

Vinogradova N. G.¹, Polyakov D. S.^{1,2}, Berestovskaya V. S.³

¹ Lobachevsky National Research Nizhny Novgorod State University, Nizhny Novgorod, Russia

² Privolzhsky Research Medical University, Nizhny Novgorod, Russia

³ Almazov National Medical Research Center, St. Petersburg, Russia

PREDICTORS OF ELEVATED NT-PROBNP LEVELS IN A HIGH-RISK OUTPATIENT POPULATION FOR HEART FAILURE: DETERMINATION USING CLINICAL DECISION LIMIT, REFERENCE INTERVALS, AND AGE- AND SEX-ADJUSTED NT-PROBNP RATIO METHODS

<i>Aim</i>	To identify predictors of increased N-terminal pro-brain natriuretic peptide (NT-proBNP) in a population of outpatients at a high risk for chronic heart failure (CHF) using methods based on the clinical decision limit (CDL), reference intervals (RI), and age- and sex-adjusted NT-proBNP ratio.
<i>Material and methods</i>	Timely diagnosis and initiation of treatment at the early stages of CHF improve the prognosis of patients. Accordingly, a program for supporting patients at a high-risk of CHF by measuring NT-proBNP was implemented in all federal districts (FDs) of the Russian Federation. The analysis included 11,740 patients at high risk of developing CHF, who had a single NT-proBNP measurement in an outpatient setting. The inclusion criteria were age ≥ 18 years, symptoms and signs of CHF and/or abnormalities on electrocardiogram and/or the presence of diseases (arterial hypertension and/or any form of ischemic heart disease). The analysis included determining the proportion of patients with NT-proBNP test results above the CDL (NT-proBNP ≥ 125 pg/ml) and above the RI (97.5 th percentile). For additional assessment, the age- and gender-adjusted NT-proBNP ratio was used. The risk of elevated NT-proBNP was assessed based on CDL, RI, and the NT-proBNP ratio.
<i>Results</i>	The median age of patients was 66 [58.0; 73.0] years, 55.8% were ≥ 65 years, and 59.3% were women. In 43.5% of patients, the NT-proBNP concentration was less than 125 pg/ml. The risk of achieving CDL was 50% higher among men, associated with the patient's age, and increased by 73% in the 45–54 age group, 2.52 times in the 55–64 age group, and 6.62 times in the ≥ 65 years age group compared to the 18–44 age group. Living in a city with a population of less than one million people increased the risk of achieving CDL by 17% compared to living in a city with a population of over a million. NT-proBNP values above the RI were achieved by 22% of patients, with the risk being 69% higher among men and 24% higher among patients living in cities with a population of less than one million. Evaluation of the NT-proBNP test results using the RI criterion showed that 44.3% of patients with normal RI values had NT-proBNP values above the CDL (≥ 125 pg/ml). The NT-proBNP ratio was the lowest in the Ural Federal District and the highest in the Far Eastern Federal District. The risk of an increased NT-proBNP ratio ≥ 1 was higher among men by 67% ($p < 0.001$), for residents of small towns by 21% ($p < 0.001$), and for residents of the Far Eastern Federal District compared to any other region ($p < 0.001$).
<i>Conclusion</i>	Independent risk factors for elevated NT-proBNP when assessed by the RI and NT-proBNP ratio included male gender, residence in cities with a population of less than one million, and residence in the Far Eastern Federal District. Assessing the NT-proBNP test solely based on the CDL, without taking into account physiological changes related to gender and age, carries a risk of overdiagnosis of CHF.
<i>Keywords</i>	Chronic heart failure; N-terminal fragment of pro-brain natriuretic peptide; clinical decision limit; reference interval; NT-proBNP ratio
<i>For citations</i>	Vinogradova N. G., Polyakov D. S., Berestovskaya V. S. Predictors of Elevated NT-proBNP Levels in a High-Risk Outpatient Population for Heart Failure: Determination Using Clinical Decision Limit, Reference Intervals, and Age- and Sex-Adjusted NT-proBNP Ratio Methods. <i>Kardiologiya</i> . 2025;65(12):62–72. [Russian: Виноградова Н. Г., Поляков Д. С., Берестовская В. С. Предикторы повышения уровней NT-проБНП в популяции амбулаторных пациентов высокого риска развития сердечной недостаточности: определение с использованием методик предела клинического решения, референсных интервалов и скорректированного по полу и возрасту соотношения NT-проБНП. <i>Кардиология</i> . 2025;65(12):62–72].
<i>Corresponding author</i>	Vinogradova Nadezhda Georgievna. E-mail: vinogradovang@yandex.ru

Introduction

Chronic heart failure (CHF) is a pressing issue in cardiology due to its increasing prevalence in many countries worldwide, as well as increasing severity of the condition in CHF patients. The risk of death from CHF remains high despite the introduction of new treatments over the past decade. Timely diagnosis and early treatment improve patient prognosis, necessitating the development of screening measures and methods for high-risk CHF patients [1, 2].

The PRIORITY-CHF study reported the leading causes of CHF in outpatients, which included arterial hypertension (AH), ischemic heart disease (IHD), atrial fibrillation (AF), type 2 diabetes mellitus, obesity, heart defects, and non-coronary myocardial diseases [3]. This suggests that early detection of CHF in outpatients should be targeted specifically at patients with these conditions and their combinations. Early diagnosis and timely initiation of treatment will improve their prognosis.

Current practice has a problem with late diagnosis of CHF, including in-hospital diagnosis, when basic therapy for CHF is initiated only during the inpatient stage. Late treatment initiation leads to a slower titration rate of basic medications and their subsequent underuse during outpatient treatment, which fails to improve the patient's prognosis. This reduces the effectiveness of the healthcare system and increases the overall cost of CHF treatment. It should be noted that the concept of early diagnosis is particularly applicable in outpatient practice, since detection of CHF during hospitalization typically indicates a high functional class and/or advanced stage [4, 5].

The literature actively discusses the issue of early diagnosis of CHF in the population based on the measurement of biomarkers, in particular natriuretic peptide (NUP), which has a high negative predictive value. The NUP test allows to exclude the diagnosis of CHF at values below the reference level or the clinical decision limits (CDLs) [6–8]. The Russian study ESSE-RF 2 that analyzed a sample of respondents aged 35–64 years showed that survival was lower with an increase in NUP above the reference values compared to respondents without an increased NUP [8]. These data allowed us to conclude that an increase in NUP in the population adversely affects the prognosis [8].

Among various laboratory tests for NUP, the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) test is the main one for the early diagnosis of HF in outpatient practice [5]. The NT-proBNP test has a class IA recommendation for the diagnosis of CHF in clinical guidelines [5, 9,

10]. For the scenario of gradual CHF development, which is typical for outpatient practice, the CDLs are applied (NT-proBNP ≥ 125 pg/mL), which has repeatedly confirmed its clinical value in the early diagnosis of CHF in patients with a high risk of CHF [11]. It should be taken into account that the positive predictive value of the NT-proBNP CDLs for confirming CHF vary from 30 to 60% depending on the characteristics of the studied cohort and the test manufacturer [12]. Furthermore, CDLs values for NT-proBNP < 125 pg/mL allow excluding CHF with a probability of 95–100% [13].

NT-proBNP levels are known to vary depending on gender, age, and other clinical parameters, while CDLs do not account for these parameters [14, 15]. The influence of gender and age can be accounted for by using reference levels (expected values) of NT-proBNP in healthy respondents. Expected values for the NT-proBNP (Elecsys proBNP II) test, based on the results of a study of the NT-proBNP concentration in the reference group of the Gutenberg Health Study participants aged 35 to 74 years, are published in the test instructions [16].

In recent years, the international literature has addressed sensitivity, specificity, and efficacy of the age- and sex-adjusted NT-proBNP ratio for diagnosing conditions associated with myocardial injury in cardiovascular diseases and COVID-19. NT-proBNP may also be highly valuable in diagnosing CHF, as several studies have reported a close correlation with the risk of death in the immediate and long-term periods [17–19].

In the Russian Federation (RF), there is a need for early diagnosis of CHF, which, through the early initiation of therapy in patients with newly diagnosed CHF, can potentially reduce the risk of CHF progression and complications. For this reason, a patient support program for NT-proBNP measurement in patients at high risk of CHF was developed and implemented in each federal district (FD) of the RF by Novartis Pharma LLC with the direct participation of Aston Health. As part of this program, patients were given the opportunity to take the NT-proBNP test upon prescription from their treating physician. This facilitated the availability of early CHF diagnosis in consistency with clinical guidelines. In accordance with the patient support program regulations, a single NT-proBNP test was performed in outpatient settings among patients aged 18 years and older with symptoms and signs of CHF and/or abnormalities on the electrocardiogram (ECG) and/or the presence of medical conditions (AH and/or any form of IHD).

This article focuses on the analysis of the results of NT-proBNP test as part of the patient support program and the search for predictors of increased NT-proBNP values in patients at high risk of CHF.

Aim

The aim of the study was to identify predictors of increased NT-proBNP values in a population of outpatients at high risk of CHF using methods based on the CDLs, reference intervals, and the sex- and age-adjusted NT-proBNP ratio.

Additionally, the following objectives were set in this study: to determine regional features of variation in NT-proBNP values in study patients; to determine differences in the evaluation of the NT-proBNP test results when using the above methods; and to determine the clinical portrait of a modern outpatient with a high risk of CHF.

Material and methods

A total of 11,740 patients participated in the patient support program from September 2023 through September 2024. Each patient took a single NT-proBNP test with the Elecsys proBNP II test (manufactured by Roche) using the approved method within the Helix laboratory service network in all FDs of the RF, which ensured the consistency of the results.

Inclusion criteria for the study. Adult patients (18 years and older); NT-proBNP test has not been performed within the previous month. Presence of one or more symptoms and signs; history of AH and/or IHD (myocardial infarction (MI), acute coronary syndrome without MI, angina pectoris, ischemic cardiomyopathy, asymptomatic myocardial ischemia, rhythm and conduction disturbances (as an independent nosological form of IHD in the absence of criteria for sudden death), hemodynamically significant coronary atherosclerosis); orthopnea; nocturnal attacks of cardiac asthma; exposure to cardiotoxic drugs; complaints of fatigue, shortness of breath, swelling of the legs, and palpitations; wheezing; bilateral swelling of the lower extremities during physical examination; heart murmurs; jugular venous distension; displaced apical impulse; abnormalities on the ECG with assessment of the heart rhythm, heart rate, morphology and QRS duration, disturbances of atrioventricular and ventricular conduction (left bundle branch block, right bundle branch block, myocardial scarring, myocardial hypertrophy).

Exclusion criteria. Lack of informed consent, patient age under 18 years, previous diagnosis of CHF, and/or NT-proBNP test performed less than 1 month ago.

Patients signed informed consent to participate in the program, to the processing of personal data, and blood sampling. Only treating physicians had access to patients' personal data and medical records. All patients and their treating physicians were promptly informed of the NT-proBNP test results, and patients were invited to a follow-up appointment with a physician/cardiologist. Clinical investigators did not have access to patients' personal data, except for the patient's gender, age, city and FD of residence, and the NT-proBNP test result.

An analysis of the types of localities in which patients resided was performed. All localities were divided into two types. Cities with a population of 1 million or more were assigned to type 1. Cities with a population of over one million included Moscow, St. Petersburg, Novosibirsk, Yekaterinburg, Kazan, Nizhny Novgorod, Krasnoyarsk, Chelyabinsk, Samara, Ufa, Rostov-on-Don, Krasnodar, Omsk, Voronezh, Perm, and Volgograd, according to official data as of January 1, 2024 [20]. Cities and other localities with a population of less than 1 million were classified as type 2.

The study was conducted in accordance with the principles of the Declaration of Helsinki (2024 revision of the World Medical Association).

The number and proportion of patients with NT-proBNP test results above the CDLs specified in national clinical guidelines ($\text{NTproBNP} \geq 125 \text{ pg/mL}$) were determined for the overall group and depending on gender, age, category of locality, and FD [10]. At the next stage, the increase in NT-proBNP was assessed based on the reference interval (RI), which was taken as the 97.5th percentile for the NT-proBNP reference level in a gender- and age-matched subgroup [16]. An additional assessment of the increase in NT-proBNP used the NT-proBNP ratio, which was defined as the NT-proBNP value of a particular patient divided by the upper RI of NT-proBNP in the control (the 97.5th percentile for the gender and age group). The NT-proBNP ratio was introduced to compensate for gender- and age-related changes in NT-proBNP.

Statistical analysis was performed in the R environment, version 4.3.2. Prior to the analysis, quantitative variables were tested for normality using the Anderson-Darling test. The distribution of quantitative variables differed from normal. Descriptive statistics are presented as median and quartiles (Me [Q1; Q3]) for quantitative variables and as absolute values and percentages for qualitative variables. For inter-group comparisons, the chi-square test for qualitative variables and the Mann-Whitney test for quantitative variables were used to assess the significance of differ-

ences. The Benjamini-Hochberg procedure was used for correction for multiple comparison. For multivariate analysis, a binary logit model (or logistic regression) was used, which allows for the assessment of the independent influence of predictors. Differences were considered statistically significant at $p < 0.05$.

Results

Patients from various FDs participated in the program. The largest number of patients was from the Northwestern FD (3,800, 32.4%), followed by the Volga Federal District (2,107, 18%), the Central FD (1,699, 14.5%), and the North Caucasian FD (1,730, 14.7%). They were followed by the Siberian FD (914, 7.8%) and the Ural FD (752 people, 6.4%). The smallest number of patients was from the Southern FD (528, 4.5%) and the Far Eastern FD (210, 1.8%). The number and proportion of patients participating in the program reflected the high population density (Central and Volga FDs) and the engagement of specialists in the patient support program (Northwestern and North Caucasian FDs). 4,336 patients (37%) were from type 1 localities, and 7,404 patients (63%) were from type 2 localities.

The median age of the patients was 66 [58.0; 73.0] years. The patients were distributed into age groups, which corresponded to the division by age of the reference group of healthy respondents in accordance with the instructions for the NT-proBNP test (Elecsys proBNP II) [16]. The absolute number and proportion of program participants were as follows: 18–44 years old, 788 (6.71%); 45–54 years old, 1,447 (12.3%); 55–64 years old, 2,953 (25.2%); 65 years and older, 6,552 (55.8%). The distribution by gender was 6,964 women (59.3%) and 4,776 men (40.7%).

The NT-proBNP concentration in the overall group, determined on the basis of CDLs, was <125 pg/mL in 43.5% of all program participants, and ≥ 125 pg/mL in 56.5%.

Female participants of the program were significantly older than males. The age group ≥ 65 years contained more women (62.9%), while in all other age groups, men predominated. The majority of both men and women lived in type 2 localities. The median NT-proBNP concentration was higher in men (176 pg/mL) than in women (145 pg/mL). Among men, there were significantly more patients with a NT-proBNP concentration ≥ 125 pg/mL (achieving the CDLs).

Table 1 shows NT-proBNP concentrations by gender and age of the program participants. In the overall group aged 18–44 years, the median NT-proBNP concentration in women was significantly higher than

Table 1. NT-proBNP values depending on gender and age in the general group of examined patients and when distributed by type of locality

Parameter	NT-proBNP, Me [Q1; Q3], pg / mL		
	Females	Males	p
General group			
18–44 years	61.2 [33.5; 120]	46.1 [12.9; 149]	0.001
45–54 years	75.9 [34.5; 155]	95.2 [33.9; 286]	0.002
55–64 years	96.2 [49.4; 210]	155 [60.2; 462]	<0.001
65 years and older	199 [96.4; 482]	272 [114; 808]	<0.001
Locality type 1			
18–44 years	65.2 [37.7; 128]	43 [11.5; 131]	0.001
45–54 years	65.8 [31.8; 130]	94.5 [34; 310]	0.005
55–64 years	87.1 [48.1; 179]	132 [56.9; 404]	<0.001
65 years and older	183 [91.8; 409]	258 [108; 801]	<0.001
Locality type 2			
18–44 years	59.4 [31.4; 109]	48.4 [14.4; 152]	0.09
45–54 years	81.8 [37.2; 170]	95.7 [34.1; 280]	0.1
55–64 years	103 [51.6; 236]	176 [60.3; 517]	<0.001
65 years and older	211 [99.6; 536]	282 [116; 809]	<0.001

NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide

in men, which is consistent with the normal distribution pattern of NT-proBNP reference values in men and women [16]. Among participants without CHF, this pattern remained in any age group (NT-proBNP values were higher in women); however, in this sample of high-risk CHF patients, starting from the age of 45 years and older, NT-proBNP values became higher in men, which is possible only in the presence of a pathological deviation of this indicator.

When distributing patients by locality type, NT-proBNP values above the CDLs (≥ 125 pg/mL) were found in 2,345 (54.1%) patients from locality type 1 and 4,285 (57.9%) patients from locality type 2 ($p < 0.001$). When distributing by locality type, the median age of patients was 66 years in both subgroups; also, when distributing by age group, there were no statistically significant differences between locality types 1 and 2.

In type 1 cities, men younger than 45 years consistently had lower NT-proBNP values than women. However, at age of 45 years and older, men in any age group had significantly higher NT-proBNP values than women, which may be associated with the development of neurohumoral system stress. In type 2 cities and towns, men even younger than 45 years had NT-proBNP values comparable to values in women, which may indicate an earlier onset of cardiovascular diseases among men in these localities. In small

Table 2. NT-proBNP concentrations depending on federal district and gender

Federal district	NT-proBNP, Me [Q1; Q3], pg /mL			
	All patients	Females	Males	p
Far Eastern	384 [91.5; 1605]	370 [109; 1466]	432 [75.9; 1974]	0.68
Volga	141 [63.6; 362]	132 [66.1; 319]	160 [53.9; 439]	0.34
Northwestern	159 [68.4; 432]	147 [69.2; 370]	178 [65.9; 552]	0.003
North Caucasian	158 [63.3; 429]	146 [65.1; 366]	178 [62.1; 512]	0.1
Siberian	158 [71.7; 442]	148 [74.2; 353]	198 [64.2; 576]	0.02
Ural	133 [57.1; 330]	133 [59.2; 314]	133 [51.7; 345]	0.85
Central	156 [67.2; 416]	141 [69.7; 325]	179 [61.1; 587]	0.007
Southern	200 [80.2; 593]	180 [79.1; 435]	230 [81.2; 702]	0.1

NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide.

towns, men and women aged 45–54 years had comparable and high NT-proBNP values. However, already at age of 55 years and older, NT-proBNP values became significantly higher in men than in women (Table 1).

NT-proBNP concentrations by FD and gender are presented in Table 2. The Far Eastern FD had the highest NT-proBNP values in the overall patient population, as well as in men and women separately. No statistically significant differences by gender were found in the Far Eastern FD. The lowest NT-proBNP values in the overall population were observed in the Ural FD, in women in the Ural and Volga FDs, and in men in the Ural FD. In the Ural and Volga FDs, no significant differences in NT-proBNP values were found between men and women. No significant differences by gender were found in the Far Eastern, North Caucasian, and Southern FDs; however, high NT-proBNP concentrations were observed in both sexes in these FDs. In the Northwestern, Siberian, and Central FDs, NT-proBNP values in men were statistically significantly higher than in women.

Differences in patient characteristics by FD were analyzed. The highest proportion of patients with NT-proBNP values above the CDL (≥ 125 pg/mL) was observed in the Far Eastern FD (66.7%), while in other FDs, NT-proBNP ranged from 51.7% (Ural FD) to 62.9% (Southern FD). However, the greatest median age (68 [60; 74]) and the proportion of patients older than 65 years (62%) were found in the Northwestern FD. In all FDs, except for the Far Eastern FD (50%) and Southern FD (49.4%), women predominated among the patients (from 53.1 to 64.8% women). In the Ural FD, the overwhelming majority of patients (85.4%) were from type 1 localities. In the Far Eastern and North Caucasian FDs, all patients lived in type 2 localities.

To study the independent effect of factors on the risk of achieving NT-proBNP CDL (≥ 125 pg/mL), a mathematical model was constructed (Table 3). This mathematical modeling used binary logistic regression, which allows assessing the independent effects of predictors. The risk of achieving CDL for NTproBNP ≥ 125 pg/mL in the age group of 18–44 years in women, and in patients from type 1 localities was taken as the reference level. In the resulting mathematical model, the risk of achieving the CDL for NT-proBNP value (≥ 125 pg/mL) was associated with the patient’s gender: among men, the probability of achieving the CDL was 50% higher. This risk was also associated with the patient’s age: compared with the age group of 18–44 years, the risks of achieving a NT-proBNP value ≥ 125 pg/mL was increased by 73% in the 45–54-year age group, 2.52 times in the 55–64-year age group, and 6.62 times in the age group ≥ 65 years. Living in a type 2 city or town increased the risk of achieving the CDL by 17% compared to living in a city with a population of over a million, and this association was independent of gender and age.

At the next step, the increase in NT-proBNP was assessed based on the RI (97.5th percentile for the respective gender and age) [16]. Individual test results were compared with the reference level (expected values) of the NT-proBNP test in healthy respondents, which made it possible to distribute patients into subgroups based on the NT-proBNP value above or below the RI and to level out the effect of gender and age (Table 4). 22% of patients achieved NT-proBNP values above the RI. Patients in the subgroup with NT-proBNP above the RI were significantly older, but no statistically significant differences were found when dividing them into age groups. Among patients with NT-proBNP above the RI, men predominated;

Table 3. Results of a mathematical model for predicting the risk of achieving CDL based on the concentration of NT-proBNP

Predictors	OR	95% CI	p
Age group 45–54 years	1.73	1.43–2.10	<0.001
Age group 55–64 years	2.52	2.12–3.01	<0.001
Age group 65 years and older	6.62	5.6–7.85	<0.001
Male gender	1.5	1.38–1.62	<0.001
Locality type 2	1.17	1.08–1.27	<0.001

CDL, clinical decision limit; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; OR, odds ratio; CI, confidence interval.

the differences were significant compared to the subgroup with the NT-proBNP value below or equal to the RI. The subgroup with values above the RI contained significantly more patients from type 2 localities compared to patients in the subgroup with values below or equal to the RI. Noteworthy, in the subgroup with NT-proBNP below or equal to the RI, 44.3% of patients had NT-proBNP values that reached the CDL in accordance with clinical guidelines (≥ 125 pg/mL).

A mathematical model was constructed to assess the independent effect of patient characteristics on the risk of exceeding the RI. The model used binary logistic regression, which allows evaluating the independent effect of predictors. The reference level was set to the risk of reaching the NT-proBNP reference interval threshold $>97.5^{\text{th}}$ percentile in the 18–44 age group, in women, in patients from type 1 localities (Table 5). Since the 97.5th percentile accounts for the adjustment for the patient's age and gender, age did not affect the patient's risk of a NT-proBNP level above the 97.5th percentile in this mathematical model. However, in the study sample, the risk of exceeding the NT-proBNP RI was 69% higher in men and 24% higher in those living in type 2 localities, which proves the independent influence of these predictors.

The increase in NT-proBNP was assessed for each patient based on the age- and gender-adjusted NT-proBNP ratio. The median NT-proBNP ratio in women was 0.3 [0.15; 0.7], which was lower than that in men (0.37 [0.14; 1.11]) in the overall study group ($p<0.001$) (Figure 1).

When distributing the NT-proBNP ratio by age group with an adjustment for multiple comparisons, the analysis of individual age subgroups did not reveal any significant differences. Distribution by locality type showed significant differences in the NT-proBNP ratio between patients from cities with a population of over a million and patients from localities with

Table 4. Distribution of patients depending on the excess of the NT-proBNP value above the reference interval (97.5th percentile for the respective age-sex group)

Parameter	Below or equal to RI	Above RI	p
Number of patients	n=9 159	n=2 581	–
Age, Me [Q1; Q3], years	66 [58; 72]	66 [58; 74]	0.001
Age group			
18–44 years, abs. (%)	620 (6.77)	168 (6.51)	0.127
45–54 years, abs. (%)	1096 (12.0)	351 (13.6)	
55–64 years, abs. (%)	2 297 (25.1)	656 (25.4)	
65 years and older, abs. (%)	5 146 (56.2)	1406 (54.5)	
Sex			
Females, abs. (%)	5 692 (62.1)	1272 (49.3)	<0.001
Males, abs. (%)	3 467 (37.9)	1309 (50.7)	
Locality type:			
Type 1, abs. (%)	3 487 (38.1)	849 (32.9)	<0.001
Type 2, abs. (%)	5 672 (61.9)	1732 (67.1)	
NT-proBNP, Me [Q1; Q3], pg/mL	107 [53.1; 213]	1080 [669; 1855]	<0.001
Distribution by NT-proBNP CDL:			
< 125 pg/mL, abs. (%)	5 104 (55.7)	6 (0.23)	<0.001
≥ 125 pg/mL, abs. (%)	4 055 (44.3)	2 575 (99.8)	

NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; RI, reference interval; CDL, clinical decision limit.

a population of less than a million (0.29 [0.14; 0.73] vs. 0.33 [0.15; 0.91], respectively, $p<0.001$).

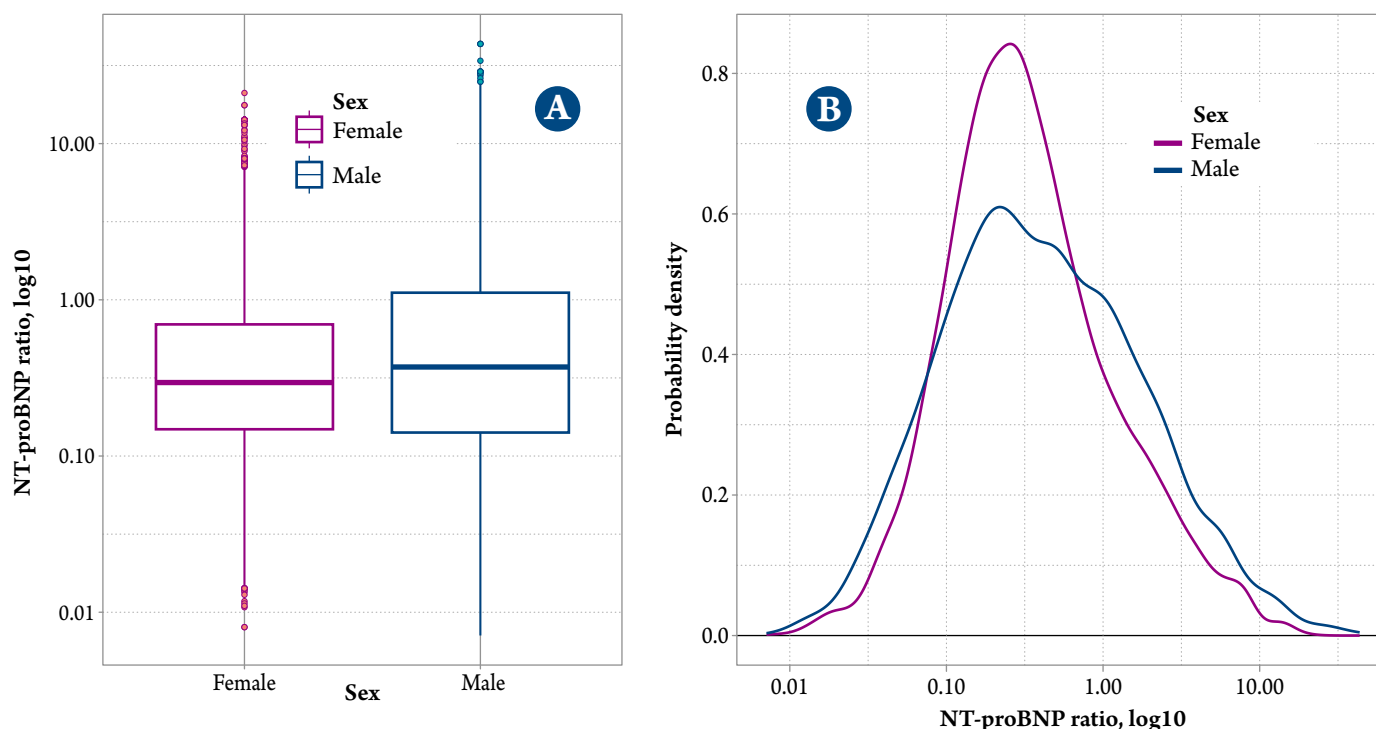
The NT-proBNP ratio was the lowest in the patient population of the Ural FD (0.28 [0.13; 0.66]), followed in ascending order by the Volga FD (0.3 [0.14; 0.77]) and Northwestern FD (0.3 [0.14; 0.83]), Central FD (0.33 [0.15; 0.81]), North Caucasian FD (0.33 [0.15; 0.95]), Siberian FD (0.34 [0.15; 0.8]) and Southern FD (0.40 [0.18; 1.19]). The highest NT-proBNP ratio was observed in the Far Eastern FD (0.78 [0.2; 2.63]). The differences between the Far Eastern FD and other FDs were statistically significant ($p<0.001$).

Table 5. Results of the mathematical model for predicting the risk of exceeding the reference interval for NT-proBNP

Predictors	OR	95% CI	p
Age group 45–54 years	1.22	0.99–1.5	0.069
Age group 55–64 years	1.07	0.89–1.3	0.484
Age group 65 years and older	1.12	0.94–1.35	0.214
Male gender	1.69	1.55–1.85	<0.001
Locality type 2	1.24	1.13–1.37	<0.001

NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; OR, odds ratio; CI, confidence interval.

Figure 1. Age- and sex-adjusted median NT-proBNP ratio: differences between sexes (A) and probability density plot (B)



The graphs are logarithmically transformed along the NT-proBNP ratio axis, since extremely high and extremely low ratio values occur.

All patients were divided into 4 quartiles based on the NT-proBNP ratio: 1st quartile (Q1) <0.15; 2nd quartile (Q2) >0.15 and <0.32; 3rd quartile (Q3) >0.32 and <0.86; and 4th quartile (Q4) >0.86. It was shown that among patients in the Far Eastern FD, the 3rd and 4th quartiles of increase in the NT-proBNP ratio prevailed, whereas in the Ural FD, the proportion of values in the 3rd and 4th quartiles was smaller (Figure 2).

It is important to analyze the risk of achieving a sex- and age-adjusted NT-proBNP ratio ≥ 1 , which indicates a deviation from normal values for a given patient. A mathematical model was constructed to establish the independent influence of patient characteristics on the risk of an increase in the sex- and age-adjusted NT-proBNP ratio ≥ 1 . This mathematical model was constructed using binary logistic regression, which allowed for the independent assessment of the effect of predictors. The reference level was set as the risk of achieving an NT-proBNP ratio ≥ 1 in the Far Eastern FD, among women aged 18–44 years, and those living in type 1 localities (Table 6).

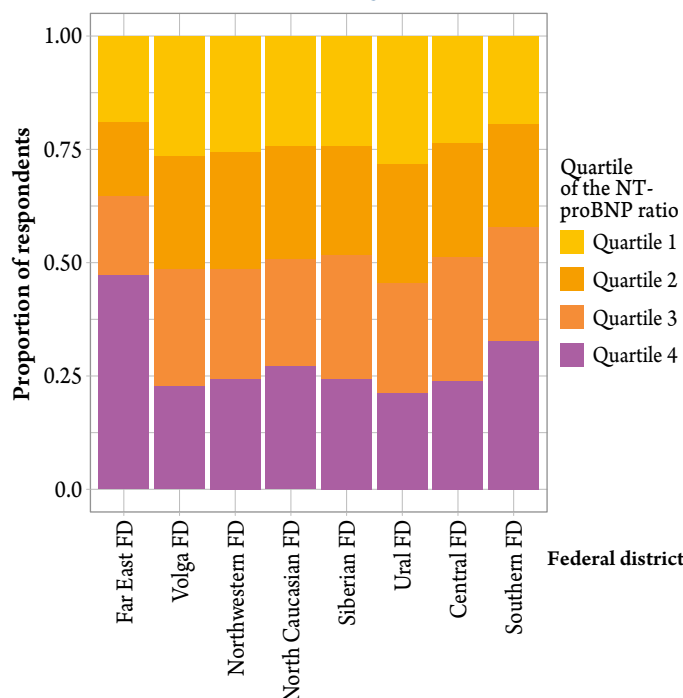
Thus, the risk of an increased NT-proBNP ratio ≥ 1 was influenced by male gender (67% higher risk, $p < 0.001$) and residence in localities with a population of less than 1 million people (21% higher risk, $p < 0.001$). Residence in any FD, compared with the Far Eastern FD, had a significantly lower risk of

an increased NT-proBNP ratio ≥ 1 ($p < 0.001$). Age group did not affect the risk of a NT-proBNP ratio ≥ 1 due to the fact that this indicator was age-adjusted (Table 6).

Discussion

In our study, more than a half of patients at high risk of CHF had NT-proBNP values higher than the CDLs provided in the National Clinical Guidelines. However, this fact alone does not allow to conclude that this cohort of patients had CHF, since the positive predictive ability of the NT-proBNP test is lower than the negative predictive ability that allows excluding CHF at values <125 pg/mL [10, 13]. Therefore, NT-proBNP test values above the CDL (≥ 125 pg/mL) cannot automatically confirm the diagnosis of CHF due to the risk of overdiagnosis. Specifically, it was shown that in persons aged 65 years without risk factors for CHF, the CDL for a NT-proBNP ≥ 125 pg/mL had a positive predictive value of 25.3%, which was associated with a probability of overdiagnosis based on this laboratory criterion of $\leq 75\%$ [21]. In the ESSE-RF2 study, 24.5% of respondents aged 35–64 years with CHF diagnosed according to mild criteria (presence of cardiovascular disease, weakness, and shortness of breath) had NUP values above the CDLs. At the same time, NUP levels above the CDLs were noted in 11.9% of respondents of the same age without CHF. This confirms

Figure 2. Distribution of patients by quartiles of the NT-proBNP ratio depending on the federal district



the need for a thorough assessment of NUP test results [8].

NT-proBNP concentrations are known to vary markedly among healthy individuals depending on age and gender. Some authors suggest that NT-proBNP reference intervals for healthy individuals based on gender and age should be used to formulate the CDLs in the future, which will allow for a more accurate characterization of the risk of abnormalities [14, 22].

M. Averina et al. (2022) assessed the diagnostic accuracy of the NT-proBNP test in the general population ($n=1936$) to identify patients with subclinical CHF. That study is interesting because it compared the diagnostic accuracy of the CDL, that is, the previously established uniform cutoff value of 125 pg/mL, and the NT-proBNP reference values in healthy individuals depending on gender and age (97.5th percentile). The authors showed that the cutoff NT-proBNP values established based on gender and age had a higher specificity for subclinical CHF compared to the previously established uniform cutoff value of 125 pg/mL [23].

In our study, we used the RI for the respective age and gender group (97.5th percentile) to analyze the probability of CHF in high-risk patients. We found that in the subgroup of patients with NT-proBNP values $\leq$ RI, 44.3% of patients had NT-proBNP values that reached the CDL indicated in the clinical guidelines (≥ 125 pg/mL). Therefore, in this cohort of patients with NT-proBNP values ≥ 125 pg/mL but below or equal to the RI for their gender and age, when

Table 6. Results of the mathematical model for predicting the risk of exceeding the NT-proBNP ratio to a value of 1 or more

Predictors	OR	CI	p
Age 45–54 years	1.2	0.97–1.48	0.088
Age 55–64 years	1.05	0.87–1.27	0.637
Age 65 years and older	1.09	0.91–1.31	0.363
Male gender	1.67	1.52–1.82	<0.001
Locality type 2	1.21	1.09–1.34	<0.001
Volga FD	0.35	0.26–0.47	<0.001
Northwestern FD	0.41	0.31–0.55	<0.001
North Caucasian FD	0.42	0.31–0.56	<0.001
Siberian FD	0.42	0.30–0.58	<0.001
Ural FD	0.38	0.27–0.54	<0.001
Central FD	0.38	0.28–0.51	<0.001
Southern FD	0.58	0.42–0.82	0.002

NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; OR, odds ratio; CI, confidence interval

diagnosing CHF in outpatient setting, the lab test results should be critically assessed and correlated with the clinical picture and comorbidities that could affect the NT-proBNP test. On the one hand, according to reports, the phenomenon of decreased NT-proBNP values in patients with CHF and obesity is known, and on the other hand, comorbidities, such as AF and chronic kidney disease, can increase this lab result [6, 24, 25].

The age- and sex-adjusted NT-proBNP ratio is a new approach to evaluating test results. The primary purpose of this method, which is similar to the RI method for assessing NT-proBNP described above, is to compensate for physiological test variations depending on sex and age, as well as to simplify the presentation of test results. The NT-proBNP ratio does not correct for pathological test deviations, as the calculation formula uses the 97.5th percentile of expected values in healthy subjects. We found no reports in the international or Russian literature of using the age- and sex-adjusted NT-proBNP ratio for diagnosing CHF. However, the high predictive value of the NT-proBNP ratio has been demonstrated in studies of the effect of NT-proBNP ratio on early and long-term mortality in patients with mixed aortic valve disease, even in patients with mild aortic stenosis and regurgitation [17], and the independent effect of a high NT-proBNP ratio on long-term prognosis in patients with obstructive hypertrophic cardiomyopathy [18]. A retrospective study by D. Li et al. [19] showed that in adult Chinese patients with COVID-19, the NT-proBNP ratio exhibited a high prognostic ability for in-hospital mortality compared with several established risk factors, including NT-proBNP CDLs, C-reactive protein, and neutrophil/lymphocyte ratio.

In our study, the NT-proBNP ratio clearly identified the FD with the highest probability of a positive CHF diagnosis (Far Eastern FD), as well as regions with a more favorable situation in terms of the prevalence of probable CHF among high-risk patients (Volga, Ural, and Central FDs). Furthermore, the mathematical model based on the NT-proBNP ratio revealed that male patients and patients residing in cities with a population of less than 1 million were at higher risk of developing CHF. These differences could be due to the organization of medical care, accessibility of medical care (especially for patients with IHD), genetic factors, and climatic and other living conditions in various FDs and localities of the Russian Federation.

Thus, after applying the above-mentioned methods for assessing NT-proBNP test results adjusted for gender and age, a profile of a patient at high risk for developing CHF was formed: a man aged 45 years or older, residing in a community with a population of less than 1 million, with AH and/or any form of IHD. Identifying sensitive patient cohorts is crucial for further planning of programs similar to this patient support program for determining NT-proBNP at the outpatient stage of CHF diagnosis. This will increase coverage of the target population and improve the effectiveness of early CHF diagnosis, which will positively impact health-care system costs for managing this category of patients.

Conclusions

1. In 43.5% of patients at high risk of chronic heart failure, the NT-proBNP concentration was less than 125 pg/mL.
2. Men aged 45 years and older compared to women, patients from cities with a population of less than 1 million compared to those living in cities with a population of over a million, and patients residing in the Far Eastern Federal District compared to other federal districts had higher median NT-proBNP concentrations.
3. Age was a risk factor for elevated NT-proBNP only in the model of using clinical decision limits. Male gender and residence in small towns increased the risk of high NT-proBNP values by the clinical decision limit criterion.
4. Evaluation of the NT-proBNP test by the reference interval criterion showed that 44.3% of patients with normal reference interval values had NT-proBNP above the clinical decision limit (≥ 125 pg/mL) and could be classified as having confirmed chronic heart failure according to clinical guidelines, which carries the risk of overdiagnosis.

5. Risk factors for elevated NT-proBNP, as assessed by the reference interval and NT-proBNP ratio, included male gender and residence in cities with populations of less than 1 million. Age was not a risk factor for elevated NT-proBNP. Therefore, the use of these methods helps avoid misdiagnosis of chronic heart failure, possibly due to a physiological increase in NT-proBNP depending on gender and age.
6. The use of the NT-proBNP ratio assessment method allowed us to determine that residence in the Far Eastern Federal District significantly increases the risk of high NT-proBNP test results compared to any other federal district, regardless of gender, age, and type of locality.

Further research prospects and application of results in practical healthcare

In the future, given the large sample size of patients participating in the program, it is possible to conduct a subanalysis for specific localities within a single FD. When planning further studies of using the NT-proBNP test for diagnosing CHF, it is recommended to consider the gender and age dependence of the test results. Targeted patient support programs and widespread implementation of the NT-proBNP test in outpatient settings will improve early diagnosis of CHF and prevent complications in this patient population.

Study limitations

This study was conducted without definitive verification of the CHF diagnosis or assessment of the impact of individual comorbidities on NT-proBNP concentrations. Studies designed to clinically verify CHF are needed to evaluate the feasibility of using the NT-proBNP ratio for the timely diagnosis of CHF in high-risk patients and to assess its advantages over the CDL-based diagnostic method. The NT-proBNP ratio may potentially serve as a population-based screening test for the early detection of CHF in high-risk populations.

Funding

This publication was prepared without sponsorship.

Conflict of interest

The publication was prepared using data obtained in the non-profit patient support program "Diagnostics of NT-proBNP levels in patients with a presumptive diagnosis of CHF", organized by Novartis Pharma LLC.

The article was received on 18/09/2025

REFERENCES

1. Polyakov D. S., Fomin I. V., Belenkov Yu. N., Mareev V. Yu., Ageev F. T., Artemjeva E. G. et al. Chronic heart failure in the Russian Federation: what has changed over 20 years of follow-up? Results of the EPOCH-CHF study. *Kardiologiya*. 2021;61(4):4–14. [Russian: Поляков Д. С., Фомин И. В., Беленков Ю. Н., Мареев В. Ю., Агеев Ф. Т., Артемьева Е. Г. и др. Хроническая сердечная недостаточность в Российской Федерации: что изменилось за 20 лет наблюдения? Результаты исследования ЭПОХА -ХСН. *Кардиология*. 2021;61(4):4–14]. DOI: 10.18087/cardio.2021.4.n1628
2. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *The Lancet*. 2020;396(10244):121–8. DOI: 10.1016/S0140-6736(20)30748-0
3. Shlyakhto E. V., Belenkov Yu. N., Boytsov S. A., Villevalde S. V., Galyavich A. S., Glezer M. G. et al. Interim analysis of a prospective observational multicenter registry study of patients with chronic heart failure in the Russian Federation 'PRIORITET-CHF': initial characteristics and treatment of the first included patients. *Russian Journal of Cardiology*. 2023;28(10):93–103. [Russian: Шляхто Е. В., Беленков Ю. Н., Бойцов С. А., Виллевальде С. В., Галявич А. С., Глезер М. Г. и др. Результаты промежуточного анализа проспективного наблюдательного многоцентрового регистрового исследования пациентов с хронической сердечной недостаточностью в Российской Федерации 'ПРИОРИТЕТ-ХСН': исходные характеристики и лечение первых включённых пациентов. *Российский кардиологический журнал*. 2023;28(10):93–103]. DOI: 10.15829/1560-4071-2023-5593
4. Crespo-Leiro MG, Barge-Caballero E. Advanced Heart Failure: Definition, Epidemiology, and Clinical Course. *Heart Failure Clinics*. 2021;17(4):533–45. DOI: 10.1016/j.hfc.2021.06.002
5. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Journal of Cardiac Failure*. 2021;27(4):387–413. DOI: 10.1016/j.cardfail.2021.01.022
6. Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L et al. Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: A clinical consensus statement from the Heart Failure Association of the ESC. *European Journal of Heart Failure*. 2023;25(11):1891–8. DOI: 10.1002/ehf.3036
7. Talha KM, Januzzi JL, Meng T, Greene SJ, Vaduganathan M, Janicijevic TK et al. Use of natriuretic peptides and echocardiography for diagnosing heart failure. *European Journal of Heart Failure*. 2024;26(3):551–60. DOI: 10.1002/ehf.3165
8. Shalnova S. A., Kutsenko V. A., Yakushin S. S., Kapustina A. V., Evstifeeva S. E., Balanova Yu. A. et al. Associations of elevated levels of brain natriuretic peptide and heart failure and their contribution to survival in the Russian middle-aged population: data from the ESSE-RF study. *Cardiovascular Therapy and Prevention*. 2023;22(6):6–13. [Russian: Шальнова С. А., Куценко В. А., Якушин С. С., Капустина А. В., Евстифеева С. Е., Баланова Ю. А. и др. Ассоциации повышенного уровня мозгового натрийуретического пептида и хронической сердечной недостаточности и их вклад в выживаемость в российской популяции среднего возраста. По данным исследования ЭССЕ-РФ. *Кардиоваскулярная терапия и профилактика*. 2023;22(6):6–13]. DOI: 10.15829/1728-8800-2023-3553
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 2021;42(36):3599–726. DOI: 10.1093/eurheartj/ehab368
10. Galyavich A. S., Tereshchenko S. N., Uskach T. M., Ageev F. T., Aronov D. M., Arutyunov G. P. et al. 2024 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology*. 2024;29(11):251–349. [Russian: Галявич А. С., Терещенко С. Н., Ускач Т. М., Агеев Ф. Т., Аронов Д. М., Арутюнов Г. П. и др. Хроническая сердечная недостаточность. Клинические рекомендации 2024. *Российский кардиологический журнал*. 2024;29(11):251–349]. DOI: 10.15829/1560-4071-2024-6162
11. Pausmüller S, Resl M, Arfsten H, Spinka G, Wurm R, Neuhold S et al. Performance of the recommended ESC/EASD cardiovascular risk stratification model in comparison to SCORE and NT-proBNP as a single biomarker for risk prediction in type 2 diabetes mellitus. *Cardiovascular Diabetology*. 2021;20(1):34. DOI: 10.1186/s12933-021-01221-w
12. BNP, NT-proBNP, and MR-proANP Assays: Analytical Characteristics Designated by Manufacturer IFCC Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) v062024. Av. at: <https://pub-180a8d00f517477ba49634e6b2b147e3.r2.dev/2024/03/BNP-NT-proBNP-and-MR-proANP-Assays-Analytical-Characteristics-Designated-By-Manufacturer-v062024.pdf>.
13. Vinogradova N. G., Berestovskaya V. S., Blankova Z. N., Vavilova T. V., Gomyranova N. V., Masenko V. P. et al. Laboratory Aspects of Using the Results of NT-ProBNP Concentration Immunochemical Determination in the Management of Patients With Heart Failure: Support For Clinical Decision-Making. *Kardiologiya*. 2024;64(8):68–78. [Russian: Виноградова Н. Г., Берестовская В. С., Бланкова З. Н., Вавилова Т. В., Гомыранова Н. В., Масенко В. П. и др. Лабораторные аспекты использования результатов иммунохимического определения концентрации NTпроBNP при ведении пациентов с хронической сердечной недостаточностью: поддержка принятия клинических решений. *Кардиология*. 2024;64(8):68–78]. DOI: 10.18087/cardio.2024.8.n2720
14. Mu S, Echouffo-Tcheugui JB, Ndumele CE, Coresh J, Juraschek S, Brady T et al. NT-proBNP Reference Intervals in Healthy U. S. Children, Adolescents, and Adults. *The Journal of Applied Laboratory Medicine*. 2023;8(4):700–12. DOI: 10.1093/jalm/jfad024
15. Ezekowitz JA, Alemayehu W, Rathwell S, Grant AD, Fiuzat M, Whellan DJ et al. The influence of comorbidities on achieving an N-terminal pro-b-type natriuretic peptide target: a secondary analysis of the GUIDE-IT trial. *ESC Heart Failure*. 2022;9(1):77–86. DOI: 10.1002/ehf2.13692
16. Roche Diagnostics GmbH H. Instruction for use Elecsys proBNP II. Av. at: <https://elabdoc.rochediagnostics.ru/api/documents/download/33d4faf3-b354-ef11-2b91-005056a71a5d>.
17. Bernard J, Jean G, Bienjonetti-Boudreau D, Jacques F, Tastet L, Salaun E et al. Prognostic utility of N-terminal pro B-type natriuretic peptide ratio in mixed aortic valve disease. *Open Heart*. 2023;10(2): e002361. DOI: 10.1136/openhrt-2023-002361
18. Hutt E, Mentias A, Alashi A, Wadhwa R, Fava A, Lever HM et al. Prognostic value of age-sex adjusted NT-proBNP ratio

- in obstructive hypertrophic cardiomyopathy. *Progress in Cardiovascular Diseases*. 2022;74:11–8. DOI: 10.1016/j.pcad.2022.08.002
19. Li D, He W, Yu B, Wang DW, Ni L. NT-proBNP ratio is a potential predictor for COVID-19 outcomes in adult Chinese patients: a retrospective study. *Scientific Reports*. 2024;14(1):5906. DOI: 10.1038/s41598-024-56329-2
 20. Russia's million-plus cities. Av. at: <https://www.statdata.ru/goroda-millionniki-rossii-po-naseleniu>. [Russian: Города-миллионники России. Доступно на: <https://www.statdata.ru/goroda-millionniki-rossii-po-naseleniu>]
 21. Nogi K, Yamamoto R, Ueda T, Nogi M, Ishihara S, Nakada Y et al. Derivation and validation of a clinical predictive model of NT-proBNP ≥ 125 pg/mL to detect pre-heart failure. *Journal of Cardiology*. 2023;82(6):481–9. DOI: 10.1016/j.jjcc.2023.05.011
 22. Alehagen U, Goetze JP, Dahlström U. Reference intervals and decision limits for B-type natriuretic peptide (BNP) and its precursor (NT-proBNP) in the elderly. *Clinica Chimica Acta*. 2007;382(1–2):8–14. DOI: 10.1016/j.cca.2007.03.005
 23. Averina M, Styliadis M, Brox J, Schirmer H. NT-ProBNP and high-sensitivity troponin T as screening tests for subclinical chronic heart failure in a general population. *ESC Heart Failure*. 2022;9(3):1954–62. DOI: 10.1002/ehf2.13906
 24. Singh S, Pandey A, Neeland IJ. Diagnostic and prognostic considerations for use of natriuretic peptides in obese patients with heart failure. *Progress in Cardiovascular Diseases*. 2020;63(5):649–55. DOI: 10.1016/j.pcad.2020.09.006
 25. Bayés-Genis A, Taylor CJ. Elevated NT-proBNP in Heart Failure and CKD: A Genuine Red Flag for Worse Prognosis-Not a False Positive. *JACC: Heart Failure*. 2025;13(1):40–2. DOI: 10.1016/j.jchf.2024.10.012