical durations (p = 0.003). Nevertheless, there was no significant difference in surgical ischemia times between the SBP and non-SBP groups (cold ischemia p-value: 0.106; warm ischemia p-value: 0.322).

The post-LT outcomes were also evaluated. Overall, 68 patients (28.9%) experienced rejection, 29 patients (12.3%) required reoperation, and 8 (3.4%) underwent retransplantation. There was no statistically significant difference between the two groups in terms of rejection (p = 0.430), reoperation (p = 0.343), or retransplantation (p = 0.67). Post-LT surgical complications, predominantly infectious syndromes, occurred in 104 cases (44.3%). The most common infectious complications were pneumonia (17.02%, n = 40) and intra-abdominal infections, including peritonitis, intra-abdominal abscess, and cholangitis (14.46%, n = 34). Urinary tract infections and sepsis syndrome were detected in 5.1% and 4.3% of the patients, respectively. Infectious syndromes were notably more frequent in the SBP group (p = 0.038) (Table 2).

The overall mortality rate after transplantation among the study participants was 14.9% (n = 35), with similar rates observed between the two groups (p = 0.249).

To adjust for the confounding effects of variables that significantly differed between the two groups, binary logistic regression and linear regression analyses were performed. These analyses assessed the impact of SBP on mortality, infectious syndromes, and retransplantation rates. The results indicated that neither the duration of surgery (P > 0.9, OR = 1.052) nor the history of hospitalization before LT in SBP patients (P > 0.9, OR = 0.000) influenced the rate of retransplantation. The mortality risk in patients with primary peritonitis and more severe underlying liver disease, as indicated by a high MELD score, was 1.4 times lower than in those with a lower MELD score (P = 0.21, OR = 1.022).

Among patients with a history of SBP, the risk of rejection was higher in those with longer surgery durations (P = 0.016, OR = 1.023) or a higher CHILD score (P = 0.038, OR = 1.866). However, a history of antibiotic use and hospitalization did not increase the risk of rejection. Furthermore, the duration of surgery (P = 0.72, OR = 1.022), transfusion of packed red blood during operation (P = 0.653, OR = 1.097), history of antibiotic use (P > 0.99, OR = 0.000), and hospitalization (P > 0.99, OR = 1767) did not contribute to increased mortality rates (Tables 3 and 4).

Table 1: Clinical Characteristics by SBP Status in Liver Transplant Patients

Characteristic	SBP- (n=160)	SBP+ (n=75)	Odds Ratio (95% CI)	P-value
Gender			1.358 (0.695 to 2.654)	0.371
- Female	67 (42%)	25 (33%)		
- Male	93 (58%)	50 (67%)		
Primary	154 (96%)	73 (97.3%)	0.478 (0.060 to 3.840)	0.488
Hospitalization History	5 (3.12%)	14 (18.7%)	0.547 (0.071 to 4.231)	0.564
Antibiotic Use History	2 (1.25%)	14 (18.7%)	26.594 (2.400 to 294.691)	*0.008
Rejection	45 (28.12%)	23 (30.7%)	1.333 (0.652 to 2.725)	0.43
Syndromic Infection	62 (38.75%)	42 (56%)	2.053 (1.039 to 4.056)	*0.038
CMV Infection	28 (17.5%)	20 (26.7%)	1.600 (0.737 to 3.472)	0.235
Fungal Infection	6 (3.75%)	6 (8%)	5.224 (1.012 to 26.979)	*0.048
Reoperation	20 (12.5%)	9 (12%)	0.577 (0.185 to 1.800)	0.343
Mortality Post-transplant	23 (14.4%)	12 (16%)	0.538 (0.188 to 1.541)	0.249
Length of Surgery (min)	291.85±6.22	272.72±3.77	1.006 (1.000 to 1.013)	*0.049
Hospitalization Length (days)	14.6±1.22	15.24±1.022	0.978 (.945 to1.013)	0.21

Table 2: Correlation between confounding variables and re-transplantation in patients with Spontaneous Bacterial Peritonitis Pre-Liver Transplant

Variable	Odds Ratio (95% CI)	P-value
Child Score	0.011	>0.9
Warm Ischemic Time	1.402	0.999
Cold Ischemic Time	0.926	>0.9
Operation Time	1.052	>0.9
MELD Score	0.611	>0.9
Packed Cell Transfusion Dose	0.349	>0.9
Length of Hospital Stay	1.564	0.999
History of Antibiotic Use	6041.465	>0.9

Table 3: Correlation between confounding variables and mortality in patients with Spontaneous Bacterial Peritonitis Pre-Liver Transplant

Variable	Odds Ratio (95% CI)	P-value
Child Score	0.845 (0.300 to 2.378)	0.75
Warm Ischemic Time	0.954 (0.868 to 1.048)	0.322
Cold Ischemic Time	1.013 (0.997 to 1.029)	0.106
Operation Time	1.022 (0.998 to 1.046)	0.072
MELD Score	1.370 (1.049 to 1.788)	0.021
Packed Cell Transfusion Dose	1.097 (0.733 to 1.641)	0.653
Length of Hospital Stay	1.032 (0.949 to 1.123)	0.457
History of Antibiotic Use	0	* >0.99

Table 4: Correlation between confounding variables and Rejection in patients with Spontaneous Bacterial Peritonitis Pre-Liver Transplant

Variable	Odds Ratio (95% CI)	P-value
Child Score	1.866 (1.036 to 3.359)	0.038
Warm Ischemic Time	1.069 (0.998 to 1.144)	0.058
Cold Ischemic Time	0.984 (0.966 to 1.002)	0.075
Operation Time	1.023 (1.004 to 1.042)	0.016
MELD Score	0.842 (0.700 to 1.014)	0.069
Packed Cell Transfusion Dose	0.920 (0.722 to 1.173)	0.502
Length of Hospital Stay	1.010 (0.942 to 1.083)	0.783
History of Antibiotic Use	0	>0.9

5. Discussion

Patients undergoing liver transplantation face numerous short-term and long-term postoperative complications. Identifying factors that influence the prognosis of transplant recipients can enhance outcomes and reduce mortality rates. SBP is a common complication among cirrhotic patients awaiting liver transplantation, with approximately 22% of those on the transplant list experiencing an episode of SBP before surgery [20]. Although there is a general consensus on the benefits of rapid transplantation, the impact of previous SBP episodes on post-liver transplantation outcomes remains unclear [21].

Our study found no differences in mortality, rejection, or re-transplantation rates between patients with and without a history of SBP prior to liver transplantation. However, patients with SBP experienced longer hospital stays and liver transplant surgeries, along with a higher prevalence of past antibiotic use. Furthermore, these patients are believed to face more technical complications during surgery.

One study indicated that patients with SBP were more likely to require abdominal surgery after one year, primarily for hernia repair, bleeding, and vascular complications, although infection-related complications did not vary between the groups [22].

Additionally, patients with a history of SBP before liver transplantation needed mechanical ventilation and hemodialysis more frequently before the transplant, and they experienced an increase in postoperative complications. Notably, patients with a history of SBP showed a threefold increase in mortality rate (24% vs. 8%) [22].

A single-center study revealed that the presence of SBP at any time before the transplant was not associated with post-transplant mortality, although a larger experimental study noted an increased risk of reoperation after LT and death due to sepsis among SBP patients. Despite higher CHILD and MELD scores at the time of transplantation, SBP prior to LT did not influence post-transplant mortality. Nonetheless, patients with SBP had a higher likelihood of reoperation within the first year post-transplantation and an increased risk of death following sepsis. The incidence of sepsis as a cause of mortality in SBP patients was 53.8%, statistically significantly different from the control group [21].

Another study in 2015 showed that the one-year survival rate for patients with a history of SBP undergoing liver transplantation was 87%, and the ten-year survival rate was 70%, suggesting that delaying liver transplantation in patients with peritonitis could improve their survival rates [23]. These findings also corroborate other studies that noted increased mortality in patients with higher MELD scores [24].

Some studies indicate that pre-transplant SBP does not impact transplant outcomes. For example, one study found that patients with pre-transplant infections, including SBP, pneumonia, cellulitis, bacteremia, and urinary tract infections, required longer hospital stays, but mortality rates 90 and 180 days after transplantation showed no significant difference compared to individuals without pre-transplant infections [25]. Another study observed that while patients with a history of SBP before transplantation were significantly sicker and had higher mortality rates and longer hospital stays than those with-

out SBP, SBP alone, when accounting for other comorbidities, was not associated with worsened disease outcomes [26]. In our study, the length of hospital stays and surgery duration were significantly longer in patients with a history of SBP before transplantation; these patients also had a more prevalent history of antibiotic use prior to transplantation.

Patients with a history of SBP may have an increased risk of transplant rejection due to the elimination of confounding variables, prolonged surgery times, or high CHILD scores. However, these factors did not influence the recurrence of liver transplantation in these patients.

The retrospective design, single-center study nature, and varying times of liver transplantation constitute the primary limitations of our study. An international multicenter registry study is necessary to gather adequate data to determine the impact of SBP on LT prognosis.

6. Conclusion

We can conclude that a previous SBP infection should not deter liver transplantation, as this infection did not significantly impact patient outcomes, including re-transplantation rates, mortality, and transplant rejection.

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