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Modification of Cardiovascular Risk Factors and the Evolution of The Cardiovascular Phenotype of Liver Transplant Recipients in the Long -Term Postoperative Period

Aim	To evaluate the contribution of traditional and additional cardiovascular risk factors (CVRFs) to the development of chronic ischemic heart disease (CIHD) in liver transplant recipients during the long-term postoperative period.
Material and methods	A single-center prospective cohort study was conducted. The study included 740 patients with chronic end-stage liver disease (CESLD) and cirrhotic cardiomyopathy (CCMP). During the observation period (5.4±2.29 years), patients were divided into two groups: liver transplant recipients (n=420) and patients with CESLD on the waiting list who did not receive a donor organ (n=320). In patients enrolled to the study upon inclusion in the waiting list, CVRFs, history, clinical and laboratory and instrumental data were studied at all stages of the hepato-cardiac continuum.
Results	During the long-term postoperative period, liver transplant recipients belonged to the group of high cardiovascular risk: over a 5-year observation period, 35.7% (n=150) of them developed metabolic syndrome (MS), 9.8% developed verified CIHD associated with MS. The incidence of traditional CVRFs was high (arterial hypertension, 88.6%; obesity, 36.6%; hypercholesterolemia, 77.8%; hypertriglyceridemia, 43.6%; reduced concentration of high-density lipoprotein cholesterol, 35.4%; increased concentrations of low-density lipoprotein cholesterol, 66.8% and very low-density lipoprotein cholesterol, 51.2%; increased atherogenic index, 61.5%). During the long-term postoperative period as compared to the period when patients were on the waiting list, additional CVRFs appeared: increases in body mass index, calcium index, nitric oxide metabolites, endothelin-1, homocysteine, intercellular adhesion molecules VCAM-1 and ICAM-1, and decreases in endothelium-dependent vasodilation and glomerular filtration rate to less than 60 ml/min/1.73 m^2. A model for the development of CIHD was created. The model uses a complex of independent risk factors and demonstrates a predictive accuracy of 84.6%.
Conclusion	The study results indicate a modification of CVRFs and a dynamic change in the cardiovascular phenotype of liver transplant recipients: progression of CCMP during their stay on the waiting list, regression of CCMP manifestations during the first 12 months after orthotopic liver transplantation, and increases in the total cardiovascular risk and likelihood of CIHD in the long-term postoperative period.

Keywords	Cardiovascular risk factors; chronic ischemic heart disease; cirrhotic cardiomyopathy; chronic end-stage liver diseases; liver transplantation
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Introduction

The idea of preventing the development and progression of Cardiovascular diseases (CVD) was based over the years on the modification and prospective control of cardiovascular risk factors (RFs). According to the unified SCORE scale, a high-risk patient is any individual at a>5% risk of death due to chronic coronary artery disease (CAD) or cardiovascular complications within the next 10 years [1, 2]. Such an approach refutes the theory of multifactorial nature of CVD, the fundamental part of which is a complex, often neglected relationship between non-modifiable, conventional, non-conventional cardiovascular RFs and comorbidities that form the concept of overall cardiovascular risk faced by a comorbid patient [2]. The development

Central illustration. Modification of cardiovascular risk factors and evolution cardiovascular phenotype of liver transplant recipients in the long-term postoperative period

Statistical details of predictive model elements

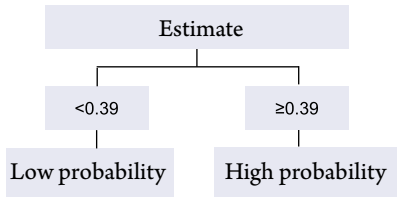
Parameter	Beta coefficient	Standard error of the coefficient	Wald test	p level	Odds ratio (95 % CI)
Intercept	-5.106	0.732	28.340	0.000	-
BMI > 30 kg/m²	1.124	0.3987	7.105	0.006	2.504 (1.288-5.107)
Early postoperative period	0.031	0.014	6.085	0.012	-
Atherogenic index > 3.5	1.003	0.365	6.735	0.008	2.034 (1.062-3.870)
TG level	0.356	0.178	5.308	0.017	-
LDL-C level	0.426	0.214	4.507	0.032	-
GFR < 6.0 mL/min/1,73m²	1.709	0.648	6.904	0.009	5.450 (1.302-18.564)
Elevated blood NT-proBNP	1.118	0.419	7.117	0.007	2.708 (1.304-5.706)

Predictive model case classification

Actual results	Results of logistic regression model	
	No outcome (code – 0)	Presence of outcome (code – 1)
No outcome (code – 0)	150	41
Presence of outcome (code – 1)	29	28

$$Y=\frac{1}{1+e^{(5{,}106-1{,}124X1-0{,}031X2-1{,}003X3-0{,}356X4-0{,}426X5-1{,}709X6-1{,}118X7)}},$$

where X1 is body mass index > 30 kg/m²
(0 = ≤ 30 kg/m², 1 = > 30 kg/m²);
X2 – early postoperative course
(0 – uncomplicated, 1 – complicated);
X3 – atherogenic index > 3.5 (0 = ≤ 3.5, 1 = > 3.5)
X4 – blood levels of triglycerides (mmol/L);
X5 – blood levels of low-density lipoprotein cholesterol (mmol/L);
X6 – glomerular filtration rate < 60 mL/min/1.73 m²)
(0 = ≥ 60 mL/min/1.73 m²; 1 = < 60 mL/min/1.73 m²)
X7 – increased blood levels of NT-proBNP (0 = normal, 1 = increase).



To facilitate calculations using this formula, Wise Calculator was used (www.wisecolculator.chat.ru).
BMI, body mass index; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; GFR, glomerular filtration rate; CI, confidence interval.

of objective personalized prediction models has become an integral part of the strategy aimed at preventing the onset and progression of chronic CAD [3].

In patients with chronic end-stage liver disease and cirrhotic cardiomyopathy (CCM) on the liver transplant waiting list, refusal to modify cardiovascular RFs with a low likelihood of complications, due to an unfavorable short-term survival prognosis while waiting for surgical intervention, inevitably leads to an increase rise in the number of patients at high cardiovascular risk in the long-term postoperative period. In fact, it turned out that the absence of verified cardiovascular RFs in patients under 50 years of age, which includes liver transplant recipients, was not directly associated with the expected low risk and improved survival. At the same time, the presence of at least one additional cardiovascular RF in a population or cohort of comorbid patients significantly increases the overall cardiovascular risk in both male and female patients [4, 5]. The cardiovascular risk of liver transplant recipients is low to moderate based on the detection of conventional cardiovascular RFs and the use of traditional scales. It never exceeds the population average. At the same time, the of signs of endothelial damage and dysfunction, elevated levels of myocardial stress markers, decreased platelet count, increased prothrombogenic potential and activity of systemic inflammation were found in this population of patients in the long-term postoperative period. The degree of responsibility of non-conventional factors for the formation of high risk of cardiovascular events after organ transplantation and the prognostic significance of their modification are not fully understood [6–13].

Objective

Evaluate the contribution of conventional and additional cardiovascular RFs to the development of chronic CAD in liver transplant recipients in the long-term postoperative period.

Material and methods

A single-center prospective cohort study included 740 patients with chronic end-stage liver disease (study cohort), of whom 420 patients (study subcohort) underwent orthotopic liver transplantation (OLT) during an observation period of 5.4±2.29 years and 320 patients did not receive liver transplant (control subcohort). Patients were enrolled based on the following inclusion criteria: signed informed consent; presence of irreversible liver disease with an unfavorable life prognosis; presence of chronic end-stage liver disease that significantly reduces the patient's quality of life and ability to work; and progressive liver disease with a life expectancy shorter than that of OLT. Exclusion criteria: a patient with chronic end-stage liver disease has relative or absolute contraindications to transplantation specified in the liver transplantation clinical protocol approved by the order No. 6 of the Ministry of Health of the Republic of Belarus as of 05.01.2010 [14];

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ischemic damage to the donor liver during the process of harvesting and preservation; a patient had chronic CAD at the inclusion in the waiting list; detection of atherosclerotic stenosis in vascular systems other than the coronary bed; endocrinopathy (diabetes mellitus type 1 or 2, thyroid dysfunction, vitamin D deficiency). Withdrawal criteria: development of acute or chronic rejection that require changing baseline immunosuppressive therapy, patient refusal to continue taking part in the study, patient death from a cause other than the outcome of interest. The examination was performed at the time of inclusion in the waiting list (Visit 0: day 0±7 days), at the time of OLT (Visit 1: day 1±1 days), at the end of the early postoperative period (Visit 2: day 30±10 days), in the long-term postoperative period in 1 year (Visit 3: day 365±30 days), and in 5 years (Visit 4: 5 years±30 days). General characteristics of patients included in the study is given in Table 1.

Propensity score matching was used to create two comparison groups of patients with metabolic syndrome (MS, Comparison group I) and MS and chronic CAD (Comparison group II), who were comparable to liver transplant recipients by age, sex, and traditional cardiovascular RFs (Figure 1).

The list and incidence of the main diseases that led to chronic end-stage liver disease and the placement of patients on the waiting list are presented in Table 2.

Manifestations of CCM were detected in 100% of patients with chronic end-stage liver disease included in the liver transplant waiting list (Table 3).

The cardiovascular examination included electrocardiography, 24-hour blood pressure monitoring, echocardiography in three modes (M mode, B mode, color Doppler) in combination with tissue Doppler and 2D speckle tracking, single photon emission computed tomography (SPECT) of the myocardium and dipyridamole stress test (verification of chronic CAD), multislice computed tomography (MSCT) for coronary calcium screening. Blood lipid profile (total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), very-low-density lipoprotein cholesterol (VLDL–C), high-

Table 1. Characteristics of the study cohort at time of placing on the liver transplant waiting list

Indicator, X±SD§	Study cohort (n=740)	
	Liver transplant recipients (n=420)	Patients with chronic end-stage liver disease on the waiting list (n=320)
Age, years	42.4±7.15	43.1±9.34
Body mass index, kg/m^2	22.7±3.56	24.8±3.23
Waist circumference, cm	127.2±6.56	129.4±5.46
Indicator, Me (25%–75%)§		
Systolic blood pressure, mm Hg	102 (90; 140)	100 (90; 130)
Diastolic blood pressure, mm Hg	60 (60; 95)	65 (60; 95)
Duration of hypertension, years	2.81 (2–3.93)	2.25 (2–5.08)
Sign, % (n)§		
Family history of early chronic CAD	34.8 % (146)	47.8 % (153)
Smoking	6.0 % (25)	10.0 % (32)
BP ≥ 130/85 mm Hg	15.0 % (63)	18.1 % (58)
Combination of two or more risk factors for chronic CAD	64.8 % (272)	65.0 % (208)

BP, blood pressure; CAD, coronary artery disease;
§ difference is not significant at p<0.05.

Figure 1. Study design

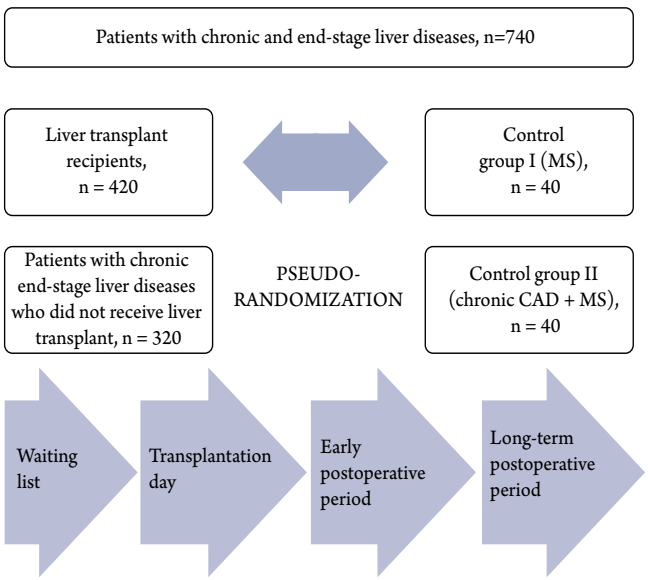

Table 2. Indications for placing the patients examined on the liver transplant waiting list

Sign, % (n)	Liver transplant recipients (n=420)	Patients with chronic end-stage liver disease on the waiting list (n=320)
Viral cirrhosis	30.7 % (129)	31.9 % (102)
Cryptogenic cirrhosis	21.9 % (92)	23.1 % (74)
Primary biliary cirrhosis	18.8 % (79)	20.0 % (64)
Wilson's disease	3.8 % (16)	4.1 % (13)
Other liver diseases	24.8 % (104)	20.9 % (67)

density lipoprotein cholesterol (HDL–C), triglycerides (TG), apolipoprotein A (apoA) and apolipoprotein B (apoB)), high-sensitivity C-reactive protein (hsCRP) was analyzed on an automated biochemical analyzer Konelab 30i (Thermo Fisher Scientific, Finland) using Thermo Scientific diagnostic liquid reagents. Plasma levels of nitric oxide (NO) were assessed by the levels of its stable metabolites, NO2- and NO3-, using BCM Diagnostics (USA) reagents. Levels of platelet sP-selectin and endothelial sE-selectin, vascular cell adhesion molecule VCAM-1, and intercellular adhesion molecule ICAM-1 were quantified by the Elisa test using Bender Medsystems (Austria) test systems. Axis Shield Diagnostics Ltd (Norway) test system was used to estimate homocysteine levels, and Biomedical ENDOTELIN 1–21 reagents from ZAO BioKhimMak (Russia) were used for endothelin-1 (ET-1) determination.

Statistical analysis of the data obtained was performed using IBM SPSS 25.0 and STATISTICA 8.0. Normally distributed quantitative values are presented as mean X and standard deviation SD (X±SD), otherwise as median (Me) and interquartile range (25–75%). Chi-squared (χ^2), Student's t-test with Bonferroni correction for multiple groups, Mann-Whitney test, and Kraskell-Wallis rank analysis of variances were used to compare independent samples; paired Student's t-test and Wilcoxon test were used for dependent samples. Univariate and multivariate binary logistic regression models were used with odds ratio (OR) and 95% confidence interval (CI). The omnibus test was used to assess the statistical significance of the regression equations. The Hosmer-Lemeshow test was used to verify the effectiveness of the models. The quality of the logistic models was evaluated, and the threshold of classification or prediction probability was determined using ROC analysis. Differences were considered statistically significant at $p<0.05$.

The study was conducted following good clinical practice and Declaration of Helsinki (World Medical Association, 2000). The study protocol was approved by the local ethics committee of the 9th City Clinical Hospital (Minsk, Belarus). Written informed consent was obtained from all the patients prior to their inclusion in the study.

Results

In the long-term postoperative period, compared with the baseline examination results at their inclusion in the waiting list, liver transplant recipients had an increase in the left heart sizes (left atrial (LA) volume 39.9±15.94 mL and 65.19±7.23 mL, respectively, p=0.007; end-diastolic volume index (EDVI) 72.2±3.19 mL/m^2 and 83.1±3.18 mL/m^2, respectively, p=0.014), left ventricular mass index (LVMI) 111,4±4.54 g/m^2 and 128.9±32.04 g/m^{2}respectively, p=0.027; diastolic left ventricular (LV) relative wall thickness index (RWTI) 0.35±0.01 and 0.48±0.12, respectively, p=0.034; decrease in inferior vena cava (IVC) diameter 24.3±3.17 mm and 17.2±3.46 mm, respectively, p=0.045; right atrial volume index (RAVI) 62.3±11.76 mL/m^2 and 26.4±4.23 mL/m^2, p=0.009, indicating regression of CCM and appearance of signs of maladaptive LV remodeling after OLT. Positive changes in the sizes of RA and IVC were first seen 1 year after OLT and persisted for the next 5 years. At the end of the observation period, patients with CCM who did not undergo liver transplantation during the observation period showed an increase in the sizes of both atria (LA volume 42.1±4.53 mL and 50.8±12.43 mL, respectively, p=0.043; PA volume index 65.8±14.42 mL/m^2 and 79.6±11.38 mL/m^2, respectively, p=0.032), right ventricular (RV) anteroposterior dimension (39.1±5.11 mm and 46.5±4.11 mm, respectively, p=0. 042), a decrease in tricuspid annular plane systolic excursion (16.8±3.11 mm and 12.7±3.18 mm, respectively, p=0.023), an increase in IVC diameter (26.1±4.52 mm and 34.3±6.32 mm, respectively, p=0.008),

Table 3. Diagnostic criteria for cirrhotic cardiomyopathy in the study groups

Diagnostic criterion, % (n)	Study cohort (n=740)	Liver transplant recipients (n=420)	Patients with chronic end-stage liver disease on the waiting list (n=320)
Left ventricular ejection fraction < 50 %	87.0 (644)	85.0 (357)	82.2 (263)
		$\chi2$=10.76; p=0.798	
Reduced increase in cardiac output during exercise	63.5 (470)	61.9 (260)	64.1 (205)
		$\chi2$=14.28; p=0.912	
E/A ≤ 0.8	72.0 (533)	70.2 (295)	73.1 (234)
		$\chi2$=12.14; p=0.654	
E/é ratio>14	88.1 (652)	89.0 (374)	88.1 (282)
		$\chi2$=14.03; p=0.521	
TR velocity>2.8 m/s	83.1 (615)	84.0 (353)	81.9 (262)
		$\chi2$=11.14; p=0.762	
Left atrial volume index>34 mL/m2	67.9 (503)	65.0 (273)	68.1 (218)
		$\chi2$=6.34; p=0.853	
Prolonged QT interval	75.9 (562)	78.1 (328)	73.1 (234)
		$\chi2$=10.24; p=0.952	
Reduced heart rate during exercise	59.0 (437)	54.0 (227)	60.0 (192)
		$\chi2$=12.46; p=0.731	
Myocardial hypertrophy	37.9 (281)	40.0 (168)	35.0 (112)
		$\chi2$=7.65; p=0.603	
Heart rhythm and conduction disorders	85.9 (636)	82.1 (345)	85.9 (275)
		$\chi2$=10.18; p=0.876	

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peak tricuspid regurgitation velocity (236.7±11.43 cm/s and 268.5±38.54 cm/s, respectively, p=0.028), indicating progression of CCM and right ventricular failure in addition to aggravation of chronic end-stage liver disease severity. 2D-speckle tracking imaging revealed significantly lower LV systolic global longitudinal strain compared to patients from the general MS population (–17.6±1.48% and –23.4±1.07%, respectively, p=0.006) and chronic CAD (–16.4±1.61% and –22.1±1.54%, respectively, p=0.008), indicating that dysfunction of the subendocardial fibers of the LV myocardium persists after OLT. The percentage of liver transplant recipients with chronic CAD who met diagnostic criteria for LV diastolic dysfunction was higher than in the general population (70.7% and 57.5%, respectively, p=0.044).

A lower percentage of individuals with normal left ventricular geometry (22.1% and 45.0%, respectively, p=0.008) and chronic CAD (19.5% and 40.0%, p=0.006) was found in liver transplant recipients compared to patients with MS in the general population in the long-term postoperative period (Table 4). Maladaptive forms prevailed in the structure of LV myocardial remodeling: the percentage of liver transplant recipients with MS having a prognostically unfavorable form of remodeling was 50.4% versus 25.0% in the comparison group consisting of patients with MS from the general population (Comparison group I, p=0.008), liver transplant recipients with chronic CAD – 58.5% versus 37.5% in the comparison group consisting of patients with chronic CAD from the general population (Comparison group II, p=0.007).

Eccentric LV hypertrophy and concentric remodeling (p<0.01) were the most common maladaptive geometric abnormalities in liver transplant recipients with MS, and eccentric and dilated (p<0.01) LV hypertrophy – in patients with chronic CAD (Figure 2).

In patients with chronic end-stage liver disease in need of OLT, the calcium score (CS) exceeded the recommended normal limits defined by the 75th percentile in 56.3% (n=152) of patients examined at the time of the inclusion in the waiting list and did not differ in the study and control subcohorts either by CS or by location of coronary calcification. In the long-term postoperative period, liver transplant recipients had a significant increase in CS, AJ-130134 (4; 176) units and 223 (38; 597) units, respectively, p=0.048; CS, Volume-130196 (8; 229) mm^2 and 314 (73;748) mm^2, respectively, p=0.009. When comparing indicators of coronary calcification at the dynamic observation cut-off points, liver transplant recipients were found to have higher CS values compared to patients with chronic end-stage liver disease who did not receive a donor organ (CS, AJ-130223 (38; 597) units and 141 (4; 176) units, respectively, p=0.045; CS Volume-130314 (73; 748) mm^2 and 203 (8; 284) mm^2, respectively, p=0.012), patients with MS (CS, AJ-130186 (78; 463) units and 74 (21; 192) units, respectively, p=0.014; CS, volume-130278 (74;623) mm^2 and 124 (74; 273) mm^2, respectively, p=0.009) and chronic CAD (CS, AJ-130274 (102; 683) units and 109 (34; 246) units, respectively, p=0.011; CS, Volume-130382 (98;834) mm^2 and 382 (98; 834) mm^2, respectively, p=0.012) of the general population. Increased CS after 5.3±2.34 years of observation was associated with the onset of chronic CADs in the study subcohort (AJ-130134 (4; 176) and 223 (38; 597), respectively, p=0.048; RR=6.127 (1.109–15.412); Volume 130196 (8; 229) and 314 (73; 748), respectively, p=0.009; RR=6.028 (2.421–12.643)).

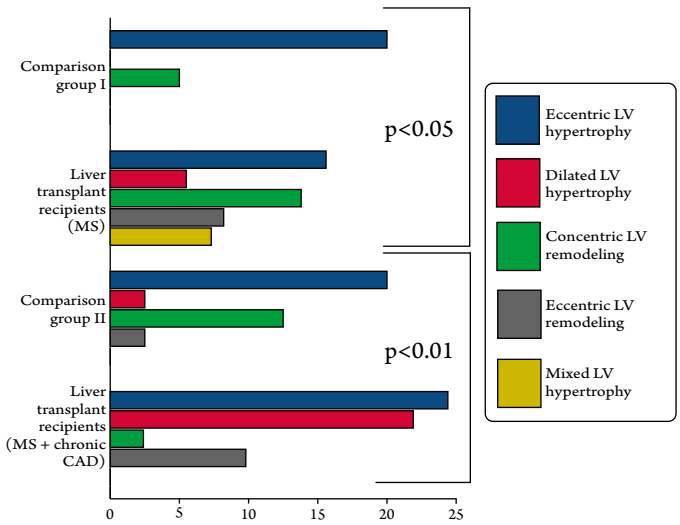
In the long-term postoperative period, elevated serum levels of nitric oxide were detected in liver transplant recipients: 56.2±9.14 μmol/L in the chronic CAD+ group and 40.4±6.15 μmol/L in the chronic CAD– group,

Table 4. Incidence of various types of LV remodeling in liver transplant recipients in the long-term postoperative period

Sign, % (n)	Liver transplant recipients (MS), n=109	Liver transplant recipients (MS + chronic CAD), n=41	Control group I (MS), n=40	Control group II (MS + chronic CAD), n=40
Percentage of individuals with normal LV geometry	22.1 % (24)**	19.5 % (8)••	45.0 % (18)	40.0 % (16)
Percentage of individuals with physiological LV hypertrophy	17.4 % (19)	4.9 % (2)	17.5 % (7)	5.0 % (2)
Percentage of individuals with concentric LV hypertrophy	10.1 % (11)	17.1 % (7)	12.5 % (5)	17.5 % (7)
Percentage of individuals with eccentric LV hypertrophy	15.6 % (17)	24.4 % (10)	20.0 % (8)	20.0 % (8)
Percentage of individuals with dilated LV hypertrophy	5.5 % (6)*	21.9 % (9)••	0 % (0)	2.5 % (1)
Percentage of individuals with mixed LV hypertrophy	7.3 % (8)*	0 % (0)	0 % (0)	0 % (0)
Percentage of individuals with concentric LV remodeling	13.8 % (15)*	2.4 % (1)••	5.0 % (2)	12.5 % (5)
Percentage of individuals with eccentric LV remodeling	8.2 % (9)*	9.8 % (4)••	0 % (0)	2.5 % (1)

* Significance of the differences compared to Comparison group I of liver transplant recipients with MS at p<0.05; ** p<0.01;
• significance of the differences compared to Comparison group II of liver transplant recipients with chronic CAD and MS at p<0.05; •• p<0.01.

Figure 2. Incidence of maladaptive forms of LV remodeling in liver transplant recipients in the long-term postoperative period



p=0.011. In liver transplant recipients without chronic CAD after 5 years of dynamic observation (chronic CAD– group), preoperative nitric oxide levels were comparable to those in the chronic CAD+ group – 42.3±8.42 μmol/L and 41.8±9.34 μmol/L, respectively, p=0.034. Thus, liver transplant recipients who developed chronic CAD within five years after OLT had higher postoperative levels of NO compared to the preoperative period (56.2±9.14 μmol/L and 41.8±9.34 μmol/L, respectively, p=0.010), which is associated with increased number of manifestations of endothelial dysfunction that can influence the terms of coronary atherosclerosis formation in this population of patients.

The serum levels of endothelin-1 in liver transplant recipients in the chronic CAD+ group was significantly higher in the long-term postoperative period compared to patients in the chronic CAD– group: 1.3±0.04 pg/mL and 0.4±0.03 pg/mL, respectively, p=0.014. The preoperative levels of ET-1 did not have significant differences between the chronic CAD+ group and the chronic CAD– group and did not exceed normal values: 0.8±0.04 pg/mL and 0.6±0.03 pg/mL, respectively, p=0.064.

In the long-term postoperative period, the mean serum VCAM-1 content was 2980.4±358.76 ng/mL in liver transplant recipients with chronic CAD and 634.3±106.12 ng/mL in those without chronic CAD, p=0.001. In the preoperative period, this value was lower compared to the postoperative in the chronic CAD+ group (650.6±75.84 ng/mL and 2980.4±358.76 ng/mL, respectively, p=0.001); serum levels of VCAM-1 did not change in the chronic CAD – group in the long-term postoperative period (642.9±43.58 ng/mL and 634.3±106.12 ng/mL, respectively). Thus, in the long-term postoperative period, the mean VCAM-1 concentration was significantly higher in patients with chronic CAD than in the chronic CAD– group, despite the absence of differences in the levels of adhesion molecules when recipients were included in the waiting list – 650.6±75.84 ng/mL and 634.3±106.12 ng/mL, respectively. A similar pattern was found when assessing mean concentration of intercellular adhesion molecule ICAM-1. Mean postoperative concentrations of sP-selectin were 271.3±54.28 ng/mL in the chronic CAD+ group and 299.7±61.18 ng/mL in the chronic CAD- group, p=0.059, these indicators were also comparable in the study groups before transplantation – 219.5±39.12 ng/mL and 224.7±41.15 ng/mL, respectively. The mean levels of sE-selectin in the study groups did not differ significantly and were 54.9±8.32 ng/mL in the chronic CAD+ group and 69.7±16.34 ng/mL in the chronic CAD- group before transplantation and 58.4±6.98 ng/mL and 62.4±8.15 ng/mL, respectively, in the postoperative period.

An intergroup comparison of homocysteine levels showed that the mean values before transplantation and in the long-term postoperative period (Figure 3) were significantly higher in the group of recipients who were diagnosed with chronic CAD after OLT than in the group of individuals who did not have chronic CAD.

An intra-group analysis showed that there was a significant increase in mean homocysteine levels in liver transplant recipients in both groups (chronic CAD+ (1) and chronic CAD– (2)) in the long-term postoperative period (Figure 4), indicating the worsening of endothelial dysfunction manifestations and increased cardiovascular risk.

The development of chronic CAD after 5.3±2.34 years of observation was associated with increased levels of nitric oxide metabolites (RR=3.028 (1.114–5.467)), endothelin-1 (RR=1.469 (1.006–3.924)), decreased endothelium-dependent vasodilation (7.6±0.82% and 12.4±1.03%, respectively, p=0.035, RR=2.421 (1.128–3.584)), reflecting the contribution of endothelial dysfunction to the onset and progression of myocardial ischemia in this population of patients.

Thus, in the long-term postoperative period, the high incidence of traditional (hypertension 88.6%, obesity 36.6%, hypercholesterolemia 77.8%, hypertriglyceridemia 43.6%, decreased HDL–C 35.4%, increased LDL–C 66.8% and VLDL–C 51.2%, increased AI 61.5%) and detection of additional non-conventional risk factors (increased calcium score, elevated levels of endothelial dysfunction markers) allow attributing liver transplant recipients to the group of high cardiovascular risk 5 years after organ replacement surgery. The probability of detecting chronic CAD in the long-term postoperative period was 4.8 times higher in liver transplant recipients with MS than in those without MS,

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Table 5. Dyslipidemia in liver transplant recipients: impact on long-term prognosis (onset of chronic CAD)

Parameters	Odds ratio (95 % confidence interval)	p value
TC>4.5 mmol/L	4.406 (2.231–19.005)	0.049
TG>1.7 mmol/L	8.617 (3.343–22.211)	0.003
LDL-C>3.0 mmol/L	5.804 (1.309–25.739)	0.034
Reduced HDL-C	3.732 (1.112–13.426)	0.041
VLDL-C>0.45 mmol/L	2.634 (1.213–9.387)	0.037
AI>3.5	3.199 (1.507–6.791)	0.034

AI, atherogenic index; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol, VLDL-C, very low-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol

Figure 3. Serum levels of homocysteine in liver transplant recipients while on the waiting list and in the long-term postoperative period

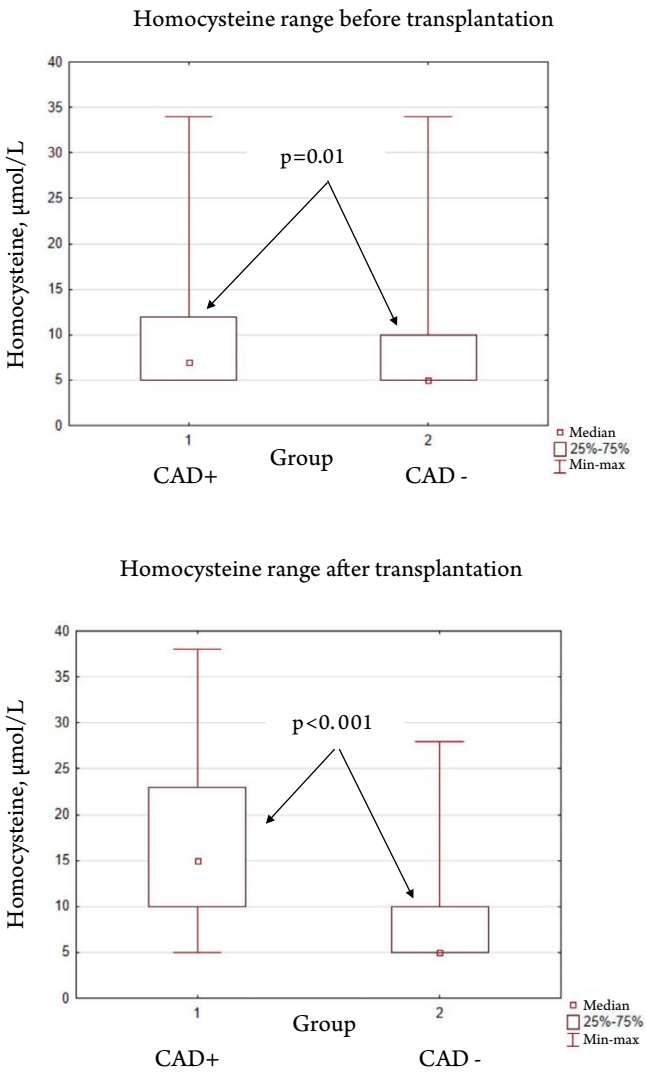
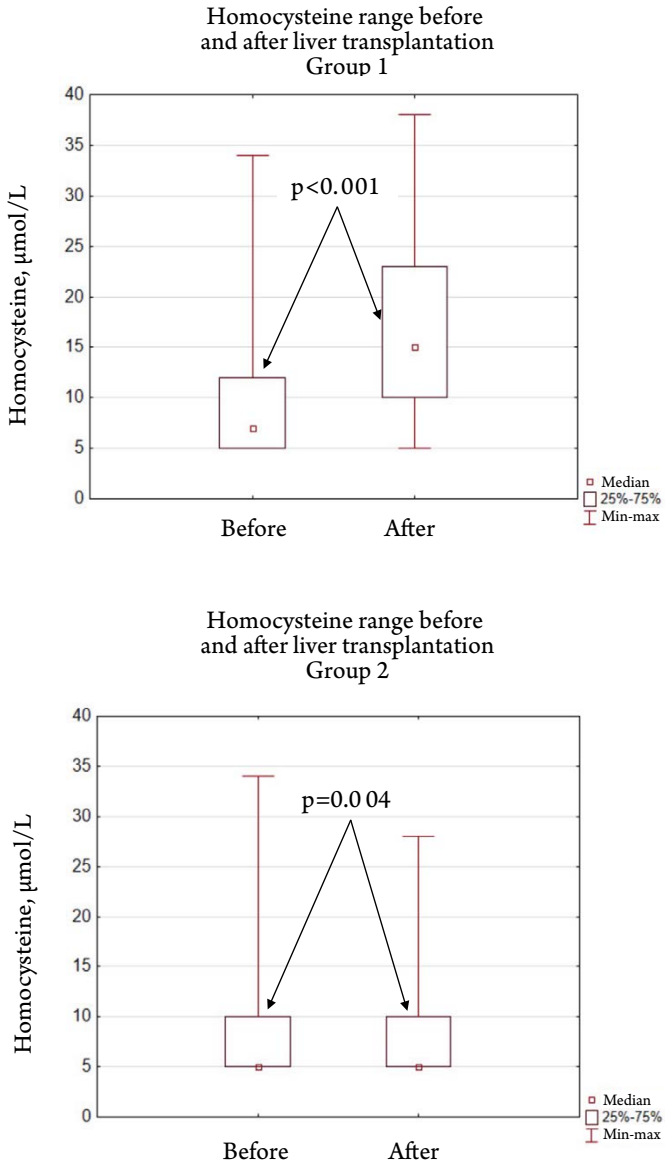


Figure 4. Changes in homocysteine serum levels in liver transplant recipients over the period of prospective observation



8.6 times higher in the presence of hypertriglyceridemia than in recipients without hypertriglyceridemia, 5.8 times higher in LDL–C>3 mmol/L than in recipients with normal LDL–C, 3.2 times higher in recipients with AI>3.5 than in those with AI ≤ 3.5. (Table 5, Figure 5).

Figure 6 shows that the median time from OLT to the onset of dyslipidemia was 1.5 (0.5–3.0) years.

TC and TG levels increased in the study cohort of liver transplant recipients over time, but the rate of change was greatest during the first two years after OLT. In the unadjusted analysis, male sex, viral hepatitis as an indication for OLT, hypertension, diabetes mellitus, and the presence of chronic CAD were the factors associated with the onset of dyslipidemia after OLT. In the adjusted model, patients with viral hepatitis as an indication for OLT were less likely to have dyslipidemia (OR 0.54; 95% CI 0.36–0.83; p=0.004), while those with chronic CAD were

Figure 5. Effect of dyslipidemia on long-term prognosis (onset of chronic CAD) in liver transplant recipients

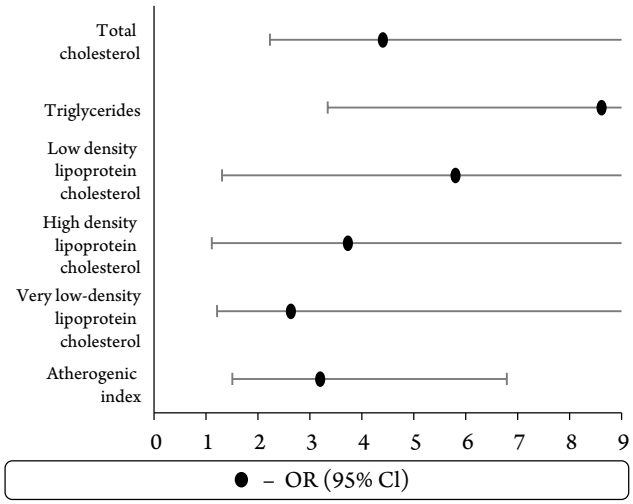
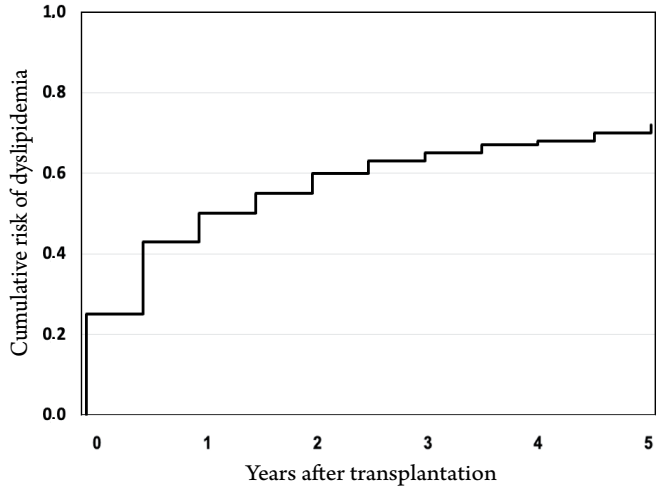


Figure 6. Dyslipidemia in liver transplant recipients in the long-term postoperative period



more likely to have dyslipidemia (OR 1.56, 95% CI 1.08–2.27, p=0.019).

Based on the results presented, a model for the development of chronic CAD in liver transplant recipients in the long-term postoperative period was developed (see central figure).

The predictive accuracy of the chronic CAD model developed using a set of independent risk factors was 84.6%.

Conclusion

The obtained results indicate the progression of cirrhotic cardiomyopathy in patients with chronic end-stage liver diseases while on the waiting list, incomplete regression of its manifestations during the first year after orthotopic liver transplantation, increase of the total cardiovascular risk and the probability of chronic coronary artery disease in liver transplant recipients in the long-term postoperative period due to the high prevalence of traditional risk factors and the emergence of additional postoperative factors: increased body mass index, calcium score, worsening of endothelial dysfunction manifestations, reduced glomerular filtration rate. Thus, modification of cardiovascular risk factors is the basis for dynamic change of cardiovascular phenotype of liver transplant recipients, formation of hepatocardial continuum, creation of personalized methods of medical prevention and treatment of this population of patients.

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