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The addition of alpha-ketoglutarate to NT-proBNP improves the prediction of long-term all-cause mortality in acute heart failure patients

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ABSTRACT

Background and Objective: Alpha-ketoglutarate (AKG), is a major intermediate metabolite of the tricarboxylic acid cycle, and is closely associated with cardiometabolic disease prognosis. Previous studies indicated that AKG is related to myocardial energy expenditure levels and reflects adverse short-term outcomes in heart failure (HF) patients. In this prospective cohort study, we examined the long-term prognostic value of AKG levels in acute HF (AHF) patients.

Methods: Plasma AKG levels were assessed in patients hospitalized with AHF. Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality were calculated via multiple Cox regression. All-cause mortality was compared between patients with NT-proBNP <1000 pg/ml and those with NT-proBNP ≥ 1000 pg/ml via subgroup analysis.

Results: Patients with AKG ≥ 9.83 μg/ml had higher heart rates and NT-proBNP and lower left ventricular ejection fraction (LVEF) and systolic blood pressure (SBP). After multiple adjustment, higher AKG was associated with an increased all-cause mortality risk (HR = 1.078, p<0.001). Compared with AKG <9.83 μg/ml, AKG ≥ 9.83 μg/ml nearly doubled (HR = 1.929, p<0.001) and quadrupled (HR = 4.160, p<0.001) the all-cause mortality risk in patients with NT-proBNP ≥ 1000 pg/ml and those with NT-proBNP <1000 pg/ml, respectively.

Conclusions and Relevance: Plasma AKG was independently associated with greater all-cause mortality risk in patients with AHF. Higher AKG levels retained prognostic value for patients with relatively low NT-proBNP.

KEY MESSAGES

- AKG was an independent factor associated with a greater risk of long-term outcomes in patients with AHF.
- Elevated AKG was significantly related to a worse prognosis in AHF patients with NT-proBNP <1000 pg/ml, especially in those patients with persevered ejection fraction.
- AKG could be used as an additive metabolic biomarker combined with NT-proBNP for long-term outcome prediction in AHF patients, especially in those with relatively low NT-proBNP levels.

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Alpha-ketoglutarate; NT-proBNP; prognosis; long-term all-cause mortality; heart failure

Introduction

Heart failure (HF), viewed as the end stage of various cardiovascular (CV) diseases, is characterized by high morbidity and mortality worldwide [1,2]. Despite the multiple introductions of new drug and device therapies for HF in recent years, the mortality and rehospitalization rates of HF remain high [3].

The plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level has been recommended by guidelines as a well-established effective biomarker for the diagnosis, risk stratification, therapeutic assessment, and prognostic evaluation of HF [2–4]. NT-proBNP is released from the myocardium and reacts to multiple physiological stimuli, such as myocardial stretch and neuroendocrine stimuli [5]. According to the latest

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guidelines, the NT-proBNP threshold of >300 pg/ml is considered one of the criteria for identifying acute HF (AHF). In addition, patients with very high NT-proBNP concentrations (NT-proBNP > 5000 pg/ml), had a poorer prognosis than do those with lower NT-proBNP concentrations [6,7]. Although studies have revealed that patients with NT-proBNP levels <1000 pg/ml were prone to lower CV death/HF hospitalization [8,9], mortality remained high [8]. These findings suggest that in AHF patients with low NT-proBNP levels, hemodynamic congestion and prognosis may be underestimated if only the NT-proBNP level is measured [10]. Hence, an additional biomarker is needed for improving prognosis prediction in patients with HF.

Metabolic remodelling and epigenetic mechanisms are central to HF pathophysiology and have facilitated the identification of novel biomarkers for HFpEF [11]. Different phenotypes of HF showed its distinct metabolic pathway, with lower fatty acid and tricarboxylic acid cycle metabolites observed in HF with persevered ejection fraction (HFpEF) compared with HF with reduced ejection fraction (HFrEF) [12,13]. Further studies also showed that circulating metabolite markers, including beta-hydroxybutyrate (β-OHB), are viewed as valuable resources for early identification of prognostic risk in HF patients [14,15]. In addition, epigenetically modified circulating CD4+ T lymphocytes may drive pro-inflammatory responses, contributing to cardiac remodelling in HFpEF, highlighting their potential utility in enhancing the accuracy of HFpEF diagnosis [16].

Alpha-ketoglutarate (AKG), also called 2-oxoglutarate, is a major intermediate metabolite of the tricarboxylic acid (TCA) cycle [17]. Recently, studies have shown that AKG plays a highly important role in various physiological processes, including cell growth performance, antioxidation, and inflammation [18]. AKG, an essential factor in cellular energy metabolism, has been revealed to be closely associated with the prognosis of CV and metabolic diseases and tumours. Murine studies have indicated that AKG reduced cellular oxidative stress [19], ameliorated inflammation, extended lifespan [20], and inhibited angiogenesis in cancer cells [21], resulting in beneficial effects. Cohort studies have also suggested plasma AKG as a metabolite marker that may predict the progression of cardiometabolic diseases [22], such as HF.

Our previous studies have shown that AKG was associated with myocardial energy expenditure levels in chronic HF patients [23] and that high baseline AKG levels were related to adverse short-term outcomes in AHF patients [24]. However, the prognostic role of AKG in AHF patients in long-term outcomes, especially in patients with NT-proBNP levels <1000 pg/ml, is still unknown. Herein, we addressed this knowledge gap by conducting a prospective cohort study to assess whether admission AKG levels are associated with increased mortality risk in HF patients and have prognostic value for HF patients with NT-proBNP levels < 1000 pg/ml.

Methods

Study design

The AHF patients were included from the NFHC-HF1.1 prospective cohort study [21]. As previously described, the NFHC-HF1.1 study was approved by the Nanfang Hospital Ethics Committee (approval no. NFEC-2017-063) and conducted in accordance with the Declaration of Helsinki. The NFHC-HF1.1 study is registered with the Chinese Clinical Trial Registry (ChiCTR-ROC-17011240) and was carried out in a double-blind manner. Written informed consent was obtained from all participants or their legal representatives [24]. A detailed study procedure was provided in Supplementary Information 1. All procedures adhered to the ethical standards of the China national research committees, in line with the principles of the Declaration of Helsinki.

Study population

The current study included participants from the NFHC-HF (The Heart Failure Cohort Study of Nanfang Hospital, Southern Medical University) from November 2017 to September 2019. Patients were diagnosed with AHF following three criteria according to the 2016 ESC guidelines: 1) worsening or new onset of symptoms (dyspnea, fatigue, or decreased exercise capacity) and the presence of one sign (edema or rales); 2) NT-proBNP levels ≥300 pg/ml; and 3) echocardiographic evidence of ventricular structural and functional abnormalities [25]. Patients aged <18 years or with acute myocardial infarction (AMI), severe renal failure [estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2], or missing AKG or NT-proBNP data were excluded.

Plasma AKG measurements

Plasma AKG levels were measured as previously described [24,26–28]. Fasting blood samples were collected in EDTA tubes within the first 24 h of admission. After immediate centrifugation at 3000 × rpm for 5 min at 4 °C, plasma sample were randomly distributed and measured using hydrophilic interaction liquid chromatography coupled with tandem mass spectrometry

(HILIC-LC/MS/MS) on an Agilent 6460 Triple Quadrupole LC–MS/MS system with an ESI interface.

Assessment of long-term outcomes

After discharge, all patients were regularly contacted by telephone until December 1st, 2023. Information of all-cause mortality was obtained from the official death certificate or household contacts. All-cause mortality and other outcomes were assessed by independent researchers who were blinded to the AKG measurements.

Statistical analysis

Baseline characteristics are summarized as continuous variables or categorical variables. Continuous variable were presented as the means and standard deviations (SDs) or median values and interquartile ranges (IQRs). Categorical variables were presented as absolute frequencies and percentages. Differences in baseline characteristics between high and low AKG were compared *via* the chi-square test and the Student's *t* test or Mann–Whitney U test for categorical variables and continuous variables, respectively. Continuous variables were log-transformed for further analyses when in nonlinear distributions. Spearman's correlation was applied to examine the correlations between the plasma AKG (log-transformed) and other laboratory measurements. Cox proportional hazard regression models were constructed to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for the all-cause mortality between the high and low AKG group, also according to the plasma AKG levels as a continuous variable (per 1-SD increase). Adjustments were made for traditional risk factors (including age, sex, heart rate, SBP, left ventricular ejection fraction (LVEF), NT-proBNP levels, ACEIs/ARBs, Beta-blockers, and statin use). Subgroup analyses were performed in the following prespecified strata: age (<65 *vs.* ≥65 years), eGFR (<60 ml/min/1.73 m^2 *vs.* ≥60 ml/min/1.73 m^2), HF phenotypes, New York Heart Association (NYHA) level, and NT-proBNP levels (300 ~ 1000 pg/ml, 1000 ~ 3000 pg/ml, 3000 ~ 5000 pg/ml *vs.* >5000 pg/ml; <1000 pg/ml *vs.* ≥1000 pg/ml; <3000 pg/ml *vs.* ≥3000 pg/ml). An interaction term was included to evaluate the effect of each subgroup on the association of mortality with AKG. The surv_cutpoint function of the 'survminer' package in R software (R Foundation, Vienna, Austria) was used to calculate the cutoff value for the AKG level. Further analysis was performed to identify whether the risk associated with AKG levels was independent of the NT-proBNP level. We used a clinically relevant NT-proBNP cutoff (1000 pg/ml or 3000 pg/ml) according to previous studies [29,30]. Therefore, we determined the corresponding AKG cutoff values according to the two different NT-proBNP cutoff values (1000 pg/ml and 3000 pg/ml) and conducted Cox regression analysis. Analyses were performed *via* IBM SPSS Statistics software (SPSS 25.0). A 2-sided $p < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

Among the 1053 patients enrolled in this cohort, a total of 672 eligible participants were included in the final analyses after applying the exclusion criteria (Figure 1). The mean concentration of AKG was 8.45 ± 3.90 μg/ml, with a median (IQR) of 7.87 (5.79 ~ 9.84) μg/ml.

The maximally selected rank statistics method was used to define a threshold of AKG that best identifies patients reaching an outcome of death. The cutoff value of 9.83 μg/ml identified in this study was slightly greater than the median value of 7.87 pg/ml.

Patient characteristics according to AKG level, as defined by an optimal cutoff value of 9.83 μg/ml, are shown in Table 1. Patients with higher AKG levels were younger (64.85 ± 13.78 years vs. 67.83 ± 13.60 years, $p = 0.048$). In general, those with higher AKG values were more likely to have higher heart rates ($p < 0.05$) and NT-proBNP levels ($p < 0.01$), as well as lower SBP ($p < 0.05$) and LVEF ($p < 0.005$) values, suggesting an overall profile of more advanced HF. Additionally, statin treatment was more common in patients in the high-AKG group ($p < 0.01$). There were no differences in comorbidities or other medication use between the two groups. Patient characteristics divided by the median AKG level are shown in Supplementary Table S1.

Clinical data correlations with AKG

Increased AKG levels were correlated with NT-proBNP levels and NYHA levels ($r = 0.145$, $p < 0.001$ and $r = 0.09$, $p = 0.019$, respectively), while were inversely correlated with LVEF levels and SBP (r = −0.157, $p < 0.001$ and r = −0.107, $p = 0.002$, respectively) (Supplementary Table S2).

Association between admission plasma AKG levels and long-term outcomes and subgroup analysis

During the median of 4.42 years (2.90 ~ 5.17 years) of follow-up, 401 deaths occurred. Univariate Cox

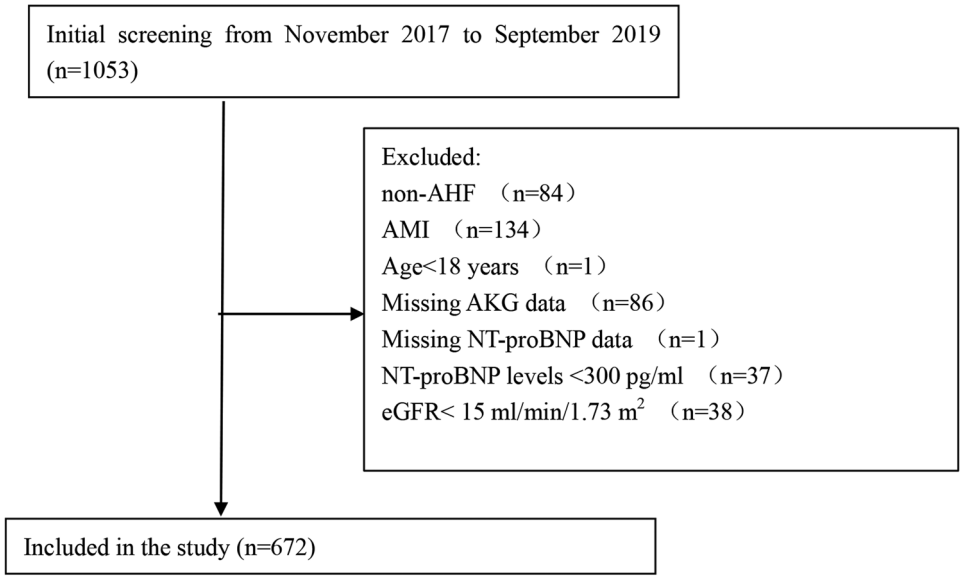

Figure 1. Flow chart for participant selection.
Abbreviations: AHF, acute heart failure; AMI, acute myocardial fraction; AKG, alpha-ketoglutarate; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide

Table 1. Baseline characteristic of the AHF cohort according to AKG level.

	Low group ($n=504$)	High group ($n=168$)	*P*
Age, mean (SD), yrs	67.83 (13.60)	64.85 (13.78)	0.048
Sex, No. (%)			
Male	320 (63.5)	120 (71.4)	0.062
Comorbidity, No. (%)			
Current smoking	116 (23.0)	52 (31.0)	0.095
Previous MI	118(23.4)	30 (19.7)	0.261
Hypertension	250 (49.6)	30 (49.4)	0.574
Diabetes mellitus	142 (28.2)	41 (24.4)	0.531
COPD	68 (13.5)	16 (9.5)	0.391
Atrial fibrillation	155 (30.8)	59 (35.1)	0.535
Stroke/TIA	40 (7.9)	17 (10.1)	0.667
Measurements at admission			
BMI, mean (SD), kg/m^2	23.30 (4.03)	23.63 (4.13)	0.514
HR, mean (SD), bpm	84.47 (19.07)	89.47 (19.90)	0.025
SBP, mean (SD), mmHg	128.42 (25.57)	124.13 (21.53)	0.042
DBP, mean (SD), mmHg	75.63 (15.75)	77.34 (14.10)	0.64
LVEF, mean (SD),%	50.12 (12.55)	46.73 (15.08)	0.005
eGFR, mean (SD), ml/min/1.73 m^2	66.54 (26.16)	65.37 (27.87)	0.598
Creatinine, mean (SD), mmol/L	108.61 (45.59)	115.15 (50.14)	0.107
ALB, mean (SD), g/L	39.43 (5.67)	39.72 (5.86)	0.965
TC, mean (SD), mmol/L	4.15 (1.17)	3.97 (1.04)	0.058
TG, mean (SD), mmol/L	1.35 (0.86)	1.23 (0.65)	0.084
LDL-C, mean (SD), mmol/L	2.61 (0.95)	2.50 (0.80)	0.116
NT-proBNP, mean (IQR), pg/ml	1997.00 (975.90–4981.50)	3164.00 (1419.50–6661.50)	0.001
AKG, mean (IQR),μg/ml	6.63 (5.43–8.33)	12.20 (10.60–14.79)	<0.001
NYHA class, No. (%)			0.374
I	11 (2.2)	1 (0.6)	
II	174 (34.5)	50 (29.8)	
III	218 (43.3)	8 (45.2)	
IV	101 (20.0)	41 (24.4)	
Medications at discharge, No. (%)			
ACEIs/ARBs	271 (53.8)	91 (54.2)	0.732
Beta-blockers	289 (57.3)	96 (57.1)	0.749
MRA	323 (64.1)	108 (64.3)	0.733
Loop diuretics	324 (64.3)	107 (63.7)	0.753
Statins	300 (59.5)	77 (45.8)	0.008

Abbreviations: AKG, alpha-ketoglutarate; MI, myocardial fraction; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; ALB, albumin; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NT-proBNP N-terminal pro B-type natriuretic peptide; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; MRA, mineralocorticoid/aldosterone receptor antagonist.

regression reported that high plasma AKG levels at admission were associated with an increased risk of long-term adverse outcomes, and the HR for all-cause mortality was 1.068 (95% CI 1.045–1.193, $p < 0.001$). After adjustment for age, heart rate, SBP, LVEF, NT-proBNP levels, and statin use, higher AKG was also a predictor of poorer outcomes, and the HR for all-cause mortality was 1.078 (95% CI 1.051–1.105, $p < 0.001$) (Table 3). In the subgroup analyses, AKG levels were associated with a greater risk of all-cause mortality across subgroups defined by age, sex, eGFR, LVEF, and NYHA classification, with no significant interactions observed (all *P* values for interactions >0.05) (Table 2). Notably, a differential association regarding mortality outcomes was found with varying NT-proBNP levels ($p < 0.05$ for all interactions); the effect of AKG was most pronounced when NT-proBNP levels ranged from 300 to 1000 pg/mL (Table 3).

Risk of adverse outcome stratified with admission NT-proBNP levels

According to the multivariable-adjusted models, an AKG concentration ≥9.83 μg/ml was associated with an increase in all-cause mortality of more than 70% (HR = 1.733, 95% CI 1.234–2.434; $p < 0.001$) (Table 3, Figure 2). There were significant associations between the AKG level and all-cause mortality in both the high- and low-NT-proBNP groups when a threshold of 1000 pg/ml was used. Moreover, among individuals whose NT-proBNP level was ≥1000 pg/ml, those with higher AKG levels (AKG ≥9.83 μg/ml) had a nearly 1.9-fold increase in the risk of all-cause mortality in patients with AHF. Moreover, there was a greater than 4.1-fold greater risk of all-cause mortality in the higher AKG level group among AHF patients with NT-proBNP

Table 2. Association Between the admission AKG levels and long-term all-cause mortality in subgroups.

	HR	95% CI	*P*	*P* for interaction
Unadjusted	1.068	1.045 ~ 1.093	<0.001	
Adjusted	1.078	1.051 ~ 1.105	<0.001	
Subgroups analysis				
				0.451
Male	1.090	1.065 ~ 1.124	<0.001	
Female	1.051	1.005 ~ 1.099	<0.001	
				0.438
Age < 65yrs	1.099	1.060 ~ 1.141	<0.001	
Age ≥ 65yrs	1.068	1.031 ~ 1.106	<0.001	
				0.849
eGFR < 60 ml/min/1.73 m^2	1.058	1.021 ~ 1.097	0.002	
eGFR ≥ 60 ml/min/1.73 m^2	1.107	1.067 ~ 1.149	<0.001	
				0.766
HFrEF	1.096	1.046 ~ 1.147	<0.001	
HFmrEF	1.069	0.998 ~ 1.145	0.056	
HFpEF	1.070	1.033 ~ 1.109	<0.001	
				0.108
NYHA II	1.066	1.018 ~ 1.116	0.007	
NYHA III	1.078	1.035 ~ 1.123	<0.001	
NYHA IV	1.093	1.040 ~ 1.149	0.001	
				0.003
NT-proBNP 300 ~ 1000 pg/ml	1.267	1.156 ~ 1.388	<0.001	
NT-proBNP 1000 ~ 3000 pg/ml	1.083	1.038 ~ 1.130	<0.001	
NT-proBNP 3000 ~ 5000 pg/ml	1.064	1.005 ~ 1.126	0.032	
NT-proBNP > 5000 pg/ml	1.071	1.022 ~ 1.121	0.004	
				<0.001
NT-proBNP < 1000 pg/ml	1.267	1.156 ~ 1.388	<0.001	
NT-proBNP ≥ 1000 pg/ml	1.069	1.040 ~ 1.097	<0.001	
				0.008
NT-proBNP < 3000 pg/ml	1.110	1.070 ~ 1.151	<0.001	
NT-proBNP ≥ 3000 pg/ml	1.066	1.028 ~ 1.106	0.001	

Adjusted for age, heart rate, systolic blood pressure, left ventricular ejection fraction, NT-proBNP levels (log-transformed), ACEIs/ARBs, Beta-blockers and Statins.
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP N-terminal pro B-type natriuretic peptide; HFrEF, heart failure with reduced ejection fraction; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction.

Table 3. Risk of all-cause mortality according to baseline AKG levels and NT-proBNP levels (log-transformed) as categorical variables.

	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*
AKG low		Reference			Reference	
AKG high	2.045	1.483 ~ 2.820	<0.001	1.733	1.234 ~ 2.434	0.001
AKG low& BNP low		Reference			Reference	
AKG low& BNP high	2.565	1.819 ~ 3.617	<0.001	0.801	0.523 ~ 1.266	0.306
AKG high& BNP low	3.659	2.064 ~ 6.486	<0.001	4.126	2.284 ~ 7.435	<0.001
AKG high& BNP high	4.578	3.300 ~ 6.937	<0.001	1.537	0.969 ~ 2.437	0.068
AKG low& BNP low		Reference			Reference	
AKG high& BNP low*	3.672	2.064 ~ 6.532	<0.001	4.160	2.208 ~ 7.834	<0.001
AKG low& BNP high		Reference			Reference	
AKG high& BNP high#	1.863	1.484 ~ 2.338	<0.001	1.929	1.516 ~ 2.455	<0.001

AKG low: AKG< 9.83 μg/ml; AKG high: AKG≥ 9.83 μg/ml; BNP low: NT-proBNP <1000 mg/dl; BNP high: NT-proBNP ≥ 1000 mg/dl.
* AKG high& BNP low versus AKG low& BNP low.
# AKG high& BNP high versus AKG low& BNP high.
Adjusted for age, heart rate, systolic blood pressure, left ventricular ejection fraction, NT-proBNP levels (log-transformed), ACEIs/ARBs, Beta-blockers and Statins.
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP N-terminal pro B-type natriuretic peptide.

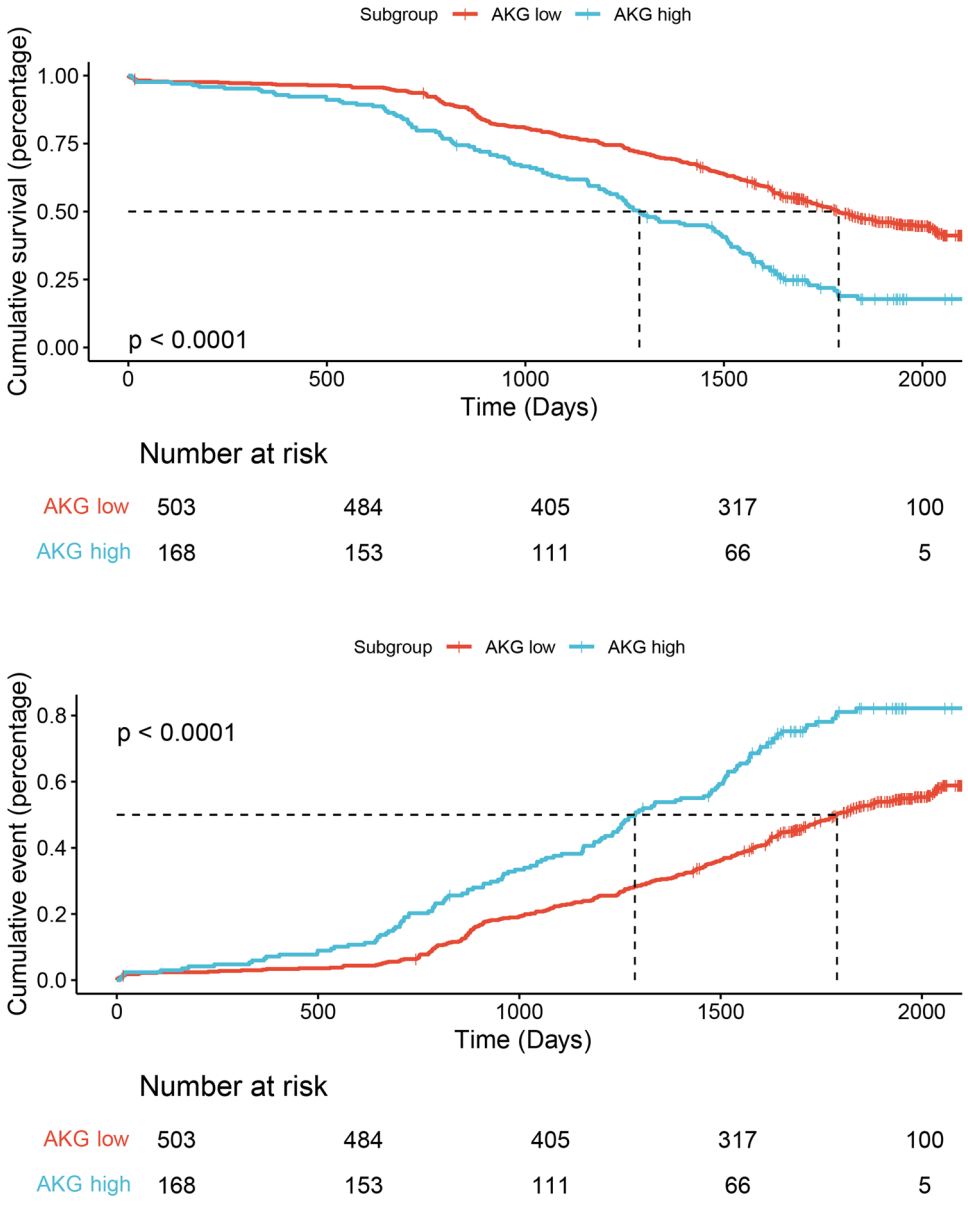

Figure 2. Overall survival rate (upper) and cumulative incidence of all-cause mortality (lower) according to baseline AKG.
AKG low: AKG< 9.83μg/ml; AKG high: AKG≥ 9.83μg/ml
Abbreviations: AKG, alpha-ketoglutarate.

< 1000 pg/ml (Table 3, Figures 3 and 4, Supplementary Figures S1–S2). Similarly, higher AKG levels were related to an increased risk for all-cause mortality regardless of whether NT-proBNP exceeded 3000 pg/ml (HR = 2.832 for the NT-proBNP < 3000 pg/ml group and HR = 1.770 for the NT-proBNP ≥ 3000 pg/ml group, both $p < 0.001$) (Table 4, Figures 5 and 6, Supplementary Figures S3–S4).

Risk of adverse outcome in patients with different HF subtypes

As different HF subtypes may own different risk factors and underlying pathology, and HFpEF ($n = 369$) was reported that often suffered from several comorbidities and the failing heart is metabolically inflexible. So we further analyzed the role AKG in different HF subtypes patients. In patients with HFpEF, high plasma AKG levels were associated with worse long-term adverse outcomes (HR = 1.677, 95% CI 1.029–2.773; $p < 0.001$) and significant relations were also seen between the AKG level and all-cause mortality in both the high- and low-NT-proBNP groups when a threshold of 1000 pg/ml was used (Table 5). In those HFpEF patients with low-NT-proBNP (NT-proBNP < 1000 pg/ml), higher AKG levels (AKG ≥9.83 μg/ml) had an above 5-fold increase in the risk of all-cause mortality (HR = 5.329, 95% CI 2.456–11.565; $p < 0.001$), while those

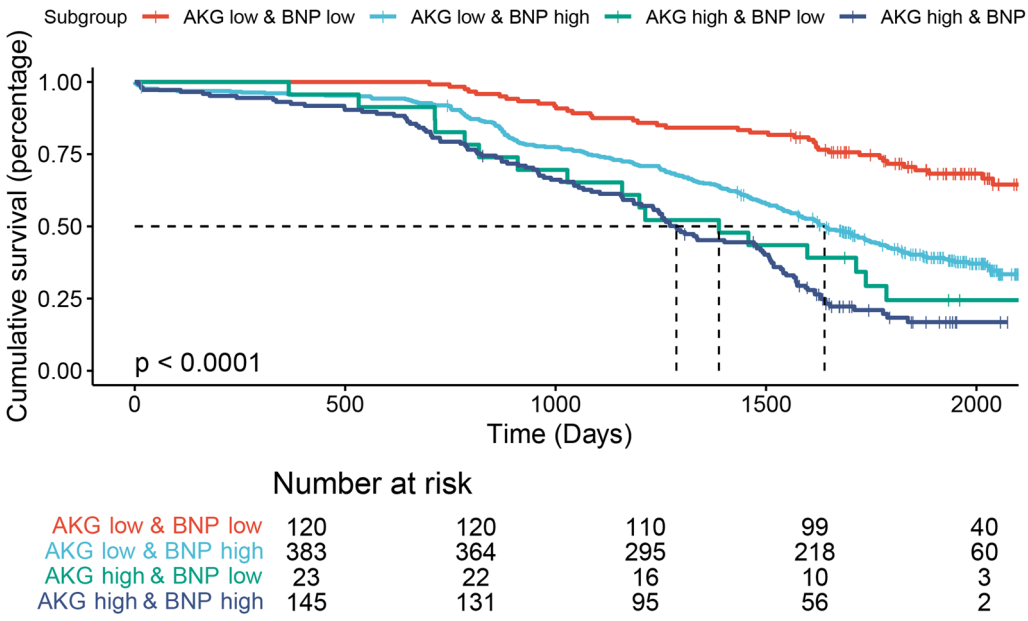

Figure 3. Overall survival rate according to baseline AKG and NT-proBNP.
AKG low: AKG< 9.83μg/ml; AKG high: AKG≥ 9.83μg/ml; BNP low: NT-proBNP <1000 mg/dl; BNP high: NT-proBNP ≥ 1000 mg/dl
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP, N-terminal pro B-type natriuretic peptide.

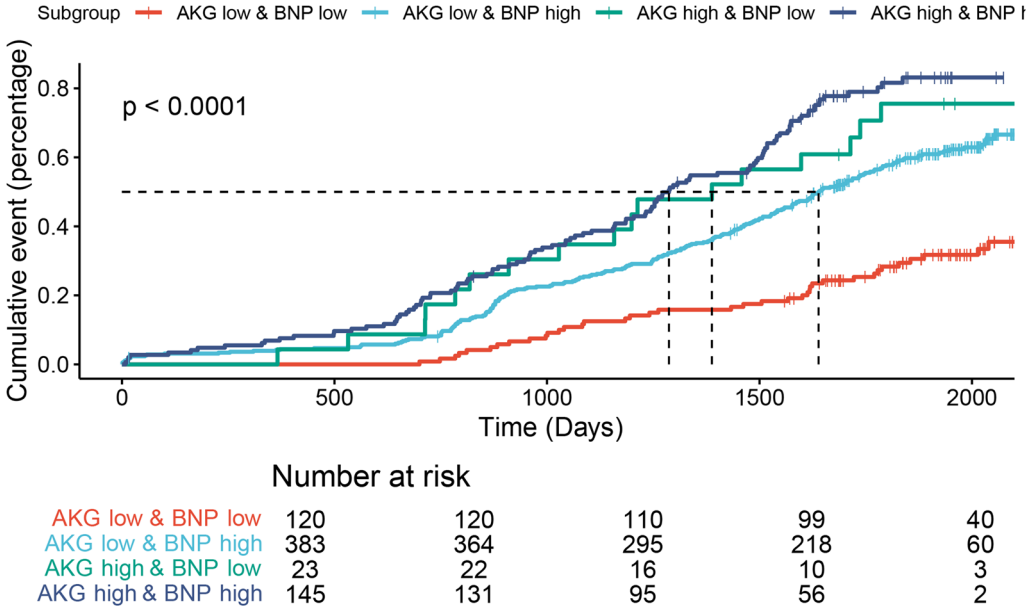

Figure 4. Cumulative incidence of all-cause mortality according to baseline AKG and NT-proBNP.
AKG low: AKG< 9.83μg/ml; AKG high: AKG≥ 9.83μg/ml; BNP low: NT-proBNP <1000 mg/dl; BNP high: NT-proBNP ≥ 1000 mg/dl
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP, N-terminal pro B-type natriuretic peptide.

with NT-proBNP ≥ 1000 pg/ml only had nearly 1.6 fold increased risk of all-cause mortality (HR = 1.685, 95% CI 1.180–2.407; $p = 0.005$, Table 5). In patients with HFrEF ($n = 186$) and HFmrEF ($n = 117$), higher AKG level had an increased risk of all-cause mortality but there were not statistically significant (Supplementary Table S3–S4).

Discussion

In this prospective study, we highlighted the prognostic value of AKG in patients with AHF, especially those with NT-proBNP levels < 1000 pg/ml. The plasma AKG level was associated with a greater risk of long-term outcomes in patients with AHF, despite adjustment for

Table 4. Risk of all-cause mortality according to baseline AKG levels and NT-proBNP levels (log-transformed) as categorical variables.

	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*
AKG low& BNP low		Reference			Reference	
AKG low& BNP high	2.506	1.971 ~ 3.186	<0.001	0.709	0.482 ~ 1.042	0.080
AKG high& BNP low	2.441	1.789 ~ 3.329	<0.001	2.277	1.512 ~ 3.430	<0.001
AKG high& BNP high	4.224	3.152 ~ 5.661	<0.001	1.036	0.638 ~ 1.681	0.887
AKG low& BNP low		Reference			Reference	
AKG high& BNP low*	2.510	1.837 ~ 3.430	<0.001	2.832	2.044 ~ 3.924	<0.001
AKG low& BNP high		Reference			Reference	
AKG high& BNP high#	1.618	1.214 ~ 2.156	<0.001	1.770	1.292 ~ 2.426	<0.001

AKG low: AKG< 9.83 μg/ml; AKG high: AKG≥ 9.83 μg/ml; BNP low: NT-proBNP <3000 mg/dl; BNP high: NT-proBNP ≥ 3000 mg/dl.
* AKG high& BNP low versus AKG low& BNP low.
# AKG high& BNP high versus AKG low& BNP high.
Adjusted for age, heart rate, systolic blood pressure, left ventricular ejection fraction, NT-proBNP levels (log-transformed), ACEIs/ARBs, Beta-blockers and Statins.
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP N-terminal pro B-type natriuretic peptide.

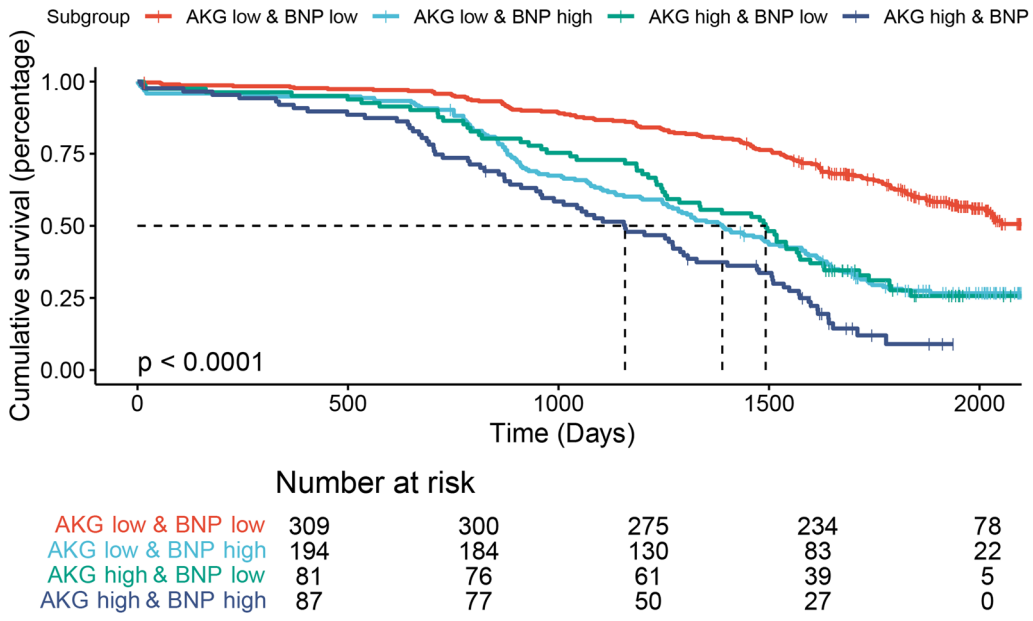

Figure 5. Overall survival rate according to baseline AKG and NT-proBNP.
AKG low: AKG< 9.83μg/ml; AKG high: AKG≥ 9.83μg/ml; BNP low: NT-proBNP <3000 mg/dl; BNP high: NT-proBNP ≥ 3000 mg/dl
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP, N-terminal pro B-type natriuretic peptide.

other prognostic variables, including NT-proBNP. Furthermore, higher AKG levels remained a prognostic indicator of outcome even when the admission levels of NT-proBNP were less than 1000 pg/ml and the association was only seen in patients with HFpEF.

Cardio-metabolic remodelling occurs during HF and manifests as the transition of the uptake of energy substrates in cardiomyocytes. In failing hearts, myocardial metabolic substrates switch from β-oxidation of free fatty acid to glycolysis, resulting in the disruption of mitochondrial function and biogenesis in cardiomyocytes, and finally leading to abnormalities in the ventricular structure and function [11,31]. Recent findings revealed changes in several constituents of the TCA cycle in plasma during cardiac ischemia and were associated with CV outcomes [32,33], suggesting that serum metabolites are able to reflect the balance of the metabolic state of the heart and can be used as biomarkers for CV diseases. Hence, tracing the changes in plasma metabolic production may reflect the progress of HF and may be useful in the diagnosis, prognosis, and treatment of HF.

As one of the major intermediates of the TCA cycle and precursors of glutamate synthesis, AKG affects various physical activities [34]. It modulates protein synthesis, stabilizes immune system homeostasis, and regulates bone development and aging, which are involved in the maintenance of mitochondrial metabolism homeostasis, antioxidation, anti-inflammation, cell proliferation, collagen synthesis, and epigenetic

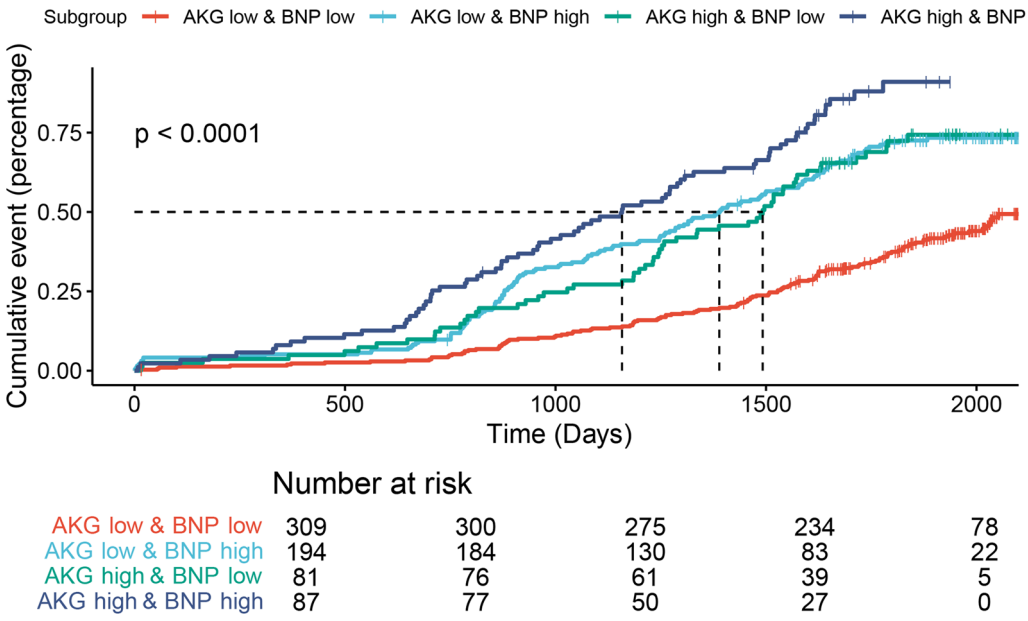

Figure 6. Cumulative incidence of all-cause mortality according to baseline AKG and NT-proBNP.
AKG low: AKG< 9.83μg/ml; AKG high: AKG≥ 9.83μg/ml; BNP low: NT-proBNP <3000 mg/dl; BNP high: NT-proBNP ≥ 3000 mg/dl
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 5. Risk of all-cause mortality according to baseline AKG levels and NT-proBNP levels (log-transformed) as categorical variables in patients with HFpEF ($n = 369$).

	Unadjusted			Adjusted		
	HR	95% CI	*P*	HR	95% CI	*P*
AKG low		Reference			Reference	
AKG high	1.911	1.211 ~ 3.015	<0.001	1.677	1.029 ~ 2.773	0.038
AKG low& BNP low		Reference			Reference	
AKG low& BNP high	2.734	1.830 ~ 4.086	<0.001	0.951	0.559 ~ 1.617	0.852
AKG high& BNP low	4.267	2.409 ~ 8.885	<0.001	4.324	2.176 ~ 8.591	<0.001
AKG high& BNP high	4.571	2.884 ~ 7.245	<0.001	1.603	0.884 ~ 2.906	0.120
AKG low& BNP low		Reference			Reference	
AKG high& BNP low*	4.641	2.402 ~ 8.965	<0.001	5.329	2.456 ~ 11.565	<0.001
AKG low& BNP high		Reference			Reference	
AKG high& BNP high#	1.677	1.196 ~ 2.350	<0.001	1.685	1.180 ~ 2.407	0.005

AKG low: AKG< 9.83 μg/ml; AKG high: AKG≥ 9.83 μg/ml; BNP low: NT-proBNP <1000 mg/dl; BNP high: NT-proBNP ≥ 1000 mg/dl.
* AKG high& BNP low versus AKG low& BNP low.
# AKG high& BNP high versus AKG low& BNP high.
Adjusted for age, heart rate, systolic blood pressure, left ventricular ejection fraction, NT-proBNP levels (log-transformed), ACEIs/ARBs, Beta-blockers and Statins.
Abbreviations: AKG, alpha-ketoglutarate; NT-proBNP N-terminal pro B-type natriuretic peptide; HFpEF, heart failure with preserved ejection fraction.

modification [35]. It also plays a vital role in the pathophysiological progress of various diseases [20,36–38], including cancers, diabetes, and CV diseases [39–41]. A serum metabolomics study of patients with an LVEF < 40% first indicated that AKG increased in HF patients, along with correlated metabolite changes [15]. Experimental studies have indicated that AKG participates in the development of HF. An increase in AKG drives the demethylation of cardiac identity genes and ensures the maturation of CMs and myofibroblasts [19,42]. We reported that in failing murine hearts, dietary AKG supplementation reduces intracellular reactive oxygen species production and repairs injury to the mitochondrial membrane potential, improving myocardial hypertrophy, fibrosis, and left ventricular systolic dysfunction [43]. Further studies revealed that AKG supplementation can alleviate myocardial cell damage through the NAD+-SIRT1 pathway, which inhibits ferroptosis and promotes mitophagy in cardiomyocytes [44]. In addition, the infarcted myocardium showed a decrease in the level of the AKG metabolite succinyl-CoA, which contributes to the misbalance of the mitochondrial energy production system [45]. It was hypothesized that the increased plasma AKG released from the oxidative deamination of glutamate reflected a decreased flux through the TCA cycle and signified an insufficient oxidative capacity of the heart [46]. Although we are unable to clarify whether AKG is

released only from the myocardium or is secreted by joint tissue and organs, we believe that the increase in plasma AKG may be a compensatory adaptation in failing hearts and that monitoring fluctuations in AKG levels could partly reveal the progression of HF. We believed that AKG was partly analogous to natriuretic peptide in HF, which means the endogenous increase may reflect the cardiac-metabolic dysfunction stage in HF and dietary AKG supplementation could attenuate the progression of the metabolic remodelling which benefit to the outcomes in AHF patients.

Previous cohort studies have shown that the AKG was an indicator of the clinical severity of HF [15,23,25]. High serum AKG levels were not only associated with myocardial energy expenditure but also related to high NT-proBNP levels and left ventricular end-diastolic diameter [23], indicating the role of AKG in reflecting the cardiac remodelling process. Moreover, higher plasma AKG levels were shown to independently predict increased 6-month all-cause mortality and HF rehospitalization in AHF patients [24], which implied that AKG serves as a novel biomarker for prognostic risk stratification in HF patients during short-term follow-up. However, whether plasma AKG can also affect the long-term prognosis of HF patients is still unknown. In this study, we first reported that higher AKG levels were independently associated with all-cause mortality during long-term follow-up in patients with AHF, suggesting that AKG could be used as a potential biomarker of HF prognosis for longer follow-up durations.

Another crucial finding of our study is that AKG levels were significantly associated with long-term outcomes at all levels of NT-proBNP, and we further detected that AKG remained a stronger predictor of long-term outcomes even in AHF patients with relatively lower NT-proBNP levels (NT-proBNP < 1000 pg/ml). These findings suggest that AKG plays a pivotal role in prognostic prediction even in AHF patients with mild or stable disease. NT-proBNP has been well established as an effective biomarker not only for diagnosis and risk stratification but also for treatment optimization and prognostic evaluation in patients irrespective of any HF classification [4,47]. Higher admission NT-proBNP levels were associated with a worse prognosis, and lower NT-proBNP levels reflected relatively better myocardial conditions [48,49]. NT-proBNP is released by the myocardium and is considered to balance the overactivation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system [50]. Studies have shown that NT-proBNP levels were strongly correlated with left ventricular dimensions, volumes, and functions [51,52], and were viewed as useful tools for identifying actual cardiac hemodynamic conditions [53]. However, as AHF represents a broad spectrum of cardiac states and diverse concomitant comorbidities, such as obesity and AF, NT-proBNP may not be able to provide adequate information to reflect cardiac stress. This indicates a crucial need to identify new biomarkers for improving risk stratification and outcomes in AHF patients with high NT-proBNP levels. As a marker of metabolic changes, AKG may reflect a different underlying pathophysiological process in HF and can provide complementary information for the assessment of patient prognosis. Our analysis revealed that the AKG value for outcome prediction in HF patients was independent of the NT-proBNP level.

Previous studies defined a cut-off value of 5000 pg/ml in AHF for predicting the risk of short-term mortality [6,54], and 1000 pg/ml to identify left ventricular systolic dysfunction [52,53]. Current studies often focus on HF patients whose NT-proBNP levels are >1000 pg/ml, and setting the target of NT-proBNP < 1000 pg/ml at discharge promises a better prognosis for AHF patients [29,49,55]. In this study, we used 1000 pg/ml as a cutoff for determining the actual status of AHF patients. While some studies reported failure of better long-term outcome achievements consistent with a reduction in NT-proBNP levels [56,57], researchers have proposed the concept of a low NT-proBNP level for estimating mortality at discharge only because of the heterogeneity of the disease state [58]. To further clarify the outcomes in AHF patients, a multibiomarker approach may be an effective tool. This study is the first to investigate the role of AKG in predicting outcomes in AHF patients with relatively low NT-proBNP levels and revealed that even in this subgroup; greater plasma AKG levels still significantly increased the risk of long-term mortality in HF patients. This finding suggested that plasma AKG can offer incremental information on prognostic risk stratification independent of NT-proBNP and is a promising potential biomarker in combination with NT-proBNP to improve the accuracy of future risk assessment in AHF patients, especially those who are relatively stable.

Study limitation

To our knowledge, this is the first prospective cohort study to explore the effect of AKG on all-cause mortality in AHF patients during long-term follow-up. However, our study had several limitations. First, a relatively small sample size and limited available variables and endpoints were used in our study, which limited its external validity. Second, the level of plasma

AKG was only measured at admission, without serial measurements at discharge and at follow-up. Thus, further studies are needed to explore whether biodynamic changes in AKG levels are associated with long-term HF prognosis. Moreover, our study only showed values of AKG in the prognosis of AHF patients and did not indicate whether other substances in TCA cycle were involved in the adverse outcomes of HF patients. Finally, as our study is a prospective cohort study, further randomized controlled trials are needed to study the causal relationship between AKG and patient outcomes and to establish whether AKG alone or in combination with other biomarkers might guide therapy decision-making.

Conclusion

In conclusion, in this study, we identified AKG as an independent factor associated with a greater risk of long-term outcomes in patients with AHF. We also demonstrated that elevated AKG was significantly related to a worse prognosis in AHF patients with NT-proBNP < 1000 pg/ml, especially in those patients with persevered ejection fraction. Our findings suggest that AKG could be used as an additive metabolic biomarker combined with NT-proBNP for long-term outcome prediction in AHF patients, especially in those with relatively low NT-proBNP levels.

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Authors contributions

Conceptualization and supervision: Dingli Xu, Yugang Dong and Qingchun Zeng. Methodology: Yuli Huang, Xianghui Zeng and Zhengliang Peng. Data analysis: Tianyu Xu, Hao Zhang, Zhuang Ma and Qiong Zhan. Data curation and writing – original draft preparation: Tianyu Xu, and Hao Zhang. Writing – review and editing: Dingli Xu, Chen Liu, and Yuli Huang. Project administration: Tianyu Xu and Qiong Zhan. All authors contributed to the article and approved the submitted version.

Disclosure statement

No potential competing interest was reported by the authors.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (Dingli Xu) on reasonable request.

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