Lipids in Health and Disease

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Free fatty acids: independent predictors of long-term adverse cardiovascular outcomes in heart failure patients

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Abstract

Background The association between plasma free fatty acid (FFA) and the outcomes in the heart failure (HF) patients remains unclear.

Methods A cohort study among HF patients was performed. Plasma FFA was analyzed as both a continuous and a categorical variable (grouped by tertiles) to assess its association with composite cardiovascular (CV) death and HF hospitalization (CV death & HHP), CV death alone, and all-cause mortality (ACM) using Cox regression models. Subgroup analyses of HF patients with preserved ejection fraction (HFpEF) and mildly reduced/reduced ejection fraction (HFmrEF/HFrEF) were performed. This work also assessed the effectiveness of combining FFA and NT-pro BNP biomarkers for risk stratification by calculating the concordance index (C-index).

Results Among the 4,109 HF patients, FFA levels exceeding 0.4–0.42 mmol/L were associated with increased risks of the three outcomes. Patients in the highest FFA tertile faced greater risks than those in the lowest tertile. Adjusted hazard ratios were 1.32 (95% CI: 1.11–1.58) for CV death & HHP, 1.45 (95% CI: 1.16–1.82) for CV death, and 1.39 (95% CI: 1.15–1.68) for ACM, with a maximum follow-up of 8 years (median: 25 months). Subgroup analyses revealed that elevated FFA levels consistently predicted worse outcomes in both HFmrEF/HFrEF and HFpEF patients. The C-index for predicting outcomes was significantly greater when NT-pro BNP and FFA were combined than when NT-pro BNP was used alone ($P < 0.01$).

Conclusion Increased plasma FFA concentrations were independently associated with greater risks of CV death & HHP, CV death, and ACM among HF patients, irrespective of the ejection fraction. The combination of FFA and NT-pro BNP biomarkers significantly improved risk stratification in HF patients.

Keywords Free fatty acids, Heart failure, Long-term follow-up, Adverse cardiovascular outcomes, All-cause mortality

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Introduction

Heart failure (HF) represents a critical progression of multiple cardiovascular conditions and poses considerable healthcare challenges and economic strain worldwide [1]. Despite significant advancements in managing hemodynamic disturbances and neuroendocrine activation, the prognosis for HF remains poor, with persistently high mortality and reduced quality of life [2]. This underscores the pressing need to pinpoint "residual risk factors" and explore new therapeutic targets.

Cardiac energetic remodelling and impairment are recognized as critical pathophysiological mechanisms driving the onset and progression of HF [3]. Free fatty acids (FFA), derived from lipolysis, are the primary energy substrate for healthy cardiac tissue. However, elevated serum FFA concentrations are increasingly identified as both a risk factor and a biomarker linked to the increased incidence of metabolic disorders and cardiovascular diseases [4–9]. Notably, compared with the general population, HF patients exhibit elevated plasma FFA levels [10]. In HF, the paradox of myocardial hypoxia coupled with the high oxygen demand required for FFA oxidation renders FFA a suboptimal energy source for the failing heart, when compared with carbohydrates [11]. In this context, elevated plasma FFA concentrations lead to excessive storage in cardiomyocytes which enhances heart dysfunction and has detrimental effects on systemic conditions, including the metabolic state and oxidative stress [9, 12–14]. While prior research has shown strong links between FFA levels and adverse cardiovascular outcomes, these studies were often limited by small sample sizes and short follow-up periods [15, 16].

To investigate the prognostic value of serum FFAs in HF patients, a cohort study was conducted on 4,608 participants at the heart failure center. This study hypothesizes that elevated serum FFA levels are independently associated with long-term adverse cardiovascular outcomes, including all-cause mortality. By examining these relationships, this research aims to provide insights into metabolic biomarkers in HF and to identify potential therapeutic targets for improving HF management.

Methods

Cohort description and population included in this analysis

Subjects were consecutively enrolled from the heart failure centre at Fuwai Hospital, part of the Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS&PUMC), during hospitalizations for acute heart failure. This cohort, established between June 2006 and December 2018, aimed to investigate the causes, prognostic indicators, and treatment outcomes of HF. Before any interventions, all participants underwent physical examinations, laboratory tests, and ECGs. A transthoracic echocardiogram was performed upon admission or within 24 h. Heart failure diagnoses—including HF with mildly reduced ejection fraction (HFmrEF), reduced ejection fraction (HFrEF), and preserved ejection fraction (HFpEF)—were initially made by the attending physicians and subsequently confirmed by chief cardiologists in accordance with the heart failure guidelines of the European Society of Cardiology throughout the 12-year study. Patients with left ventricular ejection fraction (LVEF) ≥ 50% were classified as HFpEF, while those with LVEF < 50%, including HFmrEF (LVEF 40-50%), were grouped as 'HFmrEF/HFrEF' due to sample size limitations.

This study was one of several projects conducted within this heart failure cohort and has received approval from the Ethics Committee of the Fuwai Hospital (Approval Number: 2018−1041). All patients provided written informed consent. HF patients were included unless they met exclusion criteria: (1) age < 18 years; (2) serious comorbidities, such as malignancies, immunological disorders, infective endocarditis, or chronic renal disease (eGFR < 30 ml/min/1.73 m^2); (3) insufficient data on FFA, NT-proBNP, or LVEF.

Data collection

Demographic, physical examination, laboratory, and radiological data were collected upon admission. All blood samples were drawn at approximately 6 a.m. and promptly processed in the clinical laboratory of Fuwai Hospital. For the past decade, plasma FFA levels have been measured consistently using DiaSys Diagnostic Systems assay kits based on the ACS-ACOD method. The normal FFA ranges are 0.1–0.45 mmol/L for females and 0.1–0.6 mmol/L for males. The ACS-ACOD method was strictly followed according to the kit's protocol to ensure consistency and reliability. Echocardiography was employed to measure the LVEF via the Simpson's biplane method. In addition to the baseline information, the prescribed treatment for heart failure at discharge was also recorded.

Follow-up and outcomes

The study targeted long-term adverse cardiovascular events, focusing on a composite outcome of cardiovascular mortality and heart failure readmission (CV death & HHP), cardiovascular mortality alone (CV death), and all-cause mortality (ACM). These clinically relevant endpoints were monitored through routine follow-ups, which included outpatient visits or telephone interviews conducted at 1, 6, and 12 months post-discharge, followed by annual follow-ups thereafter.

Statistical analysis

Patients were sorted into three groups based on tertiles: the lowest tertile (1st tertile), the middle tertile (2nd

tertile), and the highest tertile (3rd tertile). The baseline characteristics of these groups are presented and compared. Subsequent survival analyses were performed to assess the clinical outcomes for all participants after discharge. First, the associations between FFA levels, treated as a continuous variable, and the three clinical hard endpoints were modelled via restricted cubic splines (RCSs) with four knots within a Cox proportional hazards framework [17]. This analysis was performed in the entire HF patient population and in the HFmrEF/HFrEF and HFpEF subgroups. Next, the relationships between FFA tertiles and outcomes were examined via multiple Cox proportional hazards models, with P values for trends calculated across tertiles. Additionally, a comparison was made between the prognoses of patients with elevated FFA levels exceeding the upper limit of normal and those with normal FFA levels. To investigate potential interactions between primary covariates, such as LVEF, and the prognostic relevance of FFAs for long-term outcomes, interaction tests and stratified analyses were conducted. The Cox models were adjusted for covariates, including age, sex, body mass index (BMI), smoking and alcohol use, key comorbid conditions (diabetes, hypertension, atrial fibrillation, and coronary artery disease), serum creatinine, N-terminal pro b-type Natriuretic Peptide (NT-pro BNP), high-sensitivity C-reactive protein (hs-CRP), and discharge medications such as angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors (ACEI/ARBs/ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i).

Analyses using receiver operating characteristic (ROC) curves were conducted, and the area under the curve (AUC) values for NT-proBNP, FFA, and their combination in predicting the three clinical endpoints were calculated. The concordance index (C-index) was also assessed. All statistical evaluations and data visualizations were executed via R software (version 4.2.3).

Results

Patient characteristics

Figure 1 illustrates the patient enrolment process. Finally, 4,109 patients were included, where females accounted for 28.3%, with a median age of 58 years. The HFmrEF/HFrEF group comprised the majority (66.6%) of the cohort. According to the data in Table 1, a greater percentage of patients in the highest FFA tertile were females, and their heart rates and systolic blood pressure values were higher. Compared with those with lower FFA levels, individuals with elevated FFA levels also showed higher concentrations of white blood cells (WBCs), hs-CRP, and HbA1C, alongside reduced serum HDL-c concentrations. Additionally, elevated FFA levels were linked to increased NT-pro BNP, lower eGFRs, a greater incidence of comorbid conditions (particularly coronary heart disease), and more advanced NYHA functional classes. These findings suggest a decline in both systemic and cardiac health among patients with elevated FFA levels.

Plasma FFAs and outcomes in HFpEF and HFmrEF/HFrEF

In a median follow-up period of 25 months, extending up to 8 years, CV death & HHP occurred in 999 patients (24.3%). All-cause death and CV death were observed in 972 (23.7%) and 641 (15.6%) participants, respectively. As shown in Fig. 2, RCS curves were used to model the relationships between plasma FFA levels and the three outcomes. Figure 2A and B indicate similar curve shapes for the whole cohort and the HFmrEF/HFrEF groups. Despite wide confidence intervals, very low FFA levels (<0.4–0.42 mmol/L) tended to predict poor outcomes (adjusted *P* for nonlinearity < 0.001). For FFA levels ≥ 0.4–0.42 mmol/L, increasing FFA concentrations were associated with a greater risk of the three clinical endpoints. The associations between FFA levels and clinical outcomes in the HFpEF subgroup are depicted in Fig. 2C. The curve shapes differed slightly from those in the overall HF cohort, lacking a distinct inflection point. However, the incidence of combined cardiovascular death and heart failure hospitalization ($P_{\text{nonlinearity}}$= 0.337), cardiovascular death ($P_{\text{nonlinearity}}$ = 0.052), and all-cause death ($P_{\text{nonlinearity}}$= 0.024) still tended to increase with increasing FFA levels. Table 2 presents the associations between FFA tertiles and the three outcomes, showing that higher FFA tertiles are linked to an increased risk of mortality and adverse cardiovascular events (Ptrend <0.01). Patients in the highest FFA tertile had significantly higher risks than those in the lowest tertile, with adjusted hazard ratios of 1.32 (95% CI: 1.11–1.58) for CV death and HHP, 1.45 (95% CI: 1.16–1.82) for CV death, and 1.39 (95% CI: 1.15–1.68) for ACM. Furthermore, compared to patients with normal plasma FFA levels, those with elevated plasma FFA also showed increased risks of CV death and HHP (adjusted HR: 1.27, 95% CI: 1.10–1.47), CV death (adjusted HR: 1.37, 95% CI: 1.14–1.64), and ACM (adjusted HR: 1.28, 95% CI: 1.10–1.48) (Fig. 3). Figure 4 presents the results of subgroup analyses and interaction tests. While there were variations in HRs across subgroups (HFpEF, HFmrEF, and HFrEF), none of the adjusted *P* values for interactions were significant (all >0.05). Apart from sex (adjusted $P_{\text{interaction}}$ < 0.010), no obvious interaction was detected between FFA and other factors. In male patients, the associations between FFA levels and the outcomes of CV death & HHP (adjusted HR 1.04, 95% CI 0.96–1.13), CV death (adjusted HR 1.08, 95% CI 0.98–1.20), and ACM (adjusted HR 1.07, 95% CI 0.98–1.16) were attenuated.

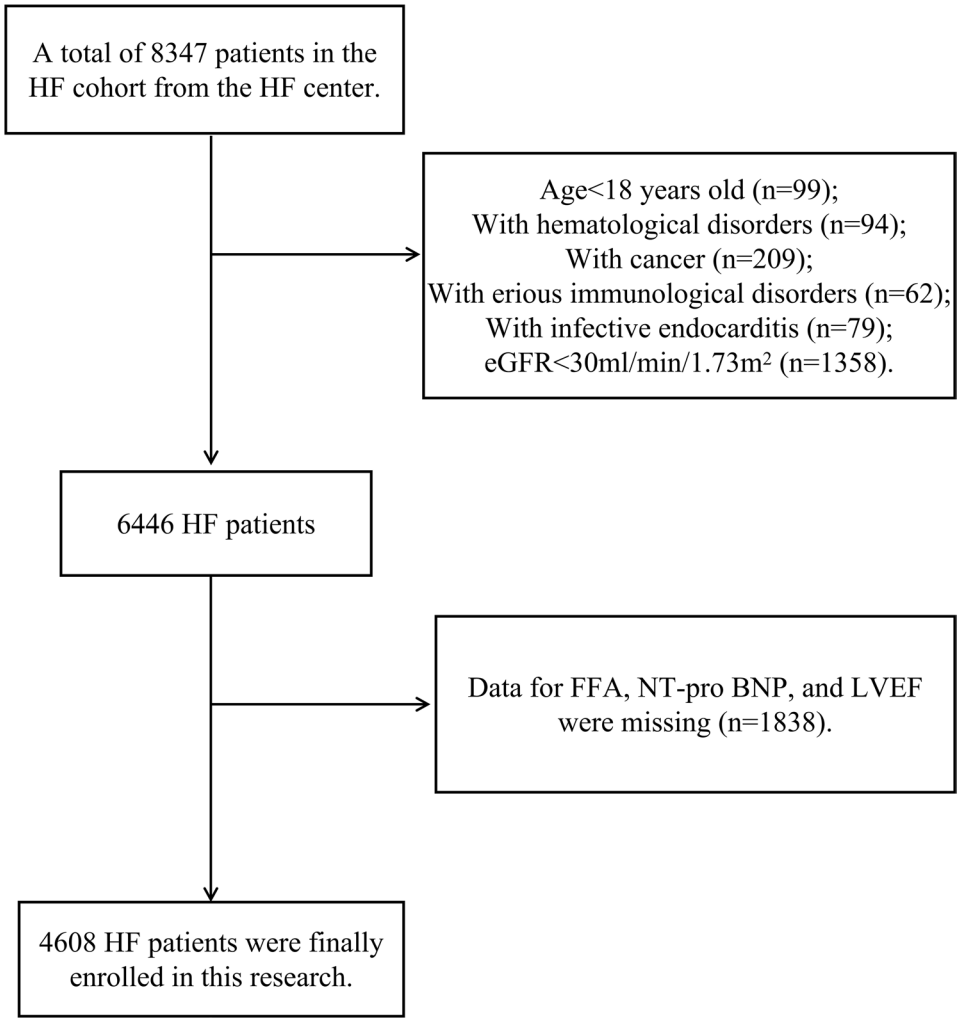


Fig. 1 Flowchart of the study subject inclusion process

The combination of plasma FFA and NT-pro BNP levels and the endpoints

Figure 5; Table 3 display ROC curves, AUC values, and C-indices. According to the ROC curves, the AUC for FFA alone was lower than that for NT-pro BNP alone; however, combining FFA with NT-proBNP improved the AUC. The C-index for the combined NT-proBNP and FFA was consistently higher than that for NT-proBNP alone in predicting CV death & HHP (C-index: 0.693, 95% CI: 0.674–0.712 vs. 0.687, 95% CI: 0.668–0.706; increase in C-index (ΔC-index): 0.006, $P<0.01$), CV death (C-index: 0.757, 95% CI: 0.736–0.778 vs. 0.750, 95% CI: 0.729–0.771; ΔC-index: 0.007, $P<0.01$), and ACM (C-index: 0.746, 95% CI: 0.729–0.763 vs. 0.739, 95% CI: 0.721–0.757; ΔC-index: 0.007, $P<0.01$).

Discussion

This study examined the associations between plasma FFA concentration, an important energy substrate for cardiac myocytes, and long-term clinical outcomes in HF patients. The findings revealed that elevated FFA levels independently predicted an increased risk of CV death & HHP, CV death alone, and ACM. These associations were observed in both the HFpEF and HFmrEF/HFrEF subgroups. Although FFA had a lower predictive value than NT-pro BNP, adding FFA improved NT-proBNP's predictive accuracy for the long-term prognosis of patients with HF.

As interest in disrupting myocardial energy metabolism in heart disease patients has grown, plasma FFAs have attracted considerable attention. Several studies found that elevated plasma FFA levels were linked to conditions preceding HF, including diabetes, hypertension, AF, and CAD [4–8]. Djousse et al. also recognized elevated FFA levels as a contributing risk factor for heart failure. However, studies on the prognostic significance of FFA in HF remain limited. A 2019 study examined the role of FFA in predicting all-cause mortality over three months in the 152 HF participants [15]. Additionally, Yu et al. conducted research in 183 acute HF subjects and

Table 1 Baseline characteristics of the three groups. Continuous variables are reported as medians [interquartile ranges] and were analyzed via the Mann-Whitney U test, while categorical variables are presented as counts (percentages) and were compared via either the chi-square test or Fisher's exact test

Variables	Overall	1st tertile group (0.02–0.43 mmol/L)	2nd tertile group (0.43–0.64 mmol/L)	3rd tertile group (0.64–2.69 mmol/L)	*P* value
Number	4109	1302	1377	1430	
Age, years	58.0 [48.0, 68.0]	58.0 [48.0, 67.0]	59.0 [48.0, 69.0]	58.0 [47.0, 69.0]	0.103
Female, n (%)	1162 (28.3)	339 (26.0)	388 (28.2)	435 (30.4)	0.039
History of smoking, n (%)	1390 (33.8)	447 (34.3)	489 (35.5)	454 (31.7)	0.098
History of drinking, n (%)	1034 (25.2)	312 (24.0)	382 (27.7)	340 (23.8)	0.026
Physical examination					
BMI, kg/cm^2	24.6 [22.0, 27.4]	24.5 [22.1, 26.8]	24.7 [22.1, 27.5]	24.5 [21.8, 28.0]	0.218
Heart rate, bpm	74.0 [64.8, 87.0]	72.0 [63.0, 82.0]	74.0 [64.5, 86.0]	78.0 [66.0, 91.0]	< 0.001
SBP, mmHg	115.0 [102.0, 130.0]	118.0 [104.5, 130.0]	115.0 [102.0, 130.0]	114.0 [101.0, 128.0]	< 0.001
DBP, mmHg	71.0 [64.0, 81.0]	71.0 [64.0, 80.0]	71.0 [64.0, 81.0]	72.0 [64.0, 81.0]	0.584
Laboratory examination					
WBC, 10^9	6.9 [5.6, 8.4]	6.8 [5.6, 8.2]	6.8 [5.6, 8.4]	7.1 [5.7, 8.7]	< 0.001
Hb, g/L	140.0 [125.0, 153.0]	138.0 [125.0, 152.0]	139.0 [124.0, 153.0]	142.0 [126.0, 156.0]	< 0.001
ALT, IU/L	22.0 [14.0, 36.0]	22.0 [14.0, 36.0]	21.0 [14.0, 34.0]	23.0 [15.0, 40.0]	0.001
FBG, mmol/L	5.2 [4.7, 6.2]	5.1 [4.6, 5.9]	5.2 [4.7, 6.2]	5.4 [4.7, 6.6]	< 0.001
HbA1C, %	6.2 [5.8, 7.0]	6.1 [5.7, 6.7]	6.3 [5.8, 7.0]	6.4 [5.9, 7.1]	< 0.001
TG, mmol/L	1.3 [0.9, 1.8]	1.3 [1.0, 1.7]	1.3 [0.9, 1.8]	1.2 [0.9, 1.7]	0.001
HDL-C, mmol/L	1.0 [0.8, 1.2]	1.0 [0.8, 1.2]	1.0 [0.8, 1.2]	0.9 [0.8, 1.2]	< 0.001
LDL-C, mmol/L	2.4 [1.8, 3.0]	2.3 [1.8, 2.9]	2.4 [1.8, 3.0]	2.4 [1.8, 3.0]	0.311
eGFR-EPI, ml/min/1.73m^2	80.2 [62.7, 96.7]	84.2 [66.8, 98.3]	80.5 [63.2, 96.9]	76.3 [59.1, 93.7]	< 0.001
hs-CRP, mg/dL	2.7 [1.0, 8.0]	1.8 [0.8, 5.0]	2.3 [0.9, 6.9]	4.2 [1.6, 10.6]	< 0.001
NT-pro BNP, pg/mL	1653.0 [556.0, 4431.0]	1189.5 [378.5, 2821.8]	1389.0 [501.0, 3794.0]	2745.0 [935.0, 6739.2]	< 0.001
Ultrasound examination					
LVEDD, mm	59.0 [50.0, 68.0]	58.0 [49.0, 66.2]	59.0 [50.0, 67.0]	61.0 [51.0, 71.0]	< 0.001
LVEF, %	40.0 [30.0, 58.0]	42.3 [31.0, 60.0]	40.0 [30.0, 58.0]	36.0 [28.0, 54.0]	< 0.001
Comorbidity					
DM, n (%)	1737 (47.9)	463 (40.7)	577 (47.7)	697 (54.4)	< 0.001
COPD, n (%)	256 (6.2)	71 (5.5)	100 (7.3)	85 (5.9)	0.132
Infection*, n (%)	694 (16.9)	163 (12.5)	222 (16.1)	309 (21.6)	< 0.001
CAD, n (%)	1737 (47.9)	463 (40.7)	577 (47.7)	697 (54.4)	< 0.001
Hypertension, n (%)	2064 (50.2)	651 (50.0)	702 (51.0)	711 (49.7)	0.784
AF, n (%)	1294 (31.5)	307 (23.6)	448 (32.5)	539 (37.7)	< 0.001
NYHA classification > II, n (%)	2459 (68.7)	658 (60.3)	796 (66.6)	1005 (77.8)	< 0.001
heart failure classification					< 0.001
HFrEF, n (%)	2026 (49.3)	561 (43.1)	661 (48.0)	804 (56.2)	
HFmrEF, n (%)	709 (17.3)	250 (19.2)	229 (16.6)	230 (16.1)	
HFpEF, n (%)	1374 (33.4)	491 (37.7)	487 (35.4)	396 (27.7)	
Prescription upon discharge					
Digoxin, n (%)	1595 (38.8)	449 (34.5)	519 (37.7)	627 (43.8)	< 0.001
Diuretic, n (%)	2803 (68.2)	895 (68.7)	903 (65.6)	1005 (70.3)	0.025
ACEI/ARB/ARNI, n (%)	2245 (54.6)	775 (59.5)	740 (53.7)	730 (51.0)	< 0.001
β-blocker, n (%)	3458 (84.2)	1104 (84.8)	1161 (84.3)	1193 (83.4)	0.609
MRA, n (%)	2660 (64.7)	799 (61.4)	868 (63.0)	993 (69.4)	< 0.001
SGLT2 inhibitors, n (%)	406 (9.9)	96 (7.4)	133 (9.7)	177 (12.4)	< 0.001

N: number; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WBC: white blood cell count; HB: hemoglobin; ALT: alanine aminotransferase; FBG: fasting blood glucose; HbA1C: glycated hemoglobin A1c; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; eGFR-EPI: estimated glomerular filtration rate by the epidemiology collaboration; hs-CRP: high-sensitivity C-reactive protein; NT-pro BNP: N-terminal pro b-type natriuretic peptide; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; AF: atrial fibrillation; NYHA classification: New York Heart Association functional classification; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; ACEI/ARB/ARNI: angiotensin-converting enzyme inhibitor/ angiotensin II receptor blocker/ angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium-glucose cotransporter 2; 1ST: the first; 2nd : the second; 3rd : the third

*Infection: Defined as an infection that requires antibiotic or antiviral treatment

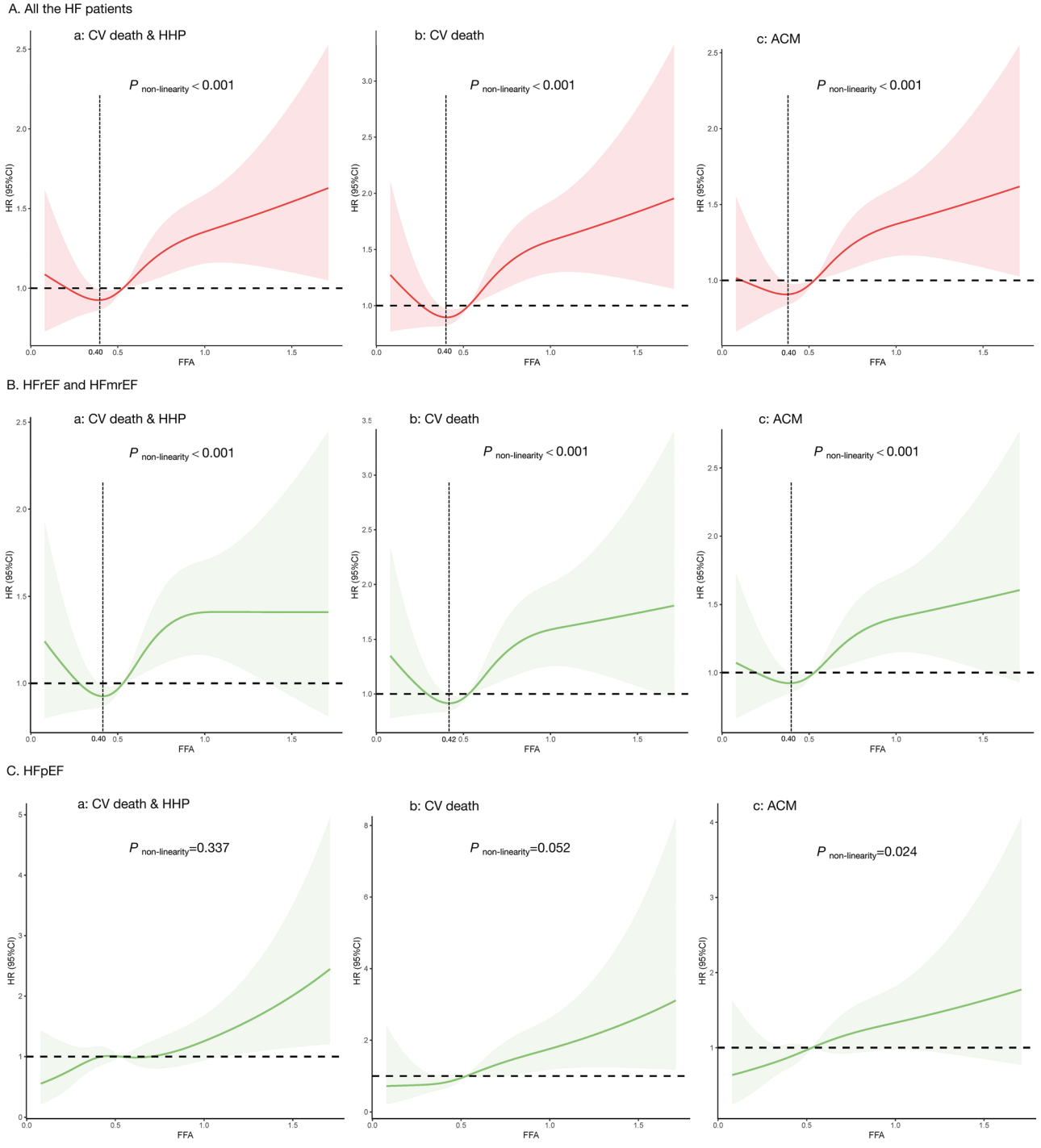


Fig. 2 RCS curves modeling the relationships between plasma FFA levels and the three long-term adverse outcomes, including CV death & HHP (**a**), CV death (**b**), and ACM (**c**). **A**) Analysis of the entire heart failure patient population; **B**) analysis of the HFrEF cohort, which included HFmrEF individuals; **C**) analysis of the HFpEF cohort. The point where the dashed line intersects the X-axis represents the plasma FFA level corresponding to the inflection point of the RCS curve. The adjusted covariates in the Cox multiple regression models included age, sex, BMI, smoking status, alcohol consumption, major comorbidities (type 2 diabetes, hypertension, atrial fibrillation, and coronary artery disease), serum creatinine, NT-proBNP, hs-CRP, and the prescription of ACE inhibitors/ARBs/ARNIs, β-blockers, MRAs, and SGLT2 inhibitors at discharge

Table 2 Associations between different tertiles of FFA levels and the three adverse outcomes

Outcomes	1st tertile group	2nd tertile group		3rd tertile group		*P* for trend
		Crude HR	Adjusted HR	Crude HR	Adjusted HR	
CV death&HHP	Ref.	1.21 (1.03,1.43)	1.09 (0.91,1.32)	1.89 (1.62,2.21)	1.32 (1.11,1.58)	< 0.01
CV death	Ref.	1.32 (1.06,1.63)	1.18 (0.93,1.5)	2.30 (1.88,2.8)	1.45 (1.16,1.82)	< 0.01
ACM	Ref.	1.39 (1.17,1.66)	1.20 (0.99,1.46)	2.23 (1.89,2.62)	1.39 (1.15,1.68)	< 0.01

1st : the first; 2nd : the second; 3rd : the third. CV death&HHP: cardiovascular death and heart failure hospitalization; CV death: cardiovascular death; ACM: all-cause mortality; FFA: free fatty acids. The adjusted covariates in the COX multiple regression analyses included age, gender, BMI, smoking, alcohol consumption, the major comorbidities (type 2 diabetes, hypertension, atrial fibrillation, and coronary artery disease), serum creatinine, NT-proBNP, hs-CRP, and the prescription of ACE inhibitors/ARBs/ARNIs, β-blockers, MRAs, and SGLT2 inhibitors at discharge

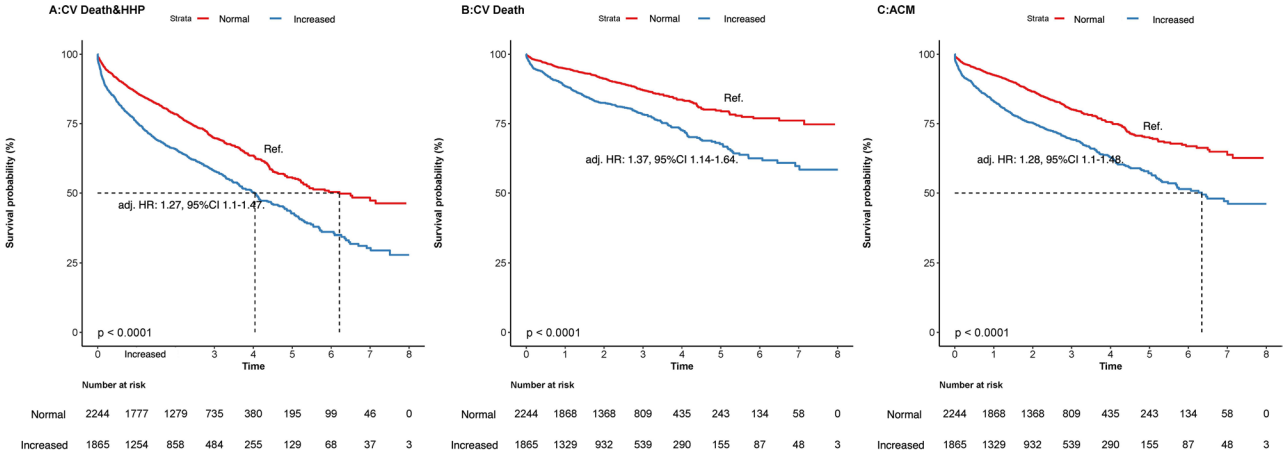


Fig. 3 Kaplan-Meier curves depicting the incidence of cardiovascular death and heart failure hospitalization (**A**), cardiovascular death (**B**), and all-cause mortality (**C**) in patients with normal versus elevated FFA levels (defined as > 0.45 mmol/L in female patients and > 0.60 mmol/L in male patients). (Note: Ref: the reference group; adj. HR: adjusted hazard ratio)

revealed positive associations between serum FFA levels and composite events of HF hospitalization and all-cause death during a one-year follow-up [16]. Although these findings suggested a link between elevated FFA levels and adverse outcomes in HF patients, the small sample sizes and limited follow-up durations diminish the reliability of these results. This research was conducted in a relatively larger cohort of HF patients encompassing a wide spectrum of LVEFs. Beyond reinforcing the significant association between increased FFA levels and the adverse outcomes in HF patients, it provided additional insights. First, the prognostic significance was consistent for HFpEF and HFmrEF/HFrEF. A subtle distinction lay in the relationship between excessively low FFA levels and adverse outcomes. In HFmrEF/HFrEF, a continuous reduction in FFA concentration (<0.4 mmol/L) was not associated with improved prognosis, as very low FFA levels might indicate severe malnutrition or cachexia—conditions common in HFmrEF/HFrEF that significantly contribute to adverse cardiovascular events and increased mortality [18]. Second, this research revealed an interaction effect between FFA and sex on all the outcomes. Specifically, the associations between FFA levels and the three outcomes were stronger in females and weaker in males. Sex-related differences in physiological responses to FFA levels might contribute to this variation [27, 28], but the exact mechanism was unclear and warranted further investigation. Finally, the combination of FFA and NT-pro BNP demonstrated greater efficacy in risk stratification for heart failure than relying solely on NT-pro BNP. NT-pro BNP is widely recognized as a valuable prognostic marker, but its specificity and sensitivity are somewhat limited [19, 20]. Including FFA levels alongside NT-pro BNP could help identify patients with a significantly increased likelihood of negative cardiovascular outcomes, offering valuable information to improve patient management.

Elevated plasma FFA levels were associated with the severity of heart failure and might also contribute to the progression of the condition to some extent. Individuals with higher NT-pro BNP levels and more advanced NYHA functional classifications tended to have elevated FFA levels (Table 1). This correlation was likely driven by heightened sympathetic nervous system activity, increased catecholamine release, and elevated inflammatory cytokines. These factors activate lipoprotein lipase, which elevated plasma FFA concentrations through the hydrolysis of triglycerides [10]. Consequently, the rise in circulating FFA levels, combined with heightened regulatory factor activity, promoted greater FFA uptake by the heart [3, 21]. However, owing to the high oxygen demand associated with fatty acid oxidation, reliance on FFA in

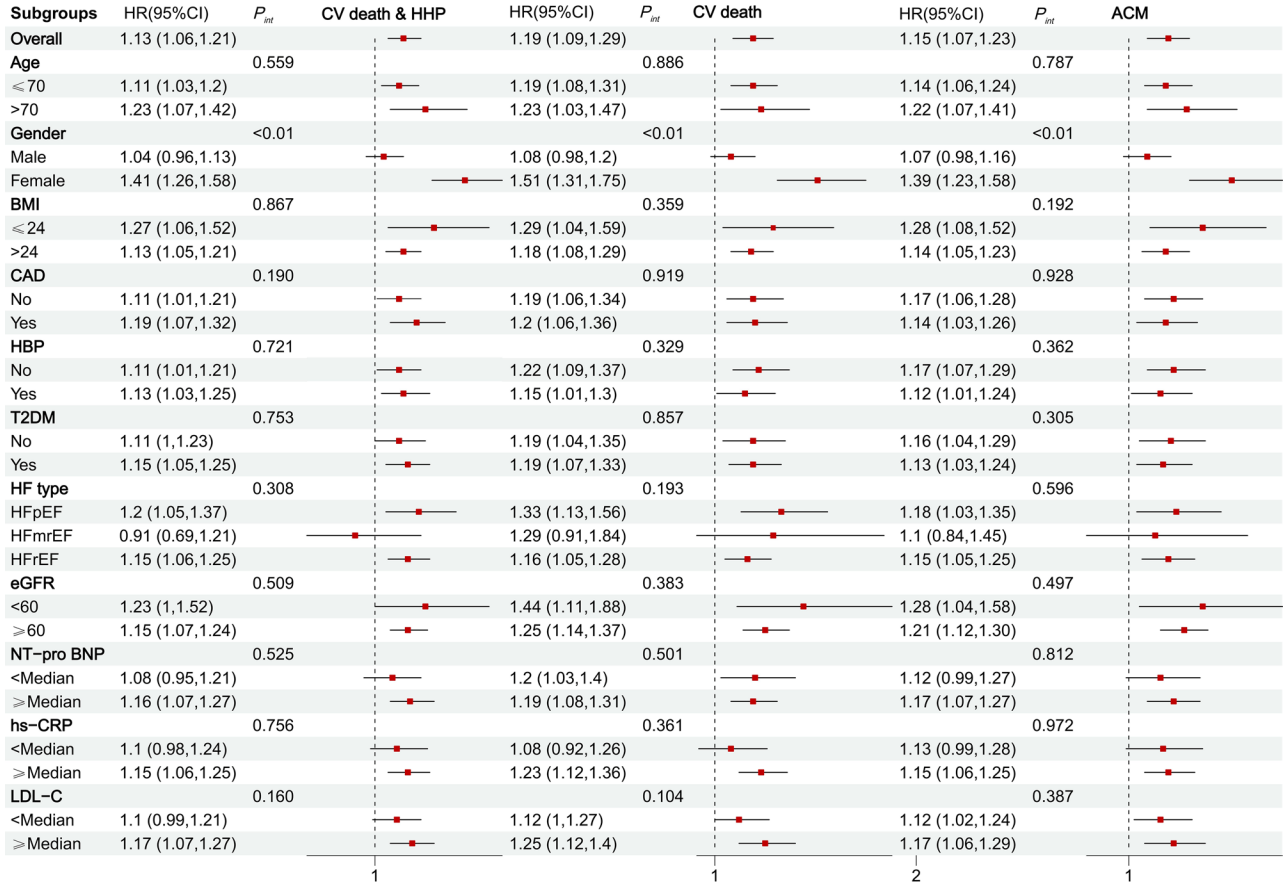
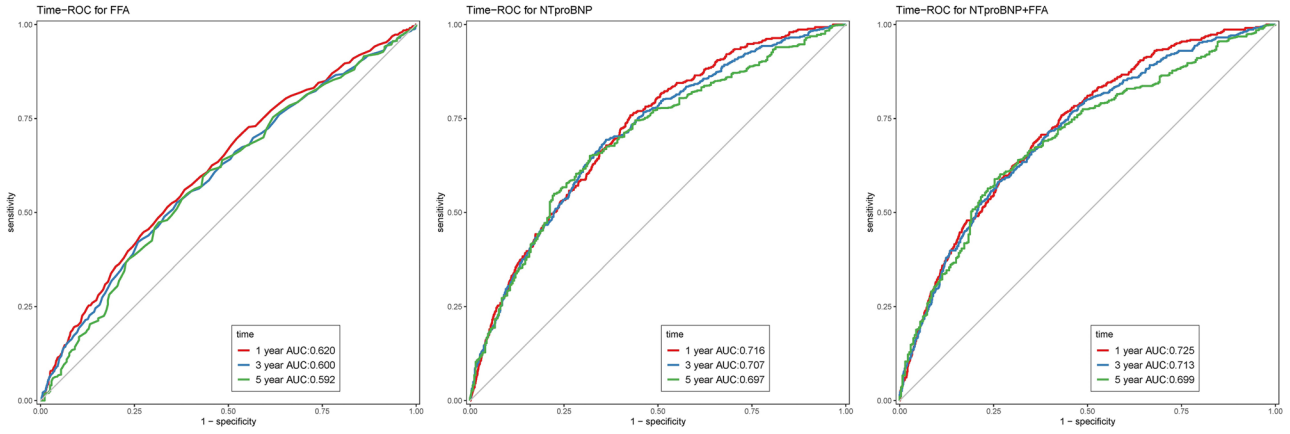


Fig. 4 Forest plots displaying the results of stratified analyses and interaction tests. In the whole cohort, the overall HRs for the three adverse outcomes were derived from a Cox proportional hazards regression model, representing the risk associated with an increase of one standard deviation (SD) in the continuous variable. P_{int}: *P* for interaction. BMI: body mass index; CAD: coronary artery disease; HBP: hypertension; HF: heart failure; HFpEF: heart failure with preserved ejection fraction. T2DM: Type 2 diabetes mellitus; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol

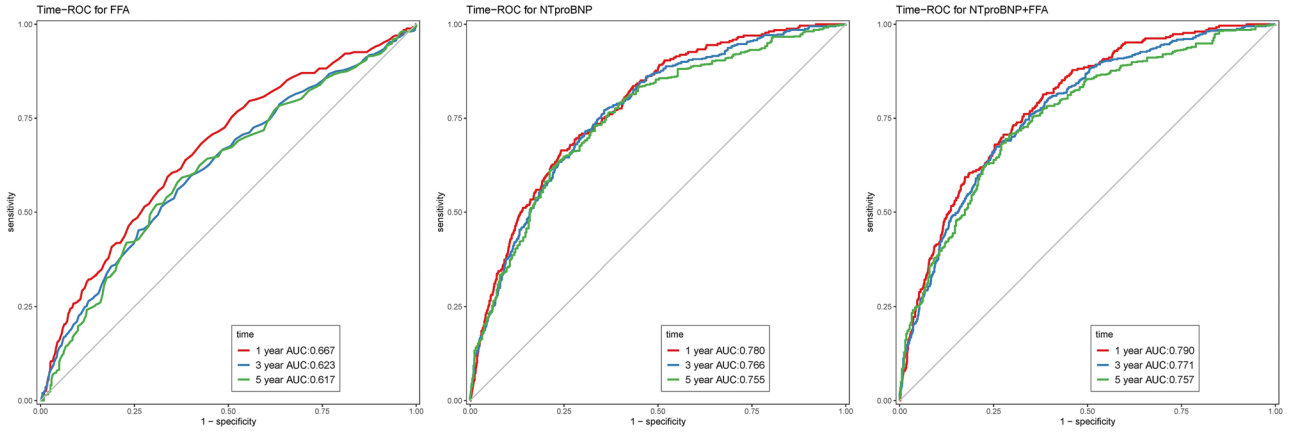
HF could exacerbate myocardial ischaemia and dysfunction. Consequently, the failing heart gradually shifted from FFA utilization to favoring glycolysis, mimicking a fetal energy metabolism pattern [3, 22–25]. An imbalance in FFA uptake and utilization could lead to lipid accumulation within myocardial cells, further impairing cardiac performance [26]. Moreover, elevated FFA levels have been reported to increase inflammation, insulin resistance, and oxidative stress, all of which can contribute to the progression of HF [13, 14].

Strengths and limitations

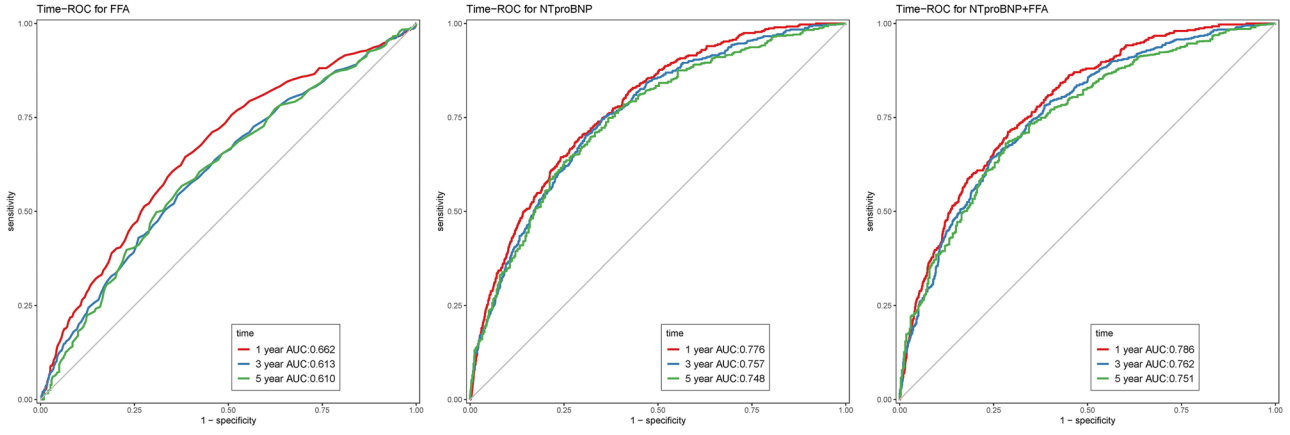
This study had several strengths, including an extended follow-up period and a large sample size, enhancing the reliability of the findings. Additionally, the subgroup analysis of HFpEF patients provided valuable insights into this patient subgroup. Unlike previous studies that focused primarily on single endpoints, this work examined a broader range of clinical endpoints, allowing a more comprehensive evaluation of the relationship between FFA and HF prognosis. However, this study also had some limitations. First, it was a single-centre study, which might restrict the generalizability of the findings to other populations or healthcare settings. Second, the observational nature of the study prevented the determination of causality between FFA levels and clinical outcomes in heart failure patients. Although efforts were made to adjust for important confounding factors, there was a possibility that some unmeasured confounders or variables were not accounted for in the analysis, potentially influencing the observed associations. Third, this study did not include a dynamic follow-up of FFA changes over time, limiting the evaluation of the impact of FFA fluctuations on clinical outcomes. Finally, the study did not examine the composition of FFA, which has been observed to be associated with the progression of heart failure and clinical outcomes [27].



A



B



C

Fig. 5 Receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) values for different models predicting cardiovascular death and heart failure hospitalization (**A**), cardiovascular death (**B**), and all-cause mortality (**C**). (Note: CV death & HHP: cardiovascular death and heart failure hospitalization; CV death: cardiovascular death; ACM: all-cause mortality.)

Table 3 Concordance index (C-index) for different models predicting various outcomes

Outcome	CV death & HHP	CV death	ACM
Model 1: NT-pro BNP	0.687 (0.668–0.706)	0.75 (0.729–0.771)	0.739 (0.721–0.757)
Model 2: FFA	0.596 (0.575–0.617)	0.628 (0.602–0.654)	0.617 (0.596–0.638)
Model 3: NT-pro BNP and FFA	0.693 (0.674–0.712)	0.757 (0.736–0.778)	0.746 (0.729–0.763)
Delta C index - P-value (Model 3 Vs. Model 1)	< 0.01	< 0.01	< 0.01

Model 1: NT-pro BNP: C-index values for predicting outcomes with NT-pro BNP as the predictor

Model 2: FFA: C-index values for predicting outcomes with FFA as the predictor

Model 3: NT-pro BNP and FFA: C-index values for predicting outcomes when both NT-pro BNP and FFA are used as predictors

The delta C index - P-value is used to determine whether the improvement in a model's discriminative ability is statistically significant. A P-value less than 0.05 indicates that Model 3, which includes additional FFA, has significantly better predictive accuracy than Model 1

(Note: CV death & HHP: cardiovascular death and heart failure hospitalization; CV death: cardiovascular death; ACM: all-cause mortality.)

Conclusion

An elevated plasma FFA concentration independently predicted an increased risk of CV death & HHP, CV death and ACM in HF patients. Subgroup analyses for HFpEF and HFmrEF/HFrEF consistently highlighted the significant predictive power of FFA levels. Combining FFA with NT-proBNP further enhanced the accuracy of risk stratification in HF patients. These findings might aid in guiding risk assessment and identifying potential therapeutic targets to improve patient outcomes.

Abbreviations

ACM	all-cause mortality
AUC	Area under the curve
ACEI/ARBs/ARNIs	Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors
CV	Cardiovascular
CAD	Coronary artery disease
CV death & HHP	Cardiovascular death and heart failure hospitalization
CI	Confidence interval
C-index	Concordance index
eGFR	Estimated glomerular filtration rate
FFA	Free fatty acid
HHP	Heart failure hospitalization
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
HFmrEF/HFrEF	Heart failure with mildly reduced ejection fraction or heart failure with reduced ejection fraction
hs-CRP	High-sensitivity C-reactive protein
MRAs	Mineralocorticoid receptor antagonists; NT-pro BNP: N-terminal pro B type natriuretic peptide
NYHA	New York Heart Association
RCS	Restricted cubic splines
ROC	Receiver operating characteristic
SGLT2i	Sodium-glucose cotransporter-2 inhibitors

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Consent for publication

NA.

Competing interests

The authors declare no competing interests.

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