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МОДЕЛЬ ПРОГНОЗИРОВАНИЯ ГИПЕРТРОФИИ МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА У ПАЦИЕНТОВ С ОБСТРУКТИВНЫМ АПНОЭ СНА

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Model for Prediction of Left Ventricular Myocardial Hypertrophy in Patients with Obstructive Sleep Apnea

Резюме

Обструктивное апноэ сна (ОАС) диагностируется у 25% взрослых лиц и сопровождается высокими фатальными рисками кардиоваскулярных осложнений. Гипертрофия миокарда левого желудочка (ГЛЖ) признается одним из маркеров таких рисков. В настоящем исследовании нами предпринята попытка создания математической модели прогнозирования ГЛЖ среди пациентов с ОАС с различной степенью тяжести заболевания. **Материалы и методы.** В проспективное когортное исследование включены 368 пациентов (358 муж. возраст 46,0 [42,0; 49,0] лет) с диагностированным ОАС, артериальной гипертензией, ожирением I-II степени (классификация ВОЗ, 1997). Характер и тяжесть апноэ сна верифицировалась в ходе ночной компьютерной сомнографии (КСГ) на аппаратном комплексе WatchPAT-200 (ItamarMedical, Израиль) с оригинальным программным обеспечением zzzPAT™SW ver. 5.1.77.7 (ItamarMedical, Израиль) путём регистрации основных респираторных полиграфических характеристик в период 23:00 — 7:30. Эхокардиография, допплерография сердца и сосудов выполнялась в одно- и двухмерном режимах в стандартных эхокардиографических позициях с помощью ультразвукового сканера Xario-200 (Toshiba, Япония) с использованием датчика частотой 3,5 МГц. Гемодинамические показатели систолической функции левого желудочка (фракция выброса (ФВ), конечный систолический объём (КСО), ко-

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нечный диастолический объём (КДО)) определялись при количественной оценке двухмерных эхокардиограмм модифицированным методом Simpson. Оценку систолической функции правого желудочка (ПЖ) проводили в «М»-режиме путём измерения систолической экскурсии фиброзного кольца трикуспидального клапана (TAPSE). **Результаты.** Наилучшими предикторами прогнозирования ГЛЖ при различной степени тяжести ОАС следует считать ESS и TSat90% (AUC = 0,975; SD = 0,00741; ДИ 95% [0,953; 0,988]), позволяющих предложить прогностическую модель с чувствительностью в 93,7% и специфичностью в 93,8%, после проведения анкетного скрининга и компьютерного сомнографического исследования. **Выводы.** Предлагаемая модель клинического прогнозирования ГЛЖ среди пациентов с ОАС различной степени тяжести основывается на тщательно спланированном анализе анкетных и инструментальных данных, хорошо применима в условиях реальных диагностических процедур широким кругом врачей терапевтической практики.

Ключевые слова: *обструктивное апноэ сна, гипертрофия левого желудочка, эхокардиография, клиническая модель предсказания, WatchPAT-200, компьютерная сомнография, КСГ, амбулаторная практика*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Obstructive sleep apnea (OSA) is diagnosed in 25% of adults and associated with high fatal risks of cardiovascular complications. Left ventricular hypertrophy (LVH) is recognized as one of the markers of such risks. In this study, we attempted to create a mathematical model for predicting LVH among OAS patients with various levels of disease severity. **Materials and methods.** In a prospective cohort study, we included 368 patients (358 male; age 46.0 [42.0; 49.0] yr.) with diagnosed OSA, arterial hypertension, grade I-II obesity (WHO classification 1997). The severity of sleep apnea was verified during nighttime computed somnography (CSG) on WatchPAT-200 hardware (ItamarMedical, Israel) with original software zzzPAT™SW ver. 5.1.77.7 (ItamarMedical, Israel) by registering the main respiratory polygraphic characteristics from 11.00 PM to 7:30 AM. Verification of LVH was performed in one- and two-dimensional modes in standard echocardiographic positions using Xario-200 ultrasound scanner (Toshiba, Japan) with 3.5 MHz transducer. Hemodynamic parameters of left ventricular (LV) systolic function (EF %, ESV, EDV) were determined by quantitative assessment of two-dimensional echocardiograms using the modified Simpson method. Evaluation of the systolic function of the right ventricle (RV) was performed in the «M»-mode by measuring the systolic excursion of the fibrous ring of the tricuspid valve (TAPSE). **Results.** ESS and TSat90% (AUC = 0.975; SD = 0.00741; CI 95% [0.953; 0.988]) should be considered the best predictors for predicting LVH in various degrees of OSA severity, allowing us to offer a predictive model with a sensitivity of 93.7% and specificity of 93.8%, after conducting a questionnaire screening and computer somnographic study. **Conclusions.** Our proposed model of clinical prediction of LVH among patients with various degrees of OAS is based on a carefully planned analysis of questionnaire and instrumental data, and is well applicable in real diagnostic procedures by a wide range of therapeutic practitioners.

Key words: *obstructive sleep apnea, left ventricular hypertrophy, echocardiography, clinical prediction model, WatchPAT-200, computed somnography, outpatient practice*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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AHI — apnea-hypopnea index, BMI — body mass index, BP — blood pressure, BSA — body surface area, cMRI — cardiac magnetic resonance imaging, CPAP — continuous positive airway pressure therapy, CVC — cardiovascular complications, DT — deceleration time, ECHO CG — cardiac echocardiography, EDV — end diastolic volume, EFT — epicardial fat thickness, ESV — end systolic volume, GCP — good clinical practice, HbA1c — glycated hemoglobin, HDL — high density lipoproteins, IVRT — isovolumic relaxation time, LA — left atrium, LAVI — left atrial volume index, LDL — low density lipoproteins, LV — left ventricle, LVDD — left ventricular diastolic dysfunction, LVEF — left ventricular ejection fraction, LVH — left ventricular hypertrophy, LVMMI — left ventricular myocardial mass index, NPS — night polysomnography, OSA — obstructive sleep apnea, PASP — pulmonary artery systolic pressure, RAVI — right atrial volume index, REM — rapid eye movement sleep (paradoxical sleep), STOP-BANG — questionnaire for the markers of obstructive sleep apnea, TAPSE — tricuspid annular plane systolic excursion, URT — upper respiratory tract, VE/VA — ratio of early to late ventricular filling velocity, WM — waist measurement

Introduction

Obstructive sleep apnea (OSA) is a heterogeneous parasomniac disease with repeated collapses of the upper respiratory tract (URT) during sleep; it can be found in approximately 25% of the adult population and is the leading cause of excessive sleepiness, deterioration of quality of life and labor productivity, and increased risk of traffic accidents [1]. Moreover, OSA is directly associated with an increased risk of fatal and nonfatal cardiovascular complications (CVC) [2, 3]. The typical manifestation of severe sleep apnea is left ventricular myocardial hypertrophy (LVH) — increased left ventricular myocardial mass, with its structural remodeling as a result of overload with excessive volume/pressure. LVH in patients with OSA should be considered as a risk factor for coronary heart disease, chronic heart failure, cardiac rhythm disorders, myocardial infarction and stroke [4]. Twelve-lead electrocardiography (12-lead ECG), echocardiography (ECHO-CG), and cardiac magnetic resonance imaging (cMRI) are considered the best methods for detecting LVH. Currently, cMRI is regarded as the "universal standard" for studying cardiac structure [5]. However, there is an ongoing intensive search for medical models for predicting LVH in patients of different therapeutic groups intended to be clearer to practitioners. Our study aimed to identify LVH predictors regardless of systolic blood pressure (SBP) and body mass index (BMI) that will allow proposing a model of LVH probability in patients with OSA of different severity.

Materials and methods

Study design. This cohort observational study included 368 patients (358 males (97.3%), age 46.0 [42.0; 49.0] years) with confirmed obstructive sleep apnea, arterial hypertension, obesity grade I–II according to the WHO classification (1997) who signed an informed consent form. It was a single-center prospective parallel group study with visits on the 3rd, 6th and 12th months in order to assess the metabolic effects of long-term CPAP therapy. The inclusion criteria were: 1) complaints of night snoring and/or respiratory failure at night and scoring more than 3 points on the STOP-BANG scale [6]; 2) obesity BMI > 30 kg/m^2 and/ or abdominal obesity (WM > 94 cm in men, WM > 80 cm in women), and any two of the following metabolic signs:

- fasting plasma glucose level > 5.6 mmol/l and/or HbA1c > 5.7%;
- SBP > 140 mm Hg or DBP > 90 mm Hg or taking antihypertensive drugs during the last 12 months;
- dyslipidemia with increased plasma triglycerides > 1.7 mmol/l; high LDL level > 3.0 mmol/l or low HDL level < 1 mmol/l for men and < 1.2 mmol/l for women, or treatment for dyslipidemia.

Individuals with clinically significant comorbidities and the following conditions were excluded from the study: pregnancy and lactation; type 1 and 2 diabetes mellitus; syndromic forms of obesity; severe somatic comorbidity (thyroid function abnormality, renal and hepatic failure, decompensated heart failure, severe hemodynamic cardiac rhythm disorders, previous myocardial infarction and stroke three months before screening, systemic inflammatory disease, cancer); use of systemic glucocorticosteroids three months before screening; medical history of mental illness and/or that detected during clinical examination; drug and alcohol dependence; patients with pronounced airway obstruction (FEV_1 < 50%), restrictive diseases (VC < 80%), daytime arterial blood saturation SpO_2 < 90% (FiO_2 = 21%).

All patients received optimal antihypertensive and hypolipidemic therapy, followed recommendations on lifestyle changes, dietary intervention and developed physical activity programs. Baseline parameters of patients are shown in Table 1.

This study was carried out at the Department of Phthisiology and Pulmonology of the Faculty of Medicine of the A. I. Evdokimov Moscow State University of Medicine and Dentistry (A. I. Evdokimov MSUMD of the Russian Ministry of Health) at the Central Union Hospital of the Russian Federation (Moscow); it met good clinical practice (GCP) standards and the principles of the Helsinki Declaration and was approved by the Interacademic Ethics Committee of A. I. Evdokimov MSUMD.

Table 1. *Baseline patients' parameters*

Parameter	Patients (n=368)
Age, years	46,0 [42,0; 49,0]
Gender, (male/female, n, %)	358 (97,3)/10 (2,7)
BMI, kg/m²	33,3 [31,7; 35,3]
Neck circumference, cm	44,0 [43,0; 45,0]
Waist circumference, cm	112 [106; 117]
Visceral Adiposity Index, (VAI)	3,11 [2,67; 3,62]
Systolic blood pressure (SBP), mm Hg	145,5 [136; 150]
Diastolic blood pressure (DBP), mm Hg	93,0 [88; 97]
Current smokers (n, (%))	38 (10,3)
Former smokers (n, (%))	210 (57,1)
Never smoked (n, (%))	120 (32,6)
Epworth sleepiness scale (ESS), score	12,0 [9,0; 13,0]
Apnoea-hypopnea index (AHI) (events/h)	28,9 [14,8; 54,0]
Oxygen desaturation index (ODI), (events/h)	18,75 [8,57; 45,28]
Percentage of time with oxygen saturation < 90%, (TSat90), %	18,75 [8,57; 45,28]
Total cholesterol, mmol/L	5,13 [4,83; 5,76]
HDL, mmol/L	0,95 [0,89; 1,02]
LDL, mmol/L	3,52 [3,04; 3,97]
Triglycerides, mmol/L	2,11 [1,98; 2,34]
Apolipoprotein B, g/L	1,31 [1,19; 1,43]
Leptin, ng/ml	25,53 [18,58; 31,05]
Uric acid, μmol/L	440,5 [420,0; 4679,0]
HOMA-IR	4,31 [3,43; 5,37]
Creatinine, μmol/L	84,0 [80,0; 89,0]
Glomerular filtration rate (GFR), ml/min/1.73m2	94,5 [88,0; 101,0]

Echocardiography and Doppler ultrasound of heart and blood vessels were performed in M- and 2D modes in standard echocardiographic views using the Xario 200 ultrasound scanner (Toshiba, Japan) with a 3.5 MHz sensor. Hemodynamic parameters of the LV systolic function (ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV)) were defined by quantitative assessment of 2D echocardiograms using a modified Simpson method. Left ventricular myocardial mass index (LVMMI) was calculated as the ratio of LV myocardial mass calculated by the ASE formula to body surface area (BSA). LVMMI of more than 115 g/m² in men and 95 g/m² in women was considered as LVH [7]. To determine the geometry (type) of LV (normal, concentric remodeling, concentric and eccentric hypertrophy), relative thickness index (RTI) was calculated according to the formula (2xPWTd)/EDD, where PWTd is posterior wall thickness at the end of diastole and EDD is the end-diastolic diameter [8]. The volume of the left atrium (LA) was determined by the biplane formula area/length indexed to body surface area (BSA). The right atrium volume index (RAVI) was calculated by the formula: RAVI = (0.85 × S2/L)/BSA, where S is the area of LA; L is the length of LA; BSA is body surface area [9]. The LV diastolic function was investigated using pulsed-wave Doppler and color Doppler flow mapping [10]. Assessment of the systolic function of the right ventricle (RV) was performed in M-mode by measuring tricuspid annular plane systolic excursion (TAPSE). Epicardial fat thickness (EFT) was determined perpendicularly to the right ventricular free wall in B mode from the parasternal position, along the left ventricular long axis, at end systole, on the line which most perpendicular to the aortic ring [12].

Night somnography (NSG). To detect obstructive sleep apnea, we performed night somnography using a computer-based somnography (CSG) method based on the technology for determining apnea episodes and their consequences by varying changes in peripheral arterial tone (PAT technology) in accordance with unified rules and recommendations of AASM (American Academy of Sleep Medicine) [13, 14]. OSA was found using a WatchPAT-200 portable device for CSG (ItamarMedical,

Caesarea, Israel) with original zzzPAT™SW software ver. 5.1.77.7 (ItamarMedical, Caesarea, Israel) by measuring the main respiratory polygraphic parameters during the period between 11:00 p.m. and 7:30 a.m. Sleep apnea-hypopnea index (AHI) from 5/h to 15/h corresponded to mild OSA, from 15/h to 30/h — to moderate OSA, more than 30/h — to severe OSA. Assessment of nocturnal desaturation ODI, mean and minimum nocturnal saturation (SpO_2), heart rate (HR), and sleep stages was performed in accordance with international recommendations [15, 16].

Statistical analysis. Statistical analysis was performed with the Medcalc statistical software package® ver. 19.2 (MedCalc Software, Belgium; https://www.medcalc.org) and StatPlus:mac® ver. 7 (AnalystSoft Inc.; www.analystsoft.com/ru/). Quantitative data were checked for normal distribution using the Kolmogorov-Smirnov test (with Lilliefors correction) and D'Agostino-Pearson test. Nonparametric data were presented as median (Me), upper and lower quartile (LQ-UQ) as Me [25%; 75%]. To develop a rule that allows estimating the probability of an event, we used simple logistic regression (with the determination of the predictors of the greatest weight) and multiple logistic regression (to build a predictive model). The quality of the obtained model was evaluated by its sensitivity, specificity, and the area under the ROC curve. Model quality assessment was performed according to the value of the expert logistic regression scale in accordance with the criteria set by Hosmer DW (2000), Julkowska MM (2019) [17, 18].

Table 2. *Clinical characteristics OSA patients*

Characteristics	Group A (n=102)	Group B (n=98)	Group C (n=168)
Age, years	44,0 [40,3; 50,0]	47,0 [42,0; 50,0]	46,0 [43,0; 48,0]
Gender, (male/female)	100/2	94/4	164/4
BMI, kg/m^2	32,1 [30,7; 34,1]	33,6 [32,4; 34,8] *	34,1 [32,3; 35,7] ##
Neck circumference, cm	43,0 [42,0; 44,0]	44,0 [43,0; 45,0] *	45,0 [44,0; 46,0] ##
Waist circumference, cm	106 [104; 113]	112 [108; 117] **	114 [109; 118] ##
Visceral Adiposity Index, (VAI)	2,61 [2,22;3,10]	3,13 [2,84;3,49] *	3,48 [2,87;4,08] ##
Epworth Sleepiness Scale (points)	9,0 [8,0; 12,0]	12,0 [9,0; 13,0] **	12,0 [9,0; 14,0] ##

Note: Quantitative data are presented as Me [25%; 75%].
Description: *p <0.05 between group A-B; * * p <0.0001 between group A-B
#p <0.05 between group A-C; ##p <0.0001 between group A-C

Table 3. *Basic polygraphic parameters OSA patients*

Parameter	Group A (n=102)	Group B (n=98)	Group C (n=168)
Apnea–hypopnea index (AHI), h^{-1}	12,7 [9,9; 14,2]	25,7 [21,4; 28,3] **	55,0 [40,9; 68,4] ##
Desaturation index, (ODI), h^{-1}	5,5 [2,5; 8,7]	17,6 [10,8; 20,3] **	47,1 [23,9; 59,1] ##
TSat90, %	1,7 [0,2; 6,9]	12,0 [1,68; 17,0] **	28,5 [13,7; 39,0] ##
SpO_2 mean, %	94,0 [92,0; 94,8]	93,0 [90,0; 93,5] **	91,0 [89,0; 92,0] ##
SpO_2min, %	83,0 [79,0; 88,0]	78,0 [70,0; 82,0] *	72,0 [66,8; 78,3] ##
Night HR min, min^{-1}	45,5 [41,0; 50,8]	43,0 [40,0; 46,0] *	45,0 [40,0; 48,0] #
Night HR max, min^{-1}	100,0 [94,3; 103,0]	99,0 [91,0; 105,0]	102,0 [99,0; 109,0] #
Sleep stages			
REM, %	21,4 [19,1; 25,5]	19,4 [15,3; 25,5]	14,7 [12,9; 19,6] ##
Light sleep, %	59,6 [53,8; 63,1]	66,6 [56,2; 73,8] *	78,9 [71,6; 82,2] ##
Deep sleep, %	19,8 [16,6; 23,1]	13,4 [10,1; 18,5] **	6,5 [4,9; 11,0] ##

Note: Quantitative data are presented as Me [25%; 75%].
Description: *p <0.05 between group A-B; * * p <0.0001 between group A-B
#p <0.05 between group A-C; ##p <0.0001 between group A-C
Definition of abbreviations: TSat90 % — night time spent with oxygen saturation below 90%; SpO2 mean — mean night saturation; SpO2min — minimum night saturation; Night HR min — minimum night heart rate; Night HR max — maximum night heart rate; REM — rapid eye movement sleep

Results

Analysis of Cardiovascular Signs of Obstructive Sleep Apnea

All patients were divided into the following groups depending on OSA severity. Group A, with mild sleep apnea, included 102 patients (100 males; 44.0 [40.3; 50.0] years); group B with moderate course — 98 patients (94 males; 47.0 [42.0; 50.0] years); group C with severe course — 168 patients (164 males; 46.0 [42.0; 48.0] years). Table 2 presents the clinical features of these groups. The severity of excessive sleepiness correlated with OSA severity in all groups. This parameter varied widely. For example, in group A, it was mild/moderate (53.9% / 33.3%), in group B — moderate/significant (38.8% / 13.3%), in group C — moderate/significant (53.6% / 20.2%), indicating a high baseline heterogeneity of patients. The main polygraphic parameters in all groups were characterized by frequent episodes of desaturation with the events of nocturnal hypoxemia, tachy-/bradycardia, and reduced deep sleep. Nocturnal polygraphic parameters are presented in Table 3.

LV systolic function was not impaired in all groups. High intergroup difference was found in the assessment of ESV, LVEF, LV myocardial mass index (LVMI), left and right atrial volume indices, several parameters of the right ventricle, epicardial fat thickness (Table 4).

Table 4 Parameters of the left and right parts of the heart (ECHO-KG)

Parameter	Group A (n=102)	Group B (n=98)	Group C (n=168)
Left atrium (LA) size, cm	3,9 [3,7; 4,2]	4,2 [3,9; 4,5] *	4,3 [4,0; 4,6] ##
LAVI, ml/m²	27,0 [25,0; 31,0]	31,0 [28,0; 33,0] **	31,5 [29,0; 34,0] ##
EDV, ml	125,0 [120,0; 133,0]	130,0 [120,0; 138,0]	135,0 [126,0; 152,0] ##
ESV, мл	42,5 [37,0; 48,8]	47,0 [38,0; 51,0]	51,0 [45,0; 60,0] ##
EF, %	66,0 [62,3; 69,0]	63,0 [61,0; 67,8] *	60,0 [58,0; 64,0] ##
LVMI, g/m²	114,0 [103,0; 120,0]	118,0 [111,0; 129,0] **	125,0 [116,0; 132,0] ##
The normal geometry of the left ventricule, n, %	57 (55,9)	30 (30,6)	24 (14,3)
Left ventricular concentric remodeling, n, %	1 (0,9)	2 (2,0)	4 (2,4)
Concentric LVH, n, %	27 (26,5)	53 (54,1)	123 (73,2)
Eccentric LVH, n, %	17 (16,7)	13 (13,3)	17 (10,1)
RAVI, ml/m²	24,0 [19,0; 30,8]	31,0 [24,0; 35,0] **	34,0 [29,0; 37,0] ##
Right ventricular wall thickness, cm	0,44 [0,39; 0,49]	0,50 [0,46; 0,55] **	0,53 [0,49; 0,55] ##
Right ventricle long-axis diameter, cm	3,30 [2,80; 3,50]	3,40 [3,00; 3,80] *	3,70 [3,20; 4,00] ##
EF, mm	5,50 [4,50; 6,00]	6,50 [5,50; 7,00] **	7,50 [6,38; 8,00] ##
TAPSE, мм	23,0 [21,0; 25,0]	22,0 [21,0; 24,0] *	21,0 [19,8; 24,0] ##
PASP, mmHg	30,0 [27,0; 34,8]	35,0 [30,0; 38,0] **	36,0 [32,0; 42,0] ##
VE/VA, м/с	1,15 [1,00; 1,18]	1,07 [0,91; 1,12] *	1,04 [0,92; 1,13] #
IVRT, мс	95,0 [90,0; 99,8]	99,0 [92,5; 109,0] *	102,0 [96,8; 116,0] ##
DT, мс	190,0 [173,0; 202,0]	209,0 [197,0; 223,0] **	214,0 [201,0; 230,0] ##
LVDD, n (%)	15 (14,7%)	26 (26,5%)	67 (39,8%)
LVDD: type I, n (%)	15 (14,7%)	24 (24,5%)	59 (35,0%) ##
LVDD: type II, n (%)	0 (0%)	2 (2,0%)	8 (4,8%)
LVDD: type III, n (%)	0 (0%)	0 (0%)	0 (0%)

Note: Quantitative data are presented as Me [25%; 75%].
Description: *p <0.05 between group A-B; ** p< 0.0001 between group A-B
#p <0.05 between group A-C; ##p <0.0001 between group A-C
Definition of abbreviations: LA — left atrium; LAVI — left atrial volume index; EDV — end-diastolic volume; ESV — end-systolic volume; EF — ejection fraction; LVMI — left ventricular mass index; LVH — left ventricular hypertrophy; RAVI — right atrial volume index; EF — epicardial fat thickness; TAPSE — systolic excursion of the fibrous ring of the tricuspid valve; PASP — pulmonary artery systolic pressure; VE/VA — ratio of the early (E) to late (A) ventricular filling velocities; IVRT — isovolumic relaxation time; DT — deceleration time; LVDD — left ventricular diastolic dysfunction

Among patients with severe OSA (group C), individuals with the diastolic dysfunction (DD) of the left ventricle (LV) prevailed — unlike in groups A and B. At the same time, initial manifestations of DD in the form of impaired LV relaxation were found in all groups, indicating the redistribution of transmitral flow toward the atrial component. DD progression led to changes in blood flow only in 2% of patients (n = 2) in group B and 4.8% of patients (n = 8) in group C, which was associated with increased LA pressure. LVH was found in 43.2% of patients (n = 44) in group A, 67.4% of patients (n = 66) in group B, and 83.3% of patients (n = 140) in group C. Analysis of LV remodeling types revealed an increase in LV concentric hypertrophy cases depending on OSA severity.

Development of a Model of LVH Probability in Patients with OSA

To establish the predictors/signs that have the best influence on event probability prediction, we performed preliminary statistical analysis. When developing a model of logistic regression, the method of step-by-step elimination of signs was used. The method was performed for all patients aged 46.0 [42; 49] years, with BMI of 33.3 [31.7; 35.3] kg/m².

Table 5. *Mathematical model: time on saturation less than 90%, Epworth sleepiness scale*

Logarithmic likelihood — 2 null model	**453,915**
Logarithmic likelihood — 2 complete model	135,875
Chi-square	318,040
df (degrees of freedom)	2
Level of significance	**P <0,0001**
Cox & Snell R Square	0,5786
Nagelkerke R2	0,8164

We formulated 74 logistic regression equations (based on the number of possible predictors) that assess the possibility of LVH in patients with OSA in order to find a diagnostic rule. Then, two predictors with the highest weight (out of 74 signs) were identified. The following parameters had the greatest prognostic weight: TSat90% — time for saturation less than 90%; ESS — Epworth Sleepiness Scale (points). The results are shown in Table 5.

The likelihood value was a negative double value of the logarithm of the similarity function (–2LL) that was highly significant during the test (after adding influence variables, –2LL was 135.875, which was 318.040 less than the baseline value). This virtually meant that a combination of predictors significantly improves the model. Cox/Shell R^2 ratios and Nagelkerke R^2 obtained from the ratio of likelihood functions demonstrated a high predictive value of this model of 81.64%. Moreover, $\chi 2$ predictors with a level of 318.040 at 2 degrees of freedom ($p < 0.0001$) convincingly demonstrated a high correlation of predictors with the probability of LVH detection in a patient with OSA of different severity. A summary for each variable of this predictive model is shown in Table 6.

According to the model developed, when the threshold value for ESS increases, the probability of LVH increases by 2.79 times (with a fixed value of another predictor), allowing to establish LVH in 93.75% of OSA cases reliably (AUC = 0.975; SD = 0.00741; CI 95% [0.953; 0.988]). The area under the ROC curve (AUC) with a level of 0.975 indicates the excellent quality of the model, its high sensitivity and specificity (Fig. 1).

We set «the cut-off levels» for ESS at 10 points and for TSat90% at 5.2%. This means that each predictor above these levels is already sufficient to predict LVH (ESS has sensitivity of 89.4%; specificity of 92.9%; TSat90% has sensitivity of 93.7%; specificity of 87.6%), and their combination allows not to take into account the «cut-off level» (it works for any value of the parameter) with sensitivity of 93.7% and specificity of 93.8% (Fig. 2). Therefore, there are

Table 6. *MODEL: coefficients and standard errors*

Variable	*Ratio*	*SE*	*P*	*OR*	*CI 95%*
TSat90%	0,21717	0,043	<0,0001	1,24	[1,14; 1,35]
ESS	1,02658	0,156	<0,0001	2,79	[2,06; 3,79]
Constant	-11,48453	1,563	<0,0001	-	-

Note: Definition of abbreviations: SE — standard error; P — significance level; OR — odds ratio; CI — confidence interval; TSat90% — night time spent with oxygen saturation below 90%; ESS — Epworth Sleepiness Scale (points)

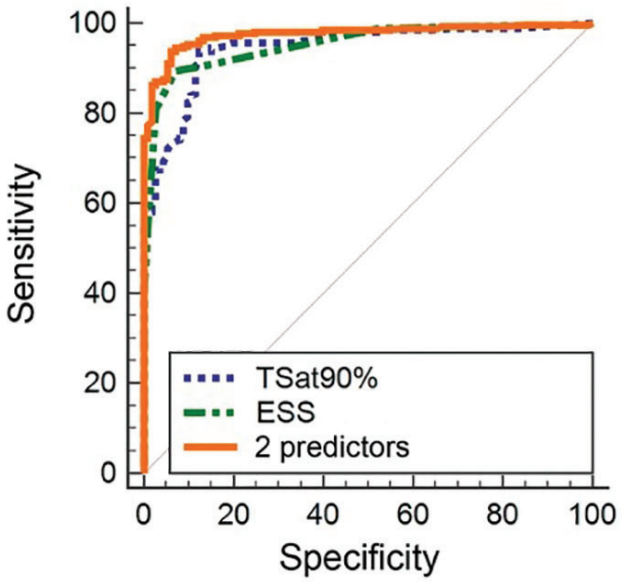

Figure 1. *Graphical representation of the sensitivity and specificity of a model using 2 predictors. Definition of abbreviations: TSat90% – night time spent with oxygen saturation below 90%; ESS – Epworth Sleepiness Scale (points); Orange line – predictive probability of 2 predictors*

objective prerequisites for developing a model for predicting LVH using ESS (patient questionnaire) and TSat90% (computer somnography) in patients with OSA of any severity.

During this work, we created a model for predicting LVH described by the following equation:

$$\mathbf{Z = (-11{,}48453) + 1{,}02658 \times (E) + +0{,}21717 \times (T)}$$

where «Z» is the sum of the numerical values of signs; «E» is the number of points according to the Epworth Sleepiness Scale, «T» is the time for saturation less than 90% (% of total sleep time).

The sum (Z) is equal to the numerical value of signs multiplied by the discriminant coefficient of the sign (1.02658 for the number of points on the ESS Sleepiness Scale and 0.21717 for TSat90%) and summed with a constant (–11.48453). Given the logistic function of the following type: $f(z) = \frac{1}{1+e^z}$, where e = 2.71828947 (base of natural logarithm), we can calculate the probability of LVH using "the probability formula" [15]:

$$p = \frac{e^z \times 100}{1 + e^z} = \frac{e^{(-11{,}48453)+1{,}02658\times(E)+0{,}21717\times(T)} \times 100}{1 + e^{(-11{,}48453)+1{,}02658\times(E)+0{,}21717\times(T)}}$$

Probability ρ > 50% shows a high risk of LVH in a patient with OSA.

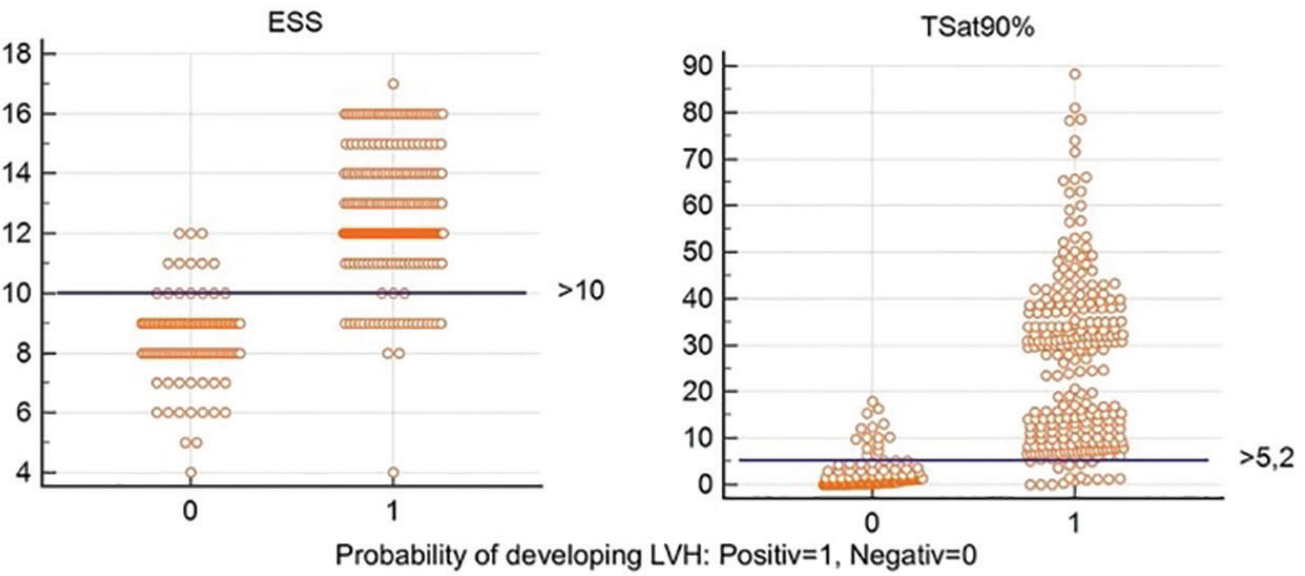

Figure 2. *Graphical representation of the «feature cut-off threshold» for 2 predictors. Definition of abbreviations: TSat90% – night time spent with oxygen saturation below 90%; ESS – Epworth Sleepiness Scale (points); LVH – left ventricular hypertrophy*

Clinical Examples of LVH Probability Calculation

Let us consider the data of a patient with OSA, male, 42, who has 16 points on the ESS Sleepiness Scale (during the survey) and TSat90% = 8.83% (according to the results of computer somnography).

$$Z = (-11{,}48453) + 1{,}02658 \times 16 + \\ + 0{,}21717 \times 8{,}83 = 6{,}86$$

$$p = \frac{e^z \times 100}{1+e^z} = \frac{2{,}71828947^{(6{,}86)} \times 100}{1+2{,}71828947^{(6{,}86)}} = \\ = \frac{953.38545294278 \times 100}{1+953.38545294278} = \frac{95338.545294278}{954.38545294278} = \\ = 99.9\ (\%)$$

The risk of LVH probability in this patient with OSA is 99.9% (> 50%) — **HIGH.**

Another patient with OSA, male, 49, with 5 ESS points (during the survey) and TSat90% = 1.05% (according to the results of computer somnography).

$$Z = (-11{,}48453) + 1{,}02658 \times 5 + \\ + 0{,}21717 \times 1{,}05 = -6{,}12$$

$$p = \frac{e^z \times 100}{1+e^z} = \frac{2{,}71828947^{(-6{,}12)} \times 100}{1+2{,}71828947^{(-6{,}12)}} = \\ = \frac{0.0021984 \times 100}{1+0.0021984} = \frac{0.21984}{1.0021984} = 0.22\ (\%)$$

The risk of LVH probability in this patient with OSA is 0.22% (< 50%) — **LOW.**

Results and Discussion

When a patient with OSA develops a persistent "vicious loop" of systemic inflammation, chronic damage to vital organs and systems develops. Results of a series of studies revealed that the heart and blood vessels are the most exposed organs. The relationship between OSA and cardiovascular conditions such as resistant arterial hypertension (RAH), atrial fibrillation (AF), and chronic heart failure (CHF) was confirmed in large prospective clinical studies [2, 3]. In our opinion, left ventricular myocardial hypertrophy (LVH), increased left ventricular myocardial mass and its structural remodeling as a result of overload by volume/pressure in patients with OSA, can be considered as the best marker of such cardiovascular risks. Despite the high accuracy and diagnostic value of cardiac magnetic resonance imaging (cMRI) as a universal standard for LVH diagnosis, its low accessibility and high cost in real clinical practice make urgent the search for alternative approaches, including medical prediction models. Our proposed model is based on a carefully planned analysis of clinical and instrumental data that can be performed in an outpatient and inpatient setting. Moreover, the predictors we defined, i.e. TSat90% — time for saturation less than 90% (CSG parameter) and ESS — sleepiness according to the Epworth scale (questionnaire parameter), not only have high sensitivity and specificity of LVH prognosis in patients with OSA of different severity, but also allow the practitioner to change the diagnostic and treatment strategy towards early prescription and extending of combination therapy of obstructive sleep apnea.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

M.V. Gorbunova (ORCID: https://orcid.org/0000-0002-2039-0072): contribution to the development of the concept and design, the author's role in the collection, analysis and interpretation of data, the author's consent to be responsible for all aspects of the work

S.L. Babak (Scopus Author ID: 45560913500, ORCID: https://orcid.org/0000-0002-6571-1220): contribution to design development, author's role in data analysis, responsibility for English translation of scientific material

V. S. Borovitsky (ORCHID): the role of the author in conducting medical statistical analysis, responsibility for building a mathematical model and regression equations

Zh. K. Naumenko (Scopus Author ID: 687383, ORCID: https://orcid.org/0000-0002-4804-6142): the role of the author in conducting all types of ultrasound examination of patients and interpreting the data obtained

A.G. Malyavin (ORCID: https://orcid.org/0000-0002-6128-5914): the role of the author in the justification and writing of the manuscript, in the verification of critical intellectual content, and in the final approval for publication of the manuscript

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