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The impact of late liver allograft dysfunction on physical activity of liver transplant recipients

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Abstract

Liver transplantation restores patients' physical and social life, and its quality.

The prevalence of low physical activity in liver recipients is unknown as well as the impact of late liver allograft dysfunction on it. Liver transplantation enhances patient's return to the usual physical and social activity and improves the quality of life. However, the prevalence of low physical activity among liver recipients and the impact of the late allograft dysfunction on it, which is a risk factor for obesity and cardiovascular diseases, require studying.

***The aim** of the study was to identify whether the late liver allograft dysfunction influences the physical activity of recipients.*

***Material and methods.** The study included 87 liver recipients. We measured anthropometric parameters, physical performance (SPPB, LFI, 6-min walk test), mean step count per day.*

Late liver allograft dysfunction was determined if elevated transaminases and/or cholestatic enzymes or hepatic failure have been diagnosed later *than 3 months posttransplant. Activity trackers were provided to assess physical activity.*

Results. *Median age was 54 years [45;61], 33% were men. The median follow-up period was 36 months [16;64]. The median of the average steps count was 5.9 [4.1;8.7] thousand per day. 60.5% of recipients were sedentary and low active, 24.4% were somewhat active, 15.1% were active. In cases of liver allograft dysfunction, the mean step count was significantly lower than in patients with normal liver function: 4.1 thousand [2.6;5.3] versus 6.8 thousand [4.2;9.4], p=0.003, despite no differences in the physical activity test results.*

Conclusion*. In case of a late liver allograft dysfunction, the physical activity can decrease; 60.5% of liver recipients, in the absence of pathological restriction of movement, have a sedentary and low active lifestyle. Activity trackers may allow identifying patients who need additional check-up or physical training.*

Keywords: activity tracker, wearable device, liver transplantation, obesity, sedentary lifestyle, liver recipient, long term transplant follow-up

Conflict of interests Authors declare no conflict of interest

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BMI, body mass index

LAD, late allograft dysfunction

LT, liver transplantation

NAFLD, non-alcoholic fatty liver disease
ULN, upper limit of normal

Introduction

Thanks to advances in surgery, anesthesiology and improvements in immunosuppressive and maintenance therapy, the survival rate of transplant patients has significantly improved in recent decades, both in the early and long-term postoperative periods. According to the American and European Transplant Registry, a 1-year survival rate of liver recipients is 85-90%, and a 20-year survival rate is 40-60%.

End-stage liver disease causes huge economic losses due to the disability of this cohort of patients, because most of them are of working age. Liver transplantation (LT) allows the patient both to avoid a fatal outcome, and also to return to the usual physical and social activity, ensures a high quality of life in the long-term postoperative period.

Late graft dysfunction is often asymptomatic and is manifested by abnormalities in laboratory parameters. In most cases, clinical signs are added later, when the pathological process leads to severe fibrosis and a decrease in the protein-synthetic function of the graft. Severe and progressive dysfunction of the graft leads to its loss, which is the need for retransplantation.

Obesity, diabetes mellitus, hyperlipidemia, and decreased physical activity are all risk factors for non-alcoholic fatty liver disease (NAFLD) of the graft, metabolic syndrome, and cardiovascular disease. Steatohepatitis, which develops secondary to NAFLD, increases the risk of cardiovascular diseases, and can also lead to graft fibrosis, and even to its loss in a long course.

Unfit lifestyle choices and high-calorie diets play a significant role in the development of these conditions. Activity trackers, not being a medical device, help patients to keep track of the number of steps taken, hours of sleep and rest, that is, follow recommendations for the time of active movement. The software allows you to configure the tracker according to individual needs and characteristics of the patient's condition. Notifications on it display help to take into account the content of food consumed and contribute to better control of calories, the number of steps taken, the time of physical activity and rest, which is important for the prevention of obesity.

It is known that drug compliance can affect the treatment efficacy. The use of trackers can increase patients' adherence not only to their lifestyle, but also to their medication regimen. So, the study of more than 600,000 patients taking medications for dyslipidemia, diabetes, and hypertension, demonstrated that patients who wore an activity tracker and kept records of weight and diet were less likely to miss dosing of their prescribed medications than those who did not.

Studying the physical performance of recipients, the impact of late dysfunction on the level of physical activity, as well as checking the level of liver recipients' adherence to drug and non-drug recommendations can allow individualizing the recipient management in order to improve the long-term results of LT.

The aim of the study was to identify the effect of late graft dysfunction on physical activity.

Material and methods

The study included 87 liver recipients followed-up at Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy.

Late allograft dysfunction (LAD) was defined as a disrupted function of the transplanted liver, manifested by cytolysis, cholestasis, or hepatic-cell insufficiency syndrome, or life-threatening complications (ascites, hepatic encephalopathy, esophageal and/or gastric varices with a risk of bleeding) that occurred after normalization of liver function in the post-transplant period. The following abnormalities in laboratory parameters were chosen as the thresholds: the blood total bilirubin of over 2 upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase levels of over 1.5 ULN, gamma-glutamyltransferase, and alkaline phosphatase of over 1.5 ULN, international normalized ratio of over 1.6. In accordance with these criteria, the recipients were divided into 2 groups with respect to the LAD presence (21 patients with LAD and 66 with a normal function).

The inclusion criteria were: age over 18 years, LT, post-transplant period of more than 1.5 months. The exclusion criteria were: the refusal to participate in the study or wear a bracelet, a serious clinical condition requiring hospitalization and intensive care. The study protocol and the informed consent form were approved at the meeting of the Local Ethics Committee. After signing the informed consent, patients underwent the measurements of anthropometric parameters and physical performance tests, which included: the 6-minute walk test, Short Physical Performance Battery (SPPB) test (used to assess the asthenia severity, includes three tests: the total balance assessment, gait speed test for a distance of 4 meters and a 5-time repeated standing up from a chair without using the arms), the handgrip strength measure by using a hand dynamometer. Based on the obtained data, the Liver Frailty Index (LFI) was calculated. Liver elastometry was also performed using a FibroScan 502 device (Echosens, France). Then the patients were given a physical activity bracelet-tracker (hereinafter referred to as the tracker): OneTrak c320 Pulse (manufactured by Sportidea LLC, Russia). Measurements of the number of steps and sleep duration were automatically transmitted from the tracker to the smartphone app, then to the server, from where they were sent to the database. Measurements were performed for 6 weeks.

The following classification was used to assess the level of physical activity that was defined as sedentary lifestyle in less than 5000 steps per day, as low activity in 5000-7499 steps per day, as medium activity in 7500-9999 steps per day, as active lifestyle in 10,000-12,500 steps per day, high activity in more than 12,500 steps per day.

Patients' compliance in wearing the bracelet was evaluated as the ratio of the number of days when the number of steps transmitted to the server was greater than 0 to the total number of days of wearing the tracker. This parameter was chosen because it was important for the patient both to have a bracelet on his/her arm, but also to be aware of the number of steps taken, the number of steps to reach the goal. Coming the data to the server meant that the patient did wear the bracelet, and also paid attention to the data received during the day by opening the app.

Liver biopsy was performed on indications in case of graft dysfunction, once during the study period. Histological activity was evaluated on the Knodell scale, the fibrosis stage was assessed by METAVIR score, steatosis was evaluated using the NAS score. The cases of the revealed rejection and autoimmune hepatitis de novo were grouped into one category "immune disorders" due to a difficult differential diagnosis of the morphological pattern and similar treatment approaches.

Statistical processing

The study material was subjected to statistical processing with using nonparametric analysis methods. Statistical analysis was performed using the Statistica 8.0 (Statsoft) and Jamovi (The Jamovi Project (2020)) software package. Quantitative variables were assessed for normal distribution using the Shapiro–Wilk, Kolmogorov–Smirnov tests, skewness and kurtosis. Sets of quantitative variables, which distribution differed from the normal one, were described using the values of the median (Me) and the lower and upper quartiles [25%;75%] and the interquartile range (min-max). Nominal data were described as absolute values and percentages. Differences in the parameters were considered statistically significant at $p<0.05$. The Mann-Whitney U-test was used to compare independent variable sets in cases where there were no signs of a normal data distribution. In order to assess the level of difference significance when comparing frequencies, Pearson's $\chi2$ test and Fisher's exact test were used for four-field tables.

Results

At the start of the study, the median follow-up period after LT was 3 years [1.3;5.3] (0.1–13.5). During the study period, all 87 patients were followed-up on an outpatient basis and were in a satisfactory condition that did not require an inpatient examination and treatment. The characteristics of donors and recipients are presented in Table 1.

Table 1. Characteristics of patients included in the study

Parameters	LAD	Normal Function	All patients	p
Number of patients	21	66	87	
Patient age, years	51 [46;61] (29-70)	55 [45;61] (25-71)	55 [45;61] (25–71)	0.7
Males	8 (38%)	25 (38%)	33 (38%)	1
MELD (Model for End-stage Liver Disease)	19 [17;21] (7-41)	17 [14;20] (7-41)	18 [15;20] (7–41)	0.09
Indications for LT				0.9
Liver cirrhosis of viral etiology	5 (24%)	24 (36%)	29 (33%)	
Liver cirrhosis resulted from autoimmune and cholestatic diseases	7 (33%)	21 (32%)	28 (32%)	
Hepatocellular carcinoma	3 (14%)	8 (12%)	11 (13%)	
Liver cirrhosis of unknown etiology	1 (5%)	2 (3%)	11 (13%)	

Liver cirrhosis of alcoholic etiology	3 (14%)	5 (8%)	8 (9%)	
Other	2 (10%)	6 (9%)		
Donor type				
Donor with brain death	21 (100%)	63 (96%)	84 (96.5%)	0.3
Living related donor			3 (3.5%)	
Immunosuppressive therapy				1
Tacrolimus + steroids ± mycophenolates	9 (43%)	28 (42%)	37 (43%)	
Tacrolimus + everolimus	4 (19%)	10 (16%)	14 (16%)	
Tacrolimus	8 (38%)	28 (42%)	36 (41%)	
Elastometry				
Liver elasticity, kPa	**7.5 [6.1;8.8] (4.0-15.8)**	**6.3 [5.7;7.0] (3.2-22)**	**6.4 [5.7;7.3] (3.2–22)**	**0.02**
Fibrosis stages				0.3
F0-F1	7 (39%)	47 (78%)	55 (63%)	
F2	6 (33%)	8 (14%)	15 (17%)	
F3-F4	4 (22%)	3 (5%)	6 (7%)	
No valid measurements obtained	1 (6%)	2 (3%)	11 (13%)	

LAD was observed in 21 patients (24%) at the time of the study. The LAD etiology was as follows: biliary in 5 patients, unknown in 6 patients, viral in 4 patients, immune (autoimmune hepatitis and rejection) in 6 patients. The LAD was manifested in laboratory abnormalities, their limits are given the section "Material and methods". There were no clinical manifestations of severe hepatic-cellular failure and portal hypertension.

The groups of patients with LAD and with normal graft function did not differ in age, gender, severity of the condition and body mass index (BMI) at the time of surgery, in donor type, and immunosuppressive therapy regimens. When analyzing the elastometry data, statistically significant differences were found between the data in the groups of patients with LAD (median 7.5 kPa, which corresponds to

F2 fibrosis stage) and of those with satisfactory function (6.3 kPa, which corresponds to F1) (see Table 1).

Most patients showed minimal or no fibrosis, both according to elastometry and graft biopsy (Table 2). Given a small number of steatosis cases (5 of 24) as detected by histological examination of the liver graft, it was not possible to identify any patterns in the physical activity differences between the patients with the non-alcoholic fatty liver disease of transplanted liver and without it.

Table 2. Results of morphological examination of liver graft biopsies

Parameters	LAD	Normal function	All biopsies	p
Number of biopsies, proportion of all patients, %	9 (33%)	15 (23%)	24 (28%)	0.09
Histology conclusion				0.2
Normal histology	2	6	8 (33%)	
Immune disorders	4	2	6 (25%)	
Hepatitis of unknown etiology	2	5	7 (29%)	
Other	1	2	3 (13%)	
Steatosis	2	3	5 (21%)	
Fibrosis assessment by METAVIR score, stage				0.2
0	1	4	5 (21%)	
F1	1	6	7 (29%)	
F2	6	5	11 (46%)	
F3	1	0	1 (4%)	
F4	0	0	0	

Anthropometry and physical performance

According to the results of anthropometry measurements in dynamics, there was a statistically significant increase in BMI in the postoperative period (the median increased by 2 kg/m^2), p=0.008. When divided into groups, a statistically significant increase in BMI was found in recipients with LAD: by 5 kg/m^2 (p=0.002), and by 2 kg/m^2 in recipients with satisfactory function (p<0.0010). There were no statistically significant differences in BMI between the groups of patients with and without dysfunction: both before surgery and at the time of the study, the BMI was 26 and 28 kg/m^2, respectively. However, there was a tendency for BMI differences between these groups to appear (p=0.055) in the postoperative period. Keeping low activity could lead to an increase in BMI in patients with LAD and the appearance of statistically significant differences between these groups (Table 3).

Table 3. Results of the tests performed

Parameters	LAD	Normal function	All	p
Physical performance tests				
Short physical performance battery test (SPPB) scored				
10–12 points	19 (91%)	63 (95%)	82 (94%)	0.5
9 points	1 (5%)	1 (2%)	2 (2%)	
5–6 points	1 (5%)	2 (3%)	3 (3%)	
6 minute walk test				0.2
More than 350 m	19 (91%)	64 (97%)	83 (95%)	
Less than 350 m	2 (9%)	2 (3%)	4 (5%)	
Liver Frailty Index	3.6 [3.2;4.0] (1.8–5.2)	3.5 [3.0;3.9] (2.1–4.3)	3.5 [3.1;3.9] (1.8–5.2)	0.5
Robust	5 (24%)	20 (30%)	25 (29%)	0.2
Pre-frail	15 (71%)	46 (70%)	61 (70%)	
Frail	1 (5%)	0	1 (1%)	
Anthropometry				
BMI at the time of LT, kg/m^2	23 [21;30] (16–37)	24 [21;26] (17–37)	24 [21;27] (16–37)	0.8
BMI at the time of the study, kg/m^2	28 [25;29] (20–42)	26 [22;29] (19–40)	26 [23;29] (19–42)	0.055
Physical activity				
Daily physical activity, thousand steps per day	**4.1 [2.6;5.3] (1.1–9.8)**	**6.8 [4.2;9.4] (1.4–17.1)**	**5.9 [4.1;8.7] (1.0–17.1)**	**0.003**
Compliance				
More than half of the data missed	2 (10%)	6 (9%)	8 (9%)	0.9
Sleep duration				
Sleep hours per 24-hour day	5.8 [5.4;7.1] (3.7–11)	6.3 [5.5;7.5] (2.3–11.2)	6.1 [5.4;7.6] (2.3–11.2)	0.4

According to the results of SPPB, LFI, and the 6-minute walk test assessments, it was found that most patients were in a satisfactory physical condition, only 1 patient showed a decrease in the results of all tests below the normal limit. In addition, this patient suffered from coxarthrosis and gonarthrosis. Other 3 patients showed decreased number of points in the tests scorring for SPPB and 6-minute walk test, but when calculating the LFI, they were referred to as “pre-frail” patients (see table. 3). One of those patients suffered from neuropathy of femoral and tibial nerve, and 2 patients older than 70 years had ischemic heart disease and chronic obstructive pulmonary disease.

The parameters of physical performance of patients with LAD and patients with a satisfactory function did not differ (see Table 3).

Physical activity

The median number of steps was 5.9 thousand [4.1;8.7] (1.0–17.1) per day. 60.5% of liver recipients had very low and low physical activity (Fig. 1).

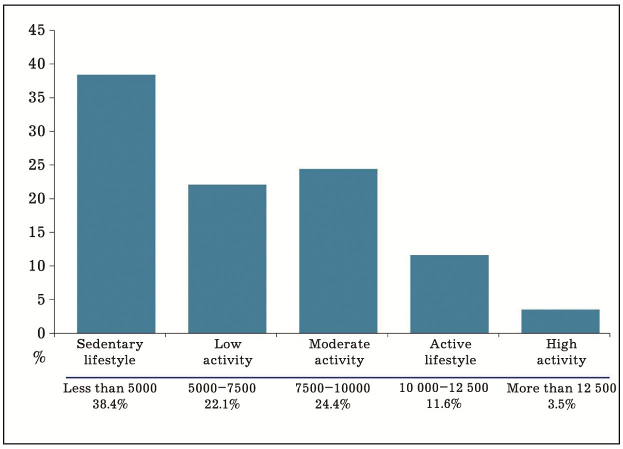

Fig. 1. Distribution of liver recipients by the daily activity level

The patients who demonstrated a limited physical performance according to the 6-minute walk test had an expected statistically significantly lower number of steps than the patients with a satisfactory test result: 2.0 thousand steps [1.3;2.8] (1.1–3.4) versus 6.2 thousand steps [4.3;8.8] (1.5–17.1), respectively, p=0.003

When comparing the groups of patients allocated according to the number of steps (less than 7,500, 7,500-10,000, and more than 10,000), after exclusion of patients who fulfilled the 6-minute walk test unsatisfactorily, no statistically significant differences between the groups were seen in test results, physical performance, and BMI, age, peculiarities of surgery or immunosuppressive therapy (the hospital length of stay, MELD, taking prednisolone, the period after surgery).

At the time of the study, the mean number of steps in LAD recipients was significantly lower than in patients with normal function (Table 3, Fig. 2).

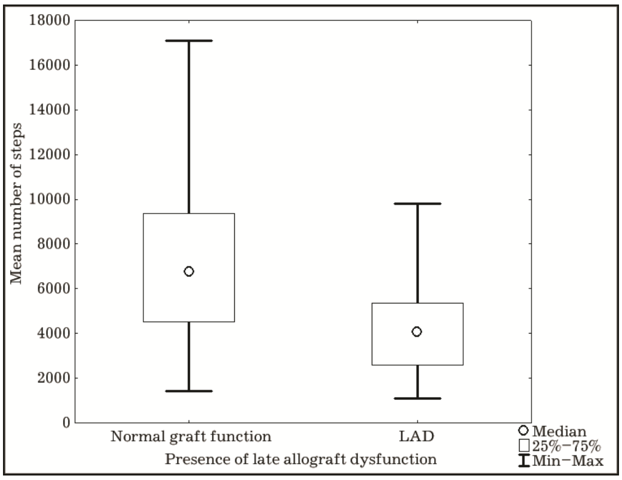

Fig. 2. Differences in the mean number of steps per day in patients with a normal graft function and those with a late allograft dysfunction

Compliance

Only 9% of patients had more than half of the missed days of wearing the bracelet-tracker or transmitting the data recorded from the tracker. There was no relationship found between the proportion of missed days and BMI, body composition, or complications. It was not possible to identify the impact of missed days of wearing the tracker on the rejection rate.

Sleep duration

Only a quarter of patients slept about 8 hours daily (from 7 to 9). Most patients had less than 8 hours of sleep per 24-hour day (Fig. 3) Sleep duration of less than 6 hours per 24-hour day did not affect BMI, body composition, number of steps per day, and results of physical performance tests. There were no statistically significant differences in sleep duration between the patients with and without LAD.

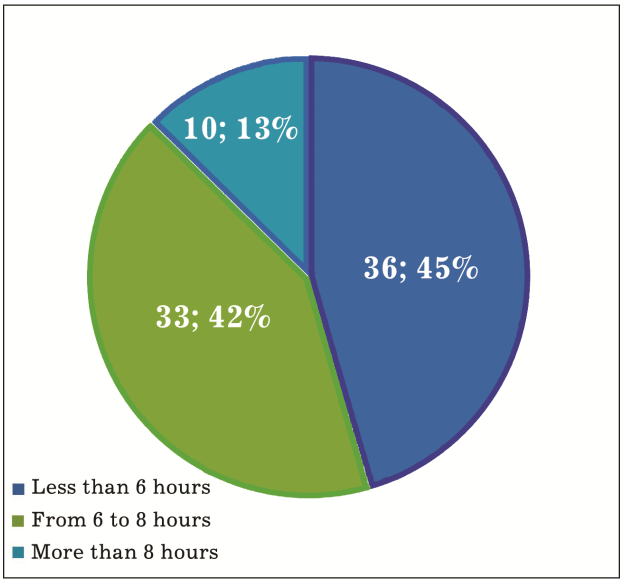

Fig. 3. Distribution of mean sleep duration among liver transplant recipients

Discussion

Physical activity and performance can be reduced in transplant recipients and candidates for many reasons. Patients on the waiting list often have severe weakness, rapid fatigue, ascites and edema, anemia, sarcopenia, and malabsorption of nutrients. While liver failure is controlled in normal graft function within the first few days, the physical activity and performance are not always quickly and completely restored. For a one-time assessment of physical characteristics, objective methods (measurement of muscle strength, energy consumption in metabolic equivalents, peak oxygen consumption) and subjective ones (questionnaires) are used. However, according to literature reports, there are currently no results of studying the daily activity of liver recipients.

We found that most patients walked less than 10,000 steps a day. More than half (60.5%) of patients led a sedentary lifestyle. Only 4 patients had low scores on physical performance tests (less than 350 meters in the 6-minute walk test), which was due to neurological, cardiovascular or orthopedic diseases, and therefore they were excluded from the analysis of differences in the number of steps between groups of recipients stratified by the LAD presence. In the remaining patients, physical abilities were not limited by any diseases.

Comparison of baseline characteristics (peculiarities of surgery and of the postoperative course) of patients stratified by the number of steps (less than 7500, 7500-10,000, and more than 10,000), revealed no statistically significant differences. That was, the recipients who moved a lot and a little did not differ in the severity of their condition, the severity of the early postoperative course, and the immunosuppression regime. There were no differences between those groups in the results of the physical performance tests and the Liver Frailty Index either. Thus, less active patients had no physiological reasons for hypodynamia and could have increased their activity had they wished.

Low physical activity is known to be a poor prognostic sign both before and after liver transplantation. It is associated with obesity, depression, and a decreased quality of life in solid organ recipients. In addition, physical inactivity is a known risk factor for NAFLD and cardiovascular disease. Consequently, more than half of liver recipients are at risk of developing various complications due to a low-activity lifestyle.

The study revealed a decrease in physical activity in patients with liver LAD compared to those who had no dysfunction. These differences were found in the group of recipients where LAD was observed exactly at the time of the study. It is worth noting that there was no severe functional impairment that included the development of ascites, edema, or encephalopathy in the recipients with LAD during the study period. Also, the groups of patients with and without LAD did not differ from each other in the results of the physical performance test and in body composition.

The most likely cause of a reduced physical activity in LAD is assumed to be weakness and fatigue, usually associated with liver diseases. Considering that patients who have experienced complications of liver cirrhosis and transplantation may underestimate these symptoms, the step counting is used as an objective method, and this can help to timely detect physical inactivity in the development of LAD.

Sedentary lifestyle increases the risk of NAFLD. In our study, of 24 who underwent a biopsy only 5 recipients showed steatosis of the transplanted liver without signs of steatohepatitis. In order to study the effect of physical inactivity on the risk of developing graft NAFLD, it is necessary to conduct a long-term prospective study with repeated morphological verification.

When analyzing the sleep duration, no relationship to obesity was found. However, this does not exclude the relationship between insomnia and metabolic problems. Perhaps a more accurate assessment of the sleep effect on health requires more sophisticated equipment than wearable devices of the current technical level.

Almost all patients followed the recommendations for wearing the tracker and syncing with the app. We could not identify a trend towards a lower incidence of rejection in patients who were fully compliant in wearing the tracker due to the relatively small number of cases and a limited time period for data collection, on the one hand, and due to the non-mandatory participation of patients in the study, on the other hand. A significant number of patients refused the proposed experiment, which in itself may be a sign of reduced adherence to the recommendations of the transplant center doctor.

Activity trackers can be considered as an additional objective tool to assess the condition of recipients. When recording a decreased physical activity, the patient may be assigned an unscheduled examination to exclude complications from both the graft and other organs and systems.

Both in the absence of a late graft dysfunction and when it is revealed, the objective data obtained using the tracker will be the basis for recommendations to correction physical activity and include the patient in physical rehabilitation programs. To confirm the diagnostic value of monitoring the physical activity, further investigations are required, preferably in the format of a multicenter study.

Thus, the implementation of remote monitoring systems in clinical practice will make it possible to reasonably include liver transplanted recipients in physical rehabilitation programs and motivate them to maintain physical activity in the long term.

Conclusions

1. With the development of late liver graft dysfunction, a decreased physical activity of liver transplant recipients by 2.7 thousand steps per day was revealed compared to recipients with graft satisfactory function.

2. Despite the absence of pathological movement restriction, 60.5% of liver recipients lead a sedentary lifestyle and are at risk of complications and reduced quality of life.

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