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# CORONARY ARTERY CALCIFICATION IN LIVER TRANSPLANT RECIPIENTS

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**Objective**: To study the dynamics of changes in the calcium index (CI) as a cardiovascular risk factor in patients with terminal liver diseases.
**Methods**: A prospective, single-center cohort study included 250 patients who needed liver transplantation. The duration of the follow-up period was 5.4±3.29 years from the moment of their inclusion on the waiting list. In addition to the assessment of prevalence and dynamics of traditional cardiovascular risk factors, indicators of the CI were determined by the method of multispiral computed tomography at the time of patients' inclusion in the study and after 5 years of dynamic follow-up.
**Results**: The CI in patients with terminal liver diseases requiring transplantation was found to exceed the limits of the recommended norm determined by the 75$^{th}$ percentile in 152 (56.3%) subjects at the stage of their inclusion on the waiting list. Comparison of coronary calcification after 5 years of dynamic observation in liver transplant recipients revealed higher values of the CI compared with those in patients with terminal liver diseases who did not receive a donor organ (CI, AJ-130 – 223 (38; 597) and 141 (4; 176) units respectively, p<0.05; CI, Volume-130 – 314 (73; 748) and 203 (8; 284) mm$^2$ respectively, p<0.01) as well as in patients with metabolic syndrome (CI, AJ-130 – 186 (78; 463) and 74 (21; 192) units respectively, p<0.01; CI, Volume-130 – 278 (74; 623) and 124 (74 ; 273) mm$^2$ respectively, p<0.01) and/or coronary artery disease (CI, AJ-130 – 274 (102; 683) and 109 (34; 246) units respectively, p<0.01; CI, Volume-130 – 382 (98; 834) and 382 (98; 834) mm$^2$ respectively, p<0.01) in the general population.
**Conclusions**: The results of the study indicate that in the long-term postoperative period, liver transplant recipients receiving immunosuppressive therapy, despite a radical solution to the problem of liver failure, developed coronary artery disease during five years of dynamic follow-up. In the study cohort, in the post-transplant period, there was an increase in the calcium index in comparison with the indicators obtained when patients were included in the waiting list, as well as in comparison with the value of the calcium index of patients with metabolic syndrome and coronary artery disease from the general population.
**Keywords**: *Chronic liver diseases, terminal liver diseases, orthotopic liver transplantation, coronary atherosclerosis risk factors, coronary artery calcification, calcium index.*

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## КАЛЬЦИНОЗ КОРОНАРНЫХ АРТЕРИЙ У РЕЦИПИЕНТОВ ТРАНСПЛАНТАТА ПЕЧЕНИ

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**Цель**: изучить динамику изменения кальциевого индекса (КИ) как фактора сердечно-сосудистого риска у пациентов с хроническими терминальными заболеваниями печени, нуждающихся в трансплантации.
**Материал и методы**: проведено проспективное одноцентровое когортное исследование, в которое было включено 250 пациентов, нуждающихся в трансплантации печени. Продолжительность периода наблюдения составила 5,4±3,29 года с момента их включения в лист ожидания. Помимо оценки распространённости и динамики традиционных сердечно-сосудистых факторов риска, методом мультиспиральной компьютерной томографии определяли показатели КИ при включении пациентов в исследование и через 5 лет динамического наблюдения.
**Результаты**: установлено, что у 152 (56,3%) обследуемых пациентов с хроническими терминальными заболеваниями печени на этапе их включения в лист ожидания КИ превышал пределы рекомендуемой возрастной нормы, определённой 75-м процентилем. При сравнении коронарной кальцификации через 5 лет динамического наблюдения у реципиентов трансплантата печени выявлены более высокие значения КИ по сравнению с таковыми у больных хроническими терминальными заболеваниями печени, не получивших донорский орган (КИ, AJ-130 – 223 (38; 597) и 141 (4; 176) ЕД соответственно, p<0,05; КИ, Volume-130 – 314 (73; 748) и 203 (8; 284) мм$^2$ соответственно, p<0,01), а также с пациентами с метаболическим синдромом (КИ, AJ-130 – 186 (78; 463) и 74 (21; 192) ЕД соответственно, p<0,01; КИ, Volume-130 – 278 (74; 623) и 124 (74; 273) мм$^2$ соответственно, p<0,01) и/или ишемической болезнью сердца (КИ, AJ-130 – 274 (102; 683) и 109 (34; 246) ЕД соответственно, p<0,01; КИ, Volume-130 – 382 (98; 834) и 382 (98; 834) мм$^2$ соответственно, p<0,01) из общей популяции.
**Заключение**: полученные результаты свидетельствуют о том, что в отдалённом послеоперационном периоде у реципиентов трансплантата печени, принимавших иммуносупрессивную терапию, несмотря на радикальное решение проблемы печёночной недостаточности, в течение пяти лет динамического наблюдения развивалась ишемическая болезнь сердца. В исследуемой когорте в посттрансплантационном периоде происходило увеличение кальциевого индекса по сравнению с показателями, полученными при включении пациентов в лист ожидания, а также в сравнении с величиной кальциевого индекса пациентов с метаболическим синдромом и ишемической болезнью сердца из общей популяции.
**Ключевые слова**: *хронические терминальные заболевания печени, ортотопическая трансплантация печени, факторы риска коронарного атеросклероза, кальцификация коронарных артерий, кальциевый индекс.*

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## Introduction

According to the definition of the World Health Organization atherosclerosis is a change in the artery inner lining manifested by focal lipid deposits, complex combinations of carbohydrates, blood elements and their circulating substances as well as by the formation of connective tissue with inclusions of calcium deposits. Atherocalcinosis is one of the pathologic manifestations in the vascular wall of patients with atherosclerosis. It has been proved that calcium deposits in the atherosclerotic plaque are formed in the very early stages of its development, i.e. similar changes in the vascular wall in atherosclerosis are observed at the stage of lipid «spots» and «streaks» [1]. In the process of the pathological development of atherosclerotic plaque the proportion of calcium compounds in its composition increases [2, 3].

It should be noted that for a long time the soft tissue component of the atherosclerotic plaque was considered as potentially dangerous, but in recent studies there has been a clear reassessment of the significance of the atherosclerotic substrates calcified component [4-6]. Data on the strength and resistance of calcified atherosclerotic plaques to ruptures are highly contradictory. At the same time, the existing methods of radiological diagnosis without clinical data and total cardiovascular risk evaluation do not allow specialists to assess completely the prognostic significance of the structure, density and nature of calcium distribution within the plaque [7].

The basis of the modern approach to cardiovascular risk assessment from the point of view of coronary calcium quantitative assessment was developed by A. Agatson in 1990, when he proposed a system for determining the degree of calcification and a scale, which was later named after him. Currently, in addition to risk assessment based on of the calcification degree, the quantitative evaluation of the coronary artery calcium index (CI) is also applied. Patients with CI values of coronary arteries in absolute units above the 75th percentile, corresponding to their age and sex, are believed to be at a high risk of fatal coronary events [8].

Terminal liver diseases (TLD) remain one of the most important problems of modern gastroenterology. This is primarily due to their high prevalence, increased proportion among gastroenterological patients, long recurrent course, serious complications, including damage to the cardiovascular system, insufficient effectiveness of therapeutic treatment resulting in high mortality rates, persistent impaired working capacity and disability of young patients [9].

In a retrospective cohort study of 420 patients with non-alcoholic fatty liver disease followed up for 7.6 years, mortality rate from any causes (however, mostly cardiovascular diseases and cancer) in patients with non-alcoholic steatohepatitis or cirrhosis was higher than in the general population. The relationship of liver dysfunction and cardiovascular system was proved by the fact that in 100% of patients with liver cirrhosis left ventricular diastolic relaxation disturbances and increased levels of NT-proBNP were detected [10].

Currently, it has been established that the mechanisms of damage to the cardiovascular system in TLD are not limited to neuroreflex and non-electrolyte disorders, but have a systemic dismetabolic character. The circulatory system is affected by three main groups of factors: etiological (viral infection, alcohol intoxication), protein metabolism changes and hemodynamic disturbances. Disturbances of central hemodynamics in patients with TLD occur most frequently according to the hyperkinetic type, which contributes to the progression of portal hypertension and subsequent heart failure development [11]. At the same time the pathogenic mechanisms leading to such problems in TLD patients remain unknown, the incidence and nature of hemodynamic disturbances depending on the stage of chronic liver disease are still elusive.

The severity of painful cardiac syndrome, rhythm disturbances and decompensation of cardiac insufficiency in patients with terminal liver diseases are associated with the progression of anemia, increase in hepatocellular insufficiency, cytolytic and cholestatic syndromes [12, 13]. At the same time, the issues of early diagnosis of cardiovascular atherosclerotic lesions in this category of patients, necessary for the selection of effective therapy, remain unresolved. There is an urgent need to find and implement in healthcare practice new non-invasive, effective methods of examining comorbid patients with hepatobiliary and cardiovascular system pathology [14, 15].

Calcium compounds due to their high roentgenologic contrast are the most accessible diagnostic markers of atherosclerosis allowing the doctors not only to determine the presence of the athero-

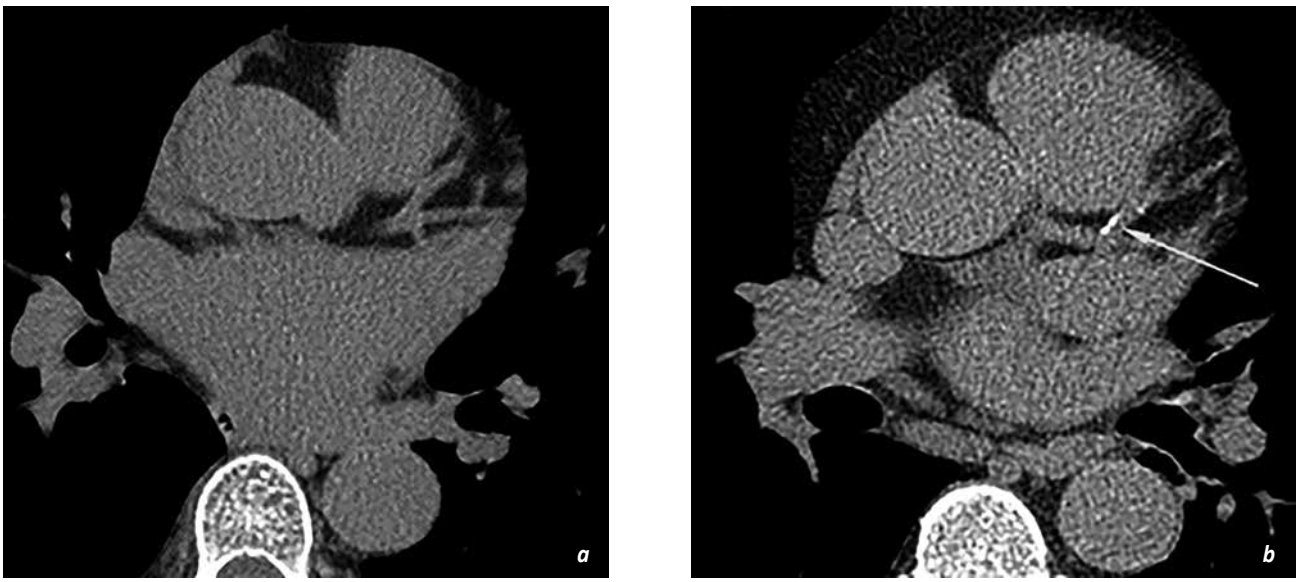


***Fig. 1*** *Absence of calcification of the coronary arteries in liver transplant recipients in the preoperative period (a) and deposits of calcium in the projection of left anterior descending artery (b) in the long-term postoperative period*

sclerotic substrate, but also to evaluate the dynamics of the atherosclerotic process development during prospective follow-up of patients with terminal liver diseases (Fig. 1).

The aim of the study is to determine the dynamics of changes in the calcium index as a cardiovascular risk factor in patients with terminal liver diseases who need transplantation.

## Methods

A single-center prospective cohort epidemiological follow-up analytical study including the evaluation of the coronary calcification dynamics in patients with c terminal liver diseases was conducted. In accordance with the design of the study a cohort of patients (n=150) from liver transplant recipients was formed. The opportunity to participate in the study was provided to patients with terminal liver diseases who signed an informed consent in case of positive decision of their inclusion on the waiting list if they met the inclusion criteria, developed on the basis of the aim and objectives of the study. A control group was formed from TLD patients on the waiting list who did not receive a liver transplant during the follow-up period (n=100).

The calculation of the sample size for the study was based on the assumption that orthotopical liver transplantation (OLT) followed by immunosuppressive therapy can increase the number of patients with a high risk of coronary artery disease (CAD) development. It was recognized, that a clinically significant effect was the increase in this number by 10%. To determine the number of patients to be included in the study, the Epi In-foTM program was used (official website http://www.cdc.gov/epiinfo/).

The examination of patients, including their questioning, clarification of anamnestic data, clinical, laboratory and instrumental assessment was carried out (visit 1: day 0±7 days) at the time of their placement on the waiting list and in the long-term postoperative period 5 years (visit 2: 5 years±30 days) after the orthotopic liver transplantation.

During the prospective follow-up of the patients included in the study and those on the waiting list, liver transplantation was performed in 150 patients over the period of 5.4±3.29 years. Among the recipients there were 72 males and 78 females, whose average age was 41.8±7.29 (28-56) years, the average score according to the MELD scale was 18.9±3.18 (6-35). 100 of patients with chronic liver disease did not receive a liver transplant during the follow-up period. There were 54 males and 46 females on the waiting list with the average age of 41.5±4.26 years, the average score according to the MELD scale was 17.2±5.17 (4-36). The mortality rate among them was 18.0% and the average MELD score was 26.4±3.72 (16-36). The causes of non-cardiac death included liver failure (n=11), hepatorenal syndrome (n=5) and bleeding from esophageal/gastric varicose veins (n=2).

The list and incidence of the underlying diseases resulting in the development of liver insufficiency and the inclusion on the waiting list presented in Table 1.

The terms of liver transplantation to the recipients from the waiting list were determined based on the degree of liver failure, group AB0 and Rh-compatibility, combined HLA-compatibility, crossmatch, the presence of preformed cytotoxic antibodies and the dynamics of presensibilization, the presence of viral hepatitis, constitutional characteristics of the recipient, state of the donor organ depending on the urgency of transplantation.

Immunosuppressive therapy to the recipients of liver transplants in the study group was carried out according to protocol, the purpose of which implied the use of tacrolimus as the basic drug. 12 hours after the operation tacrolimus in the dose of 0.05-0.1 mg/kg/day was administered orally (n=22) or as intravenous 24-hour infusion (n=128).

During the 1$^{st}$ month after OLT, the oral dose of tacrolimus was 0.2-0.3 mg/kg/day with maintaining its concentration in the range of 10-15 ng/ml, from the 2$^{nd}$ month – 0.1-0.2 mg/kg/day with maintaining a concentration of 5-10 ng/ml. In the presence of renal failure in the early postoperative period (n=98), immunosuppressive therapy with tacrolimus was performed in the dose providing the minimum acceptable concentration of the drug. The first administration of daclizumab was carried out intravenously prior to the wound suturing or in the ward of the intensive care unit in the dose of 1 mg/kg, repeated administration – on the 7$^{th}$ day after the operation.

The scheme of glucocorticoids administration according to protocol is presented in Table 2.

Glucocorticoids were canceled after intravenous administration of the first dose (500-1000 mg) in liver transplant recipients infected with hepatitis B or C viruses (n=36).

Mycophenolate mophetil (1000 mg/day) was administered from the 3$^{d}$-4$^{th}$ days and was divided into two doses – at 10am and at 10pm for 3 months. If the number of leukocytes decreased by less than $2.0\times10^{9}$/l, the drug was canceled.

Antibiotic therapy and antifungal drugs in patients included in the study were prescribed for intestinal decontamination, prevention and/or treatment of infectious and fungal complications, protection of invasive procedures in accordance with the recommendations of the clinical protocol during the pre-, intra- and early postoperative periods. Pneumocystic pneumonia was prevented by daily administration of cotrimoxazole (80 mg of trimethoprim and 400 mg of sulfamethoxazole) in the dosage of 1 tablet for life.

Prevention of cytomegalovirus infection (CMV) after liver transplantation was performed in high-risk patients (transplantation from CMV of a positive donor of CMV-negative or CMV-positive recipient; transfusion of more than 10 doses of blood products) by administration of ganciclovir intravenously in the dose of 5 mg/kg in case of normal renal function for 14 days followed by valganciclovir 2 times 450 mg/day for 3 months in case of normal renal functioning.

Nonfractioned heparin (5000 U/day) under the control of activated partial thromboplastin time was prescribed to the re-

***Table 1*** *Indications for inclusion of patients on the waiting list for liver transplantation*

| Liver diseases | The number of liver transplant recipients subjected to the effect of the studied factor (n=150) | The number of patients with TLD who did not receive a liver transplant during the follow-up period (n=100) |
|---|---|---|
| Liver cirrhosis of viral etiology | 46 (30.7%) | 32 (32.0%) |
| Cryptogenic cirrhosis | 33 (22.0%) | 23 (23.0%) |
| Primary biliary cirrhosis | 39 (26.0%) | 28 (28.0%) |
| Wilson's disease | 20 (13.3%) | 11 (11.0%) |
| Other liver diseases | 12 (8.0%) | 6 (6.0%) |

***Table 2*** *Scheme of glucocorticoids administration in the study group of liver transplant recipients*

| Drug | Application time | Dosage and route of administration |
|---|---|---|
| Methylprednisolone | In the ahepatic period | 500-1000 mg intravenously |
| | 0 day after surgery | 250 mg intravenously |
| Prednisolone | 1st-3rd day after surgery | 1 mg/kg |
| | 4th day after surgery | 0.5 mg/kg |
| | 5-7th day after surgery | 0.4 mg/kg |
| | 8-14th day after surgery | 0.25 mg/kg |
| | 15-21st day after surgery | 0.2 mg/kg |
| | 22-28th day after surgery | 10 mg/kg |
| | 29-42nd day after surgery | 7.5 mg/kg |
| | 48-56th day after surgery | 2.5 mg/kg |

cipients of liver transplants during the first 5 days of the postoperative period; if thrombotic complications were absent, low-molecular heparin (enoxaparin 0.4 ml/day or nadroparin 0.3 ml 2 times a day) starting with the 6th day after the operation were administered; on the 15th day – acetylsalicylic acid in the dosage of 75 mg/day.

Postoperative complications in the study group of liver transplant recipients were represented as follows: infectious complications (pneumonia, bacteremia, n=64), biliary anastomosis strictures (n=2), stenosis of the hepatic artery anastomosis (n=1), gastrointestinal bleeding (n=3), renal dysfunction (n=98), nonanastomotic strictures of the bile ducts (n=24). The above complications were eliminated during the early postoperative period, which allowed the recipients of liver transplants to continue their participation in the study.

Two comparison groups matched with liver transplant recipients by age, sex and traditional cardiovascular risk factors were formed: patients with metabolic syndrome (comparison group I) and those with coronary artery disease and metabolic syndrome (comparison group II).

The average age of liver transplant recipients was 41.8±7.29 years; in the group of recipients with CAD and metabolic syndrome (MS) it was 46.95±3.12 years. The age composition was the following: 20-29 years old – 4.4% (n=11), 30-39 years old – 19.2% (n=48), 40-49 years old – 43.2% (n=108), 50-59 years old – 28.4% (n=71), 60 years and more – 4.8% (n=12).

Comparison group I had the following age structure: 20-29 years – 5%, 30-39 years – 20%, 40-49 years – 40%, 50-59 years – 30%, 60 years and more – 5%. The age structure of the comparison group II: 30-39 years – 5%, 40-49 years – 15%, 50-59 years – 65%, 60 years and more – 15%.

All organ transplant recipients were CAD free at the time of inclusion in the study. The risk factors of CAD in the study group were smoking – 9.6%; family history of early cardiovascular diseases (in women over 65 years, in men under 55 years) – 40.4%; abdominal obesity (waist circumference ≥80 cm in women, ≥94 cm in men) – 64.7%. A history of arterial hypertension was found in 53.2% of patients with TLD which lasted for 2.81 (2-3.93) years. The combination of two or more cardiovascular risk factors at the time of inclusion on the waiting list was found in 60% of all liver transplant recipients.

Multispiral computed tomography was performed step-by-step by the Light Speed 32 Pro X-ray computed tomograph (GE Medical Systems Europe) from the Valsalva sinuses to the lower border of the heart in combination with a prospective ECG synchronization with a cut-off thickness of 2.0 mm and a tube radiation intensity of 250 mAs. A series of tomograms was performed within 5-10 min. The scan was performed within approximately 25 s and was equal to one breath hold. To increase the temporal resolution, obtain still images of the heart and improve the quality of the study a single dose of β-adrenergic blockers was prescribed to patients with a heart rate over 100 beats/min. The magnitude and density of the calcified area of the coronary artery were determined in the course of the study. The areas with the density over 130 Hounsfield units were taken as coronary artery calcification foci. The value of three adjacent pixels (1.03 $mm^2$) was chosen as the threshold value of the coronary artery calcified lesion area. The obtained findings of the degree of coronary artery calcification were expressed by the calcium index value calculated by the standard method of Agatston and Volume-130. The total CI value was calculated as the sum of indices on all tomographic sections.

***Table 3*** *CI percentile distribution by age and sex*

| Percentile | Age group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <40 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 |
| **Males** | | | | | | | | |
| 25 | 0 | 0 | 0 | 1 | 4 | 13 | 32 | 64 |
| 50 | 1 | 1 | 3 | 15 | 48 | 133 | 180 | 310 |
| 75 | 3 | 9 | 36 | 103 | 215 | 410 | 566 | 892 |
| 90 | 14 | 59 | 154 | 332 | 554 | 994 | 1299 | 1774 |
| **Females** | | | | | | | | |
| 25 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 3 |
| 50 | 0 | 0 | 0 | 0 | 1 | 3 | 24 | 52 |
| 75 | 1 | 1 | 2 | 5 | 23 | 57 | 145 | 210 |
| 90 | 3 | 4 | 22 | 55 | 121 | 193 | 410 | 631 |

A package of native images obtained during the scanning procedure was saved in the DICOM format and transmitted for further processing to a multimodal independent workstation. CI of the coronary arteries was determined using the software included in the software package of the workstation. CI of the main left coronary artery, anterior descending, circumflex and right coronary arteries were separately assessed in the semiautomatic mode. To do this we marked the areas with the density of more than 130 Hounsfield units on the axial images with an electronic marker.

The clinical significance of the obtained findings, severity of atherosclerotic lesions of the coronary arteries and the risk of cardiovascular complications were assessed taking into account four CI value ranges: 0 – very low; 1-10 – low; 11-100 – moderate; 101-400 – high; >400 – very high. Using the analysis of the CI percentile distribution the range of normal indices was determined, the values above the 75$^{th}$ percentile were considered as the elevated level (Table 3).

The obtained data were processed using Statistica (Version 8.0) packages and Excel. For samples with a normal distribution we used methods of variation statistics and parametric criteria. The data are presented as the mean value (M) while the representativeness error as (m). Quantitative comparison of two independent groups was performed with the Student's t-test. The significance of differences within the same group was assessed using the non-parametric Friedman and Wilcoxon criteria for dependent variables with the introduction of the Bonferroni criterion of false discovery rate (FDR). For the intragroup analysis of qualitative characteristics the Mac-Nemar test was applied. The main tendencies and dispersion of quantitative characteristics lacking normal distribution were described by a median (Me) and an interquartile range (25$^{th}$ and 75$^{th}$ percentile). Statistical significance of the differences between the groups was checked using non-parametric dispersion analysis of Kruskal-Wallis with the subsequent pair comparison by the Mann-Whitney-Wilkoson criterion. The differences in the groups were considered relevant when the probability of an unmistakable prediction was 95.5% ($p<0.05$). In case of multiple comparisons, the critical level of p significance was calculated by the FDR method. The comparison of groups by qualitative characteristics was performed by analyzing the frequency of their occurrence. We assessed the difference between independent groups by the frequency of the variable under consideration based on the Fisher's exact test, $\chi^2$ test (Pearson method, maximum likelihood method).

## Results

In patients with TLD requiring liver transplantation the CI calculated by the A.S. Agatston (AJ-130) method was 148 (4; 376) units, by the method of Volume (Volume-130) it was equal to 208 (8; 497) mm$^2$. CI values over 100 units indicating a high risk of developing cardiovascular complications during visit 0 were detected in 94 (34.8%) patients with TLD. When calculating the percentile distribution depending on gender and age (Table 3) CI in this cohort (AJ-130) proved to be higher than the normal range determined by the value of the 75$^{th}$ percentile in 152 (56.3%) patients; CI (Volume-130) corresponded to the 90$^{th}$ percentile in 175 (64.8%) patients. The screening data of patients with TLD in the dynamics in the study and control groups is presented in Table 4.

Increased values of CI were revealed in liver transplant recipients during the follow-up period compared with the screening data at the time of their inclusion on the waiting list. During the intergroup comparison of coronary artery calcification data in patients of the study and control groups during Visit 4, higher CI values were noted in liver transplant recipients compared with those having chronic terminal liver diseases who did not receive a liver graft during the follow-up period.

When patients with TLD were included in the study the rates of coronary artery calcification in the study and control groups did not differ either in the CI value or in the localization of coronary calcification. After 5 years of dynamic follow-up liver transplant recipients showed a significant increase in the CI value estimated by the two methods, which resulted in reliable intragroup and intergroup differences between the examined cohorts.

Comparing the quantitative characteristics of coronary calcification in liver transplant recipients in the late postoperative period with those of patients from the general population we revealed that the CI value in transplanted patients of the study group was higher than in those with MS and/or CAD included in comparison groups I

***Table 4*** *Indicators of coronary calcification in patients with terminal liver diseases according to the screening results, Me (25%-75%)*

| Indicator | Study group (n=92) | Control group (n=81) | p* | Study group (n=64) | Control group (n=62) | p* |
|---|---|---|---|---|---|---|
| | visit 0 | visit 0 | | visit 4 | visit 4 | |
| CI, AJ-130, unit. | 134 (4; 176) | 152 (6; 188) | 0,17 | 223 (38; 597)** | 141 (4; 176) | 0,032 |
| CI, Volume-130, mm$^2$ | 196 (8; 229) | 214 (10; 296) | 0,09 | 314 (73; 748)*** | 203 (8; 284) | 0,008 |

Note: Reliability of differences in case of intergroup data comparison (*) and intragroup data comparison with baseline values (visit 0) of liver transplant recipients (** – in $p<0.05$, *** – in $p<0.01$).

***Table 5*** *CI in liver transplant recipients in the long-term postoperative period, Me (25%-75%)*

| Indicator | Liver transplant recipients (MS) (n=34) | Liver transplant recipients (MS+CAD) (n=30) | Comparison group I (n=40) | Comparison group II (n=40) |
|---|---|---|---|---|
| CI, AJ-130 units | 186 (78; 463)* | 274 (102; 683)** | 74 (21; 192) | 109 (34; 246) |
| CI, Volume-130, mm$^2$ | 278 (74; 623)* | 382 (98; 834)** | 124 (74; 273) | 382 (98; 834) |

Note: Reliability of differences ($p<0.01$): * – data of liver transplant recipients with MS of comparison group I, ** – data of liver transplant recipients with CAD and MS of comparison group II

and II (Table 5) and corresponded to a high risk of adverse cardiovascular events.

Given the fact that the liver transplant recipients did not have liver failure in the long-term postoperative period and were comparable with the patients from the group of comparison in gender, age and traditional cardiovascular risk factors, the aggravation of coronary atherosclerosis and the development of CAD in this category of patients is most likely caused by the intake of immunosuppressive therapy – tacrolimus and mycophenolate mophetil.

The list of complications associated with the intake of immunosuppressive therapy is big. Besides, such side effects as kidney dysfunction, hyperglycemia, arterial hypertension, disturbance in lipid metabolism are independent factors of the cardiovascular risk. Clinical presentations and morphological signs of nephrotoxicity of tacrolimus are similar to the changes in the kidneys, described earlier in patients who disturbance in lipid metabolism in patients who take tacrolimus occurs more seldom than against the background of intake of other groups of immunosuppressive medications.

## Conclusions

The calcium index in patients with terminal liver diseases requiring transplantation exceeded the recommended range determined by the 75$^{th}$ percentile in 56.3% (n=152) of the screened patients at the time of their inclusion on the waiting list. At the same time, indicators of calcification of the coronary arteries in the study and control groups did not differ either in the CI magnitude or in the localization of coronary calcification. In the late postoperative period the liver transplant recipients demonstrated a significant increase in CI (CI, AJ-130 – 134 (4; 176) and 223 (38; 597) units, respectively, p<0.05; CI, Volume-130 – 196 (8; 229) and 314 (73; 748) mm$^2$, respectively, p<0.01).

When comparing coronary calcification after 5 years of follow-up, liver transplant recipients showed higher CI values than patients with terminal liver disease who did not receive a donor organ (CI, AJ-130 – 223 (38; 597) and 141 (4; 176) units, respectively, p<0.05; CI, Volume-130 – 314 (73; 748) and 203 (8; 284) mm$^2$, respectively, p<0.01) and patients with MS (CI, AJ-130 – 186 (78; 463) and 74 (21; 192) units, respectively, p<0.01; CI, Volume-130 – 278 (74; 623) and 124 (74; 273) mm$^2$, respectively, p<0.01) and/or CAD (CI, AJ-130 – 274 (102; 683) and 109 (34; 246) units, respectively, p<0.01; CI, Volume-130 – 382 (98; 834) and 382 (98; 834) mm$^2$, respectively, p<0.01) in the general population.

The results of the study indicate that in the long-term postoperative period, liver transplant recipients receiving immunosuppressive therapy, despite a radical solution to the problem of liver failure, developed coronary artery disease during five years of dynamic follow-up. In the study cohort, in the post-transplant period, there was an increase in the calcium index in comparison with the indicators obtained when patients were included in the waiting list, as well as in comparison with the value of the calcium index of patients with metabolic syndrome and coronary artery disease from the general population.

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**Информация об источнике поддержки в виде грантов, оборудования, лекарственных препаратов**

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