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Original Article

Risk factors of postoperative ascites on hepatic resection for hepatocellular carcinoma

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Backgrounds/Aims: The aim of this study was to identify the risk factors of the development of large amounts of ascites (LA) after hepatic resection for hepatocellular carcinoma (HCC). **Methods:** The medical records of 137 consecutive patients who underwent hepatic resection for HCC from January 2010 to December 2014 were retrospectively reviewed. Patients were divided into two groups: LA group, with ascites drainage >500 cc per day over 3 days (n=37) and control group (n=100). Preoperative and intraoperative clinical variables were compared between the two groups. **Results:** Thirty-seven (27.0%) patients developed LA. Platelet counts of <100,000/mm^3, ICG-R15 >10%, CTP scores of 6 or 7 points, major resection, the presence of cirrhosis, preoperative ascites, and portal hypertension were significantly more frequent in LA group. Multivariate analysis revealed that a higher CTP score (HR=4.1), the presence of portal hypertension (HR=26.7), and major resection (HR=18.5) were independent and significant risk factors of postoperative ascites development. Persistent refractory ascites developed in 6 (16.2%) patients who succumbed to hepatic failure during follow-up. **Conclusions:** Patients with a 6 or 7 point CTP score, major hepatic resection and/or portal hypertension were more likely to develop LA and experience deterioration of liver function after surgery. The selection of patients for hepatic resection should be based on a balanced assessment of the benefits of HCC treatment and risk of postoperative liver failure. **(Ann Hepatobiliary Pancreat Surg 2016;20:153-158)**

Key Words: Hepatocellular carcinoma; Ascites; Hepatectomy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second common cause of cancer-related death worldwide.[1] Hepatic resection is the main treatment option for HCC, but the majority of HCC patients have underlying chronic liver disease, such as, viral hepatitis or liver cirrhosis. The rate of hepatic resection among HCC patients ranges from 11.9 to 18.5%.[2,3]

Some preoperative parameters, such as, Child-Turcotte-Pugh (CTP) class and indocyanine green retention rate at 15 min are useful to reduce morbidity and mortality; however, rates of postoperative morbidity (22.3-45%) and mortality (2.2-4.5%) remain high.[4-6]

Postoperative ascites is one of the most common complications after hepatic resection, and patients with a large amount of ascites (LA) require more plasma volume expansion and longer hospital stays, which increase treatment costs.[7] In particular, patients with refractory ascites are more likely to experience HCC recurrence and show greater risk of mortality.[8] Hence, it is important to identify patients that are likely to develop ascites postoperatively.

Accordingly, the aim of this retrospective study was to identify the risk factors of ascites development in HCC patients after hepatic resection and analyze patient outcomes.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of 140 consecutive patients who underwent hepatic resection for pathologically confirmed primary HCC from 1 January 2010 to 31 December 2014 in Inha University Hospital.

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Three cases of HCC rupture were subsequently excluded. A total of 137 patients comprised the study cohort. Clinical characteristics and medical records were retrospectively analyzed.

Diagnosis and treatment

Preoperative diagnosis of HCC was based on the guidelines of Korean Liver Cancer Study Group.[9] Serum alpha-fetoprotein level and serum protein induced by the absence of vitamin K or antagonist-II were evaluated as diagnostic parameters.

Anatomical resectability and liver volume were estimated by dynamic enhanced computed tomography or dynamic enhanced magnetic resonance imaging. Hepatic functional reserve and surgical extent were assessed using; CTP classification, serum bilirubin level, indocyanine green retention rate at 15 min, serum platelet count, presence of ascites, and presence of portal hypertension (PHT). Preoperative PHT was defined as the presence of esophageal varices, splenomegaly, or a platelet count of $<10^5$/μl based on criteria of the Barcelona Clinic Liver Cancer group.[10]

Hepatic resections were described using Brisbane 2000 terminology.[11] Major resections were defined as left hepatectomy and resection of >3 liver segments.[12,13] Liver parenchymal transection was performed with the clamp crushing method or by application of a Cavitron ultrasonic surgical aspirator (Valleylab Inc., Boulder, CO). A Jackson-Pratt drain was placed near the cut surface and connected to a closed drainage system to drain serosanguineous fluid or monitor bile leakage.

Postoperative care

Postoperative management included daily measurement of the ascitic drainage volume and fluid therapy to maintain a minimal urine output of >0.5 ml/kg/hr without routine transfusion of fresh frozen plasma. Routine blood laboratory tests were conducted immediately after surgery and on post-operative days 1, 3, 5, and 7.

Ascites management included diuretic therapy, albumin replacement therapy and/or volume replacement therapy. Diuresis was induced with increasing doses of an aldosterone antagonist (spironolactone) and a loop diuretic (furosemide) until loss of ascitic fluid was achieved. 20% albumin was given if the serum albumin concentrations were <3.0 g/dl. In volume replacement therapy, we routinely replaced 40% of ascitic fluid drainage with crystalloid fluids.

Patients with drainage amounts >500 ml per day over 3 days were allocated to the LA group (n=37) and the rest to the control group (n=100). The removal of Jackson-Pratt drain was considered as successful therapeutic control of ascites.

Statistical analyses

Continuous data were expressed as means±standard deviations. The LA and control groups were compared with respect to categorical and continuous data. Categorical data was analyzed using the Chi-square or Fisher's exact test; and continuous data using the independent T test.

The following clinical factors and potentially important preoperative and intraoperative factors were included in the analysis: age, gender, hospital stay, hepatitis etiology, CTP score (5 vs. 6, 7), serum alanine aminotransferase (<60 IU/L vs. ≥60 IU/L), serum total bilirubin (≤12 mg/dl vs. >12 mg/dl), serum albumin (<3.5 g/dl vs. ≥ 3.5 g/dl), prothrombin time (INR ≤1.2 vs. >1.2), pre-operative platelet count ($<10^5$/μl vs. $\geq 10^5$/μl), presence of PHT, alphafetoprotein, protein induced by antagonist-II or by the absence of vitamin K, indocyanine green retention rate at 15 minutes (≤10% vs. >10%), presence of preoperative ascites, cirrhosis, tumor size, and extent of hepatic resection (non-major resection vs. major resection).

Multivariate analysis was performed using stepwise logistic regression analysis. p-values <0.05 were considered as statistical significance. The analysis was performed using the Statistical Package for the Social Sciences version 14.0 (SPSS Inc., Chicago, IL) for Windows.

RESULTS

Risk factors affecting postoperative ascites after hepatic resection

Among the 137 patients, there were 3 cases (2.2%) of 30-day mortality and 2 cases (1.5%) of 3-month mortality. One patient died of arrhythmia due to massive bleeding during operation, the other 4 patients succumbed to liver failure after hepatic resection.

Table 1. Characteristics of the large amount of ascites (LA) group and the control group

Variables	Control (n=100)	LA group (n=37)	*p*-value
Age	56.6±10.8	56.4±7.0	0.053
Gender (M:F)	84:16	35:2	0.084
Hospital stay (days)	10.3±4.0	17.8±12.0	<0.001
Etiology			
HBV	77 (77.0)	25 (67.6)	0.477
HCV	2 (2.0)	4 (10.8)	
NBNC	20 (20.0)	7 (18.9)	
HBV & HCV	1 (1.0)	1 (2.7)	
CTP score			
5 points	75 (75.0)	19 (51.4)	0.006
6-7 points	25 (25.0)	18 (48.6)	
ALT >60 IU/L	5 (5.0)	8 (21.6)	0.006
Total bilirubin >1.2 mg/dL	6 (6.0)	4 (10.8)	0.267
Albumin <3.5 g/dL	17 (17.0)	11 (29.7)	0.083
Prothrombin time (INR) >1.2	6 (6.0)	6 (16.2)	0.067
Platelet counts <100,000/mm^3	5 (5.0)	15 (40.5)	<0.001
Portal hypertension	12 (12.0)	19 (51.4)	<0.001
AFP	1,113.0±460.9	1,313.7±1,095.6	0.842
PIVKA II	844.4±3,019.4	1,032.7±2,871.0	0.760
ICG- R15 >10%	18/74 (24.3)	15/28 (53.6)	0.006
Presence of the preoperative ascites	15 (15.0)	12 (32.4)	0.024
Cirrhosis	48 (50.5)	26 (70.3)	0.016
Size of tumor	4.14±2.94	4.68±4.74	0.515
Major resection	18 (18.0)	15 (40.5)	0.007

Continuous variables are expressed as means±standard deviations and categorical variables as numbers (%). HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C; CTP, Child-Turcotte-Pugh; ALT, alanine aminotransferase; INR, international normalized ratio; PIVKA II, protein induced by vitamin K absence or antagonist-II; AFP, alphafetoprotein; ICG-R15, indocyanine green retention rate at 15 minutes

Table 2. Independent prognostic factors of the development of large amount of ascites postoperatively

Variables	Hazard ratio	95% confident intervals	*p*-value
CTP score 6-7	4.1	1.3-13.5	0.019
Portal hypertension (+)	26.7	6.1-116.8	<0.001
Major resection	18.5	4.2-81.1	0.001

CTP, Child-Turcotte-Pugh

Thirty-seven (27%) patients developed LA. Mean preoperative platelet count was significantly lower; whereas, mean hospital stay, CTP score, serum alanine aminotransferase, presence of PHT, presence of preoperative ascites, and extent of hepatic resection were higher/greater in the LA group (Table 1). Factors that showed significant association with LA on univariate analysis were subjected to multivariate logistic regression analysis. The results revealed that CTP score, presence of PHT, and extent of hepatic resection were the 3 significant factors associated with the development of LA (Table 2).

Management of postoperative ascites

In LA group, 25 (67.6%) patients received diuretic therapy, 4 (10.8%) patients were treated with volume replacement therapy only, and 8 (21.6%) patients were placed under observation. Most patients in LA group received albumin replacement therapy. The mean level of serum albumin was increased after postoperative 3 days in the control group, whereas it showed continuous decrease throughout the postoperative period in the LA group. Serum albumin concentrations were significantly lower in the LA group than in the control group before surgery and on postoperative days 1, 3, 5, and 7 (Fig. 1).

Mean times to ascites control were 14.1±7.8 days for diuretic therapy, 16.8±8.3 days for volume replacement therapy, and 10.9±2.7 days for observation.

In the patients who received diuretic therapy, the median period of diuretic use was 27 days (range: 9-567 days); diuretics were discontinued in 14 patients within 6 month; and 5 patients withdrew from diuretics after 6 months. The remaining 6 patients showed persistent re-

fractory ascites and subsequently died of liver failure (median [range], 72 [23-323] postoperative days). The specific clinical characteristics of patients were presented in Table 3.

DISCUSSION

In the present study, a high proportion (27%) of patients developed LA postoperatively. Although hepatic resection is the main treatment option for HCC, patients must be carefully selected to diminish the high risk of postoperative liver failure with increased risk of death. Multivariate analysis showed that higher CTP score, portal hypertension, and major resection significantly and independently increased the risk of LA.

The underlying mechanism of post-hepatic resection ascites is not well understood, but previous studies have shown PHT and cirrhosis can facilitate ascites. The combination of PHT and splanchnic arterial vasodilatation alters intestinal capillary pressure and permeability and stimulates neurohormonal systems, facilitating the accumulation of ascites.[14] According to the American Association for the Study of Liver Diseases practice guidelines, PHT with cirrhosis is a relative contraindication of hepatic resection.[15] However, in some studies, mortalities were similar in patients with or without PHT.[16,17] Nevertheless, the present study showed that PHT is a significant risk factor of ascites development, and post-operative prolonged or persistent ascites or refractory ascites is associated with a poor prognosis and an increased risk of mortality.[8] Thus, although resection can be performed in patients with PHT, careful patient selection considering other risk factors of LA would help reduce morbidity and mortality after hepatic resection.

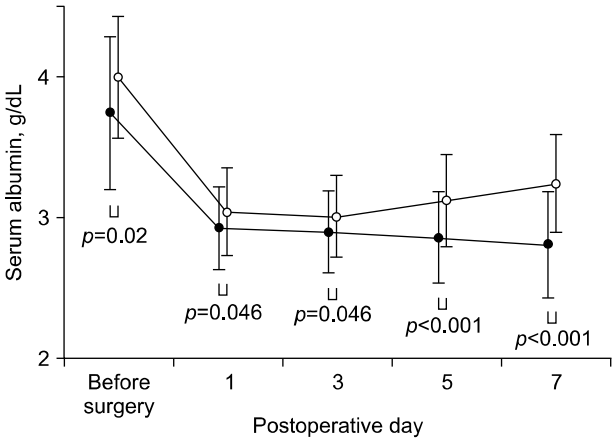

Fig. 1. Postoperative serum albumin concentrations in patients with (solid circles) and without (open circles) a large amount of ascites. Circles indicate mean values; whiskers, standard deviations.

Major resection is associated with a significant and persistent increase in portal pressure. PHT after hepatic resection may cause insufficient urinary output in the early postoperative period and subsequent ascites.[14,18]

We managed LA after hepatic resection using two strategies including diuretic therapy combined with supportive volume therapy, or volume replacement therapy alone. However, we did not evaluate differences between the two strategies. Further study is required to determine the most effective treatment for LA.

Management of LA after hepatic resection without the use of plasma expanders is associated with derangement in circulatory function, characterized by a reduction in effective arterial blood volume and activation of vasoconstrictor and antinatriuretic factors. Circulatory dysfunction in patients with cirrhosis who undergo large-volume paracentesis without the use of plasma expanders can result in subsequent renal impairment, hepatic impairment

Table 3. Summary of patients with persistent refractory ascites

Patient	Sex/Age	CTP score	Presence of PHT	Operation name	Management of ascites	Outcome
1	M/60	5	No	Right posterior sectionectomy	Diuretics	Died POD 30 due to hepatic failure
2	M/51	5	No	Right hemihepatectomy	Diuretics	Died POD 77 due to hepatic failure
3	M/60	6	No	Right hemihepatectomy	Diuretics	Died POD 135 due to hepatic failure
4	M/71	7	Yes	Left lateral sectionectomy	Diuretics	Died POD 23 due to hepatic failure
5	M/45	7	Yes	Tumorectomy	Diuretics	Died POD 67 due to hepatic failure
6	M/48	6	No	Right posterior sectionectomy	Diuretics	Died POD 323 due to hepatic failure

CTP, Child-Turcotte-Pugh; PHT, portal hypertension; POD, postoperative day

and/or dilutional hyponatremia, and shortened survival.[7,14,19] In the present study, albumin was administered for volume expansion and protein replacement. The use of albumin remains controversial due to its high cost and the lack of documented survival benefit; however, albumin has a greater protective effect on the circulatory system than other expanders.[14]

While albumin synthesis is reduced after hepatic resection, its half-life is around 20 days, which does not explain the rapid decrease in serum albumin concentration immediately after surgery. The most significant cause of the reduced albumin level is apparent redistribution, catabolism, or both. In this study, greater distribution to ascitic fluids and loss might explain hypoalbuminemia in LA group postoperatively. However, a previous study indicated that correction of hypoalbuminemia has no benefit in terms of morbidity and mortality over untreated controls.[20]

Previous studies have identified several risk factors of ascites after hepatic resection. However, important risk factors were not always related to liver function, but rather, were associated with other coexisting conditions, operative stress (use of the Pringle maneuver, operation time, blood loss) or blood transfusion.[5,7,8,21,22] In the present study, we determined risk factors related to preoperative liver function and not operative stress. Further evaluations of operative stress are needed to improve understanding of the risk factors of LA and improve treatment strategies.

In the present study, patients with a CTP score of 6 or 7 points and/or portal hypertension needed major hepatic resection. Furthermore, LA development and liver function deterioration worsened in some of these patients after surgery. These findings suggested that non-surgical treatment should be considered for the management of HCC patients at high risk of developing large amounts of ascites and the balance between the benefit of surgical HCC treatment and the risk of postoperative liver failure should be considered when selecting patients for hepatic resection.

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