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The relationship between the level of Nt-proBNP and indicators of clinical and metabolic status in comorbid elderly patients with type 2 diabetes mellitus

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Aim – to determine the specific features of the use of the semi-quantitative Nt-proBNP immunochromatographic assessment technique for the diagnosis of chronic heart failure (CHF) in comorbid elderly patients with type 2 diabetes mellitus (DM2) in relation to indicators of clinical and metabolic status.

Material and methods. The study was performed using a cross-sectional design; 97 clinical and laboratory-instrumental indicators were studied, including the determination of Nt-proBNP by a semi-quantitative method, in a sample of 50 comorbid elderly patients with T2DM; groups were identified according to the threshold value of Nt-proBNP 450 pg/ml; the interrelationships and significance of differences in variables in the groups were analyzed, including the number of average values of biomarkers for achieving the goals of DM2 treatment and the structure of drug therapy.

Results. A high prevalence of comorbid pathology (arterial hypertension: 90%, obesity: 74%, dyslipidemia: 72%) and a high proportion of participants' failure to achieve therapeutic goals, comparable in the Nt-proBNP groups, were revealed; a significant association between the Nt-proBNP group and the previously established stage of CHF (χ^2 = 6.4; p = 0.041), a positive correlation with the ratio of transmittal blood flow rates in early and late diastole E/A (r = 0.309; p = 0.003); Indirect evidence has been obtained for the high sensitivity of the semi-quantitative assessment of Nt-proBNP for the diagnosis of early-stage CHF.

Conclusion. The majority of comorbid elderly patients with DM2 (72%) have Nt-proBNP levels above the general population threshold of 125 pg/ml and need to verify the diagnosis of CHF. The assessment of the Nt-proBNP test result in T2DM has its own specifics due to polymorbid pathology (obesity and CKD) and the presence of multidirectional "disturbing" factors. When planning a follow-up program for elderly patients with DM2 and hypertension, the indications for Nt-proBNP screening should be taken into account, and if the result is positive, for an in-depth Echocardiography examination.

Keywords: old age, type 2 diabetes mellitus, N-terminal brain-promoting natriuretic peptide, chronic heart failure, comorbid pathology.

Conflict of interest: nothing to disclose.

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Взаимосвязь уровня Nt-proBNP и показателей клинико-метаболического статуса у коморбидных пожилых пациентов с сахарным диабетом 2 типа

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Аннотация

Цель – определить специфические особенности применения иммунохроматографической полуколичественной методики оценки Nt-proBNP для диагностики хронической сердечной недостаточности (ХСН) у коморбидных пожилых пациентов с СД 2 типа (СД2) во взаимосвязи с показателями клинико-метаболического статуса.

Материал и методы. Исследование выполнено по кроссекционному дизайну. Изучено 97 клинических и лабораторно-инструментальных показателей, включая определение Nt-proBNP полуколичественным методом, в выборке 50 коморбидных пожилых пациентов с СД2. Выделены группы по пороговому значению Nt-proBNP 450 пг/мл. Проанализированы взаимосвязи и значимость различий переменных в группах, в том числе средних значений биомаркеров достижения целей лечения СД2 и структуры медикаментозной терапии.

Результаты. Выявлены высокая распространенность коморбидной патологии (артериальной гипертензии (АГ) – 90%, ожирения – 74%, дислипидемии – 72%) и высокая доля недостижения терапевтических целей участников, сопоставимые в группах Nt-proBNP. Определена значимая ассоциация между группой Nt-proBNP и ранее установленной стадией ХСН (χ^2=6,4; p=0,041), а также положительная корреляция с показателем соотношения скоростей трансмитрального кровотока в раннюю и позднюю диастолу E/A (r=0,309; p=0,003). Получены косвенные доказательства высокой чувствительности полуколичественной оценки Nt-proBNP для диагностики ХСН ранних стадий.

Выводы. Большинство (72%) коморбидных пожилых пациентов с СД2 имеют уровень Nt-proBNP выше общепопуляционного порогового значения 125 пг/мл и нуждаются в верификации диагноза ХСН. Оценка результата теста Nt-proBNP при СД2 имеет специфику, обусловленную полиморбидной патологией (ожирение и ХБП) и наличием разнонаправленных «возмущающих» факторов. При планировании программы диспансерного наблюдения пожилых пациентов, имеющих СД2 и АГ, следует учитывать показания к скринингу Nt-proBNP, а при положительном результате – к углубленному эхоКГ-обследованию.

Ключевые слова: пожилой возраст, сахарный диабет 2 типа, N-терминальный промозговой натрийуретический пептид, хроническая сердечная недостаточность, коморбидная патология.

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Список сокращений
АГ – артериальная гипертензия; АД – артериальное давление; АРМЭ – автоматизированное рабочее место врача-эндокринолога; ДАД – диастолическое АД; иДПП-4 – ингибитор дипептидилпептидазы 4 типа; ИБС – ишемическая болезнь сердца; ИММ – индекс массы миокарда; ИМТ – индекс массы тела; иНГЛТ-2 – ингибитор натрий-глюкозного котранспортера 2-го типа; ИС_СКФ – индекс снижения скорости клубочковой фильтрации; КДР – конечный диастолический размер; КСР – конечный систолический размер; ЛП – левое предсердие; ЛЖ – левый желудочек; ОИМ – острый инфаркт миокарда; ОНМК – острое нарушение мозгового кровообращения; САД – систолическое АД; СКФ – скорость клубочковой фильтрации; СППВР – система поддержки принятия врачебных решений; СД2 – сахарный диабет 2 типа; ТЗС – толщина задней стенки; ТМЖП – толщина межжелудочковой перегородки; ХБП – хроническая болезнь почек; HbA1c – гликированный гемоглобин; Nt-proBNP – N-терминальный промозговой натрийуретический пептид.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) significantly increases risks of cardiovascular complications win an inevitable outcome of chronic heart failure (CHF) [1]. In many T2DM patients, CHF may manifest as the first cardiovascular event [2]. Even the clinical manifestations of pre-diabetes vs. normoglycemia increase the risk of CHF development [3], cardiovascular death and all-cause mortality [4] by 9–58%.

CHF of clinically manifested stages is confirmed in 10–30% patients with T2DM, and it is especially often registered in the age over 70 [5]. At the same time, the prevalence of non-diagnosed CHF (specifically, pre-heart failure) in T2DM patients [6], as well as non-diagnosed disorders of carbohydrate metabolism (impaired glucose tolerance, pre-diabetes, T2DM) in the general population is significant [6]. For example, the results of a meta-analysis of a screening study in the Netherlands showed that up to 4.2% of adults has objective EchoCG signs of CHF, which was considerably higher than the official registry data of 1-2% [7]. According to epidemiology data, the overall survival of patients 10 years after diagnosis of CHF is 24.5% [8].

Many scientists now consider T2DM the major risk factor of CHF onset, and patients with T2DM are regarded as patients likely having Stage A CHF (ACC/AHA Guidelines) [9].

One of priority components of T2DM management strategy in the senior age is prevention of cardiovascular risks and mortality, which necessitates search for and studies of methods of early diagnostic confirmation or exclusion of CHF. Studies of clinical significance of evaluation of natriuretic peptide concentration, including Nt-proBNP, for the screening of CHF have confirmed that this method allows for a reliable exclusion of CHF diagnosis in patients [10] and is economically feasible for the public health care [11]. It was established that values over the threshold level of Nt-proBNP are an indication for further in-depth diagnosis, confirmation of CGF status, identification of its form and severity [12].

The main goal of any screening method is to provide an answer of what threshold level of a biomarker allows for a highly reliable establishment or exclusion of some diagnosis or other. To that end, available simple qualitative and semi-quantitative tests are used [13]. We performed a focused search for studies with evidence-based findings of a relation between the level of natriuretic peptides and the parameter of clinical and metabolic status of comorbid patients with T2DM; however, it yielded no results.

The key factors complicating the determination of threshold values of Nt-proBNP in diabetes mellitus are the specific phenotype of CHF with preserved ejection fraction and prevalence of restrictive lesions of the myocardium, and status of comorbid factors and conditions significantly affecting the concentration of Nt-proBNP (obesity, diabetic nephropathy, age).

AIM

To determine the specific features of the use of the semi-quantitative Nt-proBNP immunochromatographic assessment technique for the diagnosis of chronic heart failure (CHF) in comorbid elderly patients with type 2 diabetes mellitus (T2DM) in relation to indicators of clinical and metabolic status.

MATERIAL AND METHODS

Study design. One-time cross-sectional clinical study in the population sample of comorbid elderly patients with T2DM.

Clinical base. The study is performed by the Department of Endocrinology and Geriatrics of the Samara State Medical University at the Department of endocrinology of the Samara Regional Clinical Hospital named after V.D. Seredavin.

Characteristics of participating group. The sample of participants (n=50) was formed on a random basis. It consisted of comorbid patients with a confirmed T2DM diagnosis hospitalized to the Department of endocrinology for a planned correction of therapy.

Inclusion criteria: patients with T2DM aged 60 to 74.9 years with confirmed concomitant diseases (arterial hypertension, coronary heart disease, obesity), GFR within 30 to 120 ml/min/1.73 m^2. Exclusion criteria: acute complications of diabetes mellitus, exacerbation of comorbid diseases at the moment of hospitalization, acute vascular diseases within 3 preceding months, availability of objective signs of a severe cardiac stasis (Stage II on the classification of the Russian Society of Cardiology of 2023 [14]), CKD Stage 4 and later, concomitant system pathology with a significant impact on the heart and kidney function (anemia with hemoglobin concentration below 90 g/l, gouty arthritis, malignant growth), dementia, limited functional self-care capacity, lack of informed consent.

Forming of the study sample and identification whether or not the participants meet the selection criteria were performed on the basis of medical data of preceding stages of outpatient observation, i.e. in the period before the official approval of the new CHF classification. Considering these circumstances, the old Strazhesko-Vasilenko classification was used.

The clinical characteristics of the general sample of participants follows in **Table 1**.

Since the value of the mean square deviation of creatinine level was comparable with the absolute value, the data is presented in two variants, the arithmetic mean and the standard deviation (M±SD), and the median and quartiles (Me [Q1; Q3]).

The laboratory tests included the classic indicators of clinical monitoring of DM patients as well as methods of in-depth analysis of objective parameters of CHF. Firstly, the concentration of N-terminal brain natriuretic peptide (Nt-proBNP) was determined using a domestic semi-quantitative immunochromatographic assay test (Scientific Production Company "BioTest" LLC, Novosibirsk). The test earlier demonstrated high diagnostic value as compared to the quantitative assessment of Nt-proBNP with an immunochemical assay test in the DREAM study [15], allowing identification of five ranges of values: 0-124 pg/mL; 125-449 pg/mL; 450-899 pg/mL; 900-1799 pg/mL; ≥1800 pg/mL. Secondly, an assessment of diastolic dysfunction (DD) and structural and functional disorders was performed by non-contrastive transthoracic echocardiography using the Vivid E9 ultrasonic scanner.

Collection of primary clinical material. The software suite "Endocrinologist's Automated WorkplaceARME 2.0" was used to collect the primary material. The software complex systematizes the data and stores them on digital media during outpatient visits. The matrix of formalized consultation protocol of the ARME 2.0 includes 97 history, clinical and laboratory indicators of DM patients that belong to the standard of dispensary monitoring;

Participants, n	50	
Sex (M/F), n (%)	13/37 (26,0/74,0)	
Mean age, years	65,64±4,01	
Diabetes age, years	14,52±8,12	
BMI, kg/m2	34,07±5,99	
HbA1c, %	8,93±2,58	
Creatinine, μmol/L	94,21±39,97	84,25 [73,85; 107,66]
GFR CKD-EPI (ml/min/1.73 m^2)	65,42±19,15	

Table 1. *Clinical characteristics of the general sample*
Таблица 1. *Клиническая характеристика генеральной выборки*

Clinical parameter	N	% in the group
CKD 3a-b (GFR < 60 mL/min/1.73 m²)	20	40,0
Retinopathy	15	30,0
Foot polyneuropathy	42	84,0
Stable angina	20	40,0
History of acute MI	4	8,0
History of ACVA	9	18,0
Chronic obliterative arterial disease of the lower limbs	4	8,0
Confirmed CHF	12	24,0
Arterial hypertension	45	90,0
Obesity	37	74,0
Dyslipidemia	36	72,0

Table 2. *Prevalence of complications of DM and comorbid pathology in the general sample*

Таблица 2. *Распространенность осложнений СД и коморбидной патологии в генеральной выборке*

Clinical parameter	M±SD
HbA1c, %	9,47±2,92
delta HbA1c = HbA1c-ЦУ, %	1,48±2,59
Glycaemia on admission, mmol/L	8,49±3,53
Glycaemia on self-control, min, mmol/L	7,31±2,51
Glycaemia on self-control, max, mmol/L	15,54±3,80
Glycaemia variability, mmol/L	8,23±4,06
Cholesterol_ mmol/L	5,00±1,27
LDL_ mmol/L	2,82±1,01
delta LDL = LCL-TL, %	1,41±0,96
SBP_office	131,60±6,50
DBP_office	78,48±12,99

Table 3. *Indicators of therapeutic control of diabetes in the general sample*

Таблица 3. *Показатели терапевтического контроля СД в генеральной выборке*

integrated and external modules of the medical decision-making support system (MDMSS) ensure identification of the variables (BMI, GFR under the CKD-EPI formula, stages of obesity and CKD, dyslipidemia status, arterial hypertension risk groups, target values of HbA1c, blood pressure, LDLs, SCORE2 risk, and others).

Statistical analysis. The primary material from the ARME DM database to a Microsoft Excel file was done with automation tools and a pre-set query script. Specialized software was used for the purposes of statistical analysis and mathematical modeling: SPSS 26.0 (IBM Corporation, Armonk, New York, USA). Nominal features were coded with numbers with respective labels assigned. The values of text fields of pharmacological therapy were validated using the nominal scale with segregation of drug classes.

Normality of distribution for quantitative variables was assessed graphically using visual analysis of histograms and the Shapiro-Wilk test. In cases of significant deviations from normality, non-parametric analytical methods were applied. Descriptive statistics for quantitative variables are presented as mean standard deviation (M±SD) or, in cases of substantial non-normality, as median and quartiles [Me (Q1; Q3)]. Categorical variables are described using counts and percentages of the group size.

Mann-Whitney and Student's tests were used to compare the quantitative parameters in groups. The frequencies of nominal features were compared by calculating the Pearson's χ^2 test and Fisher's two-tail exact test. The strength of associations between variables was assessed using Spearman's rank correlation for quantitative variables and Kendall's tau-b correlation for pairs of ordinal and quantitative variables. Results were considered statistically significant at $p < 0.05$ for all types of statistical analysis.

RESULTS AND DISCUSSION

The structure of the concomitant pathology and vascular complications in elderly T2DM patients is shown in **Table 2**.

Among the microvascular complications of the DM, worthy of note are the high prevalence of CKD with filtration function value below 60 mL/min/1.73 m² (40%) and polyneuropathy of the lower limbs (84%). The incidence rate of chronic forms of CHF was between 8% and 40%. The diagnosis of CHF in the study participants was established and verified by outpatient cardiologists in the preceding stages of outpatient monitoring. Considering the dedicated profile of the department and decompensated progression of diabetes in the majority of patients, the evaluation of functional disorders of the myocardium was performed using standard EchoCG parameters without functional stress tests. The CHF prevalence, according to history data, was 24%.

The concomitant comorbid diseases were present in all participants of the sample: the incidence of arterial hypertension was close to 100%, BMI was higher than the threshold value of obesity diagnosis in 74% cases, and dyslipidemia found in 72%.

Quantitative indicators of therapeutic control of elderly comorbid T2DM patients are shown in **Table 3**.

The average values of HbA1c (9.47±2.92%), its difference with the target and actual value (delta HbA1c 1.48±2.59%), glycaemia on admission (8.49±3.53 mmol/L), as well as its high variance in self-control (8.23±4.06 mmol/L) shows unsatisfactory control of glycemic status of T2DM patients. One of the most important parameters of the lipid profile, the LDL, are also outside the target range with the average value being 2.82±1.01 mmol/L, which is 1.41±0.96 mmol/L different from the target value. According to current recommendations, the target level of systolic BP is 120–130 mmHg, and the evaluation of its average value (131.60±6.50 mmHg) leads to believe that it is close to the target value. However, the analysis of the qualitative parameter of SBP meeting the target range shows a less positive situation (**Table 4**).

Clinical parameter	N	% in the group
Glycemic control (HbA1c < 7.5%)	17	34,0
Lipid control (LDL < 1.4 mmol/L)	3	6,0
SBP < 130 mmHg	7	14,0
DBP < 80 mmHg	41	82,0
All parameters (HbA1c, LDL, BP)	0	0,0

Table 4. *Frequency of achieving target levels of therapeutic control in elderly patients with DM*

Таблица 4. *Частота достижения целевых уровней терапевтического контроля у пожилых пациентов с СД*

Drug	n (%)	% in the group
Insulin	40	80,0
Sulphonylurea	18	36,0
Biguanides	29	58,0
DPP4i	6	12,0
Gliflozins	27	54,0
Monotherapy	7	14,0
Two drugs in tablets	21	42,0
Three drugs in tablets and more	10	20,0

Table 5. *Structure of hypoglycemic therapy in elderly patients with DM2*

Таблица 5. *Структура гипогликемической терапии пожилых пациентов с СД2*

Nt-proBNP	Range	N	% in the sample
0-124 pg/mL	1	12	24,0
125-449 pg/mL	2	7	14,0
450-899 pg/mL	3	16	32,0
900-1799 pg/mL	4	10	20,0
≥1800 pg/mL	5	5	10,0

Table 6. *Distribution structure of elderly patients with DM2 by Nt-proBNP ranges*

Таблица 6. *Структура распределения пожилых пациентов с СД2 по диапазонам Nt-proBNP*

The data shows that the goals of glycemic control were formally met in 34% of examined elderly T2DM patients, lipid control, in 6%, SBP, in 14%, the DBP meeting the target level in the majority of participants (82%). Thus, two most serious problems of efficient compensation of DM in the elderly age were localized, viz. meeting the SBP and LDL target levels.

The analysis of drugs used to control carbohydrate metabolism in the group of elderly T2DM patients is shown in **Table 5**.

The vast majority of hospitalized elderly patients with T2DM received insulin therapy (80%). Among oral antidiabetic drugs, biguanides were the most prescribed (58%), followed by SGLT-2 inhibitors (54%). The most common regimen involved two concomitant medications (42% of cases). Analysis of the table indicates that glucose-independent insulin secretagogues and irrational pharmacotherapy regimens were used with considerable frequency.

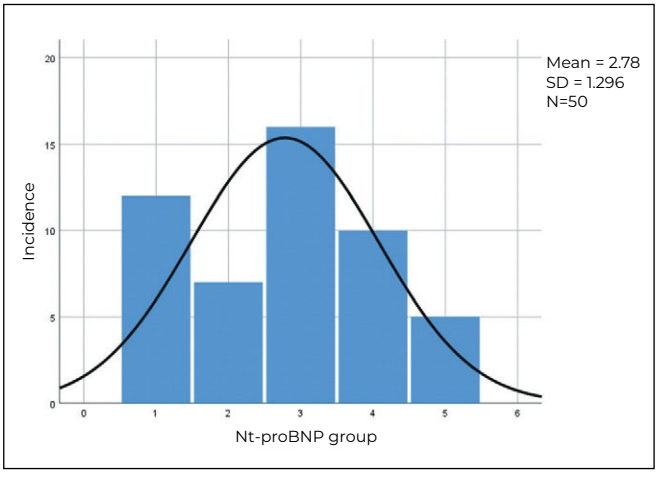

Figure 1. *Histogram of the sample distribution over the Nt-proBNP ranges.*

Рисунок 1. *Гистограмма распределения выборки по диапазонам Nt-proBNP.*

	Nt-proBNP < 450 pg/mL, n=19		Nt-proBNP ≥ 450 pg/mL,		p
	n=31	%	N	%	
No Ds CHF	14	73,7%	24	77,4%	1,000
CHF Stage 1	5	26,3%	2	6,5%	0,089
CHF Stage 2a	0	0,0%	5	16,1%	0,142

Note: p – significance of difference between groups as per Fischer's exact test
Примечания: p – значимость различий между группами: по точному критерию Фишера.

Table 7. *Frequency of previously established stages of CHF in the Nt-proBNP groups*

Таблица 7. *Частота ранее установленных стадий ХСН в группах Nt-proBNP*

The frequency of distribution of the sample participants by ranges of Nt-proBNP determined by semi-quantitative method is shown in Table 6.

The majority of comorbid elderly T2DM patients belong to range 3 with Nt-proBNP values of 450 to 899 pg/mL, which, according to the current clinical recommendations [12], is to be regarded as the necessity for further in-depth examination for CHF. The histogram of distribution of participants of the sample over the Nt-proBNP ranges is shown in **Figure 1**.

Considering the limitations of the semi-quantitative method of Nt-proBNP determination, it order to evaluate the correlations with clinical and metabolic indicators the sample was divided into groups with the threshold value of 450 pg/mL: groups A (Nt-proBNP < 450 pg/mL, n=19) and group B (Nt-proBNP ≥ 450 pg/mL, n=31). The histogram of participant distribution in the groups is shown in **Fig. 2**.

Based on a preliminary analysis of this histogram, it is admissible to suggest the following: semi-quantitative immuno-chromatographic assay of Nt-proBNP shows high sensitivity, especially in the subclinical stage of CHF development. In 22 participants (44%) with no history of CHF diagnosis, Nt-proBNP ≥ 450 pg/mL was found. This may indicate low detection of initial manifestations of CHF in elderly T2DM patients.

The diagram of incidence rates based on the threshold value of 125 pg/mL, standard cutoff point in CHF screening for general population (**Fig. 3**) clearly demonstrates that over a half of study participants (72%) without a confirmed

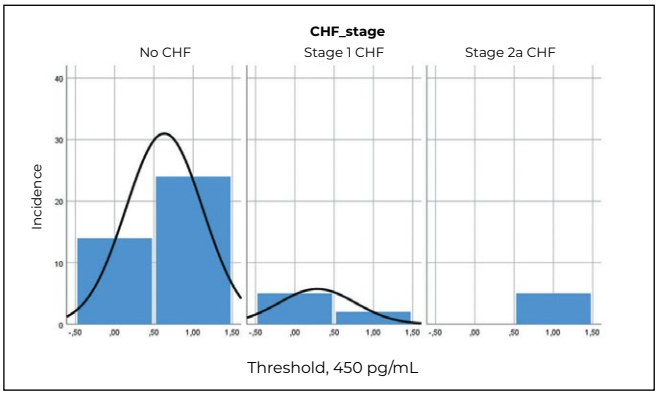

Figure 2. *Histogram of the distribution of NT-proBNP groups with a threshold value of 450 pg/ml according to previously established stages of CHF.*

Рисунок 2. *Гистограмма распределения групп NT-proBNP с пороговым значением 450 пг/мл по ранее установленным стадиям ХСН.*

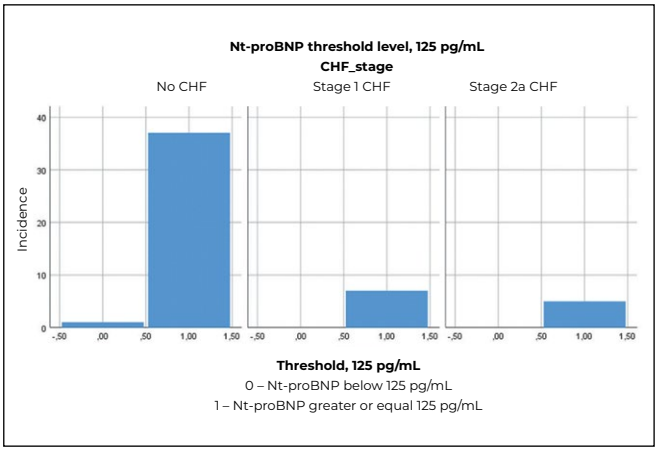

Figure 3. *Histogram of the distribution of NT-proBNP groups with a threshold value of 125 pg/ml according to previously established stages of CHF.*

Рисунок 3. *Гистограмма распределения групп NT-proBNP с пороговым значением 125 пг/мл по ранее установленным стадиям ХСН.*

diagnosis of CHF as per previous stages of dispensary follow-up, require a deeper diagnostic [12].

A closer assessment of the strong relation of the Nt-proBNP groups with the earlier established CHF stages allows for an analysis of contingency tables (**Table 7**).

The general Pearson's χ^2 for the contingency table was χ^2=6.4; p=0.041, which allows for a conclusion of a significant association between the Nt-proBNP group and the clinical CHF stage. The number of patients with 2a CHF stage was only 5 patients, but they all were within the elevated Nt-proBNP group. In the assessment of paired contingency tables, in accordance with the strict rules of medical statistics, Fisher's exact test was used. However, if Pearson's χ^2 test is to be used as maximum likelihood (p=0.024), a trend for higher incidence of CHF stage 2a is identified in patients with Nt-proBNP ≥ 450 pg/mL.

To clarify the correlation between groups identified as per Nt-proBNP category, with DM complications and comorbid pathologies, paired contingency tables were analyzed by nominal features (**Table 8**).

Following from literature data, a concomitant pathology may have various effects on the Nt-proBNP concentration. Excessive body mass and obesity may reduce the Nt-proBNP level thus masking the CHF [16]; patients with reduced kidney filtration function may accumulate the Nt-proBNP, which reversely affects the level of this parameter [17]. In our study, we checked the incidence rate of concomitant diseases in the Nt-proBNP groups but found no significant differences, which might have been related to non-inclusion of patients with extreme manifestations of these pathologies in the sample. The interaction of these competing factors (high BMI and reduced GFR), characteristic for most elderly T2DM patients, and their joint effect on the Nt-proBNP concentration necessitates a separate in-depth analysis on large samples.

To clarify the effect of conventional indicators of DM therapeutic control on the Nt-proBNP value in the groups, their average values were compared (**Table 9**).

No significant differences were found in the average values of the glycemic, lipid and hemodynamic control as well as rated parameters of reaching their target values mediated by the level of. One may suggest that despite the common links in the pathogenetic mechanism of DM and CHF, concentration of Nt-proBNP reflects only the increased extension of the cardiac chambers and has no direct connection with the compensation of DM. Noteworthy is the trend of the indicator of glycaemia variance towards significance (p=0.065) that had not reached the threshold value: this is a new indicator of glycemic control that demonstrated a significant relation with the development of vascular complications in DM patients [18, 19]. The data on the lack of relation between HbA1c and Nt-proBNP were tested by correlation analysis, and a single relation was found: that between the relative proportion of patients who reached the target level of glycemic control, and adherence to the segregated Nt-proBNP groups, Spearman's correlation having a negative sign and nearing the significance threshold (r=-0.276; p=0.052).

The following stage included a comparison of the average values of standard indicators of blood biochemical test in the Nt-proBNP groups (**Table 10**).

Clinical parameters	Group A, n (%)	Group B, n (%)	p
3a-b CKD (GFR < 60 mL/min/1.73 m²)	6 (31,6)	14 (45,2)	0,387
Retinopathy	4 (21,1)	11 (35,5)	0,351
CAD	12 (63,2)	18 (58,1)	0,774
Stable angina, FC2	10 (52,6)	10 (32,3)	0,235
History of acute MI	2 (10,5)	2 (6,5)	0,629
History of ACVA	2 (10,5)	7 (22,6)	0,452
Chronic obliterative arterial disease of the lower limbs	1 (5,3)	3 (9,7)	1,000
Arterial hypertension	19 (100,0)	30 (96,8)	1,000
Obesity	14 (73,7)	23 (76,7)	1,000
Dyslipidemia	14 (52,6)	26 (32,3)	0,474

Note: p – significance of difference between groups as per Fischer's exact test
Примечания: p – значимость различий между группами по точному критерию Фишера.

Table 8. *Structure of DM complications and concomitant pathology in the Nt-proBNP groups*

Таблица 8. *Структура осложнений СД и сопутствующей патологии в группах Nt-proBNP*

Clinical parameters	Group A M±SD	Group B M±SD	p
HbA1c, %	8,58±1,66	9,14±3,01	0,395
delta HbA1c = HbA1c-ЦУ, %	1,10±1,65	1,71±3,02	0,365
Glycaemia on admission, mmol/L	8,51±3,79	8,48±3,43	0,977
Glycaemia on self-control, min, mmol/L	7,66±2,46	7,08±2,55	0,436
Glycaemia on self-control, max, mmol/L	14,63±2,93	16,14±4,22	0,151
Glycaemia variability, mmol/L	6,97±3,29	9,06±4,35	0,065
Cholesterol_ mmol/L	2,62±0,95	2,93±0,96	0,284
LDL_ mmol/L	1,22±0,95	1,53±0,96	0,283
SBP_office	132,11±6,31	131,29±6,70	0,667
DBP_office	79,47±5,24	80,97±5,98	0,374

Note: p – significance of differences
Примечания: p – значимость различий

Table 9. *Indicators of therapeutic control of diabetes in the Nt-proBNP groups*

Таблица 9. *Показатели терапевтического контроля СД в группах Nt-proBNP*

Clinical parameters	Group A M±SD	Group B M±SD	P
Cholesterol, mmol/L	4,82±1,27	5,16±1,20	0,342
HDL, mmol/L	1,22±0,23	1,26±0,41	0,699
TG, mmol/L	2,18±0,92	1,99±0,85	0,445
Creatinine, μmol/L	87,32±27,99	98,44±45,72	0,345
GFR CKD-EPI (ml/min/1.73 m²)	69,35±20,82	63,02±17,98	0,261
IS_GFR, ml/min/1.73 m² per year	1,20±1,14	2,92±3,71	0,023*

*Note: p – significance of differences, * – p<0.05*
*Примечания: p – значимость различий; * – p<0,05.*

***Table 10.** Biochemical parameters in Nt-proBNP groups*

***Таблица 10.** Биохимические показатели в группах Nt-proBNP*

Clinical parameters	Group A M±SD	Group B M±SD	P
LV end diastolic size, mm	48,28±4,60	48,61±3,71	0,790
LV end systolic size, mm	32,11±4,56	31,46±3,60	0,595
LV posterior wall thickness, mm	11,14±1,19	11,52±1,15	0,287
IV septum thickness in diastole, mm	11,88±1,39	12,52±1,41	0,138
MMI_LV, g/m²	117,24±40,21	119,98±30,16	0,807
LA, mL	34,84±4,29	37,56±11,75	0,366
Ejection fraction, mL	61,89±6,88	62,68±6,04	0,684
E/A	0,83±0,24	0,89±0,25	0,528
TAPSE, mm	21,62±1,19	22,76±4,04	0,328
LA, mm	22,13±1,89	22,77±1,99	0,305

Note: p – significance of differences
Примечания: p – значимость различий.

***Table 11.** Indicators of instrumental examinations in Nt-proBNP groups with a threshold value of 450 pg/ml*

***Таблица 11.** Показатели инструментальных обследований в группах Nt-proBNP с пороговым значением 450 пг/мл*

The concentration of all studies biomarkers demonstrated no significant differences in the Nt-proBNP groups. These data confirm, yet again, the high diagnostic value of the Nt-proBNP level providing to the researcher some unique highly selective information about the pathological process of CHF development that finds no specific reflection in no other biochemical parameters of the blood. The exception was the calculated parameter IS_GFR (p=0.023), the original diagnostic parameter developed in the Department of Endocrinology and Geriatrics of SamSMU, that allows for a quantitative characteristics of the rate of progression of CKD in diabetes. Our earlier research provided a detailed clinical justification of the predictive value of IS_GFR exceeding the threshold value of 3.83 mL/min/1.73 m² per year as a new biomarker of adverse outcome in elderly patients with T2DM[1]. The control analysis of the paired contingency table confirmed the established correlation of the IS_GFR groups with the threshold value of 3.83 mL/min/1.73 m² and Nt-proBNP groups with the threshold value of 450 pg/mL with a high level of significance (Fisher's exact test value was 0.018).

Most interesting is the analysis of average values of EchoCG in the Nt-proBNP groups (**Table 11**).

The key EchoCG indicators of CHF demonstrated a monotonous line of values with no significant differences in the Nt-proBNP groups. At the same time, the correlation analysis identified a highly significant correlation of the diastolic function of the myocardium, i.e. ratio of velocities of transmitral flow in the early and late diastole E/A (r=0.309; p=0.003) with a complete absence of correlation with ejection fraction (r=-0.031; p=0.784). One may suggest that the data stem from a specific CHF phenotype with preserved ejection fraction and predominantly restrictive damage of the myocardium, characteristic of T2DM [20] and obese patients [21]. In a recent study [22], an attempt was made to identify independent EchoCG indicators to establish a prognosis for CHF patients with preserved ejection fraction. The authors make it a point that such indicators are only the global longitudinal strain of the left ventricle and the ratio of the systolic excursion of the ring of the triscupid valve and the systolic pressure in the pulmonary artery. In any case, the obtained data emphasize the necessity of studying and clarifying the changes in the EchoCG parameters specific for elderly T2DM patients, and of a wider use of up-to-date methods of instrumental confirmation of CHF (tissue Doppler velocimetry with E/e' ratio measurement, assessment of systolic pressure in the pulmonary artery, LV global longitudinal strain, LA index), the indications for which may be provided by the Nt-proBNP semi-quantitative test.

Brugs	Group A M±SD	Group B M±SD	P
Insulin	15 (78,9)	25 (80,6)	0,884
Sulphonylurea	6 (31,6)	12 (38,7)	0,610
Biguanides	13 (68,4)	16 (51,6)	0,242
DPP4i	2 (10,5)	4 (12,9)	0,802
Gliflozins	12 (63,2)	15 (48,4)	0,309
Monotherapy	5 (26,3)	2 (6,5)	0,049*
Two drugs in tablets	8 (42,1)	13 (41,9)	0,991
Three drugs in tablets and more	4 (21,1)	6 (19,3)	0,884

*Note: p – significance of differences, * – p<0.05*
*Примечания: p – значимость различий; * – p<0,05.*

***Table 12.** Structure of hypoglycemic therapy in Nt-proBNP groups with a threshold value of 450 pg/ml*

***Таблица 12.** Структура гипогликемической терапии в группах Nt-proBNP с пороговым значением 450 пг/мл*

One of the most important factors determining the dynamics of CHF progression is the timely prescription of a complex multi-component pharmacological therapy. In this study, we evaluated the structure of hypoglycemic drugs in groups of various levels of NT-proBNP, determined frequency of their prescription by pharmacological classes, and significance of differences in the segregated groups (**Table 12**).

Significant differences between the Nt-proBNP groups were observed only for the frequency of monotherapy prescription, which is primarily used in the early stages of DM. It is reasonable to assume that such patients are less prone to developing macrovascular complications and, even more so, clinically manifest CHF. This likely explains why the relative proportion of patients receiving

[1] Первышин Н.А. Способ прогнозирования риска высокого темпа прогрессирования хронической болезни почек у пациентов пожилого возраста при сопутствующем сахарном диабете 2 типа. Патент на изобретение № 2825048. Доступно по: https://www.fips.ru/cdfi/fips.dll/ru?ty=29&docid=2825048

a single glucose-lowering drug is higher in Group A compared to patients exceeding the 450 pg/mL threshold.

Limitations of study. The present study was designed as a phase analysis, and its clinical interpretability was limited by the insufficient sample size. The application of more advanced medical statistics methods, particularly logistic regression, requires a more extensive primary dataset and additional participant enrollment, which is currently underway.

CONCLUSIONS

1. In three out of four elderly comorbid patients with T2DM, the level of Nt-proBNP was found to be higher than the general population threshold value, which necessitates further verification and clarification of the CHF stage in such patients.

2. All elderly comorbid patients with T2DM, previously diagnosed with CHF in earlier stages of outpatient monitoring, demonstrated an elevation of the Nt-proBNP level above 125 pg/mL, which allows to conclude that the sensitivity of the semi-quantitative Nt-proBNP test is 100%.

3. The application of the semi-quantitative Nt-proBNP test in elderly T2DM patients has its proper specifics stemming from the polymorbid pathology and presence of competing contributing factors, i.e. BMI, GFR, age.

4. Insufficient specificity of the semi-quantitative Nt-proBNP test in elderly T2DM patients may be accounted for by low detection of early-stage CHF in T2DM, and availability of concomitant diseases (obesity and CKD).

5. When planning outpatient management of elderly comorbid patients with T2DM and concomitant arterial hypertension, it is to be taken into account that Nt-proBNP screening is indicated for this group. Its positive result is an indication for a detailed echocardiographic examination.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval: Protocol LEC of the SamSMU No. 269 of September 13, 2023.	***Этическая экспертиза.*** Протокол ЛЭК СамГМУ №269 от 13 сентября 2023 г.
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. N.A. Pervyshin: study design, criteria for matching participants, statistical processing of clinical material, writing of the text. S.V. Bulgakova: organization of research, editing. O.A. Shtegman: clinical interpretation of the results, editing of the text. V.N. Vasilkova, L.A. Sharonova: clinical interpretation of results. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Н.А. Первышин – дизайн исследования, критерии соответствия участников, статистическая обработка клинического материала, написание текста. С.В. Булгакова – организация исследования, редактирование рукописи. О.А. Штегман – клиническая интерпретация результатов, редактирование текста. О.Н. Василькова, Л.А. Шаронова – клиническая интерпретация результатов. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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