

# Clinical Practice of Unsedated Colonoscopy Among the Liver Transplant Recipients

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## Research article

**Keywords:** colonoscopy, liver transplantation, visual analogue scale, polyps

**Posted Date:** December 30th, 2019

**DOI:** <https://doi.org/10.21203/rs.2.19615/v1>

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# Abstract

**Background:** The incidence of colorectal cancer was increased in the liver transplant recipients and clinical practice of unsedated colonoscopy among the liver transplant recipients hasn't been fully studied. Our prospective and observational study was conducted in a tertiary hospital to investigate the clinical practice of unsedated colonoscopy among the liver transplant recipients.

**Methods:** Between June 2017 and June 2018, clinical data of the 72 liver transplant recipients received the screening colonoscopy conducted by a same endoscopists was collected. And a group of asymptomatic health examiner of same age and same gender was chosen as control group at a ratio of 1:3. Data of the colonoscopy performance, patient satisfaction and colonoscopy finding were compared between the two groups.

**Results:** No difference was observed between the two groups in the bowel clearance ( $P = 0.273$ ), however, cecal intubation time was longer ( $P = 0.024$ ) and the auxiliary abdominal compression by nurses was more frequent ( $P \leq 0.01$ ) in liver transplantation group. In term of patient's satisfaction, postprocedural visual analog scale, the willingness of repeat the same procedure and the four-point Likert scale (no pain, slight pain, moderate pain, severe pain) on the second day were comparable between the two groups. Compared with control group, the incidence of polyps was higher in the liver transplantation group (50.00% (36/72) vs 37.04% (80/216),  $P = 0.036$ ), and the incidence of adenomatous polyps (33.33% vs 24.07%,  $P = 0.084$ ) and advanced polyps (11.11% vs 5.56%,  $P = 0.094$ ) were also higher in the liver transplantation group, but no statistical difference was observed.

**Conclusions:** Liver transplantation mildly increases the difficulty of colonoscopy with experienced practitioners, although the patient's satisfaction was comparable with the common people.

**Key words:** colonoscopy, liver transplantation, visual analogue scale, polyps

## Introduction

Due to the high prevalence of HBV infection, huge population and the relatively low economic status, the incidence of end stage liver disease was high in China which accelerated the development of LT in the past decade. According to the Chinese scientific report of liver transplantation in 2015, for the recipients with pre-transplantation benign disease, the cumulative survival rate of 1 year, 3 year and 5 year was 84.09%~81.19% and 78.99%, respectively. However, long-term survival after LT was still a big challenge in clinical practice and de novo malignant tumor was an important risk threatening the long-term survival. It was reported that about 5.2%~10.7% of the liver transplant recipients was diagnosed with de novo malignant tumor after LT<sup>[1, 2]</sup>. Different from western countries, de novo malignant tumor of digestive system was more frequent in Asian liver transplant recipients, mainly stomach cancer and colon cancer, which was consistent with the high incidence of digestive system carcinoma among the general population in Asia<sup>[3-7]</sup>. Recently, Japanese authors demonstrated that de novo colorectal cancer was one of the most common de novo malignant tumors after LT<sup>[2]</sup>. Additionally, we reviewed the de novo

malignant tumor among the liver transplant recipient in our country and found that colorectal cancer was the second most common malignant tumor which further demonstrated the necessity of colonoscopy [8]. However, the clinical data of colonoscopy among the liver transplant recipients was limited and no study demonstrated the clinical practice of colonoscopy among the liver transplant recipients. Until now, it was unknown whether there was any difference between the liver transplant recipients and general population in the bowel preparation, difficulty of examination, patient's satisfaction and the incidence of abnormalities such as adenoma detection rate (ADR) and so on. Herein, a prospective cohort study was designed to elucidate clinical practice of the colonoscopy among the liver transplant recipients which may help the endoscopists understand this area well

## Methods

### 1 Patient enrollment

Between June 2017 and November 2018, 48 liver transplant recipients received screening colonoscopy by a same endoscopist (Dr. Xie) in the Affiliated Hospital of Qingdao University was named as LT-group and clinical data related to the procedures was prospectively collected. A group of asymptomatic healthy examiners of same age and same gender were chosen as control group at a ratio of 1:3 which named as control group. The colonoscopy of the control group was performed by the same endoscopist at the same time. The basic demographic data of the two groups was presented in the Table 1. Clinical data of LT-group was collected, included age, gender, indication of LT, date of operation, digestive symptoms, body mass index (BMI), medical history. All the liver transplant recipients underwent classical orthotopic LT because of the liver failure and/or HCC caused by HBV infection except two patients were diagnosed with alcoholic cirrhosis and one patient was diagnosed with cryptogenic cirrhosis. All the recipients were received a donor from citizen's death. The immunosuppressive regimen after LT was based on tacrolimus, and mycophenolate mofetil was combined during early postoperative period to prevent rejection, except few patients received sirolimus or cyclosporine based regimens. The HBV prophylaxis strategy after LT was based on entecavir combined with hepatitis B immunoglobulin. This is a real world observation study and the Affiliated Hospital of Qingdao university approved this study.

Table 1  
Basic characteristics and procedure outcomes of colonoscopy

	LT-group (N = 72)	Control group(N = 216)	P-value
Sex (n/N,%) Female Male	18/72(25.00%) 54/72(75.00%)	72/216 (33.33%) 144/216 (66.67%)	0.119
Age(year)	57.79 ± 9.02	55.31 ± 11.49	0.069
BMI(mean ± SD)	25.03 ± 3.66	26.54 ± 4.92	0.353
Bowel cleansing(n/N,%) Adequate Inadequate	55/72 (76.39%) 17/72 (23.61%)	155/216 (71.76%) 61/216 (28.24%)	0.273
Cecal intubation rate (%)	72/72(100%)	214/216(99.07%)	0.562
Intubation time(second) ≤ 240 ≥ 240	252.21 ± 56.28 29/73 (39.73%) 44/73(60.27%)	229.23 ± 34.67 126/216 (58.33%) 86/216(39.81%)	0.024 0.030
Intubation length(cm)	85.12 ± 9.15	86.84 ± 11.05	0.623
Abdominal compression(n/N,%) Yes No	44/72 (61.64%) 28/72 38.36%)	74/216 (34.26%) 142/216 (65.74%)	0.01
Position changing(n/N,%) Yes No	6/72 (8.33%) 66/72 (91.67%)	17/216 (7.87%) 199/216 (92.13%)	0.536
Anticipating of pain(n/N,%) Yes No	17/72(23.61%) 55/72(76.39%)	47/216(26.39%) 169/216(73.61%)	0.382
Post-procedure VAS(n/N,%) ≤ 3 3,≤6 ≥6	43/72(59.72%) 26/72(36.11%) 3/72(4.17%)	154/216(71.30%) 57/216(26.39%) 5/216(2.31%)	0.174
Willing of repeat (n/N,%) Yes No	67/72(93.06%) 5/72(6.94%)	189/216(87.50%) 27/216(12.50%)	0.138
Likert score (n/N,%) No pain Mild pain Moderated pain Severe pain	16/72(22.22%) 40/72(55.56%) 15/48(20.83%) 1/48(1.39%)	38/216(17.59%) 136/216(62.96%) 37/216(17.13%) 6/216(2.78%)	0.229

Table 2  
Colonoscopy findings between liver transplant patients and healthy controls

	<b>LT-group (N = 72)</b>	<b>Control group(N = 216)</b>	<b>P value</b>
No abnormalities ,n/N(%)	31/72 (43.06%)	130/216 (60.19%)	0.008
Polyps ,n/N(%)	36/72 (50.00%)	80/216 (37.04%)	0.036
Adenomatous polyps ,n/N(%)	24/72 (33.33%)	52/216 (24.07%)	0.084
Advanced polyps ,n/N(%)	8/72 (11.11%)	12/216 (5.56%)	0.094
Hyperplastic polyps ,n/N(%)	5/72 (6.94%)	16/216 (7.41%)	0.567
Inflammatory polyps ,n/N(%)	7/72 (9.72%)	9/216 (4.17%)	0.074
Serrated polyps ,n/N(%)	0	3/216 (1.39%)	0.420
Colorectal carcinoma ,n/N(%)	0	1/216 (0.42%)	0.750
Submucosal tumor ,n/N(%)	3/72(4.17%)	3/216 (1.39%)	0.167
Others ,n/N(%)	2/72(4.17%)	2/216(0.93%)	0.261

## 2. Inclusion and exclusion criteria

Inclusion criteria included: Older than 18 years; a written consent was available for the screening colonoscopy and cooperate to complete questionnaires; LT was performed at least 3 months ago before screening colonoscopy; clinical material was completed and good adherence to follow-up.

Exclusion criteria included: patients with severe comorbidities and could not tolerate the colonoscopy; patients who chose sedative colonoscopy; patients who was previously diagnosed as malignant tumor of GI tract; patients with a history of gastrointestinal surgery; Patients receiving secondary liver transplantation or combined liver and kidney transplantation; patients with severe digestive symptoms (hematochezia, hematemesis, et al) required an emergency endoscopic examination; patients with absent clinical data.

## 3. Colonoscopy

Bowel cleansing: Semi-liquid diet started 2 days before examination, and a bag (137.15 g) of compound polyethylene glycol electrolyte power (He Shuang; Wang He, Shenzhen, China) dissolved in 2000 mL of warm water 6 hours before the examination, and the patients were asked to take it within 2 hours. If defecate was less than 6 times or solid fecal was observed, 100 ml 20% magnesium sulfate was taken and colonoscopy was conducted 4 hours later. Bowel clearance was evaluated with Ottawa score, if the score was less than or equal to 4, it was considered adequate; if the score was greater than 4, it was considered inadequate.

Electronic colonoscopy was performed by a same experienced endoscopist, and all of the procedures was performed with standard colonoscopy (CF-HQ290 or CF-HQ260, Olympus Co., Japan). Before the examination, the endoscopist asked the patients about the expectation of pain for the coming procedures(yes/no). During the examination, all polyps less than 10 mm were directly removed; if polyps greater than 10 mm, patients were hospitalized for polypectomy; all submucosal tumors were subsequently examined by the endoscopic ultrasonography (EUS) with a high-frequency mini-probe (UM-3R,20 MHz, Olympus Optical Co, Ltd, Tokyo, Japan), and endoscopic mucosal dissection was performed if it was necessary. In addition, a polyp larger than 10 mm in diameter, having villous component, or showing a high grade dysplasia is classified as advanced adenoma<sup>[9, 10]</sup>.

#### 4. Evaluation of pain

After the colonoscopy, a designated nurse asked the patients about their pain score during the procedure by a visual analog scale (VAS; where 0 = no pain at all and 10 = worst possible pain), which has been validated previously<sup>[11]</sup>. On the VAS, the pain level  $\leq 3$ ,  $> 3 \leq 6$  and  $> 6$  was considered to be mild, moderate and severe pain. Before left the endoscopic unit, patients were also asked about their willingness to repeat unsedated colonoscopy (yes/no). In addition, the day after the colonoscopy, the patients were called to complete a questionnaire to re-evaluate the discomfort during the procedure by a four-point Likert scale (no, slight, moderate, or severe pain)

#### 5. Statistical analysis

Data are presented as mean  $\pm$  standard deviation (SD) or as median and range, as appropriate. Independent t tests or Mann-Whitney rank sum tests were used for continuous variables. Categorical variables were compared using the chi-square test. All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). A P value less than 0.05 was considered statistically significant.

## Results

In our study, a total of 72 liver transplant recipients received colonoscopy, 54 of them were male and 18 of them were female, and average age was  $57.79 \pm 9.02$  years. With age- and sex- matched, 216 health examiner who received colonoscopy at the same time were selected at a ratio of 1:3. The interval between the LT and colonoscopy was 3 months to 170 months, the average interval was  $41.4 \pm 36.8$  months, the number of patients received LT less than 1 year, 1 years to 3years, 3 years to 5 years and more than 5 years was 8, 31, 20 and 13, respectively. Four patients in the LT-group had intermittent abdominal pain, 5 patients had intermittent diarrhea, 2 patients had increased defecation frequency, 1 patient had intermittent fecal urgency, and the rest patients had no obvious lower gastrointestinal symptoms. The patients of control group were asymptomatic health examiners. A total of 58 recipients received tacrolimus as the main immunosuppressive regimen before enrollment, 10 patients received tacrolimus combined with sirolimus, 2 patients received cyclosporine as the main immunosuppressive regimen, and

2 patients received sirolimus alone (Table 1). Sixty-five patients received LT due to hepatitis B virus related end stage liver disease and no recurrence was observed with the prophylaxis therapy at the end of the study.

The BMI of the two groups was similar ( $25.03 \pm 3.66$  vs  $26.54 \pm 4.92$ ,  $P = 0.353$ ). There was no significant difference in bowel cleansing between the two groups, with the median Ottawa score of the two groups were both 4 points, 76.39% (55/72) of liver transplant recipients and 71.76% (155/216) of the control patients had an Ottawa score  $\leq 4$  points, indicating a good bowel preparation. Cecal intubation rate was 100% in LT groups and 99.07% in control group, which was comparable. The inserted length when the endoscopy arrived cecum were also similar between the two groups ( $78.12 \pm 9.15$  vs  $78.84 \pm 11.05$ ,  $P = 0.623$ ). However, time to reach the cecum was significantly longer in the LT groups ( $252.21 \pm 56.28$  vs  $229.23 \pm 34.67$ ,  $P = 0.024$ ). During the procedure, in order to increase efficacy and decrease the discomfort of the patients, 61.64% (44/72) patients in the LT -group and 34.26% (74/216) patients in the control group required an auxiliary nurse compressing abdomen to facilitate the insertion, and statistical difference was observed ( $P = 0.024$ ), however, the frequency of the position changing was comparable between the two groups ( $P = 0.536$ ). (Table 1)

Before examination, the percentage of patients anticipated a painful examination was similar ( $P = 0.382$ ). The median pain score measured on the VAS was 3 in both two groups, and the pain score in LT-group and control group ranged from 1 to 8 and 1 to 10, respectively. No significant difference was observed in the ratio of patients experienced pain level  $\leq 3$ ,  $>3 \leq 6$  and  $> 6$  in LT-group and control group ( $P = 0.174$ ). Additionally, 93.06% patients in LT- group and 87.50% patients in control group accepted a repeat unsedated colonoscopy ( $P = 0.138$ ). The day after the examination, the patients was phoned to complete a four-point Likert scale, and the proportion of patients with no pain, mild pain, moderate pain and severe pain in LT-group and control group was similar. ( $P = 0.229$ ) (Table 1).

In terms of the results, no abnormality colonoscopy was more frequently observed in control group than in LT-group (60.19% (130/216) vs 43.06% (31/72),  $P = 0.008$ ). The incidence of adenoma was 33.33% among the liver transplant recipients which was higher than that in the control group, although no significant difference was observed. Additionally, advanced polyp was observed in as high as 11.11% (8/72) of liver transplant recipients and 5.56% (12/216) of patients in control group, but no statistical difference was observed neither. Submucosal tumor (SMT) was observed in three liver transplant recipients, two of them were diagnosed as lipoma after EUS examination, other SMT was located in cecum, EUS showed a homogenous hypoechoic, spherical and well demarcated mass, which was  $0.6 \times 0.5$  cm in diameter, originated from submucosal layer with endophytic growth, the patient was undergoing clinical follow-up.

## Discussion

Our study showed LT could increase the difficulty of colonoscopy with longer cecal intubation time and more frequently assistant abdominal compression by nurses during the procedures, however, patient's

satisfaction for colonoscopy was compared between live transplant recipients and common people. Although no significant difference was observed between the two groups, incidence of advanced polyps was as high as 11.11% (8/72) among the liver transplant recipients which indicated that actively screening colonoscopy should be advocated after liver transplant recipients.

Colonoscopy was gold standard for diagnosis of colorectal diseases, however, colonoscopy may cause discomfort or even severe pain during the procedure. Therefore, under the background of comfort medicine, sedated colonoscopy was popular in clinical practice. Nevertheless, sedated colonoscopy has several disadvantages including sedation related complication, a necessary escort, long-term post-procedure recovery, activity inhibition, increased medical costs and higher possibility of intraprocedural perforation, therefore, several published researches elucidated that although higher level of discomfort was observed in the patient received unsedated colonoscopy, higher level of satisfaction was also reported<sup>[12, 13]</sup>. In addition, some patients weren't suitable for the sedated colonoscopy due to comorbidities and unsedated colonoscopy could significantly increase the efficiency of endoscopy centers, which was also a clinical issue needed to be considered in the context of the current shortage of medical resources<sup>[14]</sup>. In the past decades, several studies had explored the factors affecting insertion time and discomfort of patients during the colonoscopy which included female, less than 40 years old, low BMI, history of abdominal surgery, abdominal pain as the chief complaint, anxiety before the procedure, a previous painful colonoscopy and diverticulosis of colon<sup>[15-17]</sup>. Until now, clinical practice of colonoscopy among the liver transplant recipients hasn't been fully documented, it was unclear whether LT would increase the difficulty of colonoscopy and sedated colonoscopy should be advocated after LT.

In our study, Ottawa score in was similar between the two group, which meant LT did not affect the bowel preparation. Although previously abdominal surgery was thought to be a risk factor of inadequate bowel cleansing in the several published studies<sup>[7]</sup>, our study demonstrated that no more intensive bowel preparation was needed for liver transplant recipients. On the contrast, our study showed that LT did influence the performance of colonoscopy with experienced endoscopists. Compared with control group, cecal intubation time was longer and the assistant abdominal compression was more frequent in the liver transplant recipients. And our experience was that the adhesion commonly presented in the hepatic flexure of colon where assistant abdominal compression by nurses was required. Notably, cecal intubation rate in LT-group and control group was 100% and 99.07%, respectively, which meant even the difficulty of colonoscopy after LT elevated, experienced endoscopist could completed successfully.

In term of patient's satisfaction, pain level measured on the VAS, the willingness of repeat same procedure and four- Likert score on the next day was similar between the two group, which meant LT did not reduce patient's satisfaction. 95.83% of the liver transplant recipients had a mild or moderate level of pain during the colonoscopy and 93.06% of them were willing to repeat unsedated colonoscopy. Our result was consistent with the previously large-sample study in which high satisfaction (94%) of unsedated colonoscopy was observed<sup>[15]</sup>. it was interesting to notice that although cecal intubation time was longer, more patients in the LT-group (93.06% vs 87.50%) expressed a willingness of repeat

unsedated colonoscopy. Actually, due to the increased incidence of post-LT colorectal cancer and the worse prognosis compared with general population<sup>[5, 18]</sup>, whether to perform screening colonoscopy for the liver transplant candidates had bothered the hepatologists for a long time. Several published studies showed a higher incidence of colorectal adenoma among the patients with end-stage liver disease which suggested that screening colonoscopy might be necessary<sup>[19, 20]</sup>. Recently, a large sample study recruited 808 liver transplant candidates showed that the incidence of colorectal cancer and advanced polyp during the screening colonoscopy were only 0.2% and 5.4%, respectively, however, severe complication was significantly increased, especially in patients with advanced disease, and acute kidney failure and gastrointestinal bleeding were most common<sup>[21]</sup>. This study indicated that standard screening colonoscopy before LT may be questionable, according to our study, it seemed reasonable for the clinicians to perform colonoscopy after LT.

In our study, the incidence of adenoma polyp was 33.33% which was a little higher than the previous published studies. Although it had been fully documented that the incidence of colorectal cancer was elevated after liver transplantation, the studies focused on screening colonoscopy among the liver transplant recipients was relatively limited, the reported ADR ranged from 22%~28%<sup>[6, 19, 22, 23]</sup>. And it was unclear whether the incidence of colorectal adenoma was elevated among the liver transplant recipients, some studies have shown an increased ADR among the liver transplant recipients, others have not reached the same conclusion. This discrepancy could be explained by the different screening policies in different areas. A high ADR in our study may be due to the low popularity rate of screening colonoscopy and increased incidence of colorectal cancer in China. Notably, the incidence of advanced polyp was as high as 11.11% in our study and no relationship was observed between the time after LT and the incidence of advanced polyps. Recently, a large-sample study carried out by Korean scholars showed that although the incidence of the adenoma was similar with general population, the incidence of advanced colorectal neoplasm was significantly increased among the liver transplant recipients (odds ratio = 3.578), and long-term immunosuppressive therapy was suspected to facilitate carcinogenesis<sup>[22]</sup>. The reason that our study did not reach the same conclusion may be due to the smaller sample size.

Our study described the clinical practice of the colonoscopy among the liver transplant recipients with a single endoscopist, minimizing the influence of operator factor on the outcomes. There are several limitations in our study, firstly, it is a single-center, observational study, secondly, the cases in our study were limited because the screening endoscopic procedure hasn't been popularized in our country right now and the patient's willingness to accept screening colonoscopy was not strong. Nevertheless, our study provided the preliminary data of the unsedated screening colonoscopy among the liver transplant recipients which could offer some useful information for clinicians.

In conclusion, our studies showed that although liver transplantation did increase the difficulty of unsedated screening colonoscopy, majority of liver transplant recipients were satisfied with the procedure. As high as 11.11% of the liver transplant recipients were observed to have advanced polyps,

which indicated that active screening colonoscopy should be advocated after LT, especially in the area with a high incidence of colorectal cancer.

## Abbreviations

LT:Liver Transplantation, ADR:adenoma detection rate; BMI:body mix index; EUS:endoscopic ultrasonography; VAS:visual analog scale; SMT:Submucosal tumor;

## Declarations

Ethics approval and consent to participate: The conduct of our study was approved by the Ethical Affairs committee of the Affiliated Hospital of Qingdao University and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patients or guardians.

Consent for publication: Not applicable.

Competing interests: The authors do not have any disclosures to report.

Funding:No

Authors' contributions: RW proposed the study and recruited the patient. XM performed the operation , analysis the data and wrote the draft, with TZB was the supervisor, MT and ZQ managed the patient and collected clinical data. All authors contributed to the design and interpretation of the study. RW is the guarantor.

Acknowledgements: We thank the staff at the Department of Gastroenterology and Department of Organ Transplantation, the Affiliated Hospital of Qingdao University for patient management. Conflict of interest: The authors do not have any disclosures to report.

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