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Article

Post-transplant Evaluation of HBV Patients with Preoperative Risk Faktor

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Abstract

Objective: Patients diagnosed with HBV may also have with typical risk prognosis. This study aims to compare the effects of cirrhosis patients with HBV with and without risk factors on post-transplant follow-ups, and postoperative complications. **Material and method:** The data from 359 patients were retrospectively analyzed. Those without preoperative risk factors were classified as group 1 (n=224), and those with risk factors were classified as group 2 (n=135). These patients were compared in terms of complications during their postoperative follow-up. Student's t-test, ANOVA test, Mann–Whitney U test, Kruskal Wallis test, chi-square test, and Fisher's exact test were used, and $p<0.05$ was considered statistically significant. **Results:** When group 1 and group 2 were compared in terms of postoperative mortality, infections, bleeding complications, and biliary system complications, no statistically significant difference was found ($p=0.62$, $p=0.95$, $p=0.46$, $p=0.19$). Bleeding was significantly higher in patients with obesity and three comorbidities (DM, HT, and HL) ($p=0.04$, $p=0.01$). Infection, a statistically significant difference was found in patients with DM and CAD ($p=0.02$), HL and HVD ($p=0.02$), and three additional diseases (DM, HT, and HL) ($p=0.02$). **Conclusions:** Reducing the susceptibility to infection is important for those with obesity to lose weight and reduce post-transplant mortality rates.

Keywords: HBV; obesity; liver transplantation; diabetes mellitus; cirrhosis

Introduction

Hepatitis B virus (HBV) infection remains a global public health problem with changing epidemiology due to various factors, including vaccination policies and migration [1]. Cirrhosis is a disease characterized by the progression of fibrosis and nodule formation, which develops based on chronic inflammation in the liver [2]. Viral infections, toxins, nonalcoholic steatohepatitis (NASH), and hereditary and autoimmune diseases cause chronic inflammation of the liver, leading to prolonged tissue damage, fibrosis, and cirrhosis. Metabolic dysfunction-associated fatty liver disease (MAFLD) is considered the liver manifestation of metabolic syndrome. MAFLD includes a wide spectrum of liver injury including simple steatosis and NASH that may lead to serious complications such as liver cirrhosis and hepatocellular cancer (HCC) [3].

While alcohol addiction and hepatitis C virus (HCV) cause 50% of cirrhosis in developed countries, the main cause in Turkey is HBV and HCV infections[4]. It is estimated that more than 1 million people die every year in the world due to complications such as cirrhosis and liver cancer due to viral hepatitis. It is reported that HBV infection is responsible for 30-40% of cirrhosis cases and 40-50% of liver cancer. The treatment of cirrhosis and HCC is a liver transplantation (LT). Viral hepatitis constitutes more than half of in our country's LT cases performed between 2012 and 2016

[5]. Comorbidities such as obesity, overweight, diabetes mellitus (DM), coronary artery disease (CAD), and insulin resistance in the preoperative period in patients undergoing LT have known risk factors [6]. Metabolic side effects such as weight gain and diabetes may occur in liver recipients due to drug use [7]. The global prevalence of MAFLD is estimated to be 32.4%, with a higher prevalence in males (39.7%) than in females (25.6%) [8]. In recent years, there has been an increase in other medical consequences of metabolic syndrome, including NASH [9-11]. 10-15% of NASH patients continue to have inflammation and fibrosis, eventually leading to cirrhosis and HCC. A significant proportion of obese individuals also have a risk of developing hepatocellular carcinoma [12]

In this study, we aimed to compare the comorbid diseases such as Diabetes Mellitus (DM), Hypertension (HT), Hyperlipidemi(HL), Coronary arter disease (CAD), obesity in the pre-transplant period in patients who underwent LT due to cirrhosis caused by HBV and HCC with the relationship between these patients duration of hospital stay, postoperative complications (post operative infection, bleeding, reoperation, biliary complications, mortality).

Material and Method

Patients over the age of 18 who underwent LT for advanced-stage liver failure and cirrhosis due to HBV in our hospital between 2004 and 2019 were included in this study. Between these years, 1200 patients underwent LT, and 468 patients who had HBV-related transplantation were found. Due to missing records in the files of 109 patients, they were excluded from the study, and 359 patients were included in the study (Table 1A and Table 1B). Ethics committee approval was obtained by applying to the Demiroglu Bilim University ethics committee. Patient data were obtained from the hospital's automation system and patient files and scanned retrospectively. Demographic characteristics (age, gender, height, weight, comorbidity, body mass index (BMI)), laboratuar tests including complete blood count, BUN, creatinine, AST, ALT, ALP, GGT, albumin, total bilirubin, direct bilirubin, prothrombin time, INR, TSH, free T3, free T4, AFP, Ca19-9, fasting blood glucose, HbA1c, fasting insulin, HOMA IR, Na, K were investigated. For hepatitis B serology, HbsAg, anti-HBs, anti-Hbe, anti-HBc, anti-HDV, HBV DNA, HDV RNA tests were examined. PAP (pulmonary artery pressure), MELD and CHILD scores were recorded.

Those with preoperative risk factors such as DM, HL, CAD, and obesity were divided into group 1, and those without risk factors were divided into group 2. The groups were compared with each other in terms of complications in the postoperative follow-up, infection, biliary system stenosis or leakage, and mortality rate.

The study was conducted in accordance with the Declaration of Helsinki.
Ethical approval was obtained prior to the initiation of the study.
Demiroğlu Bilim University, Istanbul, Turkey 21.072020/2020-13-02.

	Group 1 (n:224)	Group 2 (n:135)	
	mean ± SD	mean ± SD	p
Age, year	51.45±9.70	51.60±7.65	0.88
BMI, weight/height²	27.49±4.87	27.22±4.87	0.67
Gender (F/M)	49/175	25/110	0.32

BMI: Body mass index.

Table 1A. Comparison of demographic data of patients between groups.

	Group 1 (n:224)	Group 2 (n:135)	
	mean ± SD	mean ± SD	p
Age, year	51.45±9.70	51.60±7.65	0.88
BMI, weight/height ²	27.49±4.87	27.22±4.87	0.67
Gender (F/M)	49/175	25/110	0.32

BMI: Body mass index

Table 1B. Comparison of clinical features of patients between groups.

	Group 1 (n:224)	Group2 (n:135)	p
	mean ± SD	mean ± SD	
MELD score	15.67±5.82	15,029±6,139	0.37
CHILD	2.24±19.8	8.09±2.26	0.75
Length of stay	19.21±10.24	18.14±9.99	0.35
Exitus duration	1:40/13±13/37	6.00±7.07	0.50

MELD: Model for End-stage Liver Disease, CHILD : Child-Pugh-Turcotte score

Statistical Analysis

All data were analyzed using the Statistical Package for The Social Sciences (SPSS) -14 Inc, Chicago, Illinois, USA statistical program. Groups were compared statistically with Student's t-test, ANOVA test, Mann–Whitney U test, and Kruskal test. The chi-square test and Fisher's exact test were used for categorical variables. Parametric data were given as mean ± standard deviation, and nonparametric data were given as percentages. A value of p < 0.05 was considered statistically significant.

Results

Three hundred fifty nine patients who underwent liver transplantation due to HBV-induced liver cirrhosis were included in the study. 359 (285 male,79%) patients were divided into two groups according to whether there were risk factors or not. Group 1 included 224 patients without risk factors for the preoperative period, and group 2 included 135 patients with at least one and more risk factors. A comparison of patients' demographic data between groups is shown in Table 1A and Table 1B. There were 175 males (78%) in group 1, and 110 male patients (81%) in group 2, and the difference was not statistically significant (p=0.36). The mean age was 51.45±9.70 years in group 1 and 51.60±7.65 years in group 2, and there was no statistically significant difference between both groups (p=0.88). There was no significant difference in BMI between the two groups (p=0.67).

All patients were HBsAg positive. The mean HBV DNA was 627491.02 ± 5476491.2 IU/mL in Group 1 and 41551915.39 ± 438470.21 IU/mL in Group 2, and there was no statistical difference between the two groups (p=0.16). When the comparison was made in terms of the MELD-Na score, Child score, and PAP, no significance was found again (p=0.37, p=0.75 and p=0.38).

When the biochemical parameters were evaluated, no statistically significant difference was found between the groups (Table 2).

The patients in group 2 were 135 and the distribution of risk factors is shown in Table 3. While 99 (73.3%) patients had one pre-operative risk factor, 34 (25.2%) patients had 2 and 2 (1.5%) patients had three co-morbid diseases.

A statistical comparison of preoperative risk factors and postoperative complications is shown in Table 4. Postoperative death was observed in 19 patients (8%) in Group 1 and 10 patients (10%) in Group 2. There was no statistically significant difference between the two groups in terms of mortality (p=0.62). There was no statistical difference between group 1 and group 2 in terms of postoperative infections, significant bleeding complications, biliary system complications, strictures or leaks (respectively p=0.95, p=0.46, p=0.19).

When patients with risk factors were evaluated in terms of postoperative complications, bleeding was found to be significantly higher in patients with obesity and three additional diseases (DM, HT, and HL) (respectively p=0.04, p=0.01). Postoperative Infections were seen in DM and CAH (p=0.02), HL and HVD (p=0.02) and three additional diseases (DM, HT, and HL) (p=0.02). No significant difference was found in any of the biliary complications.

Table 2. Laboratory results of patients and comparison between groups.

	Group 1 (n:224)	Group 2 (n:135)	p
	mean ± SD	mean ± SD	
HB g/dl	12.27±2.67	4:05/13±35 PM	0.05
Htc (%)	5.99 ±34.99	6.55±.91.35am	0.18
WBC (x10 ⁹ /µl)	1±3.36 AM	4.29±1.5	0.81
PLT (x10 ³ /µl),	87318.78±45220.66	99872.54±64339.30	0.80
INR	0.51±1.61	1.63±0.57	0.69
AST U/L	89.54±74.68	93.03.74.82	0.60
ALT U/L	65.91±65.31	62.37±39.51	0.54
ALP U/L	152.76±96.00	159.79±130±94	0.62
GGT U/L	86.98±86.80	118.18±205.22	0.06
Albumin g/L	3.15±0.67	3.14±0.68	0.90
T.Biluribin µmol/L	4.12±5.39	5.01±7.41	0.22
D. Biluribin µmol/L	2.24±1.98	2.80±3.24	0.48
BUN mg/dl	23.86±63.18	19.32±13.35	0.45
Creatinine	0.87±0.41	1.22±3.75	0.18
Na meq/L	135.32±5.47	133.81±13.97	0.17
Glucose mg/dl	109.88±40.85	109.98±44.35	0.90
HbA1c mmol	5.39±1.33	5.52±1.26	0.90
Insulin µIU/mL	20.69±14.76	19.73±14.55	0.64

HOMA IR mmol/L	6.61±9.68	6.56±6.73	0.97
T. Cholesterol mg/dl	127.99±44.91	134.14±55.13	0.31
Triglyceride mg/dl	80.66±31.44	87.51±42.69	0.11
FT4 picomol/L	11.76±7.26	10.57±7.12	0.19
FT3 picomol/L	3.63±1.02	3.84±1.37	0.64
TSH mcrIU/ml	1.93±1.52	2.1±1.38	0.14
CEA ng/mL	2.53±.96 am	5.44±12.88	0.13
CA 19. 9 U/ml	75.96±201.89	84.46±308±57	0.78
AFP ng/ml	46.45±153.56	54.85±151.48	0.39
HBV DNA IU/mL	627491.02 ± 5476491.2	41551915.39± 438470.21	0.64

*.p<0.05 values were considered significant. white blood cells (WBC), hemoglobin (Hb), hematocrit (Htc), platelet (PLT), alanine aminotransferase (ALT); aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT),), (thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxin (FT4), homeostatic model assessment Insulin Resistance (HOMA-IR), Hemoglobin A1c (HbA1c), Alpha Protein (AFP), Hepatitis B Virus DNA (HBV DNA).

Table 3. Distribution of risk factors in patients with HBV-related liver disease and preoperative risk factors (Group 2).

Risk factors	n(135)	
DM	39	(28.88%)
COPD	6	(4.44 %)
HT	14	(10.37%)
HL	3	(2.22 %)
CAD	22	(16.22%)
Obesity	3	(2.22 %)
Heart valve diseases	12	(8.88%)
DM and COPD	6	(4.44%)
DM and HT	10	(7.40%)
DM and Heart valve diseases	2	(1.48%)
DM and CAD	5	(3.70%)
HT and CAD	4	(2.96%)
HT and Heart valve diseases	4	(2.96%)

HL and Heart valve diseases	1	(0.74%)
CAD and Heart valve diseases	2	(1.48%)
DM, HT and HL	1	(0.74%)
DM, HT and CAD	1	(0.74 %)

Diabetes Mellitus: DM, Chronic obstructive pulmonary disease: COPD, Hypertension: HT, Hyperlipidemia: HL, Coronary artery disease: CAD, Heart valve diseases: HVD

Table 4. Comparison of preoperative risk factors and postoperative complications.

Risk Factors (n)	Mortality(n)	p	Bleeding (n,%)	p	Biliary (n,%)	p	Infectious (n,%)	p
Group 1 (224)	19 (%8)	0.62	14(%6)	0.46	32(%14)	0.19	53(%23)	0.95
Group 2 (135)	10(%7)		12(%8)		12(%8)		37(%27)	
HT (14)	0(%0)	0.60	1(%7)	0.50	1(%7)	0.43	3(%21)	0.11
CAD (22)	1(%4)	0.41	3(%13)	0.43	2(%9)	0.33	5(%22)	0.83
HL (3)	0(%0)	0.61	1(%33)	0.66	1(%33)	0.50	1(%33)	0.06
Obesity (3)	1(%33)	0.04*	1(%33)	0.11	2(%66)	0.06	0(%0)	0.48
DM (39)	2(%5)	0.62	1(%2)	0.46	3(%7)	0.19	10(%25)	0.95
HVD(12)	2(%16)	0.68	1(%8)	0.08	1(%8)	0.74	4(%33)	0.93
COPD (6)	1(%16)	0.23	0(%0)	0.51	0(%0)	0.62	2(%33)	0.67
DM+HT(10)	1(%10)	0.22	1(%10)	0.64	0(%0)	0.68	4(%25)	0.67
HT+CAD(4)	0(%0)	0.87	0(%0)	0.93	0(%0)	0.69	1(%25)	0.08
HT+HVD(4)	0(%0)	0.87	1(%25)	0.38	0(%0)	0.69	1(%25)	0.08
DM+CAD(5)	1(%20)	0.53	1(%20)	0.35	1(%20)	0.53	2(%40)	0.02*
DM+HVD (2)	0(%0)	0.62	1(%50)	0.08	0(%0)	0.72	0(%0)	0.68
DM+COPD (6)	0(%0)	0.80	0(%0)	0.10	1(%16)	0.68	2(%33)	0.68
CAD+HVD(2)	0(%0)	0.80	0(%0)	0.10	0(%0)	0.72	1(%50)	0.06
HL+HVD(1)	0(%0)	0.86	0(%0)	0.94	0(%0)	0.92	1(%100)	0.02*
DM+HT+HL(1)	1(%100)	0.01*	0(%0)	0.94	0(%0)	0.92	1(%100)	0.02*
DM+HT+HVD(1)	0(%0)	0.94	0(%0)	0.94	0(%0)	0.92	0(%0)	0.06

Diabetes Mellitus: DM, Chronic obstructive pulmonary disease: COPD, Hypertension: HT, Hyperlipidemia: HL, Coronary artery disease: CAD, and Heart valve disease: HVD. *:p<0.05 values were considered significant.

Discussion

There are studies showing that patients develop obesity, diabetes, and hyperlipidemia after LT. This has been reported to be related to the medications used [7]. In cirrhosis patients, many co-morbid diseases such as DM, CAD, HL, and obesity can accompany the disease that affects the prognosis. LT is the curative treatment of cirrhosis. Patients with cirrhosis are prepared for operations by evaluating perioperative risks according to Child and MELD scores. Even cirrhosis alone poses a perioperative risk [13]. There are studies showing that intraoperative hypoxia rates in advanced-stage cirrhosis patients with ascites are between 5-32% [14]. In a retrospective study by Teh et al, including 772 patients, perioperative risks were evaluated with the MELD score in patients with cirrhosis. In terms of MELD score, postoperative mortality rates for those with MELD scores <7, MELD scores=8-11, and MELD scores >11 are 5.7%, 10.3%, and 25%, respectively [15]. Bleeding, infections, biliary system stenosis, or leaks can be seen in the early and late periods after LT, and these cause an increase in mortality. F. Baganete et al. found that 67977 LT patients, the early (>90 days) mortality rate was 5% and the mortality rate within the first year was 10% [16]. In our study, the first 1-year mortality was found to be 7% in the group with risk factors and 8% in the group without risk factors, and no significant difference was found between the groups.

In the subgroup analysis in the group with preoperative risk factors, mortality was found to be significantly higher in obese patients than in non-obese patients.

The small number of patients is a limitation of this study. Further studies with larger patient groups are necessary.

Our study suggests that it may be possible to predict postoperative complications [mortality, length of hospital stay) among patients with and without preoperative risk factors after LT in patients with HBV-related cirrhosis.

Post-LT biliary complications [leakage, stenosis, bilioma) are an important cause of morbidity and mortality [17,18]. The rate of biliary stenosis is 5-15% in cadaveric LT and 28-32% in living donor transplantation [19]. In our study, post-transplant biliary complications, biliary strictures, biliary leak, and bilioma were considered in total. There was no significant difference between group 1 [8%] and group 2 [8%] in terms of biliary complications. The biliary complications we detected in our study are similar to those of previous studies [1,15]. Post-operative bleeding is usually seen in the early period and requires urgent intervention. Jung JW et al. found 9% intra-abdominal bleeding among a group of 1039 liver transplant patients [n=94] [20]. In our study, postoperative bleeding [intra-abdominal) complication rates were similar in both groups and were not found to be statistically significant.

Post-transplant infections are an important cause of mortality and morbidity in the first year after the operation. It is 80% during the year, with 70% bacterial infections, 20% viral infections, and 8% fungal infections [21] and the difference is not significant.

In subgroup analyses, postoperative bleeding [intra-abdominal) was significantly higher in patients with obesity and three comorbidities [DM, HT and HL).

In terms of postoperative complications were compared with those without risk factors; bleeding was significantly higher in patients with obesity and three additional diseases [DM, HT, and HL). When evaluated in terms of infection, a statistically significant difference was found in the patient group with DM and CAD, HL and HVD, DM, HT, and HL. Similarly, mortality in the obesity group was found to be significantly higher in the obesity group when compared to the non-obese group.

In a previous study including 184 normal weight, 136 overweight, and 50 obese liver transplant patients, a total of 370 patients were included, Von Son et al. found that obesity rates were 2 times higher than those with normal weight and found it statistically significant [22]. In our study, mortality rates were found to be high in the obesity group, which is similar to previous studies in this respect.

Conclusions: Preoperative obesity is a significant risk factor for post-LT infections and post-transplant mortality. Taking precautions such as ensuring that those with obesity problems lose weight before surgery, taking diet and exercise programs, and making lifestyle changes can reduce complications in the post-operative period.

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