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Risk factors for incisional hernia after liver transplantation in the era of mammalian target of rapamycin inhibitors use: a retrospective study of living donor liver transplantation dominant center in Korea

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Purpose: Incisional hernia (IH) is a common complication after liver transplantation (LT) with an incidence rate of 5% to 46%. This retrospective study aimed to evaluate the risk factors for IH development after LT in the era of mammalian target of rapamycin (mTOR) inhibitors use.
Methods: Data on patients who underwent LT between 2015 and 2021 were retrospectively reviewed. The patients were divided into 2 groups (IH group and non-IH group) according to the postoperative occurrence of IH.
Results: We analyzed data from 878 patients during the study period, with 28 patients (3.2%) developing IH. According to multivariate analysis, body mass index exceeding 25 kg/m² and the use of mTOR inhibitors within the first month after LT were the sole significant factors for both IH occurrence and the subsequent need for repair operations. Notably, a history of wound complications, a Model for End-stage Liver Disease score, and the timing of LT—whether conducted during regular hours or at night—did not emerge as significant risk factors for IH after LT.
Conclusion: Our study reveals a higher incidence of IH among obese patients following LT, often requiring surgical repair, particularly in cases involving mTOR inhibitor usage within the initial month after LT. Consequently, it is crucial to exercise increased vigilance, especially in obese patients, and exercise caution when considering early mTOR inhibitor administration after LT.
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Key Words: Incisional hernia, Liver transplantation, mTOR inhibitors

INTRODUCTION

Incisional hernia (IH) is a complication that occurs after abdominal surgery, with a reported incidence rate of 5% to 20% [1,2]. Obesity, older age, male sex, wound infection, steroids, ascites, smoking, malnutrition, diabetes mellitus, previous surgery, emergency surgical procedures, and chronic pulmonary disease have been described as risk factors for IH [3,4]. Liver transplant patients have several risk factors for IH, and the incidence of IH after liver transplantation (LT) is 5% to 46% [5-8]. This increased risk is because of the large incision size and the use of immunosuppressive drugs [9,10]. Many previous studies have reported various etiologies of IH such as obesity, advanced age, wound infection, ascites, steroids, diabetes mellitus, surgical technique, suture material, and the surgeon's experience [6-8,11]. Compared with other abdominal surgeries,

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immunosuppressive agents interfere with the wound-healing process [12,13].

Mammalian target of rapamycin (mTOR) inhibitors are immunosuppressive and antiproliferative agents widely used in the transplant field [11]. In LT patients, mTOR inhibitors are often used to minimize exposure to calcineurin inhibitors (CNIs) to prevent their adverse effects, particularly renal impairment and long-term malignancy [11]. Reduced usage of CNIs within the first month following LT more successfully prevents renal impairment and recurrence of hepatocellular carcinoma (HCC) [14]. The early use of mTOR inhibitors with reduced tacrolimus appears as a promising approach for LT patients with risk factors for renal impairment [15] and/or recurrence of HCC [16]. However, mTOR inhibitors attach to FK-binding proteins and act on mTOR. mTOR regulates the phosphoinositide 3-kinase/Akt pathway, which is stimulated by interleukin-2 and other cytokines [17]. It also affects cell cycle progression and angiogenesis. Consequently, inhibiting mTOR leads to a reduction in lymphocyte, endothelial, and fibroblast proliferation. Nitric oxide and vascular endothelial growth factor levels are also decreased by mTOR inhibition [18]. The inhibition of endothelial and fibroblast cells by mTOR inhibitors leads to impaired angiogenesis and decreased fibroblast activity [19].

Although several studies have been published on the incidence of IH after LT [6,9-11,20], few studies have included variables such as the history and level of mTOR inhibitors use. Therefore, the purpose of this study was to identify the incidence of and risk factors for IH after adult LT in this era of mTOR inhibitors use.

METHODS

We retrospectively reviewed the medical records of patients after adult LT from January 2015 to December 2021 at Seoul National University Hospital, Seoul, Korea. The following patient characteristics and clinical data were recorded to determine potential risk factors for the development of IH: demographics (age, sex, and body mass index [BMI]), preoperative comorbidities associated with impaired wound healing or IH (diabetes mellitus, preoperative immunosuppressive therapy, and smoking), and perioperative data (deceased or living donor and Model for End-stage Liver Disease [MELD] score). In the present study, IH was defined as IH diagnosed radiologically on dynamic liver CT or MRI, and/or clinically judged during an outpatient visit or hospitalization. IHs at any site other than the transplant incision site, stoma hernia, internal hernias, and umbilical hernias were excluded.

This study protocol was reviewed and approved by the Institution's Review Board of Seoul National University Hospital (No. 2301-089-1395). It was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature.

Surgical procedure and immunosuppressive protocol

The surgical procedures were slightly different depending on the preference of the surgeon in charge of abdominal closure; however, all procedures were performed according to the following protocol. The posterior fascia was closed with a 1-0 polyfilament running suture, and the anterior fascia was closed with a 1-0 monofilament. In addition, the 1-0 polyfilament was used as an interrupted suture to prevent the loosening of sutures and to reinforce the incision.

After transplantation, maintenance immunosuppression was based on the administration of a triple regimen, which included tacrolimus, mycophenolate mofetil (MMF), and a steroid. For far advanced HCC (larger than 10 cm, more than 10 numbers, or with macrovascular invasion) or HCC with a high recurrence rate based on high tumor marker results, we considered using mTOR inhibitors for immunosuppression [21,22]. In this study, patients who developed IH and subsequently used mTOR inhibitors after IH occurrence were referred to as mTOR inhibitor non-users. Intravenous methylprednisolone was initiated intraoperatively and gradually tapered, transitioning to oral prednisolone, which was then discontinued within 1–3 months after transplantation. Optimal plasma concentrations of tacrolimus were adjusted to maintain trough plasma concentrations of 10 ng/mL during the first month (which was decreased to 5–8 ng/mL after the first month). The patients also received 500 mg of MMF twice daily. The patients were regularly followed up with at the outpatient clinic after discharge. Postimplantation follow-up continued for more than 2 years until death or their current status.

Statistical analysis

Results are expressed as mean ± standard deviation or median (interquartile range) for continuous data and as numbers with percentages for categorical data. The Mann-Whitney U-test was used to analyze continuous variables, and the chi-square test or Fisher exact test was used to analyze categorical variables. Risk factors associated with IH were analyzed using univariate and multivariate logistic regression analyses. Multivariate Cox proportional hazard regression in a backward manner was used to determine the effect of variables that were identified as statistically significant in the univariate analysis. The log-rank test was used to compare patient survival using the Kaplan-Meier method. Statistical analysis was performed using IBM SPSS Statistics ver. 26.0 (IBM Corp.), and a P-value of less than 0.05 was considered statistically significant.

RESULTS

Data on 878 patients were obtained during the study period and analyzed. Among these 878 patients, 28 patients (3.2%) developed IH. Preoperative demographics are shown in Table 1. The mean time to IH occurrence was 17.1 months (range, 0.5–43.2 months) (Fig. 1). The mean age at transplantation was 55.9 years, and 68.8% were male; The mean BMI was 23.8 kg/m^2. Of the transplantations, 718 transplantations (81.8%) were living-related transplantations, whereas 160 grafts (18.2%) were from deceased donors. A total of 470 patients (53.5%) were diagnosed with HBV, 76 with HCV (8.7%), and 68 with non-HBV and non-HCC (7.7%); 139 (15.8%) had hypertension and 215 (24.5%) had diabetes mellitus; and 253 (28.8%) drank alcohol and 138 (15.7%) smoked. The mean MELD score was 15.6, and the mean Child-Turcotte-Pugh (CTP) score was 8.2. The number of patients who received transcatheter arterial chemoembolization was 393 (44.8%), and those who received radiofrequency ablation were 162 (18.5%). There were 347 patients (39.5%) who used mTOR inhibitors as an immunosuppressant.

The mean BMI was significantly higher in the IH group than in the non-IH group (P = 0.001). The use of mTOR inhibitors was not statistically significant between the IH group and non-IH group (P = 0.448). However, mTOR inhibitors used within 1 month after LT was significantly associated with a higher incidence of IH (17.9% *vs.* 6.6%; P = 0.039). HCC was the main diagnosis for LT in both groups (67.9% *vs.* 54.9%; P = 0.176). No significant differences in age, sex, donor type, etiology, medical history, social history, MELD score, CTP score, gastrointestinal bleeding, intervention history, and wound complication history were observed between the 2 groups (Table 2).

The univariate analysis showed that a BMI of over 25 kg/m^2 (P < 0.001) and mTOR inhibitor use within 1 month after LT (P = 0.037) were associated with hernia formation (Table 3). Age, sex, donor type, etiology, medical history, social history, MELD score, CTP score, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, jaundice, varix bleeding, and intervention history were not predisposing factors for IH formation. After adjusting the multivariate analysis model for potential confounding variables, it was found that having a BMI greater than 25 kg/m^2 (hazard ratio [HR], 3.807; 95% confidence interval [CI], 1.730–8.380; P = 0.001) and the use of mTOR inhibitors within 1 month after LT (HR, 3.012; 95% CI, 1.088–9.340; P = 0.034) were identified as significant independent risk factors for IH.

A total of 347 patients utilized the mTOR inhibitor in the study. Subgroup analysis, specifically focusing on these mTOR inhibitor users, was conducted to compare the trough levels concerning the occurrence of IH. Nevertheless, no significant difference was observed (P = 0.116). In the IH group among the mTOR inhibitor users, the mean mTOR inhibitor trough

Table 1. Demographic characteristics of LT patients

Characteristic	Data
No. of patients	878
Age (yr)	55.9 ± 10.3
Sex, male:female	604:274
Body mass index (kg/m^2)	23.8 ± 3.7
Type of LT	
LDLT	718 (81.8)
DDLT	160 (18.2)
Diagnosis	
HBV	470 (53.5)
HCV	76 (8.7)
NBNC	68 (7.7)
HCC	486 (55.4)
Medical history	
Hypertension	139 (15.8)
Diabetes mellitus	215 (24.5)
Social history	
Alcohol intake	253 (28.8)
Smoking	138 (15.7)
MELD score	15.6 ± 8.9
CTP score	8.2 ± 2.7
SBP	67 (7.6)
Ascites	519 (59.1)
PSE	184 (21.0)
Cholangitis	17 (1.9)
Jaundice itching	66 (7.5)
GI bleeding	168 (19.1)
TACE	393 (44.8)
Radiofrequency ablation	162 (18.5)
Wound complication	82 (9.3)
mTOR inhibitor use	347 (39.5)
mTOR inhibitor use within 1 mo	61 (6.9)

Values are presented as number only, mean ± standard deviation, or number (%).
LT, liver transplantation; LDLT, living donor LT; DDLT, deceased donor LT; NBNC, non-HBV and non-HCV; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; CTP, Child-Turcotte-Pugh; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy; GI, gastrointestinal; TACE, transcatheter arterial chemoembolization; mTOR, mammalian target of rapamycin.

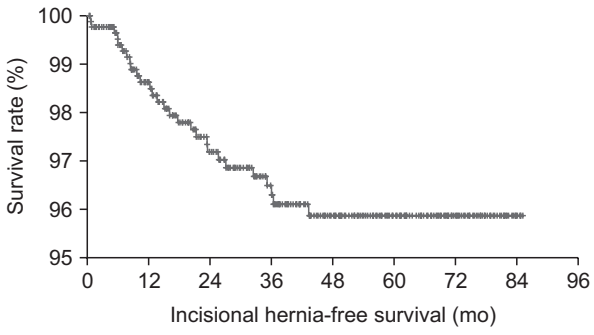

Fig. 1. Incisional hernia-free survival months.

Table 2. Comparison of the demographic characteristics of LT patients between the IH and no-IH groups

Characteristic	IH group	No-IH group	P-value
No. of patients	28	850	
Age (yr)	57.0 (51.5–62.5)	57.3 ± 9.9	0.600
Sex, male:female	21:7	583:267	0.471
Body mass index (kg/m^2)	26.6 (23.6–28.7)	23.8 ± 3.7	0.001
Type of LT			0.583
LDLT	24 (85.7)	694 (81.6)	
DDLT	4 (14.3)	156 (18.4)	
Diagnosis			0.756
HBV	14 (50.0)	456 (53.6)[a]	
HCV	2 (7.1)	74 (8.7)[a]	
NBNC	1 (3.6)	62 (7.3)	
HCC	19 (67.9)	467 (54.9)	0.176
Medical history			
Hypertension	7 (25.0)	132 (15.5)	0.177
Diabetes mellitus	7 (25.0)	208 (24.65)	0.949
Social history			
Alcohol intake	7 (25.0)	246 (28.9)	0.651
Smoking	2 (7.1)	136 (16.0)	0.205
MELD score	15.3 ± 7.5	15.6 ± 8.9	0.853
CTP score			0.823
A	10 (35.7)	312 (36.7)	
B	9 (32.1)	230 (27.1)	
C	9 (32.1)	308 (36.2)	
SBP	2 (7.1)	65 (7.6)	0.921
Ascites	16 (57.1)	503 (59.2)	0.829
PSE	10 (35.7)	174 (20.5)	0.051
Cholangitis	1 (3.6)	16 (1.9)	0.523
Jaundice itching	1 (3.6)	65 (7.6)	0.421
GI bleeding	4 (14.3)	164 (19.3)	0.507
TACE	15 (53.6)	378 (44.5)	0.341
RFA	5 (17.9)	157 (18.5)	0.934
Wound complication	77 (9.1)	5 (17.9)	0.173
mTOR inhibitor use	13 (46.4)	334 (39.3)	0.448
mTOR inhibitor use within 1 month	5 (17.9)	56 (6.6)	0.039

Values are presented as number only, mean ± standard deviation, median (interquartile range), or number (%).
LT, liver transplantation; IH, incisional hernia; LDLT, living donor LT; DDLT, deceased donor LT; NBNC, non-HBV and non-HCV; MELD, Model for End-stage Liver Disease; CTP, Child-Turcotte-Pugh; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy; GI, gastrointestinal; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; mTOR, mammalian target of rapamycin.
[a]Eight patients had underlying HBV and HCV coinfection.

level tended to increase at 1 year after LT but was within the normal range (Supplementary Fig. 1A), and when the individual data were analyzed, the level remained high at 8 or higher in 2 patients (Supplementary Fig. 1B).

DISCUSSION

The risk factors associated with the development of IH after LT are similar to those observed after general abdominal surgery. However, individuals who undergo LT often face additional risk factors due to their chronic liver disease. These factors include mixed protein-energy malnutrition resulting from hypermetabolism, malabsorption, and conditions such as diabetes mellitus, cachexia, and muscle mass loss [7]. In our study, the incidence of IH among liver transplant recipients was 3.2%, which is lower than that after laparotomy due to several reasons [3,4]. In our study, an IH occurrence was confirmed on CT or MRI during the follow-up period after LT, by diagnosis during outpatient visits, and by the requirement of surgical intervention for the IH. We excluded cases that occurred but were not reported by the patients or documented in the medical records. CT scans are not routinely conducted in LT patients unless for liver cancer. Specifically, many cases do not undergo CT scans solely upon initial detection of an IH, making

Table 3. Regression analysis

Variable	No. of patients	Univariate		Multivariate	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)					
≤55	391	Reference			
>55	487	1.250 (0.578–2.700)	0.571		
Sex					
Male	604	Reference			
Female	274	0.738 (0.306–1.733)	0.473		
Body mass index (kg/m^2)					
≤25	585	Reference		Reference	
>25	293	3.764 (1.715–8.262)	0.001	3.807 (1.730–8.380)	0.001
Donor type					
Deceased donor	160	Reference			
Living doner	718	1.349 (0.461–3.942)	0.585		
HBV or HCV/NBNC					
HBV or HCV	538[a)]	Reference			
NBNC	63	0.526 (0.069–4.036)	0.537		
Hypertension					
No	739	Reference			
Yes	139	1.813 (0.756–4.351)	0.183		
Diabetes mellitus					
No	663	Reference			
Yes	215	1.029 (0.431–2.455)	0.949		
Alcohol intake					
No	625	Reference			
Yes	253	0.818 (0.344–1.950)	0.651		
Smoking					
No	740	Reference			
Yes	138	0.404 (0.095–1.721)	0.220		
MELD score					
<22	700	Reference			
≥22	178	0.648 (0.222–1.891)	0.427		
CTP score					
A or B	561	Reference			
C	317	0.834 (0.373–1.865)	0.658		
SBP					
No	811	Reference			
Yes	67	0.929 (0.216–4.001)	0.921		
Ascites					
No	359	Reference			
Yes	519	0.920 (0.430–1.969)	0.830		
PSE					
No	694	Reference			
Yes	184	2.158 (0.979–4.759)	0.057		
Cholangitis					
No	861	Reference			
Yes	17	1.931 (0.247–15.091)	0.531		
Jaundice itching					
No	812	Reference			
Yes	66	0.447 (0.060–3.345)	0.433		
GI bleeding					
No	710	Reference			
Yes	168	0.697 (0.239–2.037)	0.510		
HCC					
No	392	Reference			
Yes	486	1.731 (0.774–3.871)	0.181		

Table 3. Continued

Variable	No. of patients	Univariate		Multivariate	
		HR (95% CI)	P-value	HR (95% CI)	P-value
TACE					
No	485	Reference			
Yes	393	1.441 (0.677–3.065)	0.343		
RFA					
No	716	Reference			
Yes	162	0.960 (0.359–2.563)	0.934		
Wound complication					
No	796	Reference			
Yes	82	2.182 (0.807–5.903)	0.124		
mTOR inhibitor use					
No	531	Reference			
Yes	347	1.339 (0.629–2.850)	0.449		
mTOR inhibitor use within 1 month					
No	817	Reference		Reference	
Yes	61	2.915 (1.069–7.943)	0.037	3.012 (1.088–9.340)	0.034

NBNC, non-HBV and non-HCV; MELD, Model for End-stage Liver Disease; CTP, Child-Turcotte-Pugh; SBP, spontaneous bacterial peritonitis; PSE, portosystemic encephalopathy; GI, gastrointestinal; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; mTOR, mammalian target of rapamycin.
[a]Eight patients had an underlying HBV and HCV coinfection.

additional IH confirmation challenging. Hence, it is possible that the number of reported IH cases in the present study might have been underestimated, potentially resulting in a lower incidence than that reported in other studies.

Previous studies have identified several risk factors associated with the occurrence of IH following LT, including acute rejection with steroid pulse therapy, low posttransplant platelet count, bilateral subcostal incision with midline extension, muscle wasting, cirrhosis related to viral infections, a BMI greater than 25 kg/m^2, severe ascites, wound infection, and potential immunosuppression [8,23,24]. Higher rates of wound healing complications and hernia recurrence following complex abdominal wall reconstruction are associated with obesity and a higher BMI [25]. Patients who are obese are widely recognized to have a higher prevalence of comorbid medical conditions, which further increase their risk during the perioperative period [26]. Surgical management becomes more complex due to obesity, as obesity significantly increases the likelihood of experiencing surgical complications such as nosocomial infections, readmissions, blood transfusions, impaired wound healing, surgical site infections, and abscess development [27].

According to one study, surgical site infection is an independent risk factor for the development of IH [10]. In the present study, wound problems were retrospectively assessed using the Clavien-Dindo classification, ranging from grades I to IV. Out of 82 patients documented with wound issues, 5 were subsequently diagnosed with IH (P = 0.173). Specifically, 2 patients had grade 2 wounds, while the remaining 3 had grade 4 wound problems, all of whom underwent hernia operations.

The use of an mTOR inhibitor combined with reduced doses of tacrolimus compared with conventional doses of tacrolimus has been shown to reduce renal impairment [28]. However, these advantages are associated with various side effects such as anemia, leukopenia, dyslipidemia, pitting edema, buccal ulcers, and IHs [29]. mTOR inhibitors are used for patients who require an anti-cancer effect or who have experienced side effects from CNI in LT. In an earlier study, patients treated with mTOR inhibitors during the initial month after LT exhibited a significantly higher IH rate compared to those treated with CNIs [20]. Conversely, another study noted that, even when mTOR inhibitors were administered within 1 month after transplantation, there was no significant difference in IH incidence as long as the dose was appropriately maintained within the range of 3 to 8 ng/mL [30]. Our findings indicate that IH was more frequently observed in patients with a high BMI or those who used mTOR inhibitors within 1 month after LT. Additionally, subgroup analysis limited to mTOR inhibitor users was performed to compare the trough level of mTOR inhibitor according to whether or not IH occurred. However, there was no significant difference (P = 0.116).

Throughout the study duration, no urgent surgeries were conducted due to strangulation. The decision to proceed with surgery at an outpatient clinic was carefully weighed, taking into account factors such as pain, progressive enlargement, abdominal discomfort, and limitations in daily activities. Thus, for this study, it was assumed that the physicians performing

the surgery deemed the cases to be of significant severity. A BMI greater than 25 kg/m² (HR, 1.210; 95% CI, 1.038–1.410; P = 0.015) and the use of mTOR inhibitors within 1 month of LT (HR, 4.106; 95% CI, 1.040–16.205; P = 0.044) were the only significant factors for IH repair operations, which is a similar result to that for IH occurrence. A subgroup analysis was conducted to specifically explore the link between mTOR inhibitor usage and the occurrence of severe IH necessitating hernia repair. Among the patients diagnosed with IH, 53.3% of non-mTOR inhibitor users (8 out of 15) required hernia repair, while 69.2% of mTOR inhibitor users (9 out of 13) underwent hernia repair, with no statistical significance observed (P = 0.390). Although the difference also did not reach statistical significance when we narrowed it down to mTOR inhibitor users within 1 month of LT (56.5% *vs.* 80.0%, P = 0.619), it is worth noting that 4 out of 5 patients (80.0%) in this group underwent hernia repair operations. In general, IH could be a minor hernia caused by local or slight loosening of a suture due to negligence in the surgical procedures. In contrast, regarding IH caused by mTOR inhibitors use, the delayed wound healing mechanism due to the mTOR inhibitors combined with the regular hernia mechanism results in the occurrence of a serious or general hernia, and this may cause deterioration after LT [13,20].

Among 28 patients who experienced IH, 2 patients experienced IH within 3 months after LT. Another subgroup analysis, limiting the IH group as IH occurring 3 months after LT to exclude immediate postoperative complications, still showed that BMI of >25 kg/m^2 (P = 0.002) and mTOR inhibitor use within 1 month from LT (P = 0.029) were significantly related with IH.

In a prior study by Montalti et al. [20] in 2012, research findings were presented based on a MELD score of 22. Similarly, in our study, we employed 22 as the cutoff value for the MELD score. We further conducted analyses using MELD score cutoff values of 30 (HR, 0.352; 95% CI, 0.047–2.622; P = 0.308) and 35 (HR, 0.663; 95% CI, 0.088–4.986; P = 0.689), but no statistical significance was observed. Thus, it appears that the MELD score is not significantly associated with the occurrence of IH.

The occurrence of IH may be influenced by the surgeon's focus and attention. However, a comparative analysis was conducted between cases where the skin incision started during regular hours (08:00–18:00) and later, showing no statistically significant difference (P = 0.465).

This study had several limitations, most of which were due to the retrospective design of the study. All data were from a single institution; therefore, the results cannot be generalized. Smoking may be an important risk factor for IH occurrence, but due to the insufficient data on smoking, we could not analyze the association. Precise preoperative nutrition evaluation was also difficult in the current study. BMI, one of the variables that can indirectly determine nutrition, is included in our study variables. However, since patients with cirrhosis and ascites were included, bias is bound to exist. As for albumin, most liver transplant patients have hypoalbuminemia, so it can be said that overall nutrition is poor. Further research with a detailed preoperative evaluation is necessary. During the study period at our institution, IHs were repaired utilizing various techniques, including primary fascial closure and mesh reinforcement with an open technique. Six cases involved primary fascial closure, while eleven cases utilized mesh reinforcement in the IH surgery. Laparoscopic herniorrhaphy was not performed in any of the cases. Importantly, there were no instances of recurrence after the surgeries were performed. Based on experiences from multiple institutions and specifically, in the context of hernia repair after LT, further studies are necessary to discover the best strategy for hernia repair.

In conclusion, IHs following LT were found to be more prevalent among obese patients and frequently resulted in surgical intervention, especially when mTOR inhibitors were used within the first month after LT. Therefore, heightened vigilance concerning IH is essential, particularly in obese patients and when contemplating early mTOR inhibitor use after LT.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1 can be found via https://doi.org/10.4174/astr.2024.106.2.115.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contribution

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Investigation: All authors
Writing – Original draft: JYK, SKH
Writing – Review & Editing: All authors

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