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Original paper

Concomitant diverticulosis among patients undergoing liver transplantation. Does it influence the length of hospitalization after the procedure?

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Abstract

Aim of the study: We tried to assess the influence of concomitant diverticulosis and other factors, e.g., Child-Pugh (C-P) and MELD scores, viral etiology, and presence of alcoholic disease, on short-term results of liver transplantation (LT) with an emphasis on duration of patient's hospitalization.

Material and methods: This prospective study was performed on 206 cirrhotic patients who were selected for LT. In order to assess the presence of diverticculosis we performed colonoscopy.

Results: The duration of hospitalization after LT did not differ significantly between patients with and without diverticulosis (27.5 [21.0-33.5] vs. 24.0 [18.0-32.0] days, $p = 0.28$). Patients with C-P class C were hospitalized longer in comparison to the class B patients. It is reflected in the positive correlation between C-P score and days of hospitalization ($r = 0.22$, $p = 0.002$). Patients with diverticulosis were significantly older (59.6 [51.1-63.3] vs. 52.9 [43.8-59.2] years, $p = 0.03$). Alcoholic liver disease (ALD) was associated with a greater risk of diverticulosis (OR = 3.89, 95% CI [1.13-15.87], $p = 0.04$).

Conclusions: Presence of diverticulosis among subjects undergoing LT did not influence the duration of hospitalization after the procedure. Significantly longer hospitalization was observed in patients with the most advanced liver disease according to C-P score. To determine the exact impact of diverticulosis on short-term results of LT additional studies are required.

Key words: liver transplantation, diverticulosis, cirrhosis, Child-Pugh score, duration of hospitalization.

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Introduction

During the last decades liver transplantation (LT) has been playing an essential role in the therapeutic path of liver diseases. It is mostly a consequence of the lack of alternative therapies and of the good post-transplant survival of approximately 90% and 80% at 1 and 5 years, respectively [1]. Based on the Eu-

ropean Association for the Study of the Liver (EASL) Clinical Practice Guidelines for LT [2], there are three types of patients who are entered on the LT waiting list: 1) patients with end-stage liver disease (ESLD), mostly decompensated liver cirrhosis, included in the waiting list on the principle of the "sickest first", based mainly on the calculation of the Model for End Stage Liver Diseases (MELD) score, 2) patients with the development of hepatocellular carcinoma (HCC) and 3) patients with acute liver failure. The MELD score (calculated from objective measures such as creatinine, bilirubin, and international normalized ratio [INR]) was developed to determine the short-term prognosis for patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) after gastrointestinal bleeding [3], and then proposed for predicting 3-month mortality in patients with ESLD.

Since the results of LT have shown significant improvement, more patients have been eligible for LT, while the indications have been evolving. As a consequence, this procedure starts pertaining to older patients as well as patients with multiple comorbidities, including diverticulosis. Diverticulosis of the colon is one of the most common anatomical colonic alterations, detected during colonoscopy or computed tomography mostly in developed countries. Diverticula of the large bowel are characterized by mucosal/submucosal herniations through outpouching in the muscle layer at anatomical weak points where blood vessels penetrate to supply the mucosa [3]. These types of diverticula occur typically in the left colon. The real prevalence of diverticulosis is unknown, although its age-dependency is proven, and it is mostly detected among patients aged 65 years or more. About 85-90% of patients remain asymptomatic; the rest develop clinically significant and symptomatic diverticulosis, leading to the so-called "diverticular disease" [4]. Despite its frequency, the pathogenesis of diverticulosis is still controversial and considered to be multifactorial. Several risk factors for diverticulosis have been identified, such as older age, constipation, a high intake of red meat, a low-fiber diet, and a low level of physical activity [5].

As mentioned above, the development in the field of solid organ transplantation, including the liver, leads to modification of characteristics of patients receiving a liver transplant. It results in an increasing number of elderly patients with all concomitant diseases typical for this age, including diverticulosis. The relevance of concomitant diverticulosis is associated with the fact that the impact of diverticular disease on patients' wellbeing and health care costs is significant. Due to its universality, diverticular disease has a leading position among the main causes of health spending for gastrointestinal diseases [6]. Furthermore, diverticulosis has been shown to have a negative impact on health-related quality of life (QOL), including emotional QOL and physical function QOL [7, 8]. It has to be mentioned that according to previous studies more than one third of patients experienced persistent symptoms 1 to 2 years after an episode of uncomplicated diverticulitis [9]. In our study we investigated the influence of such factors as body mass index (BMI), Child-Pugh (C-P) and MELD score, viral etiology, presence of alcoholic disease and especially detection of diverticulosis during colonoscopy, on short-term results of LT with an emphasis on duration of patients' hospitalization.

Material and methods

This prospective study was performed on patients who were hospitalized in the Hepatology, Gastroenterology and Liver Transplantation (HEGITO) Unit, FD Roosevelt Faculty Hospital, Banska Bystrica, Slovakia. The study included 206 cirrhotic patients who were selected for LT, i.e. patients with irreversible liver disease that was expected to be fatal without transplantation. Cirrhosis in these patients was diagnosed based on an interview (history of chronic liver disease), physical examination (typical signs of cirrhosis: spider naevi, palm erythema, ascites, spleno- and/or hepatomegaly, nail abnormalities, jaundice), imaging (ultrasound, CT, MRI) or endoscopy (presence of signs of portal hypertension, i.e., gastropathy, esophageal/gastric varices) and abnormal laboratory findings.

We defined two subgroups with respect to alcohol related (95 patients) and non-alcohol related (111 patients) etiology of cirrhosis. For further analysis, we also extracted two subgroups with viral and non-viral etiology of liver disease. The diagnosis of chronic hepatitis B (CHB) was based on raised serum transaminases for at least 6 months, positivity for hepatitis B virus (HBV) surface antigen (HBsAg) and anti-HB core IgG antibodies. Chronic hepatitis C was established in case of the presence of anti-hepatitis C virus (HCV) antibodies together with HCV-RNA for more than 6 months.

All the subjects were divided according to C-P grades A, B and C and MELD score (≤ 14 and > 14). The C-P score consists of ascites, hepatic encephalopathy (HE), prothrombin time, total bilirubin and albumin. Each measure is scored 1-3 points, with 3 indicating the most severe derangement. The sum of these points assigns the patient to one of the groups: into C-P grades A (5-6 points), B (7-9 points), C (10-15 points). The MELD

score reflects liver and renal function and is based on INR, total bilirubin, and creatinine.

To evaluate the presence of diverticulosis most of the patients underwent colonoscopy before the procedure of LT. To achieve the criteria of complete colonoscopy the bottom of cecum and proximal lip of the ileocecal valve had to be visualized, and it required good bowel preparation defined as at least 6 points on the Boston Bowel Preparation Scale (BBPS).

The statistical analysis was performed with STATISTICA 10.0 (StatSoft Polska Sp. z o.o., Cracow, Poland). The data were expressed as median (interquartile range (IQR)). The Shapiro-Wilk test was used to evaluate the distribution. The statistical significance of the difference in studied variables was tested using the Mann-Whitney *U*-test and ANOVA rank Kruskal-Wallis tests for independent groups. Fisher's exact test was used to determine the differences in diverticulosis presence. Correlations were analyzed with the Spearman rank correlation coefficient. Statistical significance was defined as values of $p < 0.05$.

Results

Comparison between females and males selected for liver transplantation

Severity of liver cirrhosis based on C-P and MELD scores did not differ significantly between females and males (10.0 [8.00-11.0] vs. 9.00 [8.00-11.0], $p = 0.55$ and 16.0 [13.6-19.0] vs. 15.0 [13.0-18.0], $p = 0.08$, respectively). We also did not observe any significant differences with respect to age or duration of hospitalization ($p = 0.30$ and $p = 0.36$). Females presented significantly lower BMI in comparison to males (24.0 [21.5-27.5] vs. 27.0 [25.0-30.0] kg/m^2, $p < 0.001$). Diverticulosis was observed less often among females (4.0%) than among males (9.9%), but the difference was not statistically significant [OR = 0.43 (95% CI: 0.11-1.61, $p = 0.24$)].

Comparison of liver transplant patients with and without diverticulosis

As mentioned above, in our study we also analyzed the presence of colonoscopy proven diverticulosis among subjects undergoing LT. Diverticulosis was detected among 13 patients, which represents 6.3% of all patients undergoing investigation. Patients with diverticulosis were significantly older (59.6 [51.1-63.3] vs. 52.9 [43.8-59.2] years, $p = 0.03$). None of the other analyzed parameters differed between these two subgroups.

Duration of hospitalization after liver transplantation

The main purpose of this study was to analyze factors that could have an impact on the period that patients had to spend in hospital after transplantation. The duration of hospitalization did not differ significantly between patients with and without diverticulosis (27.5 [21.0-33.5] vs. 24.0 [18.0-32.0] days, $p = 0.28$). Significantly longer hospitalization was observed only among patients in C-P class C in comparison to class B. It is reflected in the positive correlation between C-P score and days of hospitalization ($r = 0.22$, $p = 0.002$).

Comparison of liver transplant patients with respect to BMI

The patients were divided into two subgroups based on BMI (BMI < 30 kg/m^2 and ≥ 30 kg/m^2). There were no significant differences concerning C-P score, MELD score and days of hospitalization in the groups of patients with different BMI ($p = 0.68$, $p = 0.08$, and $p = 0.31$, respectively). Patients with obesity were older in comparison to non-obese patients (56.4 [52.0-62.7] vs. 52.1 [42.2-57.8] years, $p = 0.002$). Diverticulosis was found less often among obese patients (3.0% vs. 8.6%), but the difference was not statistically significant [OR = 0.33 (95% CI: 0.04-2.64, $p = 0.46$)].

Comparison of liver transplantation patients according to severity of cirrhosis based on Child-Pugh and MELD score

Data comparing patients with various C-P score are presented in Table 1. According to the C-P score patients were divided into 3 groups. No significant differences in age and BMI were found with respect to liver disease severity as assessed with the C-P score. When patients with different stages of liver dysfunction according to C-P score were compared, we observed significantly longer hospitalization in class C compared to class B (30.0 [20.0-44.0] vs. 22.0 [17.0-27.7] days, $p < 0.001$). Surprisingly, there was no such difference comparing class A and B ($p = 0.17$) as well as A and C ($p = 0.45$).

The patients were also divided according to MELD score into two groups: MELD ≤ 14 and MELD > 14. There were no significant differences with respect to BMI in the groups of patients with different MELD scores ($p = 0.13$). Contrary to the C-P score, we did not observe any significant differences in duration of hospitalization between these two subgroups ($p = 0.23$). Surprisingly, patients with a higher MELD score were

Table 1. Analyzed parameters according to the severity of cirrhosis, as assessed by the Child-Pugh score

Parameter	Child-Pugh A (*n* = 17)	Child-Pugh B (*n* = 87)	Child-Pugh C (*n* = 102)	Child-Pugh A vs. B *p*	Child-Pugh B vs. C *p*	Child-Pugh A vs. C *p*
Hospitalization duration (days)	27.0 (16.7-39.0)	22.0(17.0-27.7)	30.0 (20.0-44.0)	0.17	< 0.001	0.45
Age (years)	52.1 (38.5-56.6)	53.4 (44.0-60.5)	51.6 (38.9-57.5)	0.25	0.22	0.73
BMI (kg/m^2)	25.0 (22.7-28.7)	25.0 (22.0-28.0)	26.0 (24.0-28.0)	0.90	0.46	0.57
MELD score (points)	11.0 (7.54-12.4)	15.0 (12.9-16.0)	19.0 (16.9-22.7)	< 0.001	< 0.001	< 0.001
Diverticulosis (%)	13.3	3.4	7.8		0.28	

Table 2. Analyzed parameters according to the severity of cirrhosis, as assessed by MELD score

Parameter	MELD ⩽ 14 (*n* = 70)	MELD > 14 (*n* = 136)	*p*
Hospitalization duration (days)	23.5 (17.0-30.0)	25.0 (19.0-33.0)	0.23
Age (years)	56.1 (47.3-61.6)	52.3 (41.9-57.5)	0.01
BMI (kg/m^2)	27.0 (23.0-29.5)	26.0 (23.0-28.0)	0.13
Child-Pugh score (points)	8.0 (6.75-9.0)	10.0 (9.0-11.0)	< 0.001
Diverticulosis (%)	7.1	5.8	0.76

Table 3. Analyzed parameters among patients with disease of viral and non-viral etiology

Parameter	Viral	Non-viral	*p*
Hospitalization duration (days)	24.5 (18.5-27.5)	24.0 (18.0-34.0)	0.56
Age (years)	54.5 (45.6-57.3)	52.1 (42.2-59.3)	0.63
BMI (kg/m^2)	26.0 (24.0-28.0)	26.0 (22.0-28.0)	0.46
Child-Pugh score (points)	9.0 (7.5-11.0)	9.0 (8.0-11.0)	0.63
MELD score (points)	14.0 (10.0-17.1)	15.6 (13.0-18.3)	0.07

Table 4. Analyzed parameters among patients with and without history of alcoholic liver disease (ALD)

Parameter	ALD (*n* = 95)	Non-ALD (*n* = 111)	*p*
Hospitalization duration (days)	23.5 (18.0-31.5)	25.5 (18.0-33.0)	0.38
Age (years)	55.8 (50.8-59.8)	50.1 (37.7-57.8)	< 0.001
BMI (kg/m^2)	27.0 (24.0-30.0)	25.0 (22.0-28.0)	< 0.001
Child-Pugh score (points)	10.0 (9.0-11.0)	9.0 (7.0-11.0)	0.006
MELD score (points)	15.9 (14.0-18.6)	15.2 (13.0-18.1)	0.50
Diverticulosis (%)	10.5	2.7	0.04

significantly younger (p = 0.01). There was no difference in diverticulosis frequency between patients with higher and lower MELD scores (5.8% vs. 7.1%) [OR = 0.84 (95% CI: 0.26-2.69, p = 0.76)]. For details see Table 2.

Comparison of liver transplant patients with viral and non-viral etiology of cirrhosis

In our study, we differentiated the study group according to the etiology of cirrhosis into two subgroups: viral etiology (HBV or HCV) and non-viral etiology. None of the analyzed parameters differed significantly when these two subgroups were compared (Table 3).

Comparison of liver transplant patients with and without history of alcoholic liver disease

For further analysis patients were divided into two subgroups: 1) with history of alcoholic liver disease (ALD), which included 95 patients, and 2) without ALD – 111 patients. ALD patients were significantly older (p < 0.001) and had significantly higher BMI in comparison to non-ALD patients. Moreover, patients with ALD also had significantly higher C-P (p = 0.006) but not MELD score (p = 0.50). Surprisingly, proven overuse of alcohol in the past did not have an impact on duration of hospital stay. There was no significant difference between ALD and non-ALD patients regarding number of days that patients had to stay in hospital after LT. Diverticulosis was discovered more often among ALD patients (10.5%) than among non-ALD patients (2.7%). Documented alcohol abuse in the past was associated with a greater risk of diverticulosis [OR = 3.89 (95% CI: 1.13-15.87), p = 0.04]. For details see Table 4.

Correlations between analyzed parameters

In our study, we also scrutinized correlations between analyzed parameters (such as age of patients, BMI, C-P as well as MELD score) with an emphasis on the relationship between them and the duration of hospitalization. Only C-P score was positively associated with days of hospital stay (r = 0.22, p = 0.002), where-

as MELD score was negatively associated with BMI ($r = -0.15$, $p = 0.04$) and age of LT patients ($r = -0.20$, $p = 0.004$), but it was not correlated with duration of hospitalization ($p = 0.24$).

Discussion

The development in the field of solid organ transplantation, and subsequently increasing importance of LT as a desirable therapy of chronic liver diseases, leads to modification of characteristics of patients receiving a liver transplant. As a result, various co-morbidities pose new challenges for clinicians to deal with. To the best of our knowledge, this is the first study to assess the influence of concomitant diverticulosis on short-term results of LT with an emphasis on duration of patients' hospitalization.

Initially, at the stage of research planning we had proposed that concomitant diverticulosis would have resulted in posttransplant complications and consequently would have prolonged the time of hospitalization. However, presence of diverticulosis did not influence treatment duration and was not associated with longer hospital stay.

Analyzing previous publications, there are a few similar studies investigating the presence of diverticular disease and its complications after lung, heart, or kidney transplantation [10-12]. Olson *et al.* [13] conducted a retrospective study to review patients undergoing lung transplant between 2007 and 2016 with posttransplant acute colonic diverticulitis. The study group consisted of 512 transplant recipients. According to Olson's research the incidence of posttransplant diverticulitis (3.3%) was much higher than that reported in the general population (0.7%). Over 60% of diverticulitis cases occur within 2 years after transplantation, which is consistent with previous studies [14, 15]. Higher BMI at the time of listing for transplant was identified as a risk factor for diverticulitis after transplantation and the likelihood of developing recurrent diverticulitis.

What is interesting is that Olson's study showed that patients with pretransplant diverticulosis experienced earlier posttransplant diverticulitis episodes, increased recurrence, and higher incidence of surgical intervention than patients without pretransplant diverticulosis. That fact illustrates the value of pretransplant colonoscopy. There is another crucial issue that needs to be mentioned in reference to diverticulosis and its complications among patients after solid organ transplantation. The classic presentation of diverticulitis may be complicated by immunosuppressive medications or the patient's critical condition, which may delay diagnosis and intervention [13]. Glucocorticoids reduce infection defense capabilities by the inhibition of granulocytes and macrophages. In addition, steroids inhibit the action of certain pyrogenic interleukins and pain-inducing prostaglandins [16]. As a result, symptoms and classic signs of acute abdomen are masked under immunosuppression, and this leads to a diagnostic challenge.

Liver cirrhosis is a chronic disease that affects and unhinges homeostasis of other organs and systems in the human body, especially the gastrointestinal tract. A well-known phenomenon associated with cirrhosis is bacterial translocation (BT). BT or microbial translocation is defined as the migration of microorganisms or their products from the intestinal lumen into the mesenteric lymph nodes (MLN) and other tissue and organs [17]. The most evidenced clinical expression of pathological BT is spontaneous bacterial peritonitis (SBP) or bacteremia [18]. The etiology of intestinal barrier dysfunction in liver cirrhosis, resulting in BT, is probably multifactorial. Several studies have reported that the gut microbiota is changed in patients with liver cirrhosis, which is called dysbiosis. A quantitative alteration in *Bacteroides*/*Firmicutes* ratio, with an increase in potentially pathogenic bacteria including Enterobacteriaceae together with a reduction in specific autochthonous commensals, was observed [19, 20]. Gut dysbiosis seems to participate in the disruption of intestinal epithelial tight junctions and the imbalance of proliferation and apoptosis of intestinal epithelial cells [21]. The gut epithelium plays an important role in immune homeostasis as the first barrier that prevents BT. The intestinal barrier is constituted mainly by intestinal epithelial cells and their mucinous components [22]. The gut barrier is a complex dynamic structure made of mechanical (mucus layer, epithelial cells and endothelial cells), immunological (secretory IgA, lymphatic tissue, intestinal microbiota), functional (gut motility, gastric acid secretion, bile acids) and microbiological components involved in the selective regulation of intestinal permeability [23]. According to previous publications, the rate and degree of pathological BT increase with severity of liver disease. Pathological translocation of vital bacteria to MLN is a phenomenon of the decompensated stage. Direct data on culturable BT to MLN revealed a significantly higher rate in C-P C cirrhotic patients (30%) as compared to C-P B or A (8% and 3%, respectively) patients and C-P score was the only independent predictor for pathological BT [24, 25].

A study performed by Yeh *et al.* [26] investigated the clinical significance of BT after cirrhotic liver resection. In this study, bacterial cultures of MLNs before and after liver resection were performed in 181 cirrhotic patients. According to them, the incidence of BT

after liver resection was significantly higher than before liver resection (19.9% vs. 0%, $p < 0.001$). Postoperative complications occurred in 17 patients (47.2%) in the BT group and 23 patients (15.9%) in the non-BT group ($p < 0.001$). BT group patients had a significantly higher infectious complication rate (44.4% vs. 7.6%, $p < 0.001$). In consequence, the postoperative hospital stay was significantly longer in the BT group (16.3 ±1.6 vs. 11.7 ±0.59 days, $p = 0.01$).

As we can easily notice, liver cirrhosis, per se, increases the risk of BT and consequently LT complications. Diverticulosis also predisposes to diminution of the gut barrier, leading to leaky gut. The diverticular fundus is frequently distended and thin walled. Due to the weakened resistance, microperforation can easily take place, in particular at the diverticular fundus, allowing inflammatory spread into pericolic tissues and abscess formation [27]. Additionally, stasis of fecal material within diverticula can be favored by a prolonged colonic transit, which in turn predisposes to altered microflora and bacterial overgrowth. All of these provoke an inflammatory reaction by means of cytokine release [28]. Previous publications described possible activation of Toll-like receptors (TLR) with a subsequent inflammatory reaction at the level of the perivisceral tissues [29, 30].

In our study we also analyzed the impact of alcohol intake on diverticulosis and duration of hospitalization among patients undergoing LT. Previous reports on the association of alcohol use and diverticular disease have been conflicting. Alcohol has multiple effects on the gastrointestinal tract. It can cause mucosal injury, impair motility, and inhibit the absorption of nutrients, resulting in various gastrointestinal disorders [31, 32]. Reduced rectosigmoid motility caused by alcohol consumption may be an important pathogenic factor of diverticula formation. Alcohol inhibits colonic motility through activation of the nuclear factor-κB pathway and the subsequent upregulation of inducible nitric oxide synthase expression, thus resulting in increased intracolonic pressure and colonic diverticulosis [33]. Some studies have also analyzed the influence of alcohol overuse on the probability of diverticular complications such as diverticular bleeding. The study of Nagata *et al.* [34] including 911 patients with diverticulosis presented increased odds of bleeding in moderate drinkers compared to non-drinkers. According to this information we could suppose that ALD patients were predisposed to some of the complications of diverticulosis. Surprisingly, proven overuse of alcohol in the past did not have any influence on duration of hospital stay. On the other hand, similarly to previous studies, diverticulosis was discovered more often among ALD patients (10.5%) than among non-ALD patients (2.7%).

We also differentiated the study group according to the etiology of cirrhosis into two subgroups, viral etiology (HBV or HCV) and non-viral etiology, although none of the analyzed parameters differed significantly when these two subgroups were compared. This seems to be consistent with the lack of any pathophysiological connection between hepatotropic virus infections and diverticulosis in the literature.

Taking into consideration the above data, it is clear that LT among cirrhotic patients with concomitant diverticulosis is fraught with higher risk of infectious complications that may prolong postoperative hospital stay, increase hospital costs, and even cause death. Surprisingly, according to our results there were no significant differences in duration of hospitalization of patients with and without diverticulosis. Despite the fact that we did not prove this correlation, diverticulosis still remains a challenging issue – mostly due to the persistent symptoms of diverticular disease that eventually have a negative impact on health-related QOL.

Unfortunately, our study has several limitations. First of all, the study group consisted of a relatively small number of patients, although this is related to the fact that the primary criterion of inclusion of patients in the study was LT but not presence of diverticular disease. Secondly, the follow-up of the study group comprised a short period after LT. According to previous publications diverticulosis complications mostly occur within 2 years of transplant. In consequence, some of them could have been missed in our study. The lack of analysis of such short-term LT complication as liver decompensation, bleeding, infection, and post-transplant mortality is another important limitation of our investigation. Thirdly, a more perspicacious assessment of the potential influence of diverticulosis among LT patients was hampered by the lack of data on detailed complications such as diverticulitis or diverticular bleeding.

Conclusions

In conclusion, our study revealed, for the first time, that the presence of colonoscopy proved diverticulosis among subjects undergoing LT did not influence the duration of hospitalization after the procedure. Significantly longer hospitalization was observed only among patients in C-P class C in comparison to class B, and it was reflected in a positive correlation between C-P score and days of hospitalization. Contrarily, MELD score seemed not to be an accurate instrument to predict recovery. The fact that patients with proven ALD had greater risk of diverticulosis (OR = 3.89) indicates

to us that this group of patients requiers particular colonoscopic surveillance. According to our findings, it is difficult to evaluate the value of routine pretransplant colonoscopy, due to the fact that our study was limited by a short-term follow-up. However, based on the previous publications referring to complications of diverticular disease after transplantations of other solid organs, we could suppose that pretransplant colonoscopy might decrease the risk of serious diverticulitis or even colon perforation. The aforementioned studies highlighted the fact that the rate of diverticulitis in transplant or immunosuppressed patients is higher than in the general population, and its clinical course in such patients may be more severe. Simultaneously, abdominal signs are often subtle, which may delay diagnosis and intervention. Considering all the results, to determine the exact impact of diverticulosis on short-term results of LT, additional studies are required.

Disclosure

The authors declare no conflict of interest.

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