

INVESTIGATING THE OCCURRENCE OF PERSISTENT ASCITES AFTER LIVER TRANSPLANTATION AND ITS RELATIONSHIP WITH GRAFT REJECTION

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Summary

Introduction. Ascites is caused by fluid accumulation in the abdominal cavity, which can be caused by portal hypertension. Various causes are effective for the formation of ascites, which is different according to the gradient of albumin and protein in the ascites liquid. There are various indications and etiologies for liver transplantation in cirrhotic patients. The causes of ascites after transplant are different from infectious causes to seizure rejection. In this study, the frequency of resistant ascites after liver transplantation in patients and its relationship with rejection after transplantation has been investigated.

Methodology. In this project, we retrospectively analyzed the data of patients who had liver transplantation for various causes of liver cirrhosis between December 2012 and December 2017, and the frequency and prevalence of resistant ascites after liver transplantation and its relationship with rejection after surgery were investigated.

Result. It can be mentioned in the project results that a total of 493 patients who underwent liver transplantation were reviewed and the relevant causes were isolated, and 137 patients (27.8%) had evidence of rejection during a median follow-up period of 2 years.

During this follow-up period, 48 patients (9.7%) died. 190 patients (38.5%) are women and 303 patients (61.5%) are men. 387 (78.5%) of patients have persistent ascites after liver transplantation.

Conclusions. It should be noted that the incidence of ascites after liver transplantation has a significant relationship with the incidence of rejection after liver transplantation (p value: 0.009).

INTRODUCTION

Ascites is the accumulation of an ultrafiltrate in the peritoneum of patients with cirrhosis, which often indicates an irreversible condition in this population. Splanchnic and systemic vasodilation is predominant. The primary mediator of this state is the vasodilator nitric oxide. Splanchnic vasodilation leads to a decrease in effective circulating blood volume, followed by severe sodium retention by the kidneys (in an attempt to increase blood volume) and a hyperdynamic circulation¹.

With the increase of sinus hydrostatic pressure, the formation of hepatic lymph increases, which affects and reduces the ability of the lymphatic

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system to return lymph to the venous circulation. Lymphatic transudation continues through the capsule and fluid accumulation in the peritoneum continues and is maintained by continued dilation of the splanchnic vessels. In addition, the continuation of vasodilation in the splanchnic bed can lead to vasoconstriction at the level of renal arteries, and as a result, it leads to functional kidney failure, which may progress to liver syndrome by developing resistant ascites¹.

Ascites is a common and end-stage complication of advanced liver disease¹, and refractory ascites (RA) occurs when it cannot be satisfactorily and completely reduced by drug therapy and ascites fluid. RA is known to have a poor prognosis, with a 1-year transplant-free survival in advanced cirrhotic patients of 20–50%². Patients with RA commonly have additional complications, including spontaneous bacterial peritonitis, hepatic syndrome, and hepatic hydrothorax^{3,4}. Large volume paracentesis (LVP), transjugular intrahepatic portosystemic shunt (TIPS), venous peritoneal shunts and portocaval shunts^{1–8} in the treatment of patients with have been used to RA. Liver transplantation (LT) is the best treatment option for patients with end-stage liver disease and ascites, as ascites usually disappears after LT. Ascites has been reported after LT, and its occurrence can be related to hepatic vein outflow obstruction⁸.

The prevalence of ascites after liver transplantation (LT) in adult patients ranges from 3 to 7%^{1–3}. Transient accumulation and persistence of ascites after LT is not uncommon, and it can occur in patients after liver transplantation, but in most cases, ascites disappears in the early period after LT. Long-term or persistent ascites after LT can be caused by back ligation performed at the time of surgery, inferior vena cava anastomotic stenosis, Venoocclusive disease (VOD), recurrent hepatitis C virus (HCV), and infection. The pathophysiology of ascites formation as a result of rejection after liver transplantation is not clear, but its probable cause is vascular thrombosis caused by severe inflammation and endothelial damage, which leads to sinus obstruction syndrome (SOS).

Ascites after liver transplantation, although uncommon, still presents a serious clinical problem. The hemodynamic changes that support the development of ascites before liver transplantation are largely improved after transplantation. Therefore, persistent ascites (PA) after liver transplantation is unexpected and debilitating³.

Advanced liver disease associated with intractable ascites is an indication for liver transplantation. Most patients with problematic ascites benefit significantly from liver transplantation as it increases survival and quality of life³.

Ascites resolution after liver transplantation is mainly the result of reversal of hemodynamic disturbances and renal functional failure that occur in patients with

decompensated cirrhosis. In fact, in most cases, this reversal occurs 2 weeks after the liver transplant. The reasons for maintaining this disorder are unclear. The mechanisms leading to persistent ascites (PA) after liver transplantation are still unclear. Understanding these mechanisms helps in the management of affected patients³.

Child-Pugh scores and the model for end-stage liver disease (MELD) are widely used to predict outcomes and assess the outcome after liver transplantation (LT). Both have similar prognostic values in most cases, although their benefits may differ in some specific conditions⁴.

METHODOLOGY

In this project, retrospectively, 493 patients who underwent liver transplantation were examined from the data of the transplantation department of Imam Khomeini Hospital affiliated to Tehran University of Medical Sciences from 2012 to 2017, and the relevant etiologies were isolated.

We have observed these patients on average during the 2 years after the transplant in a continuous form with the presence of the patients in the clinic and also the continuous follow-up of the patients by telephone.

The patients' MELD score and basic demographic information were separated from the patients and entered into SPSS version 2022, and the analysis was performed from the patients.

All patients with liver cirrhosis who underwent liver transplantation at Imam Khomeini Hospital Center were included in the project.

EVALUATION

Blood tests should be performed to assess liver and kidney function, including complete blood cell counts, liver enzymes, albumin levels, immunosuppressant levels, and renal parameters. Because of the relatively high incidence and available treatment options, there should be a low threshold for evaluating viral causes, primarily hepatitis C. In cases where a cardiac cause is clinically possible, N-terminal B-type natriuretic peptide (NTproBNP) levels should be measured. The next step should be a diagnostic paracentesis, primarily to evaluate for infections such as bacterial peritonitis. The slope of serum albumin to ascites should be determined. However, its use to assess portal blood pressure in the post-transplant setting is limited.

RESULT

From December 2012 to December 2017, the number of 493 patients who underwent liver transplantation was

examined and the relevant etiologies were isolated, and 137 patients had evidence of rejection during the 2-year median follow up period of the patients (27.8%).

387(78.5%) of patients have persistent ascites after liver transplantation.

During this follow-up period, 48 patients died (9.7%): 190 patients (38.5%) are women and 303 patients (61.5%) are men.

The average age of the participants is 44.84 with a standard deviation of 13.24.

The etiologies of the patient's liver failure can be seen in Table I.

8 patients had evidence of portal thrombosis after transplantation (1.62%) and 14 patients had evidence of hepatic artery thrombosis (2.83%).

14 patients have experienced hepatorenal evidence of post-transplantation syndrome (2.83%).

323 patients had hepatic encephalopathy after transplantation (65.51%).

382 patients have developed acidosis after transplantation (77.48%).

There is a significant relationship between graft rejection and post-transplant ascites (p value = 0.009).

DISCUSSION

Vascular causes of persistent ascites (PA) include outflow and inflow obstructions of blood supply to the liver parenchyma⁸. Inferior vena cava stenosis is a very rare complication after LT, the incidence of which is reported to be 1%⁹. This iatrogenic complication is usually located at the anastomosis site or just above the anastomosis site⁹. According to the results of Cirera et al.⁶, the main mechanism for the formation of massive ascites after LT is post-sinusoidal portal hypertension secondary to the problem of outflow of fluid from the hepatic vein. In their work, hemodynamic data were used; the gradient between free hepatic vein pressure and right atrial pressure in patients who had ascites was significantly higher than in patients who did not. However, ascites was diagnosed only when hepatic venous pressure, which reflects sinus pressure, exceeded a threshold of 12 mm Hg and increased⁶.

The etiology of post-LT ascites is highly variable, unclear, and sometimes poorly understood¹, but can generally be based on graft status, whether cirrhosis (due to recurrent disease) or reduced hepatic vascular compliance due to cellular rejection. Acute/chronic frequent, etc.)⁵, or non-cirrhotic transplantation (due to vascular complications such as hepatic venous outflow obstruction (HVVO) or portal vein thrombosis or stenosis leading to portal hypertension and ascites)¹⁻⁵. Idiopathic ascites after LDLT is diagnosed after all possible causes have been excluded.

Table I. Etiology of liver cirrhosis in patients.

Etiology of liver failure	Frequency	Percent
Autoimmune	57	11.6
Cryptogenic	91	18.5
HCV	48	9.7
HBV	46	9.3
Wilson's	14	2.8
PBC	8	1.6
PSC	57	11.6
HBV-HDV	4	.8
Hemochromatosis	3	.6
Acute liver failure	28	5.7
Celiac	1	.2
Nash	30	6.1
HBV-HCC	11	2.2
Ash	11	2.2
Buddchiary	13	2.6
HCV+HCC	8	1.6
HBV+HDV+HCC	4	.8
HBV+HCV	1	.2
Hyper cholestoroledi	3	.6
congenital fibrosis	1	.2
Retransplant	20	4.1
SSC	1	.2
Wilson's+HCC	1	.2
AI+HCC	4	.8
buddchiary+HCC	5	1.0
Crypto+HCC	4	.8
Liver & kidney	6	1.2
HCC	2	.4
buddchiary+PSC	2	.4
Acute on chronic	3	.6
Other	3	.6
Total	490	100

These patients usually have a good prognosis.

Some studies have shown that patient risk factors, such as gender, presence of hepatitis C virus (HCV), and cold ischemic time (CIT), may also predispose patients to ascites. Men may be at a higher risk of developing ascites, but data are limited. Before the widespread use of direct-acting antivirals (DAAs), patients who underwent transplantation for HCV-related disease were at increased risk for developing and resisting persistent ascites. HCV recurrence after liver transplantation can lead to ascites even in the absence of significant fibrosis. According to two retrospective studies, ascites was found in allograft biopsies in patients with stage 0, 1, or 2 fibrosis. Positive cryoglobulinemia in patients with positive HCV is also a predictor of ascites development. There are limited data

Table II. Frequency persistent ascites after transplant.

		Frequency	Percent
	No	106	21.50
	Yes	387	78.50
Total		493	100.0

Table III. The relationship between the presence of ascites after transplantation and rejection.

		Persistent ascites after transplant		Total	p value
		No	Yes		
Rejection	No	63	287	350	0.009
	Yes	39	94	133	
Total		102	381	483	

on the resolution of ascites after HCV treatment, particularly with the use of DAAs.

Several predictive factors for the development of ascites after LT have been reported in the literature, mostly from case series or retrospective cohort data, including preoperative, intraoperative, and postoperative factors. The present study aimed to determine the prevalence (Tabs. II-III), risk factors and describe the outcome of ascites after LDLT.

Treatment of ascites after liver transplantation is directed towards the underlying cause of its occurrence, if it can be corrected. Patients with outflow obstruction can undergo balloon angioplasty or surgical repair, and this often results in rapid resolution of ascites. Diuretics are used in patients without internally correctable causes. Unfortunately, the possibility of renal failure or electrolyte disturbances may occur, requiring treatment with repeated therapeutic paracentesis.

Transjugular intrahepatic portosystemic shunts (TIPS), commonly used as a graft bridge for patients with cirrhosis, are also used to manage post-transplant ascites. There is controversy regarding the technical difficulty of placing TIPS in a transplanted versus a native liver. However, a retrospective study found no statistical significance regarding success rates. Complications of placing TIPS in a liver transplant recipient include the risk of perforation of the liver capsule, infection, TIPS dysfunction, decreased liver function, infection, and hepatic encephalopathy^{12,13}. There is a high clinical success rate with TIPS following OLT, which has been described as 16-58%, which is lower than in the pretransplant population, and graft survival 6-12 months after TIPS is 45-50%. Due to variable success, many patients may continue paracentesis therapy after TIPS placement or may require revision of TIPS.

CONCLUSIONS

In the final result of this study, it should be noted that the occurrence of ascites after liver transplantation has a significant relationship with the occurrence of rejection after liver transplantation. Therefore, the occurrence of ascites during patient follow-up can warn the physician that there is a possibility of transplant rejection.

It is suggested that in future studies, corticosteroid pulse drug treatment should be started in patients with ascites after liver transplantation in order to prevent the possibility of rejection.

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Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

SAA, AK: have adjusted the final text. All the authors contributed equally to the work.

Ethical consideration

Not applicable.

Limitation

In the limitations of this study, it should be mentioned that the main limitation in this study was the duration of follow-up of the patients. If the follow-up period of the patients is assumed to be longer, more definite results can be presented.

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