

Original Research Article

Persistent diarrhea in living donors after donor hepatectomy: natural course and analysis of predisposing risk factors

Szu-Han Wang¹, Ping-Yi Lin^{4,5}, Yao-Li Chen^{4,6}, Mei-Feng Huang²,
Chia-En Hsieh¹, Chih-Cheng Chen^{3*}

¹Organ Transplant Center, ²Nursing Department, ³Department of Colorectal Surgery, Changhua Christian Hospital, Changhua, Taiwan

⁴Transplant Medicine and Surgery Research Centre, Changhua Christian Hospital, Changhua, Taiwan

⁵Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

⁶Department of General Surgery, Changhua Christian Hospital, Changhua, Taiwan, and School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Received: 23 April 2020

Revised: 05 June 2020

Accepted: 08 June 2020

***Correspondence:**

Dr. Chih-Cheng Chen,

E-mail: 117190@cch.org.tw

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Diarrhea is a frequent but overlooked complication of living liver donation. Thus, this retrospective study aimed to report the natural course of diarrhea and examined predictors of persistent diarrhea after living donor hepatectomy.

Methods: We enrolled 79 donors who underwent living donor hepatectomy between 2010 and 2015 at a single medical center and had diarrhea symptoms after hepatectomy. The Chinese version of the gastrointestinal quality of life index (GIQLI) was applied to evaluate the effect of diarrhea on quality of life.

Results: The onset of diarrhea was post-donation 1.1 ± 0.3 months. According to their duration of diarrhea, donors were further classified into two groups: the healed and the persistent diarrhea group, the ratio was 36 to 43 (45.6% versus 54.4%). A donor who followed a low-fat diet had a protective effect on persistent diarrhea (odds ratio [OR] = 0.18, 95% confidence interval: 0.04-0.66). Compared to healed diarrhea donors, donors with persistent diarrhea had lower GIQLI scores in the domains of physical (2.3 versus 1.9) and social functions (2.5 versus 2.3). Receiver operating characteristic curves for the duration of diarrhea after liver donation indicated that a donor was likely to develop a persistent diarrhea status if the duration of the diarrhea reached 12.5 months.

Conclusions: A donor not following a low-fat diet can be independently predictive for persistent diarrhea after living donor hepatectomy. Besides, a donor with persistent diarrhea after hepatectomy is more likely to report lower GIQLI scores in physical and social functions.

Keywords: Living donor liver transplantation, Low-fat diet, Persistent diarrhea

INTRODUCTION

Liver transplantation is often the only reasonable option for patients with end-stage liver disease.¹ Adult-to-adult living donor liver transplantation (LDLT) has become increasingly common worldwide, mainly because of a

shortage of cadaveric donor organs. Although LDLT is a lifesaving procedure for the recipient, it carries a significant risk of morbidity and mortality for the otherwise healthy donor.² However, in addition to the risk from the complexity of surgical procedures, the quality of life after hepatectomy is usually a new challenge for donors.

It has been reported that donors have experienced a number of complications including abdominal discomfort, bile leakage, minor wound infections, pleural effusion, and atelectasis.² The gastrointestinal (GI) complications rate was high (53%) after hepatectomy.² Diarrhea is the most common GI symptom for liver donors; 30% of donors experience diarrhea after hepatectomy.^{3,4} Diarrhea is a frequent but overlooked complication and their duration of diarrhea is an important outcome of living liver donations. In this retrospective generational study, we reported the diarrhea duration and condition of the diarrhea donors and investigated predisposing risk factors of persistent diarrhea in donors after hepatectomy.

METHODS

Patients

Two hundred and ninety-two living liver donors who underwent hepatectomy between 2010 and 2015 at the Changhua Christian Hospital were enrolled in the retrospective study. Donors with gallbladder surgery history (n=4), donors who did not experience diarrhea after a donor hepatectomy (n=207) and those with intestinal bowel syndrome before liver donation (n=2) were excluded. Finally, there were 79 donors who experienced diarrhea after hepatectomy and met the inclusion criteria and were recruited in the current study (Figure 1). Ethical approval for all study procedures was obtained from Institutional Review Board of the Changhua Christian Hospital.

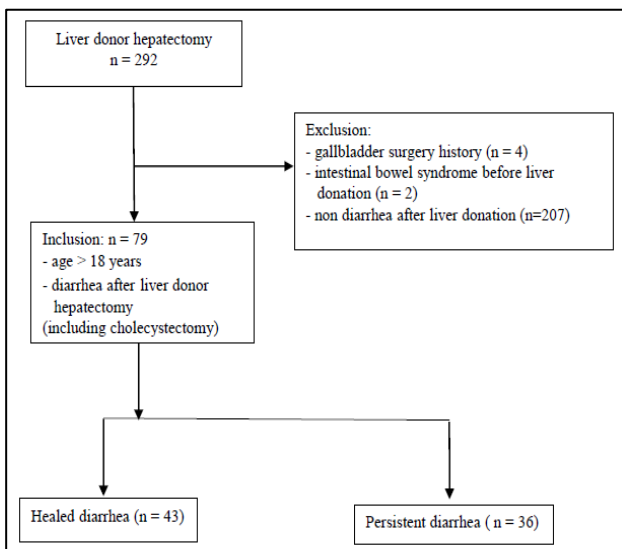


Figure 1: Screening and enrollment.

Assessments

After the donors were discharged from the hospital, they would regularly follow-up at the transplant clinic and were inquired about their gastrointestinal symptoms. Diagnosis of diarrhea requires the passing of three or

more liquid stools per day for a period of at least 6 months.^{5,6}

In this study, we reviewed the medical records up to December 2017 of 79 diarrhea affected donors. According to diarrhea status, we stratified donors into a healed diarrhea group and a persistent diarrhea group. The Chinese version of the gastrointestinal quality of life index (GIQLI) questionnaire was applied to evaluate the effect of diarrhea on quality of life at the time point of 12 months after donor hepatectomy.

The GIQLI contains five domains and 36 items. The five domains are a 19-item subscale measuring GI symptoms, a 7-item subscale measuring physical function, a 5-item subscale measuring emotional function, a 4-item subscale measuring social function, and one item measuring treatment reaction.⁷

Demographic and clinical characteristics

Donor characteristics included age, gender, education, the relationship between donor and recipient, regular exercise, remnant liver volume (RLV, %), hepatic steatosis, chronic cholecystitis, duration of surgery (minutes), low-fat diet (post donation $\leq 30\%$ energy from fat/day), body weight (Kg), body mass index (BMI, Kg/m²), onset of diarrhea (months), duration of diarrhea (months), frequency of diarrhea (per day), stool nature, frequent diarrhea status, diarrhea treatment, and ability to return to one's pre-donation job (months).⁸

Statistical analysis

Donors were classified into 2 groups according to whether their diarrhea status persisted to 12 months or not. Group comparisons were performed using the Mann-Whitney U test for continuous variables and using Fisher's exact test for categorical variables. Multivariate logistic regression analysis was conducted to identify the significant predisposing risk factors for persistent diarrhea after donor hepatectomy. To evaluate the duration of persistent diarrhea after liver donation, the receiver operating characteristic curve (ROC) and the respective areas-under-the-curve (AUC) along with sensitivity and specificity were calculated. P-value less than 0.05 was considered to indicate statistical significance. All analyses were performed using SPSS for Windows (version 18.0).

RESULTS

Of the 79 diarrhea-affected donors (mean age, 28.5 \pm 7.3 years), 51.8% of them were men. The diarrhea-affected donors' average BMI (22.5 to 23.6 kg/m²) and body weight (63.2 to 64.5 kg) increased between pre/post living donor hepatectomy. The onset of diarrhea was post-donation 1.1 \pm 0.3 months, and 97.5% of the diarrhea-affected donors experienced diarrhea 3-5 times per day. Seventy-one percent of their stools were water stools.

Many diarrhea-affected donors frequently had diarrhea after eating 3 meals (55.7%) or greasy food (43.1%), and

90% did not seek diarrhea treatment (3 donors used traditional Chinese medicine) (Table 1).

Table 1: Characteristics of living liver donors (n=79).

Characteristics ^a	Healed diarrhea (n=43)	Persistent diarrhea (n=36)	Total (n=79)	P value
Age	27.9±6.7	29.7±7.8	28.5±7.3	0.270
Male^b	20 (46.5)	21 (58.3)	41 (51.8)	0.368
Education level				
Senior high school or below	6 (14.0)	18 (50.0)	24 (30.4)	0.002
College or above	37 (86.0)	18 (50.0)	55 (69.6)	
Relationship with recipient^b				
Spouse	4 (9.4)	3(8.4)	7(8.8)	0.082
Immediate family	39 (90.6)	33 (91.6)	72 (91.2)	
Regular exercised ^b	18 (41.9)	13 (36.1)	31 (39.2)	0.649
RLV (%)	38.2±5.4	37.5±4.3	37.8±4.7	0.528
Hepatic steatosis ^b	6(14.0)	9(25.0)	15(19.0)	0.257
Chronic cholecystitis ^b	17 (39.5)	13 (36.1)	30 (37.9)	0.818
Duration of surgery (min.)	251±46	242±48	245±48	0.389
Low-fat diet ^b	32 (74.4)	17 (47.2)	49 (62.0)	0.020
Body weight (kg)				
Pre-donation	60.9±13.3	64.3±10.5	63.2±11.9	0.223
Post-donation	62.0±13.7	66.1±11.6	64.5±12.6	0.158
Weight change (kg)	+1.0±2.4	+1.7±2.6	+1.3±2.6	0.192
BMI				
Pre-donation	22.1±3.7	23.2±3.0	22.5±3.3	0.169
Post-donation	22.5±3.8	23.8±3.3	23.6±3.5	0.105
Diarrhea onset post-donation (month)	1.1±0.2	1.2±0.3	1.1±0.3	0.087
Diarrhea duration (month)	9.7±1.7	40.6±21.4		<0.001
Diarrhea frequency (per day)^b				
3-5	42 (97.7)	35 (97.2)	77 (97.5)	0.764
>5	1 (2.3)	1 (2.8)	2 (2.5)	
Nature stool quality^b				
Solid stool	1 (2.4)	0 (0)	1 (1.2)	0.207
Paste stool	9 (20.9)	13 (36.1)	22 (27.8)	
Water stool	33 (76.7)	23 (63.9)	56 (71.0)	
Frequent diarrhea status				
After breakfast	1 (2.4)	0 (0)	1 (1.2)	0.305
Eating three meals	21 (48.8)	23 (63.9)	44 (55.7)	
After greasy food	21 (48.8)	13 (36.1)	34 (43.1)	
Diarrhea treatment^b				
Anti-diarrheal medicine	3 (7.2)	2 (5.6)	5 (6.2)	0.828
Traditional Chinese medicine	0 (0)	3 (8.4)	3 (3.8)	
Nil	40 (92.8)	31 (86.0)	71 (90.0)	
Returned to pre-donation job (month)^b				
<3	13 (30.3)	17 (47.2)	30 (37.9)	0.602
3-6	30 (69.7)	17 (47.2)	47 (59.7)	
>6	0 (0)	2 (5.6)	2 (2.4)	
GIQLIS				
Gastrointestinal symptoms	1.8±0.3	1.7±0.4	1.7±0.3	0.339
Physical function	2.3±0.7	1.9±0.2	2.1±0.3	0.003
Emotional function	3.2±0.4	3.1±0.3	3.1±0.4	0.066
Social function	2.5±0.4	2.3±0.4	2.4±0.4	0.028
Treatment reaction	2.7±0.5	2.6±0.4	2.6±0.5	0.794

^a Data are shown as mean ± standard deviation and compared using the Mann- Whitney U test, ^b Data are shown as n (%) and compared using the Fisher's exact test, BMI= body mass index, RLV= remnant liver volume, GIQLIS= Gastrointestinal quality of life index score.

Table 2: Associated factors of persistent diarrhea after living liver donor hepatectomy in living liver transplant donor.

Factor	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Chronic cholecystitis	0.86	0.34-2.15	0.755	0.71	0.25-2.02	0.522
Low fat diet	0.30	0.11-0.7	0.015	0.18	0.04-0.66	0.010

Among those diarrhea-affected donors, 36 (45.6%) donors were diagnosed as persistent diarrhea. Results of group comparisons show that persistent diarrhea was significant with a lower education level (senior high school or below: 50.0% versus 14.0%, $p=0.002$), a lower rate of following low-fat diet after liver donation (47.2% versus 74.4%, $p=0.020$) and a longer duration of diarrhea (average: 40.6 versus 9.7 months, $p<0.001$), compared with healed diarrhea (Table 1).

In addition, donors with persistent diarrhea had lower average GIQLI scores in the domains of physical function (2.3 versus 1.9, $p=0.003$) and social function (2.5 versus 2.3, $p=0.028$), but not in the domains of GI symptoms, emotional function and treatment reaction compared to donors with healed diarrhea (Table 1).

Multivariate analysis revealed that low-fat diet was a significant protective factor for the development of postoperative persistent diarrhea (OR=0.18, 95% confidence interval: 0.04-0.66) (Table 2).

ROC curves for the duration of diarrhea after liver donation indicated that a donor was likely to develop a persistent diarrhea status if the duration of the diarrhea reached 12.5 months. The AUC of the ROC plots for duration of persistent diarrhea was 0.89 ($p<0.001$).

DISCUSSION

In this present study, we have showed the natural course of diarrhea for living liver donors. Ours donors were younger (mean age, 28.5 ± 7.3 years), and 12.3% of donors were classified as having persistent diarrhea. The diarrhea-affected donors frequently had diarrhea after eating 3 meals (55.7%) or greasy food (43.1%). In regard to education, 86.0% of healed diarrhea donors had a college or above education, which was significantly higher than the 50.0% of persistent diarrhea donors with a college or above education. The failure of a donor to follow a low-fat diet was independently predictive for persistent diarrhea after living donor hepatectomy. All donors in our transplant center received nutritional consultations before surgery. However, we recommended that the medical team assess each donor individually and adjust diets to meet donors' needs. In some cases it was necessary that the donor be referred to the Department of Nutrition.

In a past study, we found that the incidence of newly onset diarrhea in liver donors after hepatectomy was

30.3%; a young donor age and a lack of chronic gallbladder inflammation were risk factors of diarrhea after living donor hepatectomy.³ Diarrhea is a frequent GI complication of living liver donations. Cholecystectomy is routinely performed during living donor hepatectomy at most transplant centers.⁹ Appleby et al. found that patients post cholecystectomy have more than twice the risk of diarrhea than the general population.¹⁰ Thus, cholecystectomy was associated with an increased risk of diarrhea. However, the living donor population cannot be directly compared to general surgical patients. They are healthy and are undergoing an elective procedure rather than one for cause. Therefore, this should be kept in mind in the preoperative judgement and communicated to the donors.

The study's findings are similar to those reported on post-cholecystectomy outcomes in patients. Lublin et al noted postoperative diarrhea in 21% of their patients. The most common non-pain symptom post-laparoscopic cholecystectomy (PLC) was fatty food intolerance (41%).¹¹ Cholecystectomy may decrease the tolerance towards fatty foods and lead to diarrhea; a low-fat diet has significant negative correlations with post-laparoscopic cholecystectomy diarrhea (PLCD) at both 1 week and 3 months PLC.^{12,13} Many doctors advise to limit the consumption of lipids for several months after cholecystectomy to allow the liver to compensate for the gallbladder's absence, and they advise that fat should be introduced gradually.¹¹⁻¹⁴

The study involved 26 post-cholecystectomy patients with chronic diarrhea; their average duration of diarrhea was 3.9 years. A total of 25 (96%) had severe bile acid malabsorption.¹⁵ In this study, diarrhea duration greater than 12.5 months implied that a donor would likely develop a persistent diarrhea status. Donors with persistent diarrhea had a longer duration of diarrhea (40.6 ± 21.4 months) than donors with healed diarrhea (9.7 ± 1.7 months), and 90% of the diarrhea-affected donors did not seek diarrhea treatment. Therefore, diarrhea can spontaneously cease within 12 months. However, previous research did not mention the duration for which donors should follow a low-fat diet after hepatectomy. Therefore, all donors in our center were advised to follow a low-fat diet for 12 months to reduce the possibility of chronic diarrhea after living donor hepatectomy. Of the 79 diarrhea-affected donors in our study, the average BMI (22.5 to 23.6 kg/m²) and body weight (63.2 to 64.5 kg) increased between pre/post living donor hepatectomy. A diarrhea frequency of 3-5

times per day was reported by 97.5% of diarrhea-affected donors, and 71% of their stools were water stools. Post-laparoscopic cholecystectomy diarrhea (PLCD) is likely to be multifactorial in origin. Bile acid diarrhea is a common disorder characterized by chronic watery diarrhea and is a consequence of increased delivery of bile acids to the colonic lumen.¹⁶ Persistent diarrhea is one of the most common presentations in gastroenterology and general practice, and bile acid malabsorption is a common but frequently unrecognized cause of persistent diarrhea.¹⁷ PLCD was associated with food intolerance and abdominal bloating. Interestingly, patients with PLCD showed a tendency towards weight gain, in which 36% of patients with PLCD diarrhea had gained weight in excess of 2 kg.^{18,19}

Diarrhea in donors has been associated with lower gastrointestinal quality.³ In this study, donors with persistent diarrhea had lower GIQLI scores in the physical and social functions compared to donors in the healed diarrhea group. We can infer from this that donors could adapt to chronic diarrhea but were still worried about its impact on health and social activities.

To the best of our knowledge, this is the first study to assess the clinical outcomes of diarrhea's natural course and predisposing risk factors of persistent diarrhea for donor hepatectomy in living donor liver transplantation. The study was limited by the small sample size. Multicenter studies that include a greater number of patients are needed to confirm our findings.

CONCLUSION

The incidence of post-hepatectomy persistent diarrhea in living donors was 12.3% in this study. A donor not following a low-fat diet was independently predictive for persistent diarrhea after living donor hepatectomy. Besides, a donor with persistent diarrhea status after hepatectomy is more likely to report lower GIQLI scores (physical and social functions). Diarrhea duration greater than 12.5 months implies that a donor is more likely to develop a persistent diarrhea status.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of Changhua Christian Hospital

REFERENCES

- Xu DW, Long XD, Xia Q. A review of life quality in living donors after liver transplantation. *Int J Clin Exp Med.* 2015;8(1):20-6.
- Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. *Liver Transpl.* 2013;19(5):499-506.
- Wang SH, Ming YZ, Lin PY, Wang JY, Lin HC, Hsieh CE, et al. Predictors of diarrhea after hepatectomy and its impact on gastrointestinal quality of life in living donors. *PLOS One.* 2016;11(11):1-8.
- Sotiropoulos GC, Radtke A, Molmenti EP, Schroeder T, Baba HA, Frilling A, et al. Long-term follow-up after right hepatectomy for adult living donation and attitudes toward the procedure. *Ann Surg.* 2011;254(5):694-700.
- Bajor J, Bero T. Diarrhea, from the gastroenterologist's point of view. *Orv Hetil.* 2009;150(35):1655-61.
- Mullhaupt B. Diarrhea. *Praxis.* 2002;91(42):1749-56.
- Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmillig C, Neugebauer E, et al. Gastrointestinal quality of life index: development, validation and application of a new instrument. *Br J Surg.* 1995;82(2):216-22.
- Institute of Medicine (US) Panel on Macronutrients. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: 2005.
- Dong JH, Ye S, Duan WD, Ji WB, Liang YR. Feasibility of liver graft procurement with donor gallbladder preservation in living donor liver transplantation. *Hepatol Int.* 2015;9(4):603-11.
- Appleby RN, Nolan JD, Johnston IM, Pattni SS, Fox J, Walters JR. Novel associations of bile acid diarrhoea with fatty liver disease and gallstones: a cohort retrospective analysis. *BMJ Open Gastroenterol.* 2017;4(1):e000178.
- Lublin M, Crawford DL, Hiatt JR, Phillips EH. Symptoms before and after laparoscopic cholecystectomy for gallstones. *Am Surg.* 2004;70(10):863-6.
- Niranjan B, Chumber S, Kriplani AK. Symptomatic outcome after laparoscopic cholecystectomy. *Trop Gastroenterol.* 2000;21(3):144-8.
- Yueh TP, Chen FY, Lin TE, Chuang MT. Diarrhea after laparoscopic cholecystectomy: Associated factors and predictors. *Asian J Surg.* 2014;37(4):171-7.
- Shin Y, Choi D, Lee KG, Choi HS, Park Y. Association between dietary intake and postlaparoscopic cholecystectomy symptoms in patients with gallbladder disease. *Korean J Intern Med.* 2018;33(4):829-36.
- Sciarretta G, Furno A, Mazzoni M, Malaguti P. Post-cholecystectomy diarrhea: evidence of bile acid malabsorption assessed by SeHCAT test. *Am J Gastroenterol.* 1992;87(12):1852-4.
- Appleby RN, Walters JR. The role of bile acids in functional GI disorders. *Neurogastroenterol Motil.* 2014 26(8):1057-69.
- Barkun AN, Love J, Gould M, Pluta H, Steinhart H. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. *Can J Gastroenterol.* 2013;27(11):653-9.

18. Fisher M, Spiliadis DC, Tong LK. Diarrhea after laparoscopic cholecystectomy: incidence and main determinants. *ANZ J Surg.* 2008;78(6):482-6.
19. O'Donnell LJ. Post-cholecystectomy diarrhoea: a running commentary. *Gut.* 1999;45(6):796-7.

Cite this article as: Wang S-H, Lin P-Y, Chen Y-L, Huang M-F, Hsieh C-E, Chen C-C. Persistent diarrhea in living donors after donor hepatectomy: natural course and analysis of predisposing risk factors. *Int Surg J* 2020;7:2110-5.