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The glucose-potassium ratio as a marker of adverse prognosis in patients with chronic heart failure

V. V. Syvolap[A,C,E,F], **V. A. Lysenko***[B,C,D,E]

Zaporizhzhia State Medical and Pharmaceutical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The glucose-potassium ratio (GPR) has previously proven its prognostic role in acute pathological conditions: ischemic and hemorrhagic strokes, aortic aneurysm and dissection, myocardial infarction. However, changes in the serum GPR in patients with chronic heart failure (CHF) with preserved left ventricular ejection fraction (HFpEF) remain unclear. It is known that tubulointerstitial injury occurs in patients with CHF. The renal tubulointerstitium plays a leading role in the reabsorption of glucose, potassium, and sodium. Therefore, impaired glucose-potassium ratio in patients with CHF is expected.

Aim. To examine changes in the glucose-potassium ratio in patients with ischemic HFpEF and to determine its impact on the short-term (1 year) prognosis.

Materials and methods. The study involved 57 patients (men – 43.9 % (n = 25); women – 56.1 % (n = 32)) with ischemic CHF, stage II A–B, NYHA FC II–IV, 49.1 % (n = 28) with sinus rhythm, and 50.9 % (n = 29) with atrial fibrillation (AF). Patients with sinus rhythm and AF were comparable in age (p = 0.968), height (p = 0.167), weight (p = 0.539), BMI (p = 0.774), body surface area (p = 0.296). The serum GPR was calculated as the serum glucose level divided by the serum potassium level. ROC analysis and logistic regression analysis were performed.

Results. According to the univariate regression model, an increase in the GPR above 1.1697 increased the number of adverse cardiovascular events by 11.15 times at the end of the 1st year of follow-up (95 % CI 1.33–93.50, p = 0.0048).

Conclusions. Chronic heart failure with preserved left ventricular ejection fraction is accompanied by impaired tubulointerstitial function, which is confirmed by an increase in the glucose-potassium ratio, and its increase above 1.1697 (sensitivity 88.9 %, specificity 60.8 %) is associated with 11.15 times (p = 0.0048) higher odds ratio of adverse cardiovascular events within a year.

Keywords: chronic heart failure with preserved ejection fraction, tubulointerstitial injury, glucose-potassium ratio.

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***E-mail:** Vladm.d22@gmail.com

Глюкозо-калієве відношення як маркер несприятливого прогнозу в пацієнтів із хронічною серцевою недостатністю

В. В. Сиволап, В. А. Лисенко

Показано прогностичну роль глюкозо-калієвого відношення (ГКВ) у сироватці крові при гострих патологічних станах: ішемічних і геморагічних інсультах, розшарувальній аневризмі аорти, інфаркті міокарда. Втім, зміни відношення глюкоза / калій у сироватці крові в пацієнтів із хронічною серцевою недостатністю (ХСН) зі збереженою фракцією викиду залишаються нез'ясованими. Відомо, що у хворих на ХСН відбувається ураження тубулоінтерстицію. Тубулоінтерстицію нирок належить провідна роль у реабсорбції глюкози, калію, натрію. Отже, очікуваним є порушення ГКВ у хворих на ХСН.

Мета роботи – дослідити зміни глюкозо-калієвого відношення у хворих на ХСН ішемічного ґенезу зі збереженою фракцією викиду лівого шлуночка та з'ясувати його вплив на наближений (1 рік) прогноз.

Матеріали і методи. До дослідження залучено 57 хворих (25 чоловіків – 43,9 %; 32 жінки – 56,1 %) на ХСН ішемічного ґенезу, II А–Б стадії, II–IV ФК за NYHA. З поміж обстежених – 28 (49,1 %) пацієнтів із синусовим ритмом, 29 (50,9 %) – із фібриляцією передсердь. Хворі з синусовим ритмом і фібриляцією передсердь зіставні за віком (p = 0,968), зростом (p = 0,167), масою тіла (p = 0,539), ІМТ (p = 0,774), площею поверхні тіла (p = 0,296). ГКВ у сироватці крові обрахували, поділивши показник глюкози в сироватці крові на рівень калію в сироватці крові. Здійснили ROC-аналіз і логістичний регресійний аналіз.

Результати. За даними уніваріантної регресивної моделі, підвищення глюкозо-калієвого відношення понад 1,1697 збільшувало кількість несприятливих серцево-судинних подій на кінець першого року спостереження в 11,15 раза (95 % ДІ 1,33–93,50, p = 0,0048).

Висновки. ХСН зі збереженою фракцією викиду лівого шлуночка супроводжується порушенням функції тубулоінтерстицію, що підтверджено зростанням глюкозо-калієвого відношення, а збільшення ГКВ понад 1,1697 (чутливість – 88,9 %, специфічність – 60,8 %) асоціюється з підвищенням відношення шансів несприятливих серцево-судинних подій упродовж року в 11,15 раза (p = 0,0048).

Ключові слова: хронічна серцева недостатність зі збереженою фракцією викиду лівого шлуночка, ураження тубулоінтерстицію, глюкозо-калієве відношення.

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Chronic heart failure with preserved left ventricular ejection fraction (HFpEF) is highly prevalent worldwide. With the rapid progression of the aging population all over the world, the incidence of heart failure (HF) is increasing steadily [1]. HFpEF represents more than half of all HF hospitalizations. Effective treatment remains a significant unmet clinical need, regardless of a clear diagnosis [2]. HFpEF is associated with high morbidity and mortality, leading to a poor clinical prognosis. However, risk stratification and clinical management of HFpEF continue to be challenging [3].

Studies have demonstrated a complex interaction between blood glucose and potassium in the human

body. Given the potential combined effects of these two variables, the glucose-potassium ratio (GPR) concept has been introduced [4].

Serum glucose and potassium are key biomarkers frequently utilized in clinical practice. Glucose, as the primary energy source for cells in the human body, is essential for maintaining cellular metabolism. Potassium ions, the most abundant cations within human cells, are integral to various physiological processes, including nerve conduction, cardiac rhythm, muscle contraction, and the assurance of normal renal functions [5].

Recently, the GPR has served as a novel biomarker in several studies, demonstrating its potential as an early indicator of central nervous system injuries, including aneurysmal subarachnoid hemorrhage (aSAH), acute intracerebral hemorrhage, severe traumatic brain injury, and neuropsychiatric disorders following carbon monoxide poisoning. Additionally, a study has highlighted the prognostic value of GPR for predicting mortality in patients with ischemic stroke [5].

Although the GPR potentially integrates these chronic pathophysiological alterations, its prognostic value in chronic conditions, particularly in patients with HFpEF, remains unclear.

Aim

To examine changes in the glucose-potassium ratio in patients with ischemic HFpEF and to determine its impact on the short-term (1 year) prognosis.

Materials and methods

The study was performed at the clinical base of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Radiation Therapy of Zaporizhzhia State Medical and Pharmaceutical University and at the Cardiology Department of the Municipal Non-Commercial Enterprise "City Hospital No. 6" of the Zaporizhzhia City Council, in accordance with the Good Clinical Practice standards and the Helsinki Declaration principles. The study protocol was approved by the Ethics Committee of the Zaporizhzhia State Medical and Pharmaceutical University.

Following informed consent, 57 patients with ischemic CHF, stage II A–B, NYHA FC II–IV, were enrolled in the study. Of them, 43.9 % (n = 25) were male and 56.1 % (n = 32) were female. Among the participants, 49.1 % (n = 28) had sinus rhythm, while 50.9 % (n = 29) had atrial fibrillation (AF). Patients with sinus rhythm and AF were comparable in terms of age (69.32 ± 10.31 years vs. 69.59 ± 8.45 years, p = 0.968), height (166.57 ± 10.86 cm vs. 170.24 ± 8.68 cm, p = 0.167), weight (83.64 ± 17.73 kg vs. 86.93 ± 19.92 kg, p = 0.539), BMI (24.99 ± 4.39 kg/m^2 vs. 25.40 ± 5.08 kg/m^2, p = 0.774), and body surface area (1.92 ± 0.23 m^2 vs. 1.98 ± 0.24 m^2, p = 0.296).

Inclusion criteria: manifestation of subjective symptoms and objective signs of CHF (NYHA FC II–IV); objective evidence of left ventricular (LV) myocardial dysfunction in patients over 18 years; verification of ischemic CHF genesis (history of myocardial infarction and/or clinical symptoms of stable angina or ischemia signs based on ECG monitoring); ECG evidence of prior myocardial infarction (MI); coronary artery atherosclerosis confirmed by CAG or MSCT; previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); written informed consent from a patient.

Exclusion criteria: acute coronary syndrome (within the last 6 months); acute cerebrovascular accident (within the last 6 months); acute infectious diseases; decompensated diabetes mellitus; parenchymal kidney diseases; renal failure (GFR <30 ml/min/1.73 m^2); liver cirrhosis; oncological and oncohematological diseases; mental illnesses; patient refusal to participate in the study.

Ischemic CHF was diagnosed according to the 2021 Recommendations for the Diagnosis and Treatment of Chronic Heart Failure by the Ukrainian Cardiology Association and the Ukrainian Association of Heart Failure Specialists [6,7]. Doppler echocardiographic examination was conducted using an "Esaote MyLab Eight" device (Italy) with a standard method to determine baseline parameters [8], including end-diastolic and end-systolic dimensions of the left ventricle (LVEDD, cm; LVESD, cm), left ventricular ejection fraction (LVEF, %), relative wall thickness of the left ventricle (RWT), LV myocardial mass index (LVMI) according to the Penn Convention, left atrial volume index (LAVI, ml/m^2), early diastolic filling velocity of the left ventricle (E, cm/s), early diastolic velocity of the medial and lateral walls of the mitral valve fibrous ring (E'med and E'lat, cm/s), and the E/e' ratio, which indicates the end-diastolic pressure in the left ventricle according to tissue Doppler (E/e' med) [9].

The HFpEF diagnosis was verified by the presence of the HFA-PEFF diagnostic algorithm criteria [10]. The HFA-PEFF diagnostic algorithm can be calculated even if not all parameters are obtained, which increases its practical value.

The serum GPR was calculated as the serum glucose level (mmol/L) divided by the serum potassium level (mmol/L).

Statistical analysis of the material was performed using the Statistica 13.0 software package (StatSoft Inc., USA), license number JPZ804I382130ARCN10-J and MedCalc.10.2.0.0. The normality of the distribution of quantitative characteristics was analyzed using the Shapiro–Wilk test. The parameters with a normal distribution were given as the arithmetic mean and standard deviation (M ± SD). The results with non-normal distribution were demonstrated by descriptive statistics as median, lower and upper quartiles – Me (Q25; Q75). The normal and non-normal distributed quantitative variables in the groups were compared by T-test or the Mann–Whitney test, respectively, after ascertaining the distribution normality. To determine the optimal point for the distribution of quantitative features (optimal ratio of sensitivity and specificity), ROC analysis with characteristic curve construction was used. Logistic regression analysis was performed to construct a univariate model. Odds ratios of adverse cardiovascular events were calculated during one year of observation. Adverse events were considered to be myocardial infarction, stroke, progressive angina, and progressive HF requiring hospitalization. Data were presented as odds ratios (ORs) and confidence intervals (95 % CIs). The differences were considered significant at a p-value <0.05.

Table 1. Structural-geometric and functional parameters of the heart in patients with ischemic HFpEF

Parameter, measurement units	HFpEF, n = 57	HFpEF with sinus rhythm, n = 28	HFpEF with atrial fibrillation, n = 29	p
Age, years	69.46 ± 9.33	69.32 ± 10.31	69.59 ± 8.45	0.968
Height, cm	168.44 ± 9.90	166.57 ± 10.86	170.24 ± 8.68	0.167
Weight, kg	85.32 ± 18.78	83.64 ± 17.73	86.93 ± 19.92	0.539
BMI, kg/m^2	25.20 ± 4.72	24.99 ± 4.39	25.40 ± 5.08	0.774
BSA, m^2	1.95 ± 0.23	1.92 ± 0.23	1.98 ± 0.24	0.296
LAd, cm	5.05 ± 0.69	4.81 ± 0.67	5.29 ± 0.64	0.015
LVEDD, cm	5.30 ± 0.74	5.47 ± 0.84	5.12 ± 0.60	0.129
LVESD, cm	3.38 ± 0.67	3.47 ± 0.78	3.30 ± 0.54	0.566
LVEF, %	65.26 ± 7.82	66.46 ± 7.64	64.10 ± 7.95	0.257
RWT, cm	0.42 ± 0.15	0.43 ± 0.18	0.42 ± 0.13	0.962
LVMI, g/m^2	126.49 ± 40.71	129.86 ± 48.03	123.24 ± 32.67	0.743
PASP, mmHg	47.19 ± 11.39	44.18 ± 11.92	49.66 ± 10.50	0.145
E/e' med, c. u.	8.78 ± 5.41	8.11 ± 3.87	9.44 ± 6.57	0.534
E' med, cm/s	9.12 ± 3.41	7.61 ± 2.04	10.59 ± 3.84	0.001
E' lat, cm/s	11.79 ± 4.09	10.04 ± 3.44	13.41 ± 4.03	0.001
LAVI, ml/m^2	47.23 ± 17.23	43.40 ± 6.96	50.42 ± 22.98	0.855
SBP, mmHg	149.61 ± 12.06	149.61 ± 13.75	149.62 ± 10.43	0.774
Potassium, mmol/l	4.37 ± 0.31	4.36 ± 0.35	4.38 ±0.27	0.930
Sodium, mmol/l	143.77 ± 3.22	143.24 ± 2.95	144.28 ± 3.42	0.254
Blood glucose, mmol/l	5.08 ± 1.04	5.24 ± 1.20	4.92 ± 0.86	0.434
GPR	1.17 ± 0.25	1.21 ± 0.29	1.13 ± 0.20	0.350

Results

Initially, the probability of HFpEF was assessed using the H_2FPEF score [11] in patients with ischemic CHF included in the study.

According to the assessment criteria, each patient was assigned 1 point for the presence of arterial or pulmonary hypertension, elevated end-diastolic pressure, age over 60 years, 2 points for obesity, and 3 points for AF. The sum of the points from 2 to 6 indicated an intermediate probability, up to 2 points – low, 6–9 points – high probability of HFpEF.

All the examined patients (n = 57) with CHF had arterial hypertension and used more than two antihypertensive drugs, 84 % (n = 48) were older than 60 years, in 14 % of cases (n = 8), obesity was documented (BMI over 30 kg/m^2), systolic pressure in the pulmonary artery exceeded 35 mm Hg in 75 % (n = 43), and increased LV filling pressure (E/e' >9 conventional units) was in 100 % (n = 57). Persons with AF accounted for 51 % (n = 29) of all the examined.

Additionally, the diagnosis of HFpEF was confirmed based on the criteria outlined in the HFA-PEFF diagnostic algorithm [10], where the first stage (pretest) (P) should be performed for any patient with symptoms and/or signs compatible with the diagnosis of HF. Dyspnea on exertion (New York Heart Association class II or III) is very sensitive for the CHF diagnosis. Patients with HFpEF often report reduced physical activity and fatigue, disproportionate to cardiac abnormalities at rest.

Risk factors and comorbid conditions consistent with HFpEF in a symptomatic patient include older age (≥70 years for men and women), overweight / obesity, metabolic syndrome / diabetes mellitus, insufficient physical activity / detraining, arterial hypertension, AF. According to the diagnostic algorithm, if HFpEF is suspected after the first stage (P), a more detailed evaluation can confirm or rule out this diagnosis – it is the second stage, or echocardiographic (E).

The second stage (E) requires a comprehensive echocardiography and is usually performed by a cardiologist. Measurements involve early diastolic mitral annulus velocity (e'), LV filling pressure estimated by E/e', left atrial volume index, LV mass index, relative LV wall thickness, tricuspid regurgitation velocity, and global longitudinal LV systolic strain estimated by speckle-tracking echocardiography.

The score combines a number of functional, morphological and biomarker parameters, either of which is assigned 1 point (for minor criteria) or 2 points (for major criteria). A score of ≥5 points means proven HFpEF; ≤1 point makes the diagnosis of HFpEF unlikely. An intermediate score (2–4 points) means diagnostic uncertainty, that is functional testing (F1) with echocardiographic or invasive hemodynamic stress tests are recommended at the third stage. The HFA-PEFF diagnostic algorithm remains applicable even in the absence of certain parameters, which enhances its practical utility.

At the first stage, the primary symptoms of CHF were assessed, including dyspnea during physical exertion (functional classes II to IV according to the NYHA classification), reduced tolerance to physical activity, decreased physical capacity, and fatigue disproportionate to the degree of cardiac dysfunction at rest. Among the risk factors and comorbidities typical of HF, 100 % of the examined subjects had hypertension, with a mean BMI of 25.20 ± 4.72 kg/m^2. Also, AF was present in 51 % (n = 29) of patients, and the mean age of the cohort was 69.46 ± 9.33 years.

At the second (E) stage, an echocardiographic assessment was performed to verify the diagnosis of HFpEF. *Table 1* presents changes in the structural, geometric, and functional parameters of the heart in patients with ischemic HFpEF.

Assessment of major echocardiographic functional parameters (with a weight of 2 points) in the examined patients has revealed a decrease in early diastolic velocity of the medial (e'med) in 25 % (n = 14), lateral wall of the

Table 2. Univariate prediction models of adverse cardiovascular events during the first year of follow-up for serum glucose, potassium, and glucose-potassium ratio

Variable	Odds Ratio	95 % CI	p
Potassium	0.5561	0.0655–4.7221	0.5908
Glucose	1.5809	0.9852–2.5370	0.05769
GPR	11.1515	1.3299–93.5046	0.02623

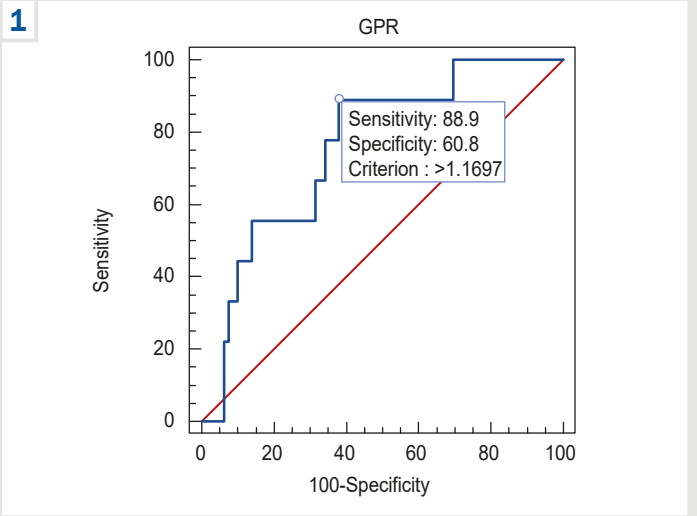

Fig. 1. Cut-off point for the glucose-potassium ratio ≥1.1697, sensitivity 88.9 %, specificity 60.8 %, p = 0.0076.

mitral annulus (e'lat) – in 37 % (n = 21), an increase in the mean E/e' index >15 standard units – in 51 % (n = 29), indicating an increase in end-diastolic pressure in the LV. An increase in systolic pressure in the pulmonary artery over 35 mmHg has been detected in 75 % (n = 43) of the examined patients. A decrease in global longitudinal systolic strain of the LV (according to longitudinal global strain ≤16 %) has been detected in 100 % (n = 57) of the examined patients. The last indicator belongs to small functional criteria and is rated at 1 point.

Major echocardiographic morphological criteria with a weight of 2 points include an increase in the left atrial volume index of more than 34 ml/m^2. This sign has been diagnosed in all 100 % (n = 57) of the examined patients. The second major morphological criterion is an increase in the LVMI of ≥149 g/m^2 for men (according to the Penn convention formula), that has been documented in 12 % (n = 7) of the examined patients, and ≥122 g/m^2 for women – in 25 % (n = 14) of the corresponding sex patients.

The minor morphological criterion of 1 point includes an increase in the LVMI (according to the Penn convention formula) of ≥115 g/m^2 for men, and ≥95 g/m^2 for women. LVMI indicators that met the minor morphological criterion were in 32 % (n = 18) of men and 39 % (n = 22) of women.

Therefore, counting the point number of major and minor criteria has generated a sum of 5 points for each patient involved in the study to confirm the presence of HFpEF in them.

In order to determine the cut-off value of the GPR for this patient population, ROC analysis was performed.

According to its results, the GPR cut-off point has been found to be ≥1.1697. The area under the curve 0.758; standard error 0.0966; 95 % CI 0.655–0.843; z statistic 2.671; p = 0.0076.

According to the univariate regression model, an increase in the GPR above 1.1697 increased the number of adverse cardiovascular events by 11.15 times (95 % CI 1.33–93.50, p = 0.0048) during the 1st year of follow-up. However, when testing the hypothesis, univariate models of the glucose (p = 0.0576) and potassium (p = 0.5908) influence in patients with HFpEF have not proven their own prognostic value, which is shown in *Table 2*.

Therefore, the GPR may be a marker of functional tubulointerstitial disorders in patients with HFpEF. An increased GPR index is associated with a higher odds ratio for adverse cardiovascular events during the one-year follow-up in HFpEF patients.

Discussion

HFpEF is a leading cause of morbidity and mortality without specific symptoms in patients with cardiovascular diseases [12]. Previously, the probability of HFpEF was calculated using the H_2FPEF scale [11]. According to the evaluation criteria, each patient was assigned 1 point for the presence of arterial or pulmonary hypertension, elevated end-diastolic pressure, age over 60 years, 2 points for obesity, and 3 points for AF. The sum of points from 2 to 6 indicated an intermediate, up to 2 points – low, 6–9 points – high probability of CHF. However, this system had its drawbacks, and in 2019 a new algorithm for verifying HFpEF was proposed, which is still valid [10].

In accordance with the recommendations of the European Society of Cardiology, the serum level of NTproBNP is a generally accepted marker of HF. However, a normal NTproBNP level does not rule out the HF presence. Therefore, the calculation of points based on the functional and morphological parameters of echocardiography is an alternative method of HFpEF verification. In our study, all the examined patients had a sum of 5 points on the HFA-PEFF diagnostic algorithm scale, that has reliably confirmed HFpEF.

Patients with AF were more likely to develop HFpEF than those with sinus rhythm. Furthermore, the risk of an unfavorable prognosis was higher for patients with AF. Therefore, to consider the impact of AF on outcomes, we have purposely formed an observation group with AF occurrence in half of the patients. This approach enabled us to adjust the prognostic model for age, sex, and heart rhythm. These factors have not affected the model statistical performance.

According to German sonologists [13], the early diastolic velocity of the mitral annulus, E', is the most feasible, reproducible, and prognostically relevant of the tissue Doppler parameters. However, no specific cut-off values for E' have been given for patients with AF. For this parameter, it would be appropriate to analyze either the septal (medial) early diastolic velocity E', lateral early diastolic velocity E', or a mean value of both.

These parameters were also monitored in our study. We have obtained a significant difference in HFpEF group between patients with sinus rhythm and AF, represented by parameters of early diastolic velocity of the medial (e'med) – 7.61 ± 2.04 cm/s vs. 10.59 ± 3.84 cm/s,

p = 0.001, respectively, and lateral wall of the mitral annulus (e'lat) – 10.04 ± 3.44 cm/s vs. 13.41 ± 4.03 cm/s, p = 0.001, respectively. This, in turn, is supported by a study of E. Fukuhara et al., proving that patients with asymptomatic AF showed a lower E/e' ratio, due to higher early diastolic velocity of the medial and lateral walls of the mitral annulus, in contrast to the group of patients with sinus rhythm [14].

Serum glucose and potassium are crucial circulating biomarkers for prognosis. Hyperglycemia is a recognized risk factor for CHF and is associated with a higher rate of hospitalizations [15]. Both postprandial and fasting glucose levels have been linked to the CHF incidence. A meta-analysis [16] has revealed that fasting blood glucose levels were correlated with an elevated risk of stroke in the general population. In addition, the GPR upon hospitalization may serve as a promising predictor of short-term outcomes in patients with ischemic stroke [5].

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) trial has demonstrated that diabetes was an independent risk factor for mortality in HF patients. The cardiovascular mortality conferred by diabetes was significantly higher in patients with HFpEF compared to patients with HFrEF. HFpEF patients with diabetes also had a higher risk of hospitalization and a trend towards a higher ventricular hypertrophy and fibrosis [17].

In the study of F. R. Khan et al., it has been shown that the association between GPR and poor endpoints was also significant in patients without diabetes in this study. Stress hyperglycemia was common in non-diabetic acute HF patients. Moreover, patients with stress hyperglycemia were associated with worse clinical outcomes than those with proven diabetes. Consequently, the predictive value of GPR for outcomes was stronger in the patient population without diabetes, where the confounding effect of diabetes was absent. It has been shown that special attention should also be paid to an elevated serum glucose levels in non-diabetic patients [18].

In our study, the mean blood glucose value was 5.08 ± 1.04 mmol, confirming the hypothesis of the study by F. R. Khan et al. about a leading diagnostic role of GPR in the patient population even without diagnosed diabetes [18].

A study by Y. Chen et al. has shown that serum GPR was closely related to the prognosis of cerebrovascular diseases. A high GPR was an independent risk factor for in-hospital mortality in patients with acute type A aortic dissection and acute chest trauma [4].

The GPR has proved to be a more comprehensive index with better predictive value compared to serum glucose or serum potassium levels alone, in cases of acute methylxanthine intoxication and blunt abdominal trauma [19]. It has been recognized as the best predictor of life-threatening cardiovascular and neurological complications among methylxanthine users (HR = 2.92; 95 % CI = 2.02–4.23). With an excellent area under the curve (0.906) and a cutoff value of 2.44, that ratio could correctly classify patients based on their prognostic risk of life-threatening events with 73 % accuracy (sensitivity 88 % and specificity 70 %) [19].

In our study, the cut-off point for GPR was 1.1697 (sensitivity 88.9 %, specificity 60.8 %). Exceeding this cut-off level significantly increased the number of adverse cardiovascular events at the end of the 1st year of follow-up (p = 0.0048).

Another study [3] has revealed a U-shaped relationship between serum glucose levels and cardiovascular mortality in acute HF patients. Meanwhile, a linear relationship has been reported between serum potassium and ischemic stroke, intracerebral hemorrhage, and all-cause mortality in the general cohort. In a study by L. Shan et al. [3], a total of 1749 patients with HFpEF were included. The mean GFR values were 1.7 ± 0.8 for men and 1.6 ± 0.8 for women with significant sex-specific differences. The cut-off point for the GPR was 1.1697 in our study, being identical to the study by L. Shan et al.

During follow-up, 514 (29.4 %) patients have reached the primary endpoint. In univariate Cox regression analysis, patients with higher levels of GPR have demonstrated a significantly increased risk of a primary cumulative endpoint (HR 1.35; 95 % CI = 1.07–1.70, p = 0.012) and hospitalization for HF (HR 1.57; 95 % CI = 1.20–2.05, p = 0.001). In multivariate Cox regression analysis, the results also have shown an independent association between the GPR and the risk of the primary cumulative endpoint (p = 0.001). The curve has demonstrated a J-shaped trend between the GPR and the primary endpoint (non-linear, p = 0.002) [3].

This finding suggests that clinicians should consider monitoring glucose and potassium levels in combination rather than alone. Notably, the GPR has demonstrated a J-shaped association with the primary outcome. An extremely low level of GPR was affected by hyperkalemia and hypoglycemia, which could increase the mortality risk [20].

Dyskalemia (including both hypokalemia and hyperkalemia) is a prevalent comorbidity in HF. While dyskalemia is generally associated with poor prognosis, the distinct prognostic impacts of hypo- and hyperkalemia have not yet been fully understood [21]. The concurrent presence of hypokalemia and hyperglycemia often indicates disrupted metabolic homeostasis and chronic inflammatory states, both of which are well-established prognostic factors in CHF [22].

The GPR has clinical significance in the prognostic assessment of patients hospitalized in the intensive care unit with such diagnoses as acute coronary syndrome, acute decompensated HF, and life-threatening cardiac arrhythmias that activate the body's stress response. Thus, a study [23] examined correlations between the serum GPR and mortality in patients hospitalized in the intensive care unit. The results have shown a significant association between the serum GPR and in-hospital mortality among intensive care unit patients. Therefore, the GPR has the potential to be a simple and rapid prognostic parameter of in-hospital mortality in cardiovascular intensive care units.

Our evidence suggests that the GPR may be a convenient and reliable biomarker of adverse cardiovascular events in patients with HFpEF and serve as a risk stratification criterion.

Our study has demonstrated the predictive value of the GPR. According to the univariate regression model, an increase in the GPR above 1.1697 was associated

with an 11.15-fold increase in the incidence of adverse cardiovascular events during the one-year follow-up (95 % CI 1.33–93.50, p = 0.0048).

Conclusions

1. Chronic heart failure with preserved left ventricular ejection fraction is associated with tubulointerstitial dysfunction, as reflected by an increase in the serum glucose-potassium ratio.

2. The glucose-potassium ratio has demonstrated its significance as an accessible and reliable biomarker in patients with chronic heart failure and preserved left ventricular ejection fraction.

3. ROC analysis has indicated the cut-off value of the glucose-potassium ratio of 1.1697 in patients with chronic heart failure and preserved left ventricular ejection fraction (sensitivity 88.9 %, specificity 60.8 %, p = 0.0076).

4. In patients with chronic heart failure and preserved left ventricular ejection fraction, exceeding this cut-off value is associated with an 11.15-fold increase in the odds ratio for adverse cardiovascular events during the one-year follow-up (p = 0.0048).

Prospects for further research are to study the influence of kidney tubulo-interstitial dysfunction markers, the GPR and a decreased serum sodium level, on the early cumulative endpoints in HFpEF patients.

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Information about the authors:

Syvolap V. V., MD, PhD, DSc, Professor of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Therapy, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0001-9865-4325
Lysenko V. A., MD, PhD, Assistant of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Therapy, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0001-7502-0127

Відомості про авторів:

Сиволап В. В., д-р мед. наук, професор каф. пропедевтики внутрішньої медицини, променевої діагностики та променевої терапії, Запорізький державний медико-фармацевтичний університет, Україна.
Лисенко В. А., канд. мед. наук, асистент каф. пропедевтики внутрішньої медицини, променевої діагностики та променевої терапії, Запорізький державний медико-фармацевтичний університет, Україна.

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