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Can we Predict Massive Ascites Formation after Liver Transplantation, and is it Related to Long-Term Adverse Effects?

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Abstract

Objective: The aim of this study was (1) to quantify post-transplantation ascites formation, (2) to identify predictive factors for postoperative ascites formation, and (3) to evaluate whether it has impact on long term graft and patient survival. Factors that contribute to post-transplantation ascites formation are unknown. Routine peritoneal drain placement to prevent ascites accumulation after orthotopic liver transplantation (OLT) is controversial.

Materials & Methods: Included were 238 adult patients who underwent primary OLT. The amount of ascites present at the start of OLT was measured. Primary outcome variables were the cumulative amount of postoperative ascites formation, the total duration of ascites drainage, and the patient and graft survival with a minimum follow-up period of three years. Predictive variables were categorized in donor, recipient and transplantation-related variables.

Results: Median amount of ascites present at the start of OLT was 100 mL (0-21,000 mL, IQR 2,000 mL) and median cumulative postoperative ascites production was 6,240 mL (0-123,820 mL, IQR 13,716 mL). Multivariate regression analysis could not identify significant predictors. Median follow-up was 8.4 years (IQR 6.4 years). Five-year graft and patient survival were 80% and 95% respectively; three-year graft and patient survival were 88% and 97% respectively. Patient and graft survival were not different in the upper versus the lower than median cumulative postoperative ascites production.

Conclusion: Our data signify that postoperative ascites production is a problem and is highly variable. We could not reliably identify predictive factors. No effect on patient and graft survival was found.

Keywords: Liver; Transplant; Outcomes; Ascites; Drainage

Abbreviations: CIT: Cold ischaemia time; DBD: Donors after brain-death; DCD: Donors after circulatory death; FAHP: Functional anhepatic phase; ICU: Intensive care unit; IQR: Interquartile range; LVP: Large-volume paracentesis; MELD: Model for end-stage liver disease; OLT: Orthotopic liver transplantation; REVT: Revascularisation time; WIT: Warm ischaemia time

Introduction

Orthotopic liver transplantation (OLT) is currently the only life-saving treatment for patients with end-stage liver disease [1]. Still, a great variety of postoperative surgical and medical complications have been reported [2,3]. Postoperative ascites formation is a serious complication and may contribute to prolonged hospital stay, increased morbidity and mortality [4,5]. Postoperative ascites after OLT occurs in 20-40% of the patients in widely varying amounts [6-11]. Factors contributing to the amount of ascites production after OLT are by and large unknown [12]. Abdominal drains are routinely placed after transplantation in 86% of the centers [13]. Recently, the necessity of routine drain placement after OLT was challenged by several studies [6-8,12,14]. However, these studies mainly focused on the effect of drain placement on complications like bleeding and bile leakage, and did not focus on postoperative ascites formation.

The aim of this study was to gain insight in the problem of ascites production after OLT, to identify risk factors for increased ascites production, and to evaluate whether it has impact on long-term patient and graft survival. To this end, we analyzed donor and recipient variables in a cohort of adult patients who underwent a primary OLT.

Materials and Methods

We analyzed data collected in our prospective liver transplant database. From 2000-2012, 494 patients underwent an OLT in our center of which we included 238 patients. We excluded 140 transplantations in patients less than 16 years of age at OLT, 64 patients with incomplete data, 30 patients with early retransplantation or mortality within 10 days after OLT, 5 patients who underwent multi-organ transplantation, and 17 patients with large-volume paracentesis (LVP) in the week before OLT or venous obstruction in the first 10 days after OLT**.** Postoperative patient and graft survival were recorded during a minimum follow-up period of three years.

Donor selection and recipient care were standardized as described earlier [15]. The amount of ascites present at the start of the OLT (intraoperative ascites) was measured by removing all of the ascites immediately after opening the abdominal cavity. Ascites production during transplantation was ignored. During the operation a restrictive fluid suppletion with maintenance of blood pressure and tissue perfusion by using inotropic support was aimed for. One or more closed suction drains (26F) were left behind at the end of the transplantation. Drains were placed in the subhepatic and the right subdiaphragmatic space. During the postoperative period we aimed at a neutral fluid-balance. Albumin was administered intravenously if serum albumin levels were below 20g/L. Doppler ultrasound examinations of hepatic artery, portal vein and hepatic veins were routinely performed on days 1,4 and 7 after OLT as described earlier [16]. In case of unexpected prolonged ascites drainage Doppler ultrasound was repeated to ensure portal and hepatic vein patency. Vacuum bottles were replaced if the vacuum was off. Drains were removed when the production was less than an arbitrary amount of 50-100 mL per day. When the drain production stopped the drains were manipulated in order to try to resume ascites drainage. If this was unsuccessful, the drain was removed. Production from the drain opening after drain removal was collected and recorded. Postoperative ascites production from the drains was measured daily, but the daily production was reported only until day 10. If drainage persisted, the cumulative amount was calculated. Total ascites production is defined as the cumulative postoperative ascites volume.

In order to identify predictive factors for postoperative ascites formation, donor, recipient, and transplantation variables were analyzed. The following donor variables were analyzed: age, sex, donors after circulatory death (DCD) or donors after brain-dead (DBD), BMI, cause of death (head trauma versus cerebral bleeding), history of hypertension with the need for medical treatment, alcohol abuse, smoker, cardiac arrest in the period before organ recovery, body temperature at donation procedure, hospital and intensive care unit (ICU) admission days, days on respiratory support, the use and dosages of inotropics, laboratory values including liver function tests obtained shortly before organ procurement and the type of preservation solution. Recipient variables that were analyzed included: age, sex, BMI, underlying liver disease (categorized in non-cholestatic, cholestatic, metabolic, alcoholic and

other), Karnofsky performance scale [17], Child-Pugh score [18], model for end-stage liver disease (MELD) score [19], preoperative serum creatinine, intraoperative blood loss, type of caval vein anastomosis. Cold ischemia time (CIT), warm ischemia time (WIT), duration of functional anhepatic phase (FAHP), revascularization time (REVT) and total operation time were calculated. CIT represents the time from in situ flushing in the donor until the graft is taken from ice to start implantation in the recipient. WIT represents the time from the removal of the graft from ice to recirculation of the graft through the portal vein, the hepatic artery, or both simultaneously. The anhepatic phase represents the time from the physical removal of the liver from the recipient to recirculation of the graft through the portal vein, the hepatic artery, or both simultaneously. The REVT represents the time from removal of the liver from ice to recirculation of the graft through the hepatic artery [20].

Routine daily laboratory chemistry was performed pre- and postoperatively. As a surrogate marker of liver function we analyzed the change in laboratory values between day 3 and 5, in which a positive value represents an increase and a negative value a decrease.

Statistical Analysis

Continuous variables were presented as median values and interquartile ranges (IQR). Categorical variables were presented as numbers and percentages. Association between the cumulative postoperative ascites formation and other variables was analyzed by calculating the correlation (R) coefficients, using the (non-parametric) Spearman-rho test.

Multivariate analysis was performed using a linear and binary regression model. The linear regression model was used to identify independent factors that were associated with the cumulative postoperative ascites volume. Based on the median cumulative postoperative ascites volume, patients were divided in two groups; one above the median value and the other below the median value. A binary logistic model was used to identify risk factors for a larger than the median value of cumulative postoperative ascites volume. Only variables with a significant ($p < 0.1$) correlation with the cumulative postoperative ascites formation were entered in the multivariate analysis. Of note, we excluded postoperative variables for this analysis because our goal was to predict the postoperative ascites formation. Survival analysis was performed using the Kaplan-Meier method. Survival was compared in the upper and lower than median cumulative ascites volume groups, using the log rank test.

Statistical analysis was performed using SPSS 20 (SPSS, Chicago, IL) for Windows. P values < 0.05 were considered statistically significant.

Results

Demographics and characteristics

Donor data, recipient demographics and postoperative recipient data are shown in Tables 1, 2 and 3 respectively. Donor livers were mainly recovered from DBD donors (86%) who died from a cerebrovascular accident (54%). Hepatocellular carcinoma was present in 15 cases. Piggy-back procedure was used in 86% of the patients and median operation time was 9 hours and 1 minute (IQR 2 hours and 39 minutes) with a range from 6 hours to 14 hours and 53 minutes. The median MELD score was 14 (IQR 12), with a range from 6 to 40. The median amount of intraoperative ascites was 100 mL (IQR 2,000 mL), with a range from 0 to 21,000 mL. The median cumulative postoperative ascites volume was 6,240 mL (IQR 13,716 mL) with a range from 0 to 123,820 mL. The median postoperative drain duration was 12 days (IQR 12 days). No significant differences were found in the different diagnosis groups regarding the intraoperative and postoperative ascites volumes.

An overview of the daily postoperative ascites production is shown in Figure 1. Due to missing drain production data of 37 patients the data of day 1 consists of only 201 patients. The ascites volume increased until day 5 and then showed a daily decrease with a plateau after day 8. In patients in whom the drain was producing for more than 10 days the cumulative ascites production from day 11 until removal of the drains was 2,943 mL (IQR 8,689 mL). Figure 2 shows the daily ascites formation starting with the intraoperative ascites formation of patients in the upper and lower decile of cumulative postoperative ascites formation, with a total of 22 patients per group. No distinguishable trend was observed.

Table 1: Donor characteristics.

Variable	
DBD	205 (86%)
Sex (female)	117 (49%)
Age at donor procedure (years)	50.0 (20.3)
BMI (kg/m^2)	24.0 (4.0)
Cause of death	
Cerebrovascular accident	129 (54%)
Head trauma	55 (23%)
Other	54 (23%)
Hypertension	48 (20%)
Alcohol abuse	17 (7%)
Smoker	99 (42%)
Cardiac arrest	43 (18%)
Body temperature (degrees Celsius)	36.0 (2.0)
ICU stay (days)	2.0 (2.0)
Respiratory support (days)	2.0 (2.0)
Admitted in hospital (days)	3.0 (3.0)
Inotropic support	188 (79%)
Hb (mmol/L)	7.0 (3.0)
White blood cell count (x10^9/L)	12.0 (7.8)
Platelet count (x10^9/L)	178.0 (117.5)
Sodium (mmol/L)	145.0 (8.0)
Creatinine (µmol/L)	70.0 (35.5)
Alanine aminotransferase (U/L)	25.0 (31.3)
Gamma-glutamyl transferase (U/L)	25.0 (31.0)
Total bilirubin (µmol/L)	10.0 (9.0)
Alkaline phosphatase (U/L)	58.0 (37.0)
Total protein (g/L)	54.5 (12.0)
Albumin (g/L)	29.0 (9.0)
Fibrinogen (g/L)	4.0 (2.0)
CRP (mg/L)	93.5 (132.3)
Blood pH	7.41 (0.1)
Preservation solution (UW)	189 (80%)

Abbreviations: DBD, donors after brain-dead ;ICU, intensive care unit; Hb, hemoglobin; CRP, C-reactive protein; UW, University of Wisconsin.

NOTE: The numbers represent median values (interquartile ranges) for continuous data, and absolute numbers (percentages) for categorical data.

Correlation between the cumulative postoperative ascites volume and study variables

Donor and recipient variables that revealed a significant correlation with the cumulative postoperative ascites volume are shown in Table 4. The strongest correlations were obtained with MELD score (R 0.411), intraoperative ascites volume (R 0.376), Child-Pugh score (R 0.326) and intraoperative blood loss (R 0.282). The postoperative serum alkaline phosphatase (R -0.299) and gamma-glutamyl transferase (R -0.260) were the strongest negative correlations found in the postoperative lab values. There were no differences between the cumulative postoperative ascites volume and the calculated difference in postoperative lab values between day 3 and 5.

Table 2: Recipient characteristics.

Variable	
Age at OLT (years)	53 (17)
Sex (female)	94 (42%)
Diagnosis of underlying liver disease	
Non cholestatic	80 (33%)
Cholestatic	71 (30%)
Metabolic	33 (14%)
Alcoholic	26 (11%)
Other	28 (12%)
BMI (kg/m^2)	24 (6)
Preoperative creatinine (µmol/L)	84 (46)
Piggy-back procedure	189 (86%)
Karnofsky score	70 (30)
Child-Pugh score	5 (7)
MELD score	14 (12)
Full size grafts	234 (98%)
Intraoperative ascites (mL)	100 (2,000)
Blood loss during OLT (mL)	2,100 (3,000)
Total operation time (min)	541 (159)
CIT (min)	468 (162)
FAHP (min)	78 (40)
WIT (min)	45 (13)
REVT (min)	96 (35)
3-year survival rate	88%

Abbreviations: OLT, Orthotopic liver transplantation; MELD, model for end-stage liver disease; CIT, cold ischemic time; FAHP, functional anhepatic phase; WIT, warm ischemic time; REVT, revascularization time.

NOTE: The numbers represent median values (interquartile ranges) for continuous data and absolute numbers (percentages) for categorical data.

Are there predictive variables for the cumulative postoperative ascites volume?

All variables that correlated significantly ($p < 0.1$) with the cumulative postoperative ascites volume were used for the regression

Table 3: Recipient postoperative characteristics.

Variable	
Cumulative postoperative ascites volume (mL)	6,240 (13,716)
White blood cell count day 3 (x10^9/L)	7.0 (6.8)
Difference day 5-3	0.0 (3.0)
Platelet count day 3 (x10^9/L)	55.0 (68.0)
Difference day 5-3	+6.0 (31.0)
CRP day 3 (mg/L)	33.0 (39.0)
Difference day 5-3	-3.0 (31)
BUN day 3 (mmol/L)	11.0 (11.0)
Difference day 5-3	0.0 (4.0)
Creatinine day 3 (µmol/L)	95.0 (72.0)
Difference day 5-3	-4.0 (29.5)
Alkaline phosphatase day 3 (U/L)	93.5(73.5)
Difference day 5-3	+6.5 (61.8)
Alanine aminotransferase day 3 (U/L)	467.0 (563)
Difference day 5-3	-94.0 (355.0)
Total billirubin day 3 (µmol/L)	39.5 (67.5)
Difference day 5-3	+1.0 (19.0)
Albumin day 3 (g/L)	23.0 (6.0)
Difference day 5-3	0.0 (4.0)
Gamma-glutamyl transferase day 3 (U/L)	123.5 (146.3)
Difference day 5-3	+20.0 (160.5)

Abbreviations: CRP, C-reactive protein.

NOTE: data are shown as medians including interquartile ranges. The lab value of day 3 is shown, with the increase (+) or decrease (-) at day 5 as compared to day 3.

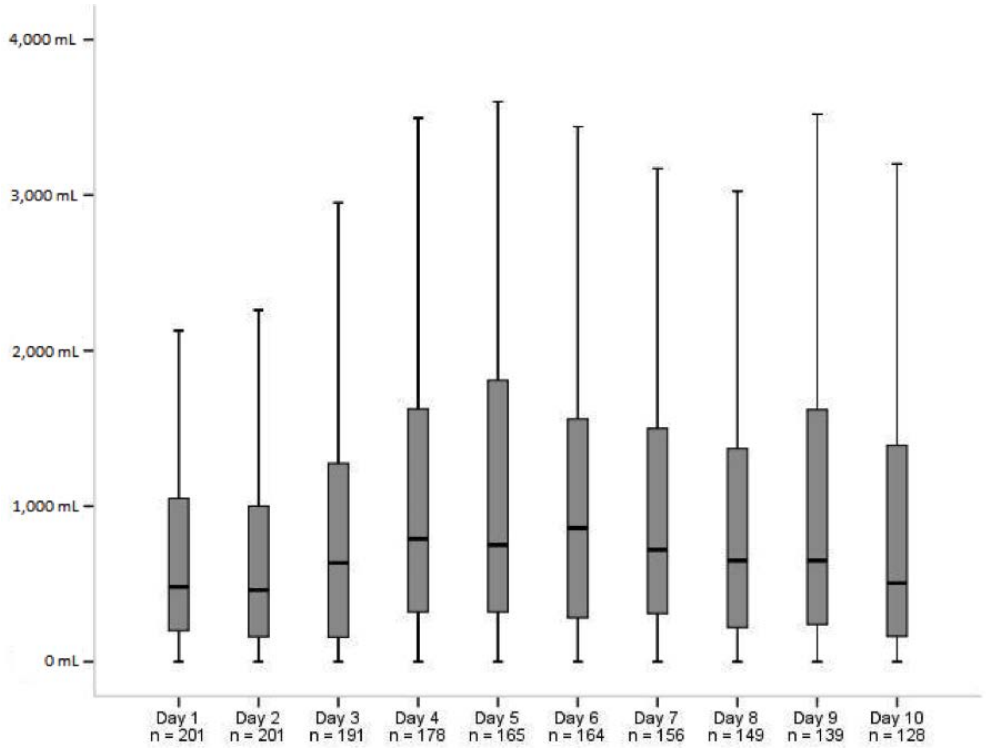

Figure 1: The bars represent box plots with median value (horizontal line), interquartile range (box) and values (whiskers) which are not outliers or extremes (both not shown) representing the daily postoperative ascites production during the first 10 postoperative days. The numbers (n) represent the number of patients for which the production was registered.

Table 4: Correlation coefficients of variables with the cumulative postoperative ascites volume. Only variables with correlation coefficients with a p value < 0.05 are presented.

Variable	*Cumulative amount of postoperative ascites*
Donor	
Hb (mmol/L)	-0.163
Total protein (mg/L)	ns
Recipient	
Age at OLT	0.146
Karnofsky score	-0.210
Child-Pugh score	0.326
MELD score	0.411
Preoperative creatinine (µmol/L)	0.274
Intraoperative ascites volume (mL)	0.376
Intraoperative bloodloss (mL)	0.282
Total operation time (min)	0.188
FAHP (min)	0.165
Platelet count day 3 (x10^9/L)	-0.286
BUN day 3 (mmol/L)	0.367
Creatinine day 3 (µmol/L)	0.306
Alkaline phosphatase day 3 (U/L)	-0.299
Albumin day 3 (g/L)	-0.260
Gamma-glutamyl transferase day 3 (U/L)	-0.260

Abbreviations: Hb, hemoglobin; MELD, model for end-stage liver disase; FAHP, functional anhepatic phase.

NOTE: Spearman-rho's correlation coefficient is shown as R. Only significant correlations are shown. Inversed correlations are shown as negative R values.

analysis. The linear regression analysis could not identify significant predictors for the postoperative ascites volume. The binary logistic model showed similar results. This was applied to identify predictors for a larger than median cumulative postoperative ascites volume (yes versus no).

Survival analysis

Median follow-up was 8.4 years (IQR 6.4 years). Five-year graft and patient survival were 80% and 95% respectively; three-year graft and patient survival were 88% and 97% respectively. No differences were found when the upper and lower than median postoperative ascites groups were compared with regard to five-year graft and patient survival (p = 0.22 and p = 0.58 respectively).

Discussion

Our goal was to quantify the amount of ascites production after liver transplantation and to predict the postoperative ascites formation. We found that 50% of the patients had a cumulative postoperative ascites volume equal to 6 liters or more, which signifies the magnitude of the problem. Independent prognostic factors could unfortunately not be identified for post-transplant ascites; however, some correlations were found.

The intraoperative ascites formation was not a predictive factor for the postoperative ascites volume, this indicates that other mechanisms play a role in the formation of postoperative ascites. The correlation between postoperative ascites formation and the Child-Pugh score indicates that the severity of liver disease pre-operatively is weakly associated with postoperative ascites formation.

The correlation between the FAHP and postoperative ascites

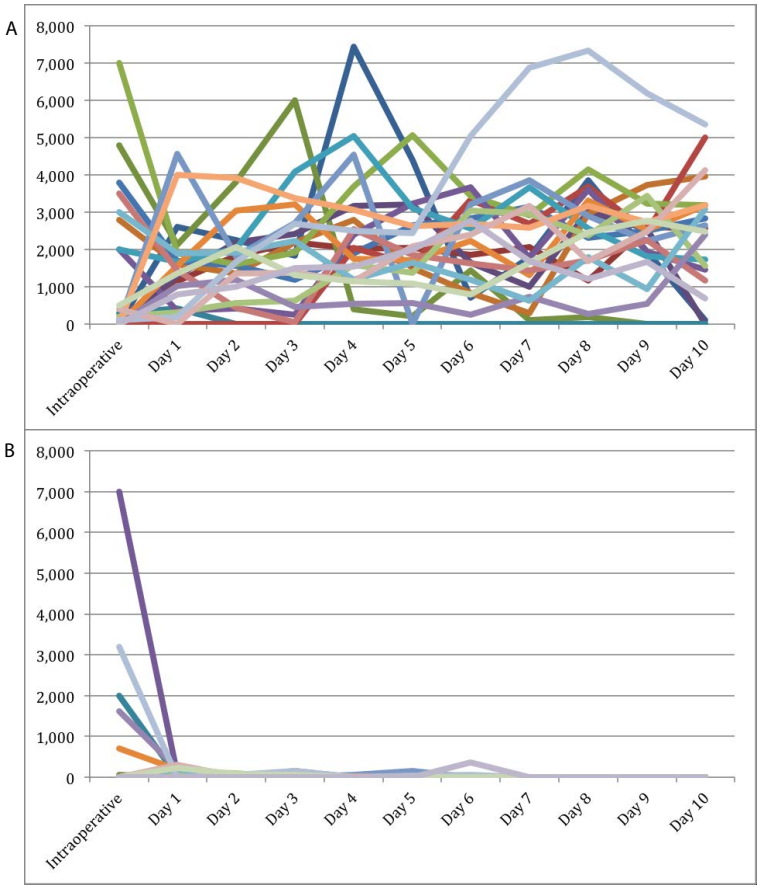

Figure 2: The daily postoperative production of ascites from day 1 to 10 starting from the intraoperative ascites volume. The Y axis shows the volume of ascites (mL).Figure 2a shows the patients in the upper decile of cumulative postoperative ascites production, figure 2b shows the patients in the lowest decile of cumulative postoperative ascites volume. Of note, each line represents 1 patient with a total of 22 patients per figure, overlapping lines are displayed as one line.

formation might be explained by the pronounced inflammatory response triggered by the start of the anhepatic phase [20]. This response consists of the release of pro-inflammatory cytokines such as IL-6 [21]. Inflammation or inflammatory response can lead to disruption of the vascular barrier function and thus to fluid extravasation, factors such as Angiopoietin-2 and VEGF have shown to promote this mechanism [22].

Postoperative ascites formation was previously described as a serious complication which is associated with increased mortality [5]. Studies have investigated the demographics, clinical and hemodynamic data of patients who developed large volumes of postoperative ascites [4,9,11,23]. Several factors such as hepatic vein outflow obstruction, the presence of hepatitis C, prolonged CIT, a Piggy-back procedure and the presence of portal hypertension without cirrhosis were reported as associated variables. In our study, we could not verify these variables as independent risk factors for the cumulative postoperative ascites volume, however, we did not include patients with venous outflow obstruction because this is a well-known condition associated with an increased risk of postoperative ascites formation [24].

Routine drain placement after OLT was challenged in several studies [6-8,12,14]. It appeared that drain placement did not result in earlier detection of complications. One study compared the postoperative complications in a drainage group (n=70) and a non-drainage group (n=35) [6]. The drains were removed routinely between postoperative day 3 and 5. This study failed to show any significant differences in complications after OLT between both groups. The percentage of patients with ascites more than 3 days was about 20% in both groups. Interventions were performed on day 5 in the drained group versus on day 11 in the non-drained groups ($p = 0.1$), without mentioning the type of intervention. A remarkable high percentage of renal failure necessitating intermittent hemofiltration was reported, in both the drain group (21%) and in the non-drain group (34%) ($p < 0.1$). A rise in intra-abdominal pressure caused by the accumulation of fluid might impair the renal blood flow, known as the abdominal compartment syndrome [25]. In our patient cohort we did not see a high postoperative renal failure rate, as can be seen in the minimal difference in serum BUN and creatinine between day 3 and 5, (Table 3).

One study compared the characteristics and complications of a non-drain (n=93) and drain (n=51) OLT group retrospectively [7]. The results showed that ascites recurred in 31.2% of the patients in the non-drain group versus 13.7% in the drain group. In the non-drain group 19.3% needed LVP versus 0% in the drain group. The postoperative in-hospital mortality rate was around 20%. Of note, this study did not report the p values and ascites amount and definition were not specified.

Another study compared a non-drain (n=70) and drain (n=70) OLT patient group prospectively [8]. The results showed that LVP was needed in 30% of the patients in the non-drain group versus 6% ($p < 0.01$) in the drain group, the LVP frequency and evacuated amount were not reported. Multivariate analysis showed that the presence of preoperative refractory ascites (> 1,000mL) increased the risk of postoperative LVP (OR 5.9, $p < 0.02$).

The latest study compared two pair-matched groups containing 58 patients each, with and without abdominal drainage after OLT [14]. Endpoints were survival and occurrence of major postoperative complications. Drains were removed between postoperative day 7 and 14. Three patients in the non-drain group required paracentesis due to ascites, compared to none in the drain group. Volumes and incidence of ascites production postoperative were not described.

Increasing evidence indicates fluid extravasation in advanced liver disease cannot be contributed to the peripheral arterial vasodilatation hypothesis alone. Bernardi et al. indicate that the inflammatory response plays an important part in fluid extravasation [26]. Determination of the amount of serum pro-inflammatory cytokines, such as IL-6 and factors that increase the vascular permeability, such as VEGF and angiopoietins, in liver transplant patients might be an interesting topic of research, following the results previously found [22,27,28].

The strengths of this study are the large sample size compared to other studies, the detailed information on the course of the postoperative ascites formation, and the long-term patient and graft survival data. The limitation of this study is its retrospective study design.

In conclusion we demonstrated that the postoperative ascites formation is a serious clinical problem. Unfortunately, we could not predict the postoperative ascites volume based on the collected variables. Our data suggest that factors contributing to the preoperative ascites formation may differ from those contributing to the postoperative ascites formation.

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