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J-shaped association between serum glucose potassium ratio and prognosis in heart failure with preserved ejection fraction with stronger predictive value in non-diabetic patients

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Background: The relationship between serum glucose/potassium ratio (GPR) and the adverse outcomes in patients with heart failure with preserved ejection fraction (HFpEF) has not been completely clarified. Methods: Patients were included from the American cohort of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. The primary endpoint was the composite of cardiovascular mortality, aborted cardiac arrest, and hospitalization for HF. The Cox regression models were applied to calculate the hazard ratio (HR) and 95% confidence interval (CI) to examine the relationship between GPR and prognosis. Restricted cubic spline (RCS) curves were performed to explore the nonlinear relationship between GPR and the primary endpoint. Receiver Operating Characteristic (ROC) curves were constructed, and the areas under the curves (AUCs) for GPR and its components were compared using the DeLong test. Subgroup analysis and interaction effect were also explored. Results: A total of 1749 HFpEF patients were included. During the follow-up, 514 (29.4%) patients reached the primary outcome. An increase in GPR was independently associated with a higher risk in the primary endpoint [Tertile 3 vs. Tertile 1: HR (95% CI), 1.35 (1.07–1.70), $P = 0.012$] and HF hospitalization [Tertile 3 vs. Tertile 1: HR (95% CI), 1.57 (1.20–2.05), $P = 0.001$]. RCS curve showed a J-shape trend between GPR and primary endpoint (non-linear $P = 0.002$). The AUC for GPR was superior to that of the glucose and potassium (De long test $P < 0.05$). Additionally, the prognostic value of GPR was stronger in patients without diabetes and with less severe heart failure symptoms (P interaction < 0.05). Conclusion: A J-shaped relationship was existed between GPR levels and the primary outcome in HFpEF patients. An increased GPR was an independent predictor of poor prognosis in HFpEF patients, especially in non-diabetic patients and those with less severe heart failure symptoms.

Keywords Serum glucose/potassium ratio, Clinical outcomes, Heart failure with preserved ejection fraction, Heart failure, TOPCAT

Heart failure with preserved ejection fraction (HFpEF) is highly prevalent worldwide[1]. It is characterized by the left ventricular ejection fraction (LVEF) of heart failure (HF) patients > 50%, accounting for up to 50% of HF patients[2]. HFpEF is associated with a higher morbidity and mortality, leading to a poor clinical prognosis[3,4]. However, the risk stratification of HFpEF and clinical interventions remained difficult. It is essential to find a convenient index for prognostic prediction in HFpEF.

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Hyperglycemia is common in HF, and correlated with a high hospitalization rate[5]. Fasting and post-load glucose were both associated with incident HF[6]. On the other hand, patients with HF experienced more frequent potassium imbalanced[7]. A lower level of serum potassium (≤ 3.71 mmol/L) was significantly associated with adverse outcome in patients with HFpEF[8]. Another retrospective observational study indicated a J-shaped association between potassium level and cardiovascular events in HFpEF patients[9]. Both patients with serum potassium < 4.1 mmol/L and serum potassium > 4.4 mmol/L had significantly higher probabilities of cardiovascular events.

Serum glucose/potassium ratio (GPR), calculated by the serum glucose level divided by the serum potassium level, has been proposed recently. Evidences showed a prognostic value of GPR for mortality in patients with severe traumatic brain injury[10] and ischemic stroke[11].

In chronic heart failure, persistent sympathetic activation led to elevated catecholamine levels, resulting in adverse cardiac remodeling characterized by impaired contractile function and electrophysiological alterations[12–14]. These pathological changes accelerated heart failure progression and worsened prognosis[15,16]. The sustained hormonal dysregulation influenced GPR, which served as an indicator of chronic metabolic perturbations and electrolyte imbalances. For instance, the combination of hypokalemia and hyperglycemia often reflected compromised metabolic homeostasis and chronic inflammatory states, both established prognostic factors in heart failure[17,18]. While GPR potentially integrated these chronic pathophysiological alterations, its prognostic significance specifically in patients with HFpEF remained unexplored. In this study, we aimed to assess the predictive value of a higher GPR level on the risk of adverse clinical outcomes in HFpEF patients.

Methods

Population

Patients enrolled in this study were participants of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT). TOPCAT was a multicenter, double-blinded, placebo-controlled randomized control trial of spironolactone. A total of 3445 patients with symptomatic HF were included from Americas, Russia, and Georgia. The inclusion criteria were: (1) LVEF ≥ 45%; (2) aged 50 years or older; (3) serum potassium concentration level of < 5.5 mmol/L prior to randomization; (4) estimated glomerular filtration rate (eGFR) > 30 ml/min/1.73 m^2, or serum creatinine level was < 2.5 mg/dl prior to randomization. The detailed design, characteristics, and results of the trial have been previously described[19]. The TOPCAT trial protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki and this study involving humans were approved by the Ethics Committee of the Cardiovascular Institute and Anzhen Hospital. Written informed consents were obtained from all survey participants. All methods in this study were carried out in accordance with relevant guidelines and regulations, ensuring the ethical use of data from the TOPCAT trial.

In the present study, patients from Russia and Georgia were excluded due to significant regional differences. In addition, patients with missing data of serum glucose and serum potassium were also excluded. Finally, the remaining 1749 patients with HFpEF from the Americas were included in the present analysis (shown in Fig. 1).

Laboratory assessment

Clinical data of patients were collected from the TOPCAT, including demographic characteristics, comorbidities, medication, and laboratory tests. Body mass index (BMI) was weight in kilograms divided by the height squared in meters. eGFR was calculated to assess renal function[20]. GPR was calculated by serum glucose (mmol/L)/potassium (mmol/L)[10]. All blood samples were collected in a fasting state. In the TOPCAT trial, diabetes was defined as either a documented history of diabetes mellitus or current use of antidiabetic medications.

Clinical outcomes

The primary outcome of the present analysis was the composite of cardiovascular mortality, HF hospitalization, and aborted cardiac arrest[21]. Secondary outcomes were all-cause mortality, cardiovascular mortality, HF hospitalization, and aborted cardiac arrest. The definition of each outcome was according to the original TOPCAT.

Statistical analysis

Patients included in this study were divided into three groups according to the tertile of GPR level: Tertile 1 ($n = 577$, GPR < 1.26), Tertile 2 ($n = 578$, 1.26 ≤ GPR < 1.62), Tertile 3 ($n = 594$, GPR ≥ 1.62). Continuous variables were presented as mean ± standard deviation for normally distributed variables, and median (interquartile range) for nonnormally distributed variables. Categorical variables were expressed as counts (percentage). The intergroup differences were assessed using the analysis of variance (ANOVA) or Kruskal-Wallis test to compare continuous variables, and chi-square ($\chi 2$) test for categorical variables. To visualize the distribution of GPR across the study population, box plots were constructed to illustrate GPR patterns between male and female subgroups. Kaplan-Meier curves and Cox regression model were used to analyze the relationship between GPR tertiles and clinical outcomes. Model 1 was an unadjusted analysis; Model 2 incorporated adjustments for age, sex, and variables that were either statistically significant ($P < 0.05$) in univariate analysis or clinically relevant, including smoking status, diastolic blood pressure (DBP), heart rate (HR), EF, eGFR, diabetes mellitus (DM), stroke, myocardial infarction, chronic obstructive pulmonary disease (COPD), coronary artery bypass grafting (CABG), atrial fibrillation, diuretics, beta-blocker, spironolactone, hemoglobin, albumin, alanine aminotransferase (ALT), and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB). The results were expressed by the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Sensitivity analysis was conducted in patients with LVEF ≥ 50% to validate our findings. Restricted cubic spline (RCS) curves were employed to visualize the nonlinear relationship between GPR and the primary endpoint. Receiver operating characteristic (ROC) curves were generated to assess the predictive performance of GPR, glucose, and serum potassium, and

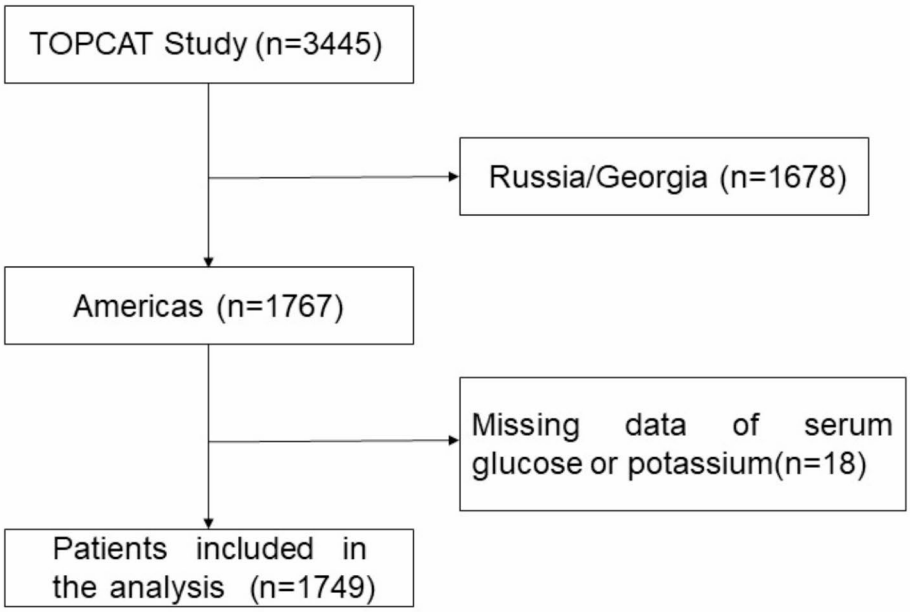


Fig. 1. Flow diagram of the patient selection process.

the area under the curve (AUC) values were compared using the DeLong test. Subgroup analysis was further conducted to evaluate the interaction effect stratified by gender, diabetes mellitus, atrial fibrillation, New York Heart Association (NYHA) class, and treatment group (spironolactone versus placebo).

All statistical analysis was conducted using SPSS 23.0., and statistical significance was defined as $P<0.05$ (two-sided tests).

Results

Patient characteristics

A total of 1749 patients were included in the present study. The mean GPR values were 1.7 ± 0.8 and 1.6 ± 0.8 for males and females, respectively, with significant gender-based differences observed (Fig. 2). As shown in Table 1, there was a significant difference among three groups in terms of age, BMI, HR, eGFR, and level of hemoglobin, creatinine, ALT, glucose and potassium. The proportion of male sex, hypertension, DM, myocardial infarction, percutaneous coronary intervention (PCI) and CABG were significantly higher in the Tertile 3 group. Additionally, the use of ACEI/ARB, calcium channel blocker (CCB), diuretics and loop diuretics was more frequent in patients with a higher level of GPR.

Association between GPR and clinical outcomes

During a median follow-up of 2.93 years, 514 (29.4%) patients experienced the primary composite outcome. In the aspect of secondary outcome, 380 (21.7%) patients experienced the all-cause mortality, 218 (12.5%) experienced the cardiovascular mortality, 394 (22.5%) experienced the HF hospitalization, and only 6 (0.3%) experienced aborted cardiac arrest. The incidence of primary composite outcome and HF hospitalization was significantly higher in the Tertile 3 group (shown in Table 2). Meanwhile, as shown in Fig. 3, the Kaplan-Meier analyses also showed a graded increased risk for primary composite outcome and HF hospitalization in HFpEF patients (Log-rank $P<0.05$).

In the univariate Cox regression analysis, as shown in Table 3, patients with a higher GPR level demonstrated a significant increase in the risk of primary composite outcome (Tertile 3 vs. Tertile 1: HR, 95% CI: 1.73, 1.40–2.14, $P<0.001$, P for trend <0.001) and HF hospitalization (Tertile 3 vs. Tertile 1: HR, 95% CI: 2.07, 1.62–2.65, $P<0.001$, P for trend <0.001). In the multivariate Cox regression analysis, the results also indicated an

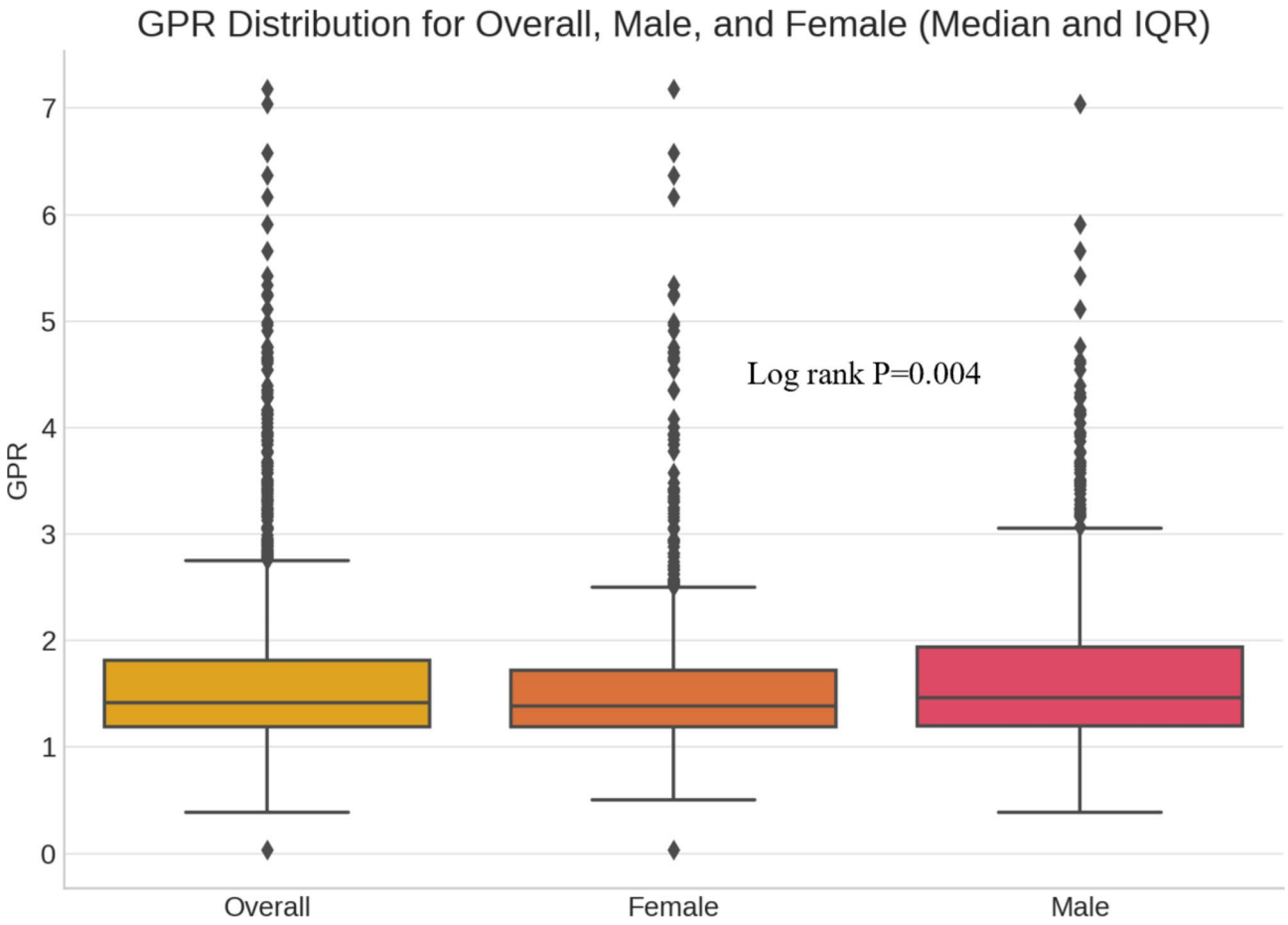


Fig. 2. GPR distribution for overall, male, and female.

independent association between GPR and the risk of primary composite outcome (Tertile 3 vs. Tertile 1: HR, 95% CI: 1.35, 1.07–1.70, $P=0.012$, P for trend = 0.012) as well as HF hospitalization (Tertile 3 vs. Tertile 1: HR, 95% CI: 1.57, 1.20–2.05, $P=0.001$, P for trend = 0.001). However, no significant association was observed between GPR and all-cause mortality, cardiovascular mortality, or aborted cardiac arrest. The sensitivity analysis yielded consistent results with our primary findings (Details in supplementary file).

In Fig. 4, the RCS curve revealed a J-shaped association between the GPR and the risk of the primary composite endpoint (non-linear $P=0.002$).

In Fig. 5, the ROC curves visually depicted the predictive capability of GPR for in-hospital mortality, yielding an AUC of 0.676 [95% CI: 0.653–0.698]. This performance surpassed that of the glucose (0.676 vs. 0.565, De-long test $P<0.001$) and potassium (0.676 vs. 0.526, De-long test $P<0.001$).

Subgroup analysis

Subgroup analyses were performed based on sex, diabetes status, atrial fibrillation, NYHA classification, and spironolactone intervention (shown in Table 4). Significant interactions were observed in the subgroups of diabetes status and NYHA classification (P for interaction < 0.05). The predictive value of GPR for the primary composite outcome and HF hospitalization was higher in patients with less severe heart failure symptoms (NYHA class I-II), and those without diabetes mellitus.

Discussion

This study examined the relationship between GPR and clinical outcomes in patients with HFpEF. Our findings suggested that a higher GPR level was a strong predictor for the primary composite outcome and HF hospitalization in HFpEF patients, and could serve as a potential marker for risk stratification in this population.

HFpEF is a leading cause of morbidity and mortality, with no specific symptoms[22]. Recent studies suggested that there were pathophysiological changes in HFpEF patients, including myocardial hypertrophy, myocardial fibrosis, and left ventricular diastolic dysfunction[23]. The etiological factors of HFpEF are complex, such as vascular stiffness, endothelial dysfunction, oxidative stress, and inflammation[24]. According to the guideline, B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide were used to diagnose the HF[25]. However, a specific biomarker for HFpEF was not referred.

	Total ($n=1749$)	Tertile 1 ($n=577$)	Tertile 2 ($n=578$)	Tertile 3 ($n=594$)	*P* value
Age (year)	71.5 ± 9.7	72.3 ± 9.8	72.6 ± 10.0	69.8 ± 9.1	< 0.001
Male (%)	870 (49.7)	275 (47.7)	267 (46.2)	328 (55.2)	0.004
Smoking status (%)	115 (6.6)	42 (7.3)	37 (6.4)	36 (6.1)	0.687
BMI (kg/m^2)	33.8 ± 8.2	32.0 ± 7.6	33.5 ± 8.1	35.9 ± 8.3	< 0.001
SBP (mmHg)	127.5 ± 15.8	126.3 ± 15.9	127.8 ± 14.9	128.4 ± 16.6	0.065
DBP (mmHg)	71.4 ± 11.5	71.6 ± 11.5	72.0 ± 11.4	70.5 ± 11.5	0.088
HR (bpm)	69.1 ± 11.3	68.0 ± 10.4	68.3 ± 12.0	69.9 ± 11.3	0.015
LVEF (%)	58.2 ± 7.8	58.1 ± 8.0	58.5 ± 7.7	58.1 ± 7.6	0.642
eGFR (mL/min/1.73 m^2)	61.2 (49.0,76.6)	62.9 (50.7,77.2)	62.4 (49.8,77.5)	57.8 (47.5,75.0)	0.009
Hypertension (%)	1574 (90.0)	498 (86.3)	523 (90.5)	553 (93.1)	< 0.001
DM (%)	779 (44.5)	154 (26.7)	168 (29.1)	457 (76.9)	< 0.001
Stroke (%)	77 (4.4)	26 (4.5)	24 (4.2)	27 (4.5)	0.937
Myocardial infarction (%)	94 (5.4)	27 (4.7)	19 (3.3)	48 (8.1)	0.001
NYHA functional class (%)					0.038
I-II	1135 (64.9)	397 (68.8)	371 (64.2)	367 (61.8)	
III-IV	614 (35.1)	180 (31.2)	207 (35.8)	227 (38.2)	
COPD (%)	288 (16.5)	98 (17.0)	88 (15.2)	102 (17.2)	0.614
PCI (%)	342 (19.6)	102 (17.7)	88 (15.2)	152 (25.6)	< 0.001
CABG (%)	330 (18.9)	99 (17.2)	91 (15.7)	140 (23.6)	0.001
Atrial fibrillation (%)	734 (42.0)	247 (42.8)	251 (43.4)	236 (39.7)	0.388
Beta blocker (%)	1371 (78.4)	441 (76.4)	448 (77.5)	482 (81.1)	0.120
CCB (%)	678 (38.8)	203 (35.2)	209 (36.2)	266 (44.8)	0.001
Diuretics (%)	1557 (89.0)	491 (85.1)	516 (89.3)	550 (92.6)	< 0.001
Loop diuretic (%)	1516 (86.7)	467 (80.9)	506 (87.5)	543 (91.4)	< 0.001
ACEI/ARB (%)	1383 (79.1)	444 (76.9)	448 (77.5)	491 (82.7)	0.030
Spironolactone (%)	881 (50.4)	275 (47.7)	292 (50.5)	314 (52.9)	0.204
WBC (10^9/L)	7.1 (5.9,8.5)	6.8 (5.7,8.1)	7.0 (5.9,8.4)	7.4 (6.0,9.1)	0.224
Hemoglobin (g/dl)	12.9 ± 1.7	13.0 ± 1.7	12.9 ± 1.7	12.7 ± 1.6	0.003
Albumin (g/dl)	4.0 ± 1.6	4.0 (3.7,4.2)	3.9 ± 0.4	3.9 ± 1.8	0.235
Creatinine (μmol/l)	97.2 (79.6,123.8)	97.2 (79.6,115.0)	97.2 (79.6,114.9)	106.1 (81.5,127.2)	< 0.001
ALT (U/l)	22.0 (16.0,31.0)	21.0 (15.0,29.0)	23.0 (16.0,32.0)	22.0 (16.0,31.0)	0.009
AST (U/l)	23.0 (18.0,29.0)	23.0 (18.0,29.0)	23.0 (19.0,30.0)	22.0 (17.0,28.0)	0.055
Glucose (mmol/l)	5.8 (5.1,7.4)	4.7 ± 0.7	5.9 ± 0.6	8.6 (7.3,11.1)	< 0.001
Potassium (mmol/l)	4.2 ± 0.4	4.4 ± 0.4	4.1 ± 0.4	4.1 ± 0.5	< 0.001
GPR	1.4 (1.2,1.8)	1.1 ± 0.2	1.4 ± 0.1	2.1 (1.8,2.7)	< 0.001

Table 1. Baseline characteristics of HFpEF patients grouped by tertiles of GPR. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular rate; HR, heart rate; NYHA, New York Heart Association; WBC, white blood cell; DM, diabetes mellitus; CCB, calcium channel blocker; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; GPR, glucose/potassium ratio.

Outcomes	Total ($n=1749$)	Tertile 1 ($n=577$)	Tertile 2 ($n=578$)	Tertile 3 ($n=594$)	*P* value
Primary composite outcome (%)	514 (29.4)	141 (24.4)	154 (26.6)	219 (36.9)	< 0.001
Cardiovascular mortality (%)	218 (12.5)	72 (12.5)	68 (11.8)	78 (13.1)	0.778
HF hospitalization (%)	394 (22.5)	98 (17.0)	112 (19.4)	184 (31.0)	< 0.001
Aborted cardiac arrest (%)	6 (0.3)	2 (0.3)	1 (0.2)	3 (0.5)	0.623
All-cause mortality (%)	380 (21.7)	123 (21.3)	117 (20.2)	140 (23.6)	0.369

Table 2. Clinical outcomes of HFpEF patients stratified by tertiles of GPR. Abbreviations: HFpEF, heart failure with preserved ejection fraction; GPR, glucose/potassium ratio; HF, heart failure.

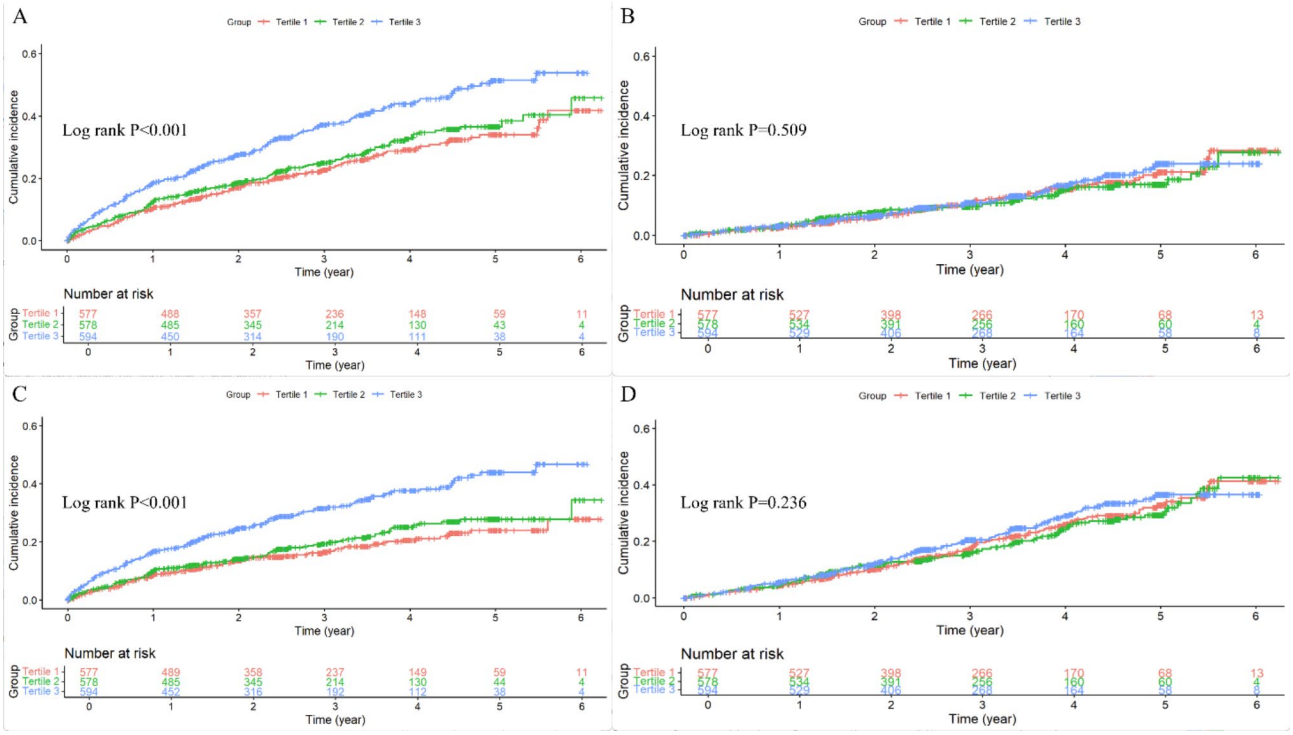


Fig. 3. Kaplan–Meier curves for cumulative events of adverse outcome in HFpEF patients (**A**) Primary composite outcome, (**B**) Cardiovascular mortality, (**C**) HF hospitalization, (**D**) All-cause mortality.

Serum glucose and potassium are two important circulating biomarkers for prognosis. A meta-analysis showed that fasting blood glucose was positively related to stroke risk in the general population[26]. Another study revealed a U-shaped association between serum glucose and cardiovascular mortality in acute HF patients[27]. Meanwhile, a linear relationship was presented between serum potassium and ischemic stroke, intracerebral hemorrhage and all-cause mortality in the general cohort[28]. Nevertheless, the correlation of decreased serum potassium levels and prognosis in patients with HF was not stable[29,30]. GPR was a more comprehensive index with a better predictive ability in comparison to the simple serum glucose or serum potassium in acute methylxanthine intoxication[31] and blunt abdominal trauma[32]. Therefore, it is meaningful to verify the diagnostic value of GPR for prognosis in patients with HFpEF.

A high GPR was an independent risk factor for in-hospital mortality in patients with acute type A aortic dissection[33] and trauma[34]. The association of GPR and poor prognosis was also shown in patients with aneurysmal subarachnoid hemorrhage[35,36]. However, the predictive value of GPR for clinical outcomes in patients with HFpEF patients was still unrevealed. In our study, we included HFpEF patients from TOPCAT trial, and found that GPR was positively associated with the risk of primary composite outcome and HF hospitalization. The pathological mechanisms behind the impact of GPR on the prognosis in HFpEF patients was multifactorial. An increased activity of the sympathetic nervous system is common in HF patients[37], resulting in excessive catecholamine and corticosteroids production. Potassium is transported acros the cell membrane via the adenosine triphosphatase sodium/potassium pump (Na+/K+-ATpase), which is regulated by catecholamines, B2 adrenergic hormones, and insulin[38], leading to a reduced serum potassium level. Serum potassium disturbance increased the automaticity and excitability of cardiac muscle cell, thereby elevating the risk of sudden cardiac death[39]. In patients with HFrEF, hypokalemia was associated with a higher risk of long-term mortality[40]. A supplemental of serum potassium could attenuate hypertension through enhancing sodium excretion and nitric oxide synthase activity[41]. Serum glucose and potassium displayed a complex interplay. A profound effect of potassium on the maintenance of glucose homeostasis was proposed[42]. ATP-sensitive potassium channels appeared to be important to regulate the release of hormones in hypoglycemia. Accumulating evidence showed a toxic effect of hyperglycemia on cardiovascular complications[43]. The increasing serum glucose level might be associated with gut microbiota in HF patients[44]. Hyperglycemia could increase the level of proinflammatory cytokines and oxidative stress[45]. Moreover, oxidative stress and apoptosis induced by a high serum glucose were further involved in the process of cardiac dysfunction in rats[46].

In our study, the superior discriminative ability of GPR compared to its individual components (as demonstrated by ROC curve analysis) highlighted its potential value as an integrated biomarker for risk stratification in clinical practice. And this finding suggested that clinicians should consider monitoring both glucose and potassium levels collectively rather than in isolation. Notably, GPR exhibited a J-shaped association with primary outcome. An extremely low level of GPR could be affected by hyperkalemia and hypoglycemia,

	Model 1			Model 2		
	HR (95%CI)	P value	P for trend	HR (95%CI)	P value	P for trend
Primary composite outcome			< 0.001			0.012
Tertile 1	Reference			Reference		
Tertile 2	1.12 (0.89,1.41)	0.321		1.11 (088,1.40)	0.357	
Tertile 3	1.73 (1.40,2.14)	< 0.001		1.35 (1.07,1.70)	0.012	
Cardiovascular mortality			0.576			0.797
Tertile 1	Reference			Reference		
Tertile 2	0.96 (0.69,1.33)	0.801		1.00 (0.71,1.39)	0.984	
Tertile 3	1.09 (0.79,1.51)	0.581		0.95 (0.67,1.36)	0.791	
HF hospitalization			< 0.001			0.001
Tertile 1	Reference			Reference		
Tertile 2	1.17 (0.89,1.54)	0.253		1.16 (0.88,1.53)	0.280	
Tertile 3	2.07 (1.62,2.65)	< 0.001		1.57 (1.20,2.05)	0.001	
Aborted cardiac arrest			0.594			0.505
Tertile 1	Reference			Reference		
Tertile 2	0.52 (0.05,5.78)	0.598		0.11 (0.00,6.84)	0.295	
Tertile 3	1.56 (0.26,9.34)	0.627		0.28 (0.01,5.28)	0.395	
All-cause mortality			0.267			0.867
Tertile 1	Reference			Reference		
Tertile 2	0.96 (0.75,1.24)	0.761		0.97 (0.75,1.26)	0.842	
Tertile 3	1.15 (0.90,1.46)	0.275		1.03 (0.79,1.34)	0.853	

Table 3. Associations of GPR with adverse outcomes in HFpEF patients. Model 1: unadjusted. Model 2: adjusted for age, sex, smoke, diastolic blood pressure, heart rate, ejection fraction, estimated glomerular filtration rate, diabetes mellitus, stroke, myocardial infarction, chronic obstructive pulmonary disease, coronary artery bypass grafting, atrial fibrillation, diuretics, beta-blocker, spironolactone, hemoglobin, albumin, and alanine aminotransferase, ACEI/ARB. Abbreviations: GPR, glucose/potassium ratio; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; CI, confidence interval; ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

which could both heighten the risk for mortality[47,48]. Further research is required to elucidate a proper cutoff range of serum potassium and glucose in HFpEF patients for a better prognosis.

Subgroup analysis showed that GPR was positively associated with a higher risk of poor clinical outcomes regardless of the treatment of spironolactone, suggested that the predictive value of GPR for prognosis was relatively stable in HFpEF patients receiving routine treatment. Additionally, a significant interaction was observed in the diabetes subgroup. A study including participants from Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program showed that diabetes was an independent risk factor for mortality in patients with HF[49]. Inflammatory, oxidative stress and apoptosis were observed in diabetic cardiomyopathy[50,51]. In particular, the cardiovascular mortality conferred by diabetes was significantly higher in patients with HFpEF in comparison to patients with HFrEF. HFpEF patients with diabetes also had a high risk of hospitalization[52] and a trend towards a higher ventricular hypertrophy and fibrosis[53]. The adverse impact of diabetes on prognosis might attenuate the prognostic value of GPR in this subgroup. In non-diabetic patients with aneurysmal subarachnoid hemorrhage, an elevated GPR was as an independent risk factor for rebleeding[54]. In line with the existing literature, the association of GPR and poor endpoints was also significant in patients without diabetes in this study. Stress hyperglycemia was prevalent in non-diabetic acute HF patients[55]. Additionally, patients with stress hyperglycemia were associated with worse clinical outcomes than those with pre-existing diabetes[56]. Consequently, the predictive ability of GPR for outcomes was stronger in the non-diabetic population, where the confounding effect of diabetes was absent. Our findings revealed that a particular attention should also be paid to an elevated serum glucose level in non-diabetic patients.

Furthermore, we found that the prognostic ability of GPR was higher in patients with NYHA class I-II compared to those with class III-IV. Evidence indicated that a left ventricular hypertrophy and diastolic dysfunction could occur in HFpEF patients[57]. Furthermore, the cardiac hypertrophy and diastolic dysfunction were significantly associated with a greater mechanical dyssynchrony[58], leading to an increased risk of death[59]. Patients with a worse cardiac dysfunction probably had a higher risk of other comorbidities[60]. Consequently, the predictive power of GPR for outcomes was more pronounced in patients with less severe heart failure symptoms (NYHA class I-II), where the confounding effects of advanced heart failure were less prominent.

In this study, the prognostic ability of GPR was more pronounced in patients with NYHA class I-II and those without diabetes. This finding highlights the importance of evaluating GPR in these subgroups to improve prognosis. In clinical practice, patients with diabetes or severe heart failure symptoms (NYHA class III-IV) are more likely to receive close attention and comprehensive management due to their apparent high-risk status. However, patients without diabetes or with less severe heart failure symptoms (NYHA class I-II)

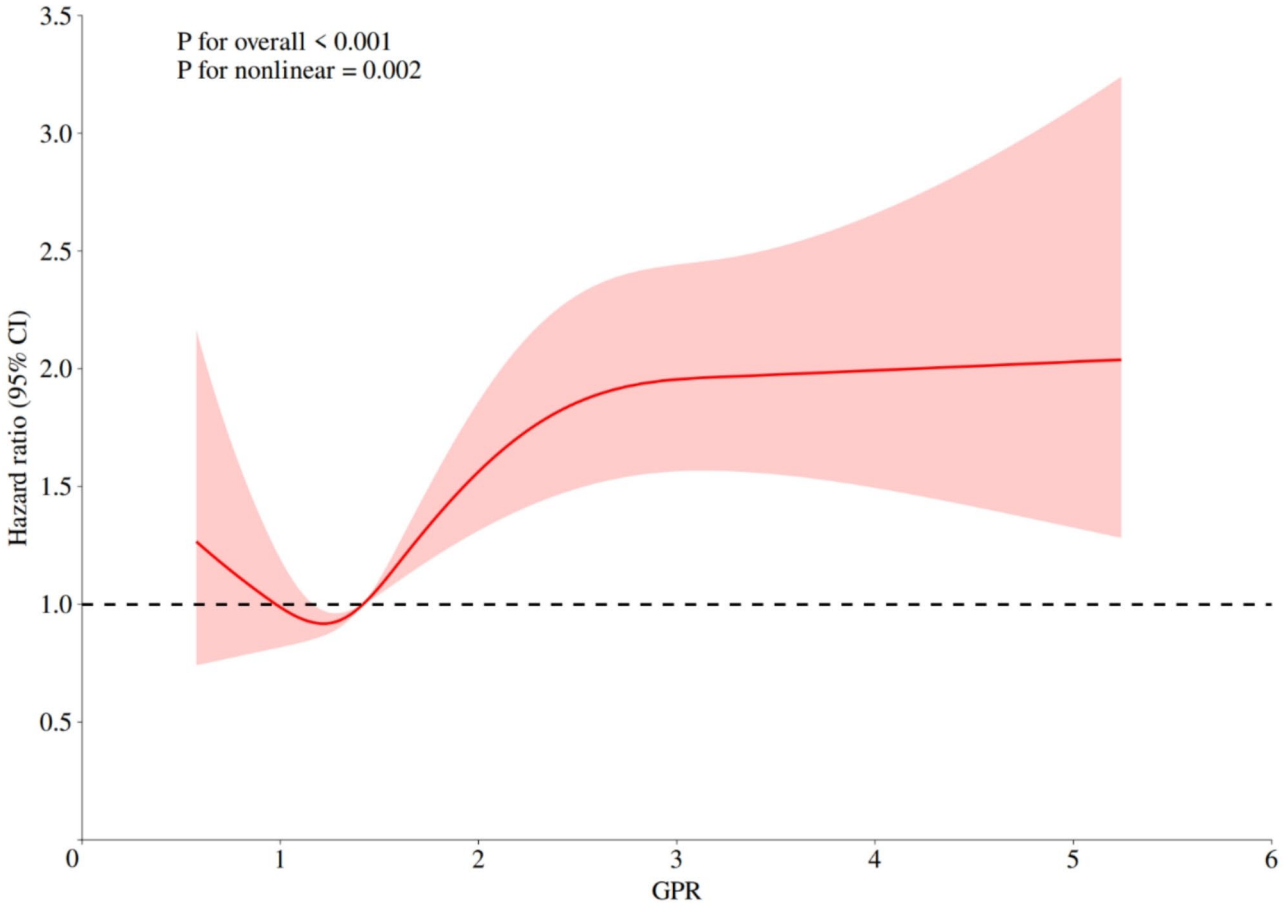


Fig. 4. RCS revealed the relationship between GPR and primary composite outcome in HFpEF patients.

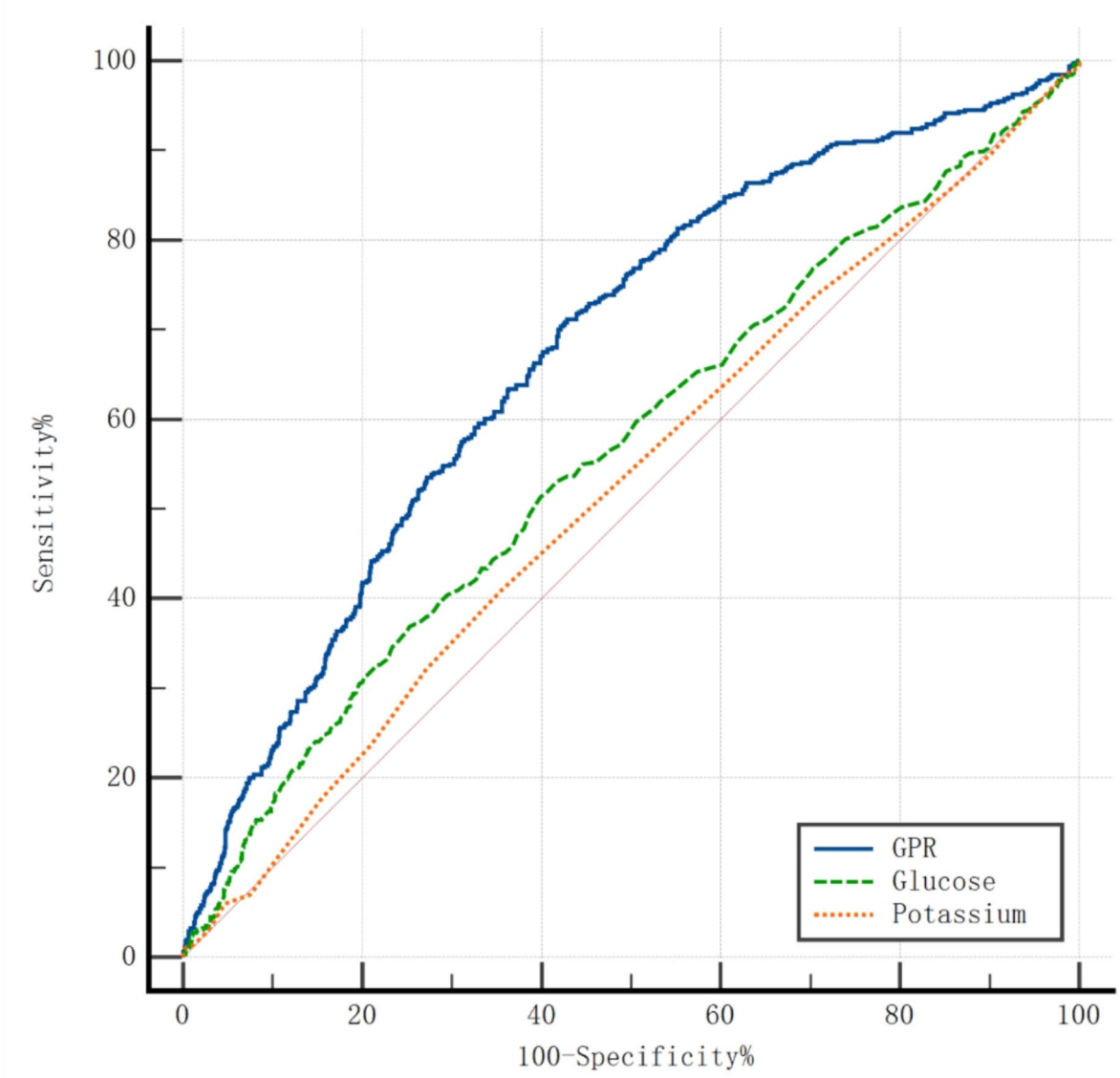
may be overlooked, leading to a potential delay in identifying and addressing risk factors. Given the stronger predictive power of GPR in non-diabetic patients and those with NYHA class I-II, clinicians should prioritize the assessment of GPR in these subgroups. By doing so, high-risk individuals can be identified early, allowing for timely intervention and personalized management strategies. This proactive approach may help prevent or delay the progression of heart failure and improve overall outcomes.

In this study, GPR demonstrated significant prognostic power for predicting HF hospitalization but did not show the same effect for mortality. This discrepancy may stem from GPR's specific ability to reflect metabolic and electrolyte status. Factors such as metabolic instability and electrolyte imbalances were more directly associated with acute exacerbations leading to hospitalization, whereas mortality prediction in HF often depended more on overall cardiac function, comorbidities, and long-term cardiovascular health[61].

However, this study has several limitations. First, the value of serum glucose and serum potassium were obtained at admission. The dynamic monitoring of GPR could improve the reliable of our results. Second, the several important parameters, including antidiabetic drugs, diuretic dosage HbA1c, cardiac biomarkers (BNP or NT-proBNP), and key echocardiographic measurements were not available in this study, which might affect the validity. Third, patients with an eGFR < 30 mL/min/1.73 m^2 prior to randomization were excluded from the TOPCAT which might lead to a bias. The study population was also limited to HFpEF patients, precluding the generalization of our findings to those with HFrEF. Furthermore, data on prediabetes status were not available in the original cohort.

Conclusion

Our results showed that higher levels of GPR were associated with an increased risk of primary composite outcome and HF hospitalization in HFpEF patients. The relationship between GPR levels and the primary outcome exhibited a J-shaped curve. The findings prompted that GPR might be a convenient and reliable biomarker for risk-stratifying patients with HFpEF. More studies are needed to confirm our results and explore the potential mechanisms.



Indicators	AUC	95%CI	De-long test P value
GPR	0.676	0.653 to 0.698	Ref.
Glucose	0.565	0.541 to 0.588	<0.001
Potassium	0.526	0.502 to 0.549	<0.001

Fig. 5. ROC curves for the prediction of primary composite outcome of GPR, glucose, and potassium.

	Primary composite outcome			HF hospitalization		
	HR (95%CI)	P value	P for interaction	HR (95%CI)	P value	P for interaction
Gender			0.147			0.429
Male	1.24 (1.10,1.40)	0.001		1.30 (1.13,1.49)	< 0.001	
Female	1.28 (1.13,1.44)	< 0.001		1.32 (1.15,1.50)	< 0.001	
DM			< 0.001			< 0.001
No	1.72 (1.19,2.36)	0.003		2.14 (1.43,3.19)	< 0.001	
Yes	1.11 (1.00,1.23)	0.060		1.12 (0.99,1.26)	0.063	
NYHA class			< 0.001			< 0.001
I-II	1.32 (1.15,1.51)	< 0.001		1.38 (1.18,1.61)	< 0.001	
III-IV	1.17 (1.04,1.31)	0.007		1.20 (1.06,1.36)	0.003	
Atrial fibrillation			0.162			0.094
No	1.23 (1.11,1.37)	< 0.001		1.26 (1.13,1.42)	< 0.001	
Yes	1.38 (1.16,1.64)	< 0.001		1.49 (1.23,1.80)	< 0.001	
Spironolactone			0.147			0.200
No	1.21 (1.07,1.36)	0.002		1.26 (1.10,1.43)	0.001	
Yes	1.33 (1.17,1.51)	< 0.001		1.38 (1.20,1.58)	< 0.001	

Table 4. Subgroup analysis for the association of GPR and prognosis in HFpEF patients. Abbreviations: HFpEF, heart failure with preserved ejection fraction; GPR, glucose/potassium ratio; HF, heart failure; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; NYHA, New York Heart Association.

Data availability

The data analyzed in this study are publicly available from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, which can be obtained from the BioLINCC website (https://biolincc.nhlbi.nih.gov/).

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Author contributions
L.S. was responsible for conceptualization, methodology, data curation, and writing the original draft. K.Z. conducted data analysis and contributed to writing by reviewing and editing. W.D. carried out investigation, provided resources, and supervised the project. P.H. and Y.W. managed the project. All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

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