


Malnutrition in acute heart failure with preserved ejection fraction: clinical correlates and prognostic implications

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Abstract

Aims This study aimed to evaluate the prognostic significance of nutritional status in post-discharge Asians with heart failure with preserved ejection fraction (HFpEF).

Methods and results We examined the prognostic implications of body mass index (BMI) and nutritional markers among consecutive patients hospitalized for HFpEF. Nutritional metrics were estimated by serum albumin (SA), prognostic nutritional index (PNI), Controlling Nutritional Status (CONUT) score, and geriatric nutritional risk index. Among 1120 patients (mean age: 77.2 ± 12.6 years, 39.4% men), mean SA levels, PNI, CONUT scores, and geriatric nutritional risk index were 3.3 ± 0.6 g/dL, 40.2 ± 8.7, 5.5 ± 2.1, and 95.9 ± 14.5, respectively. Lean body size, higher white blood cell counts and C-reactive protein levels, anaemia, and lack of angiotensin blocker use were independently associated with malnutrition (defined by SA < 3.5 g/dL). Higher SA levels [hazard ratio (HR): 0.67 (95% confidence interval, CI: 0.53–0.85)], higher PNI [HR: 0.97 (95% CI: 0.95–0.99)], and higher geriatric nutritional risk index [HR: 0.98 (95% CI: 0.97–0.99)] (all *P* < 0.05) were all associated with longer survival, with higher CONUT score [HR: 1.08 (95% CI: 1.02–1.13)] exhibited higher mortality in Cox regression models and with higher SA levels/PNI but not BMI further contributing to the reduced rate of re-hospitalization (both *P* < 0.05). Categorizing BMI (25 kg/m² as cut-off) and nutritional status showed significantly higher mortality rates among patients with lower BMI/malnutrition than among those with BMI/better nutrition (SA level, PNI, and CONUT score, all *P* < 0.01). Restricted cubic spline regression revealed a marked survival benefit of better nutrition with increasing BMI (adjusted *P*_{interaction} for both SA level and PNI: <0.001; adjusted *P*_{interaction} for CONUT score: 0.046).

Conclusions Malnutrition was frequently and strongly associated with systemic inflammation in Asian patients hospitalized for acute HFpEF. Our findings also indicate that nutrition may play a pivotal role in metabolic protection in this population.

Keywords Nutritional status; Albumin; Mortality; Body mass index; Heart failure with preserved ejection fraction

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Introduction

Managing patients with heart failure (HF) with preserved ejection fraction (HFpEF) remains a clinical challenge, partly

due to its underlying heterogeneity, multiple co-morbidities, and the lack of consensus on effective treatments.^{1,2} Hence, interventions leading to early recognition of potentially modifiable risk factors (e.g. obesity and hypertension) could offer

an alternative approach in subjects susceptible to HFpEF. Obesity or overweight directly influences haemodynamic and physiological conditions and has been linked to several co-morbidities as well as to structural and functional alterations of the heart that may predispose to HF.^{3–5} Conversely, a higher body mass index (BMI) appears to be associated with reduced mortality in patients with established HF. This association is known as the ‘Obesity Paradox’.^{3,4} This effect is possibly mediated by several factors, including better nutrition or a reservoir of metabolic expenditure,^{3,4} differential natriuretic peptide levels,⁶ and greater muscle mass with higher exercise capacity.^{4,7–9}

Cardiopulmonary fitness appears to outweigh BMI in systolic HF as increasing muscle mass and BMI improve aerobic capacity and body composition, which ameliorate functional capacity.^{4,7,10} Patients with HFpEF, however, exhibit ‘sarcopenic’ obesity, which is characterized by excessive BMI and low muscle mass with multiple co-morbidities, excessive visceral adiposity, and heightened systemic inflammation.¹¹ On the other hand, BMI alone fails to incorporate information that accurately describes a condition of protein-energy wasting and relevant harmful biological effects, which are known to be highly prognostic in HF.^{9,12–20} While it has been recently proposed that poor nutritional status in the context of hypoalbuminaemia is associated with a risk of death for patients with HFpEF,²⁰ the beneficial effects of albumin level over the course of HF syndrome (e.g. HF re-hospitalization) remain largely unknown, especially in ethnic Asians. Of note, Asians with HFpEF tend to be lean based on BMI metrics and may share a similarly high number of co-morbidities with Western patients (e.g. diabetes)²¹; thus, BMI reference values derived from a Western population may not be completely applicable to Asians. In this regard, there is a growing need in identifying alternative markers that potentially reflect metabolic reserve other than BMI in HFpEF in ethnic Asians. In light of this, we sought to investigate the clinical factors associated with hypoalbuminaemia and whether malnutrition may play a more important role as prognosticator than BMI in post-discharge HFpEF in Asians.

Materials and methods

Study setting and population

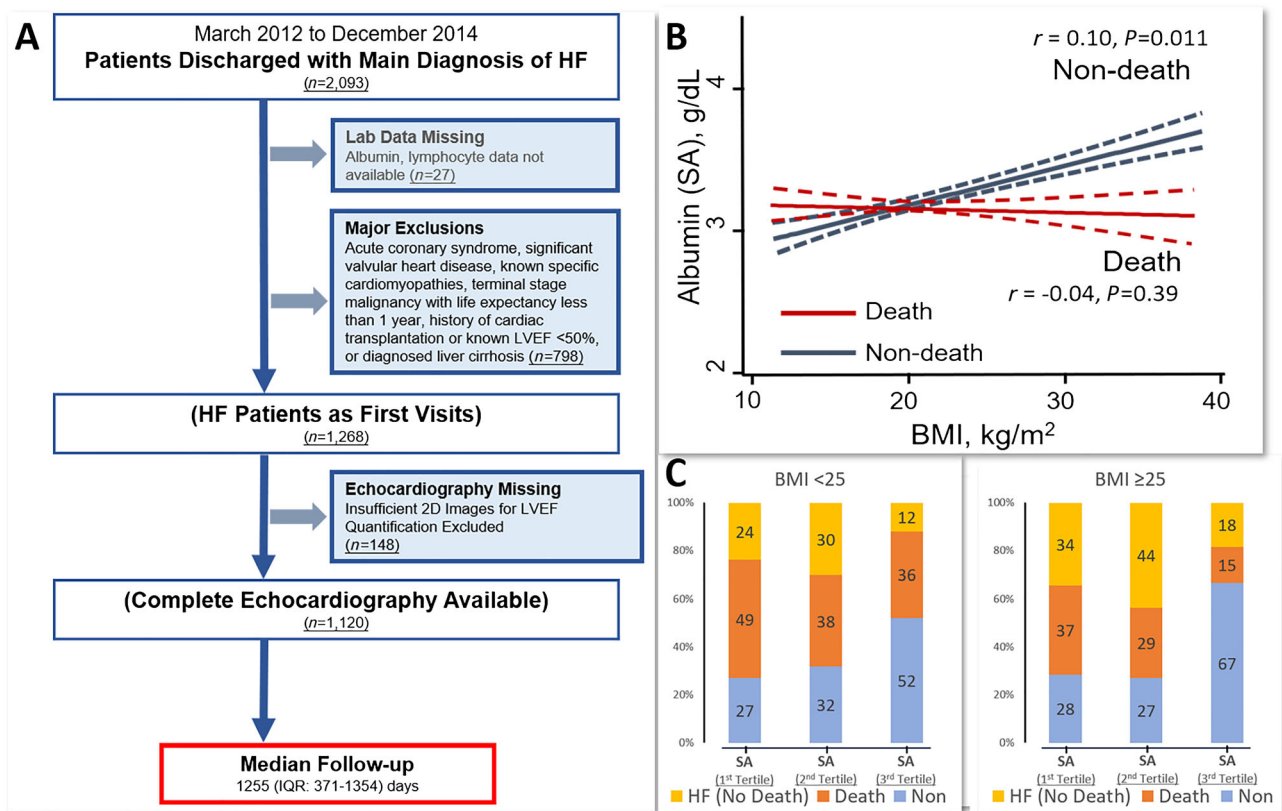
Our current study population comprised 1120 consecutively discharged patients aged >20 years with acute HF as the main diagnosis at discharge from a tertiary medical centre located in the northern part of Taiwan (from March 2012 to December 2014). Patient data included baseline characteristics and hospitalization records extracted from the electronic data capture system. Data were retrospectively analysed. Patients with main discharge diagnosis of HF (compliant with the Singapore

Heart Failure Outcomes and Phenotypes (SHOP) study inpatient cohort)²² were based on the Framingham HF criteria,² which mandated intravenous diuretic management. Left ventricular ejection fraction (LVEF) was determined by echocardiography using biplane Simpson’s method during the hospital stay (within the first 3 days of admission) or on arrival at the emergency department. Specifically, medical history of chronic HF, hypertension, diabetes, coronary artery disease, chronic kidney disease, dyslipidaemia, stroke, anaemia, and medications were extracted from electronic medical records. The main exclusion criteria were acute coronary syndrome (including diagnosed myocardial infarction or unstable angina during admission), significant valvular heart disease (more than moderate valvular regurgitation or mild valvular stenosis), terminal stage malignancy with life expectancy of less than 1 year, prior history of cardiac transplantation, known history of HF with reduced ejection fraction (LVEF < 50%), and diagnosed liver cirrhosis from any cause (*Figure 1A*). This study complied with the Declaration of Helsinki, and the local ethics board committee (15MMHIS015) waived the requirement for obtaining written informed consent for data collection and analysis owing to the retrospective design of the study.

Laboratory variables and nutritional indices

Blood samples were obtained and analysed using a Beckman LH 780 analyzer (Beckman Coulter, Miami, FL, USA) for haematological data and a Beckman Synchron LX i725 (Beckman Coulter, Brea, CA, USA) for biochemical data. Brain natriuretic peptide (BNP) was measured using a Quidel Triage BNP test (Alere, San Diego, CA, USA). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation: $175 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female). Prognostic nutritional index (PNI), Controlling Nutritional Status (CONUT) scores, and geriatric nutritional risk index (GNRI) were adopted to assess the individual’s nutritional status, where $\text{PNI} = 10 \times \text{serum albumin (SA) (g/dL)} + 0.005 \times \text{total lymphocyte count (TLC) } (\times 10^3/\mu\text{L})$. CONUT score was determined by assessing the circulating levels of three laboratory markers, SA, TLC, and total cholesterol,^{13,17} and GNRI was calculated by the following formula: $\text{GNRI} = [1.489 \times \text{albumin (g/L)}] + [41.7 \times (\text{weight/WLo})]$, where WLo represents ideal weight calculated by the Lorentz formula.²³ Patients were categorized as having either better nutrition or malnutrition status according to the level of each nutritional index using previously reported cut-offs of 3.5 g/dL for SA level, 38 for PNI, 3 for CONUT score, and 92 for GNRI.^{15,17–19} Patients were stratified by BMI in accordance with recommendations from the Department of Health in Taiwan as follows: normal weight (BMI < 24 kg/m²), overweight (24 ≤ BMI < 27 kg/m²), and obese

Figure 1 Study flowchart and the association of clinical events with serum albumin (SA) levels stratified by body mass index (BMI). Flowchart of the current study is shown (A). Associations between BMI and SA in the current study population in the death ($r = 0.10, P=0.011$) or non-death ($r = -0.04, P=0.39$) groups (B). Subjects in higher SA strata were associated with a lower proportion of death or heart failure (HF) re-hospitalization (without death) irrespective of BMI strata ($<25, \geq 25 \text{ kg/m}^2$) (C). IQR, interquartile range; LVEF, left ventricular ejection fraction.



($\text{BMI} \geq 27 \text{ kg/m}^2$).²⁴ In the current study, SA, PNI, CONUT, and GNRI were available in 1111 (99.2%), 1093 (97.6%), 1079 (96.3%), and 1068 (95.4%) study participants, respectively.

Outcome determinations

The primary endpoint of this study was all-cause mortality, with occurrence of HF re-hospitalization as a secondary endpoint, and a composite endpoint of both mortality and HF re-hospitalization. The definition of HF re-hospitalization in the present study was determined by rapidly worsening clinical HF signs/symptoms requiring urgent and unplanned hospitalization, an unplanned emergency department visit presenting with HF signs/symptoms and receiving intravenous diuretic or vasodilator treatment, or new or worsening HF with evidence of pulmonary congestion/oedema requiring admission. Re-hospitalization of enrolled patients was further adjudicated by two experienced cardiologists (S.-C. C. and C.-L. H.) based mainly on the following extracted electronic data capture information: discharge diagnoses, signs and symptoms, BNP level, chest plain film, and echocardiography.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (mean \pm SD) or median and interquartile range (IQR: 25th to 75th) for non-normal distributions and were compared by unpaired Student's *t*-test (Table 1). Categorical or binary variables were presented as proportions or relative frequencies (percentage) and compared by χ^2 test (i.e. Fisher's exact test). Pearson's correlation was used for linear relationships between any two continuous variables of interest and multivariate stepwise logistic regression models [with odds ratio and corresponding 95% confidence interval (CI)] used to establish the relationship between baseline clinical covariates (characteristics, anthropometrics, biochemical analyses, and medications, when $P < 0.05$ in univariate models) and hypoalbuminaemia ($<3.5 \text{ g/dL}$).

Regarding clinical outcomes, estimated total event numbers and rates are described by total number and expressed as proportions or percentages. All-cause mortality and HF re-hospitalization-free survival rates are displayed using Kaplan–Meier plots and further compared using the log-rank test. Cox proportional hazards regression

Table 1 Baseline characteristics of the study patients

	All patients	Without event (–)	With event (+)	P value
	N = 1120 n (%)	N = 440 n (%)	N = 680 n (%)	
Demographics, n (%)				
Age (years)	77.2 (12.6)	75.2 (13.5)	78.4 (11.8)	<0.001
Sex (men), n (%)	441 (39.4%)	178 (40.5%)	263 (38.7%)	0.553
Height (m)	1.6 (0.0)	1.6 (0.5)	1.6 (0.1)	0.125
Weight (kg)	60.5 (0.4)	62.0 (14.5)	59.6 (14.2)	0.01
Body mass index (kg/m ²)	24.6 (0.2)	25.2 (6.9)	24.3 (5.5)	0.014
Normal weight (%)	50.7	46.1	53.6	0.057
Overweight (%)	22.2	24.3	20.9	
Obesity (%)	27.1	29.6	25.5	
Systolic blood pressure (mmHg)	141.0 (1.0)	141.1 (31.0)	140.9 (33.4)	0.912
Diastolic blood pressure (mmHg)	72.9 (0.5)	73.4 (17.1)	72.6 (18.3)	0.5
Heart rate (b.p.m.)	89.5 (0.7)	88.1 (21.21)	90.4 (22.2)	0.075
NYHA FC				
≤II	154 (13.8%)	67 (15.1%)	87 (12.9%)	<0.001
III	689 (61.5%)	298 (67.3%)	391 (57.7%)	
IV	277 (24.7%)	78 (17.6%)	199 (29.4%)	
QRS duration (ms)	99.2 (23.2)	98.5 (24.6)	99.7 (22.2)	0.40
Medical history, n (%)				
Prior history of HF	614 (54.8%)	225 (51.1%)	389 (57.2%)	0.043
Hypertension	808 (72.1%)	276 (62.7%)	532 (78.2%)	<0.001
Diabetes mellitus	548 (48.9%)	201 (45.7%)	347 (51.0%)	0.076
Coronary artery disease	381 (34.0%)	137 (30.9%)	244 (36.0%)	0.08
CVA	200 (17.9%)	67 (15.1%)	133 (20.0%)	0.053
Hyperlipidaemia	215 (19.2%)	85 (19.3%)	130 (19.1%)	0.934
Atrial fibrillation	393 (35.1%)	133 (30.0%)	260 (38.5%)	0.004
COPD	170 (15.2%)	46 (10.4%)	124 (18.3%)	<0.001
PAD	78 (7.0%)	22 (5.0%)	56 (8.3%)	0.034
Active smoking	218 (19.5%)	74 (16.8%)	144 (21.2%)	0.072
Laboratory data				
White blood cells (×10 ³ /μL)	10.1 (5.2)	9.8 (5.0)	10.3 (5.36)	0.171
Total lymphocyte count (×10 ³ /μL)	15.1 (10.8)	16.3 (11.3)	14.3 (10.5)	0.003
Haemoglobin (g/dL)	10.5 (2.5)	10.7 (2.5)	10.4 (2.4)	0.02
Glucose (mg/dL)	173.8 (110.1)	171.8 (106.6)	175.2 (112.3)	0.619
Cholesterol (mg/dL)	156.9 (50.5)	161.5 (51.3)	153.9 (49.8)	0.014
ALT (U/L)	62.7 (150.4)	32.5 (50.6)	82.0 (185.8)	<0.001
HDL-C (mg/dL)	45.7 (14.9)	45.9 (14.4)	45.5 (15.3)	0.68
Na (mEq/L)	137.5 (5.5)	139.1 (1.8)	136.5 (6.7)	<0.001
K (mEq/L)	4.1 (0.8)	4.1 (0.8)	4.2 (0.8)	0.17
BUN (mEq/L)	40.5 (30.3)	37.4 (27.4)	42.5 (31.9)	0.007
eGFR (mL/min/1.73 m ²)	54.4 (38.5)	64.1 (44.0)	48.0 (32.9)	<0.001
Biomarkers				
C-reactive protein, median (IQR) (mg/mL)	2.91 (0.5–4.6)	1.59 (0.43–4.42)	2.42 (0.7–4.78)	0.008
BNP median (IQR) (pg/mL)	567 (260–1250)	554 (255.5–1225)	587 (262–1250)	0.09
Nutritional indices				
Albumin (mg/dL)	3.3 (0.6)	3.5 (0.6)	3.2 (0.6)	<0.001
PNI	41.3 (9.5)	43.7 (9.9)	39.8 (8.9)	<0.001
CONUT	5.5 (2.1)	5.2 (2.2)	5.7 (2.1)	<0.001
GNRI	95.9 (14.5)	99.5 (14.0)	93.6 (14.3)	<0.001
Medications, n (%)				
ACE-I/ARB	387 (34.6%)	183 (41.6%)	204 (30.0%)	<0.001
Beta-blocker	220 (19.6%)	107 (24.3%)	113 (16.6%)	0.002

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BUN, Blood urea nitrogen; CONUT, Controlling Nutritional Status; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; IQR, interquartile range; K, potassium level; LVEF, left ventricular ejection fraction; Na, sodium level; NYHA FC, New York Heart Association functional classification; PAD, peripheral artery disease; PNI, prognostic nutritional index.

Definition of event: mortality or HF re-hospitalization.

models [expressed as hazard ratio (HR) with corresponding 95% CI and P values] were used to assess the associations of clinical outcomes by nutritional indexes cut-offs (as binary variables) and BMI strata (<25, ≥25 kg/m²) into four categories. Assuming that hazard incidences were

proportional, stepwise regression models were separately adjusted as the following Cox proportional hazard models: Model 1 (age), Model 2 (Model 1 + age, sex, BMI, systolic blood pressure, heart rate, prior HF, hypertension, cardiovascular disease, diabetes, and atrial fibrillation), and Model

3 (Model 2 + hyperlipidaemia, eGFR, and BNP). To assess the associations between outcomes and BMI, we further tested the linearity assumption of the associations with various nutritional indices (including SA level, PNI, CONUT score, and GNRI) using restricted cubic splines with spline knots selected based on three cut-off points besides lower (5th) and upper (95th) percentile threshold values. The modifying effect on clinical outcomes by various nutritional indices (SA, PNI, CONUT, and GNRI, separately) and BMI was also tested.

All analyses were conducted using Stata (version 12, StataCorp, College Station, TX, USA) or SAS (version 9.4, SAS Institute, Cary, NC, USA). For all tests, two-tailed alpha significance level was set to 0.05.

Results

Patient population

Baseline clinical characteristics for patients are shown in *Table 1*. A total of 1120 patients (mean age: 77.2 years, 60.6% women) who met our eligibility criteria for acute HF with preserved LVEF were included (*Table 1, Figure 1A*). Among all patients, the prevalence of hypertension, diabetes, and coronary artery disease were 72.1%, 48.9%, and 34%, respectively, with median BNP level of 567 (IQR: 260–1250) pg/mL on admission. Of all patients, 680 (60.7%) developed adverse events (mortality or HF re-hospitalization) during a median follow-up of 1255 (IQR: 371–1354) days. Mean SA, PNI, TLC, CONUT, and GNRI in the current study were 3.3 ± 0.6 g/dL, 40.2 ± 8.7 , 5.5 ± 2.1 , and 95.9 ± 14.5 , respectively. Patients who developed adverse events were older, with a higher New York Heart Association functional classification grade, had lower BMIs, and were more likely to have hypertension, atrial fibrillation, HF history, chronic lung diseases, and peripheral vascular disease (all $P < 0.05$). Furthermore, these patients had, in general, poor nutritional status, higher levels of C-reactive protein (CRP), lower levels of haemoglobin, sodium, and cholesterol, lower eGFR, higher levels of alanine transaminase and Blood urea nitrogen (all $P < 0.05$), and marginally higher BNP levels (0.09). They were also less likely to receive treatment with angiotensin receptor blockers (ARBs) or beta-blockers (all $P < 0.05$). The prevalence of malnutrition as defined by hypoalbuminaemia (SA level < 3.5 g/dL) was 56% among all patients, common (60.6%) in patients with a normal BMI (< 24 kg/m²), and less prevalent in overweight and obese patients with HFpEF (49.4% and 53.8%, $\chi^2 P = 0.009$). Higher CRP levels correlated with lower SA levels and PNI, higher CONUT scores, and lower GNRI ($r = -0.13, -0.17, 0.12, \text{ and } -0.08$, respectively, all $P < 0.05$) but not BMI ($r = -0.02, 0.49$).

Determinants of malnutrition defined by hypoalbuminaemia in post-discharge heart failure with preserved ejection fraction

Serum albumin and clinical correlates are displayed in *Table 2*. In univariate models, aging, lean body size, lower blood pressure, faster heart rate, history of cerebrovascular accidents, peripheral artery disease, higher white cell counts, lower lymphocyte counts, lower haemoglobin level, lower cholesterol, higher hepatitis markers, lower sodium, higher CRP, and higher BNP, together with lack of angiotensin-converting enzyme inhibitor or ARB use, were all associated with hypoalbuminaemia (defined by SA < 3.5 g/dL) (all $P < 0.05$). Lean body size, higher white cell count, lower haemoglobin, higher CRP, and a lack of angiotensin-converting enzyme inhibitor/ARB use remained uniformly and independently associated with hypoalbuminaemia in multivariate models.

Mortality

Subjects who died during follow-up ($n = 394$: 206 cardiovascular deaths and 188 non-cardiovascular deaths) were more often in lower SA (< 3.5 g/dL: 41.5% vs. 28.5%), lower PNI (< 38 : 45.5% vs. 29.5%), and higher CONUT strata (> 3 : 38.3% vs. 19.9%) and had lower GNRI scores (< 92 : 47.6% vs. 27.8%; all log-rank $P < 0.001$) (Supporting Information, *Table S1*). In multivariate models, greater BMI, higher SA, higher PNI, and higher GNRI scores were all unequivocally associated with lower all-cause mortality [adjusted HR: 0.96 (95% CI: 0.93–0.98), 0.67 (95% CI: 0.53–0.85), 0.97 (95% CI: 0.95–0.99), and 0.98 (95% CI: 0.97–0.99), for BMI, SA, PNI, and GNRI, respectively, all $P < 0.05$]. Higher CONUT scores were associated with higher mortality risk [adjusted HR: 1.08 (95% CI: 1.02–1.13), 0.008] (*Table 3*; Supporting Information, *Table S2*), supporting the obesity paradox phenomenon in the present study (*Table 3*). In the univariate models, better nutritional scores were associated with lower risks of cardiovascular and non-cardiovascular mortality, and these associations remained significant for cardiovascular mortality rates among patients with higher SA level, higher PNI, and high GNRI in fully adjusted models [adjusted HR: 0.70 (95% CI: 0.51–0.94), 0.73 (95% CI: 0.55–0.98), and 0.59 (95% CI: 0.41–0.84), all $P < 0.05$] but not for non-cardiovascular mortality rates, except for the association with GNRI [adjusted HR: 0.68 (95% CI: 0.47–0.99), 0.046]. A modest positive relationship between higher BMI and better nutritional indices was observed in the survival group ($r = 0.10, 0.011, r = 0.11, 0.004, r = -0.18, P < 0.001, \text{ and } r = 0.77, P < 0.001$ for SA level, PNI, CONUT score, and GNRI, respectively) but not in the death group (all NS except GNRI, $r = 0.74, P < 0.001$) (*Figure 1B*, only SA shown), indicating the uncoupled association between BMI and most nutritional conditions in non-survivors.

Table 2 Associations of baseline clinical parameters and hypoalbuminaemia in the current study

	Univariate model		Multivariate model ^a (SBP in model)		Multivariate model ^a (DBP in model)	
	Coef. (95% CI)	P value	Coef. (95% CI)	P value	Coef. (95% CI)	P value
Demographics, n (%)						
Age (+10 years)	0.03 (0.06–0.003)	0.027	—	—	—	—
Sex (men), n %	0.025 (–0.047 to 0.097)	0.49	—	—	—	—
Height (m)	–0.33 (0.75–0.09)	0.13	—	—	—	—
Weight (+10 kg)	–0.04 (–0.06 to –0.01)	0.004	–0.03 (–0.054 to –0.001)	0.042	–0.03 (–0.05 to –0.003)	0.048
Body mass index (kg/m ²)	–0.01 (0.013–0.001)	0.052	—	—	—	—
Systolic blood pressure (+10 mmHg)	–0.02 (–0.03 to –0.01)	<0.001	–0.02 (–0.03 to –0.0)	0.001	NA	NA
Diastolic blood pressure (+10 mmHg)	–0.04 (–0.059 to –0.019)	<0.001	NA	NA	—	—
Heart rate (+10 b.p.m.)	0.02 (0.01–0.037)	0.008	—	—	—	—
QRS duration (+10 ms)	0.013 (–0.029 to 0.002)	0.086	—	—	—	—
Medical history, n (%)						
Prior history of HF	0.008 (–0.06 to 0.08)	0.81	—	—	—	—
Hypertension	–0.04 (–0.12 to 0.04)	0.35	—	—	—	—
Diabetes mellitus	–0.02 (–0.09 to 0.05)	0.51	—	—	—	—
Coronary artery disease	–0.066 (–0.14 to 0.008)	0.081	—	—	—	—
CVA	0.15 (0.06–0.24)	0.001	—	—	—	—
Hyperlipidaemia	–0.027 (0.12–0.06)	0.55	—	—	—	—
Atrial fibrillation	–0.07 (–0.14 to 0.004)	0.064	—	—	—	—
COPD	–0.05 (–0.15 to 0.04)	0.28	—	—	—	—
PAD	0.29 (0.15–0.24)	<0.001	—	—	—	—
Active smoking	0.02 (–0.07 to 0.10)	0.73	—	—	—	—
Laboratory data						
White blood cells ($\times 10^3/\mu\text{L}$)	0.02 (0.009–0.02)	<0.001	0.014 (0.007–0.02)	<0.001	0.014 (0.007–0.02)	<0.001
Total lymphocyte count ($\times 10^3/\mu\text{L}$)	–0.044 (–0.074 to –0.014)	0.004	—	—	—	—
Haemoglobin (g/dL)	–0.04 (–0.054 to –0.026)	<0.001	–0.037 (–0.052 to –0.021)	<0.001	–0.03 (–0.049 to –0.018)	<0.001
Glucose (+10 mg/dL)	0.001 (–0.002 to 0.004)	0.49	—	—	—	—
Cholesterol (+10 mg/dL)	–0.01 (–0.02 to –0.01)	<0.001	—	—	–0.01 (–0.02 to 0.001)	0.038
ALT (+10 U/L)	0.003 (0.001–0.005)	0.029	—	—	—	—
HDL-C	–0.001 (–0.004 to 0.001)	0.38	—	—	—	—
Na (mEq/L)	–0.01 (–0.016 to –0.003)	0.005	—	—	—	—
K (mEq/L)	–0.014 (–0.058 to 0.029)	0.51	—	—	—	—
eGFR (+10 mL/min/1.73 m ²)	0.002 (–0.001 to 0.01)	0.68	—	—	—	—
Biomarkers						
C-reactive protein (mg/mL)	0.025 (0.013–0.037)	<0.001	0.018 (0.006–0.03)	0.004	0.019 (0.007–0.03)	0.002
BNP (+500 pg/mL)	0.017 (0.001–0.033)	0.04	—	—	—	—
Medications, n (%)						
ACE-I/ARB	–0.18 (–0.26 to –0.11)	<0.001	–0.10 (–0.18 to –0.02)	0.011	–0.12 (–0.20 to –0.04)	0.004
Beta-blocker	–0.11 (–0.20 to 0.019)	0.017	—	—	—	—

ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; K, potassium level; Na, sodium level; NA, not available in model; PAD, peripheral artery disease; SBP, systolic blood pressure.

^aSBP and DBP were separately entered into multivariate models due to collinearity.

Table 3 Multivariate analyses of factors predicting mortality and heart failure re-hospitalization in patients with heart failure with preserved ejection fraction

	Univariate model		Multivariate model	Univariate model	Multivariate model 1	Multivariate model 2	Multivariate model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Mortality	(Reference group)						
SA	SA < 3.5, (Referent)	SA ≥ 3.5, 0.62 (0.50–0.76), P < 0.001	SA ≥ 3.5, 0.77 (0.62–0.96), P 0.02	0.59 (0.48–0.73), P < 0.001	0.60 (0.49–0.75), P < 0.001	0.66 (0.52–0.83), P < 0.001	0.67 (0.53–0.85), P < 0.001
PNI	PNI < 38, (Referent)	PNI ≥ 38, 0.61 (0.50–0.74), P < 0.001	PNI ≥ 38, 0.77 (0.62–0.95), P 0.003	0.96 (0.94–0.97), P < 0.001	0.96 (0.95–0.98), P < 0.001	0.97 (0.95–0.98), P < 0.001	0.97 (0.95–0.98), P < 0.001
CONUT	CONUT > 3, (Referent)	CONUT ≤ 3, 0.46 (0.33–0.65), P < 0.001	CONUT ≤ 3, 0.66 (0.47–0.93), P 0.017	1.14 (1.09–1.20), P < 0.001	1.12 (1.07–1.18), P < 0.001	1.08 (1.03–1.14), P < 0.001	1.08 (1.02–1.13), P < 0.001
GNRI	GNRI < 92, (Referent)	GNRI ≥ 92, 0.49 (0.40–0.60), P < 0.001	GNRI ≥ 92, 0.63 (0.49–0.82), P < 0.001	0.97 (0.97–0.98), P < 0.001	0.98 (0.97–0.99), P < 0.001	0.98 (0.97–0.99), P < 0.001	0.98 (0.97–0.99), P < 0.001
BMI	BMI < 25, (Referent)	BMI ≥ 25, 0.58 (0.47–0.71), P < 0.001	BMI ≥ 25, 0.65 (0.52–0.82), P < 0.001	0.94 (0.92–0.96), P < 0.001	0.95 (0.93–0.98), P < 0.001	0.96 (0.93–0.98), P < 0.001	0.96 (0.93–0.98), P < 0.001
HF re-hospitalization	(Reference group)						
SA	SA < 3.5, (Referent)	SA ≥ 3.5, 0.44 (0.35–0.54), P < 0.001	SA ≥ 3.5, 0.43 (0.34–0.54), P < 0.001	0.57 (0.46–0.70), P < 0.001	0.56 (0.45–0.69), P < 0.001	0.49 (0.39–0.62), P < 0.001	0.50 (0.39–0.64), P < 0.001
PNI	PNI < 38, (Referent)	PNI ≥ 38, 0.61 (0.50–0.75), P < 0.001	PNI ≥ 38, 0.61 (0.49–0.75), P < 0.001	0.98 (0.97–0.99), P < 0.001	0.98 (0.97–0.99), P < 0.001	0.98 (0.96–0.99), P < 0.001	0.98 (0.96–0.99), P < 0.001
CONUT	CONUT > 3, (Referent)	CONUT ≤ 3, 0.82 (0.62–1.07), P 0.14	CONUT ≤ 3, 0.93 (0.69–1.23), P 0.60	1.04 (0.99–1.09), P 0.15	1.04 (0.99–1.09), P 0.16	1.03 (0.98–1.09), P 0.23	1.03 (0.98–1.09), P 0.27
GNRI	GNRI < 92, (Referent)	GNRI ≥ 92, 0.61 (0.50–0.75), P < 0.001	GNRI ≥ 92, 0.47 (0.36–0.61), P < 0.001	0.98 (0.98–0.99), P < 0.001	0.98 (0.98–0.99), P < 0.001	0.96 (0.94–0.97), P < 0.001	0.96 (0.94–0.97), P < 0.001
BMI	BMI < 25, (Referent)	BMI ≥ 25, 0.44 (0.35–0.54), P < 0.001	BMI ≥ 25, 0.43 (0.34–0.54), P < 0.001	1.01 (0.99–1.03), P 0.43	1.01 (0.99–1.03), P 0.34	1.00 (0.98–1.03), P 0.702	1.00 (0.98–1.03), P 0.78

BMI, body mass index; CI, confidence interval; CONUT, Controlling Nutritional Status; GNRI, geriatric nutritional risk index; HF, heart failure; HR, hazard ratio; PNI, prognostic nutritional index; SA, serum albumin.

Model 1: age; Model 2: Model 1 + body mass index, sex, prior heart failure, hypertension, cardiovascular disease, diabetes, systolic blood pressure, heart rate, and atrial fibrillation; and Model 3: Model 2 + hyperlipidaemia, estimated glomerular filtration rate, and brain natriuretic peptide.

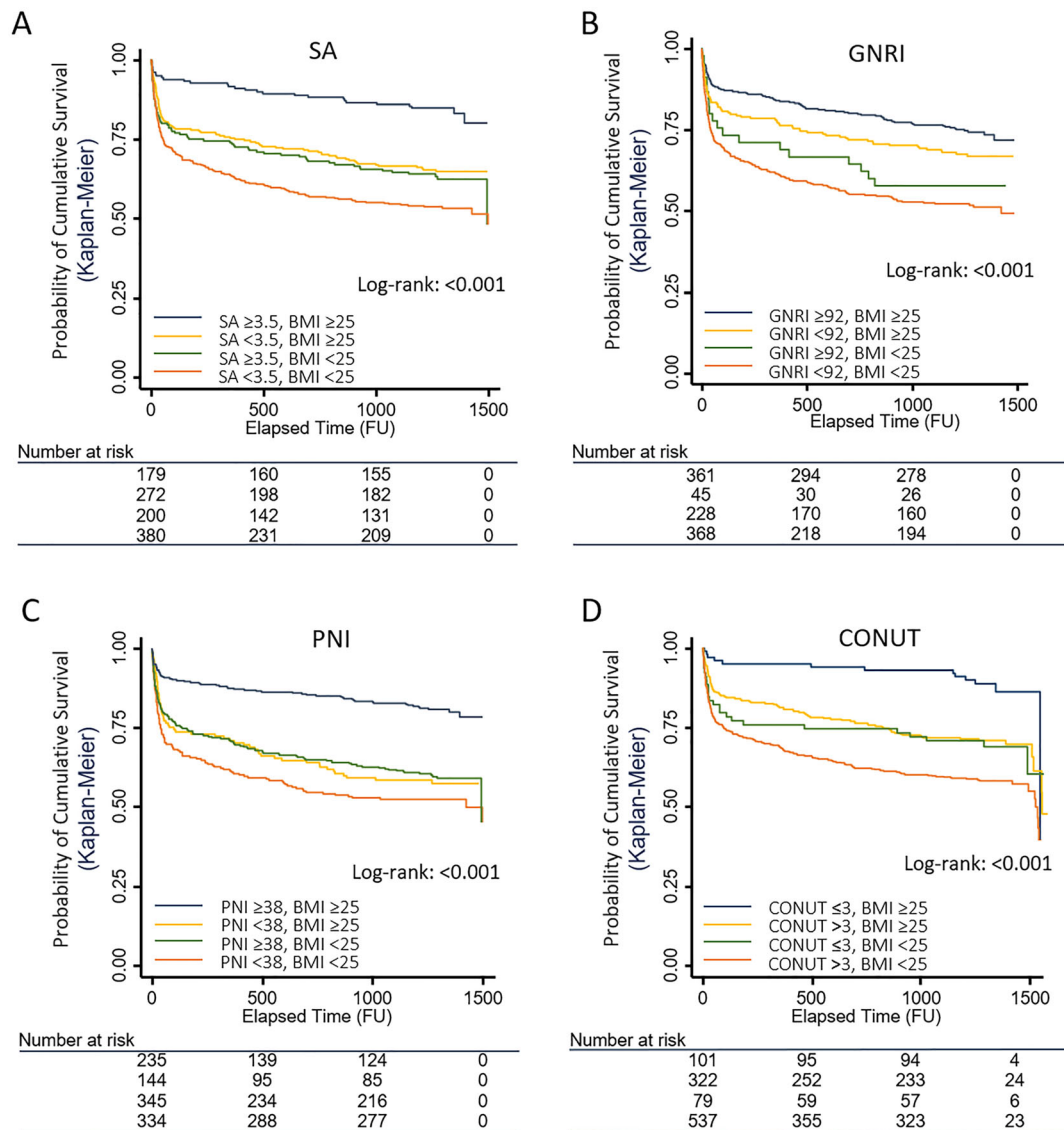
Heart failure re-hospitalization

During follow-up, 369 patients experienced at least one re-hospitalization due to HF. Patients with higher SA level, PNI, and GNRI were further associated with lower HF-related re-hospitalization rate (Supporting Information, *Table S1*; 39.8% vs. 23.6%, 35.2% vs. 31.2%, and 37.1% vs. 31.9% for lower vs. higher SA level, PNI, and GNRI groups, all log-rank $P < 0.001$). However, we found that CONUT score and TLC were not predictive markers of HF re-hospitalization (*Table 3*; Supporting Information, *Figure S1B, D, F, H*). In multivariate models, higher SA, PNI, and GNRI remained independent indicators for lower HF re-hospitalization [adjusted HR: 0.50 (95% CI: 0.39–0.64), $P < 0.001$; 0.98 (95% CI: 0.96–0.99), 0.014; and 0.96 (95% CI: 0.94–0.97), $P < 0.001$, for SA level, PNI, and GNRI, respectively]. However, we found that BMI was less predictive of HF-related re-hospitalization [HR: 1.003 (95% CI: 0.98–1.03), 0.78] (*Table 3*).

Mortality risk according to nutritional status and body mass index

Overall, discharged patients with HFpEF in higher SA strata were uniformly associated with lower clinical events including death and HF re-hospitalization in either lower or higher BMI strata (BMI of <25 and ≥25 kg/m²) (*Figure 1C*). Overall, patients in both malnutrition and lower BMI (<25 kg/m²) strata demonstrated the lowest chance of survival compared with those presenting in both better nutrition and higher BMI strata (*Figure 2*; Supporting Information, *Table S3*) [adjusted HR: 3.56 (95% CI: 2.25–5.63), 3.00 (95% CI: 2.02–4.44), 2.43 (95% CI: 1.29–4.60), and 1.78 (95% CI: 1.18–2.69) for SA, PNI, CONUT, and GNRI, respectively, all $P < 0.05$] (*Figure 2*, all log-rank $P < 0.05$). In general, subjects in the malnutrition strata (SA level < 3.5 g/dL, PNI < 38, CONUT score > 3, and GNRI < 92) were associated with a higher risk of all-cause mortality compared with their better nutrition counterparts

Figure 2 Kaplan–Meier survival curves for all-cause mortality stratified according to body mass index (BMI) and nutritional indices. Higher BMI was associated with better survival based on three BMI categories (<24 , ≥ 24 and <27 , ≥ 27 kg/m^2), indicating the existence of obesity paradox in the current study (A). Of the four categories stratified by BMI (<25 , ≥ 25 kg/m^2) and nutritional status determined by serum albumin (SA) (<3.5 , ≥ 3.5 g/dL) (B), prognostic nutritional index (PNI) (<38 , ≥ 38) (C), and Controlling Nutritional Status (CONUT) score (>3 , ≤ 3) (D), the high BMI and normal nutrition subgroup had the best prognosis, while the low BMI and malnutrition subgroup had the worst prognosis. GNRI, geriatric nutritional risk index.



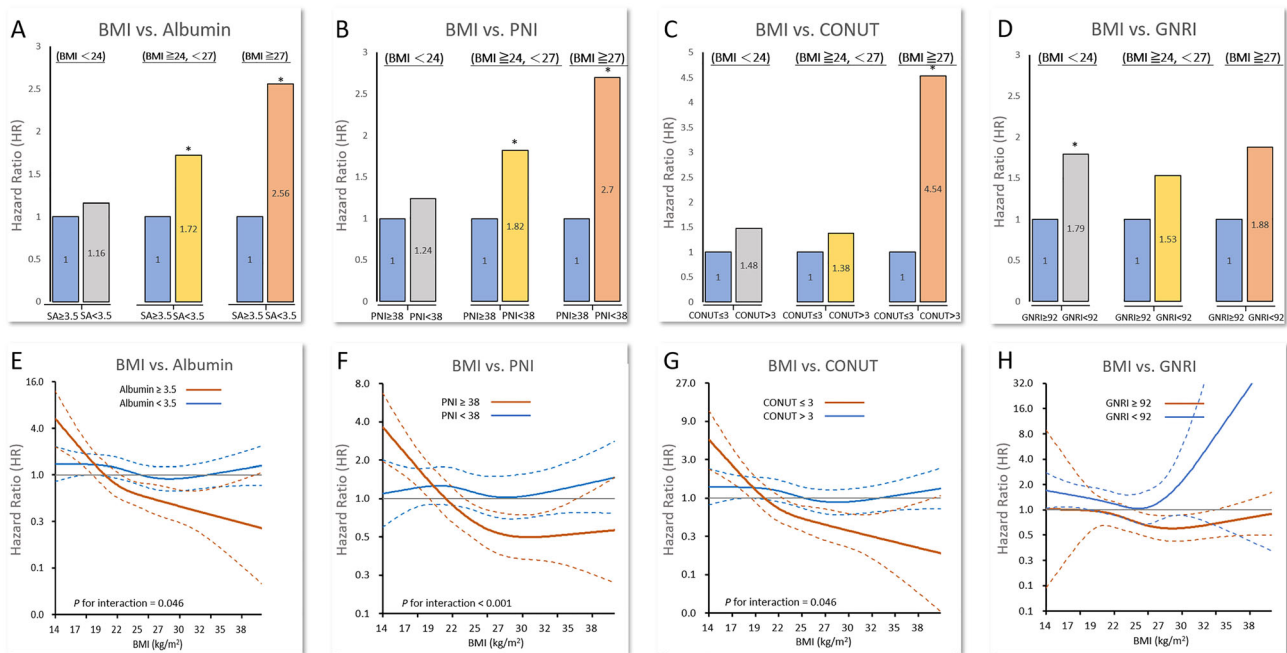
(SA level ≥ 3.5 g/dL , PNI ≥ 38 , CONUT score ≤ 3 , and GNRI ≥ 92), especially in the obese groups [BMI ≥ 27 kg/m^2 (obese), except for GNRI] (Figure 3A–D).

Restricted cubic spline analysis showed the impact of BMI on survival in terms of all-cause mortality stratified by distinct nutritional status (Figure 3E–H). Notably, effects of BMI and various nutritional indexes (SA, PNI, and CONUT) on all-cause mortality were observed, with better nutritional status exerting a more pronounced beneficial effect than greater BMI (adjusted $P_{\text{interaction}}$ for both SA and PNI: <0.001 ; adjusted $P_{\text{interaction}}$ for CONUT: 0.046).

Discussion

To the best of our knowledge, our study is the first to demonstrate the clinical correlates and prognostic impact of nutritional markers on the contemporarily established concept of the ‘Obesity Paradox’ in a large, post-discharge HFpEF cohort of Asian ethnicity. Lower body weight, anaemia, and systemic inflammation together with lack of ARB use were all determinants of hypoalbuminaemia. A modest positive linear correlation between greater BMI and better nutrition status was only observed in survivors but not in those who died. Outcomes in

Figure 3 Association of various nutritional metrics with body mass index (BMI) in predicting all-cause mortality. Malnutrition showed higher event risk in contrast to better nutrition, especially in overweight/obese categories (A–C). Multivariate regression spline curves examining the relationship of BMI and incidence of death stratified by nutritional status during follow-up (D–F). The protective effect of BMI on risk of death appeared more pronounced in subjects in better nutritional strata. CONUT, Controlling Nutritional Status; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; SA, serum albumin.



HFpEF were most optimal in overweight/obese patients with higher circulating nutritional biomarkers (including SA, PNI, CONUT score, and GNRI). Outcomes were worst in lean, undernourished patients. The overall survival benefit of a greater BMI was more pronounced in patients with better nutrition according to all circulating nutritional markers except GNRI.

Role of nutritional parameters in heart failure with preserved ejection fraction

To date, a variety of blood-based biomarkers have been identified to assess nutritional status and aid in clinical risk stratification. Among them, low circulating SA levels are common in patients with HF (25–33%) due to multiple factors, including anorexia, dietary changes, lifestyle (e.g. smoking), absorption disorder, hypercatabolic state, or possibly mediated by a ‘malnutrition-inflammation complex syndrome’, which produces excessive oxidative stress and consequent inflammatory response.^{25–28} Aside from its role in protein-energy storage as a malnutrition-inflammation complex component, SA is also considered as a measure of inflammation and serves as an antioxidant.^{25,26,29} Our findings are in accordance with the findings of Liu *et al.*²⁰ in that lower SA was associated with increased all-cause mortality. We further extended the follow-up interval to 3.5 years following discharge in HFpEF and used multiple nutritional measures.

Furthermore, both PNI and CONUT score have shown to be superior in predicting mortality in patients with HF,^{14,15,21} even with preserved EF.^{13,30} In a recently published, multi-centre prospective HFpEF registry in Japan (JASPER), multivariate analyses revealed SA levels rather than BMI to be among the strongest determinants for worse outcomes.³¹ SA levels in the present work were slightly lower compared with those in the JASPER study but higher than another prospective study in a Western population in a similar setting,²⁶ potentially indicating more severe or acute HF and greater co-morbidities in our population. Of note, the rate of HF re-hospitalization in the present work was similar to a study performed in Canada (32.5% vs. 34.9%), suggesting similar health care quality.³² As a major component of PNI and CONUT, SA levels are also influenced by several pathophysiological conditions common in HF, such as haemodilution, transcapillary loss, enteric loss, hepatic dysfunction, and systemic inflammation.^{25,33} Given the fact that higher SA was associated with lower systemic white cell counts and CRP and that its robust relationship with various physical functions has been reported, the prognostic implication of lower SA further implicates pro-inflammatory cascades as the hypothetical central pathophysiology in HFpEF from multiple co-morbidities.³⁴ While SA is also associated with erythropoietin sensitivity and transferrin production, which are in part regulated by systemic inflammation, lower haemoglobin may accompany lower SA level as in this present work.³⁵

Nutrition, body mass index, and mortality risk

The relatively low BMIs in HFpEF in the present work are consistent with a prospectively enrolled, outpatient-based HFpEF study from the same geographical region (Northeast Asia).²¹ In part, however, the BMIs in this study reflect a more debilitating, advanced form of HFpEF in hospitalized patients similar to another prospectively designed, multi-centre study of patients hospitalized with HFpEF from Japan.³¹ It is noteworthy that patients with HF frequently show evidence of muscle wasting and altered physical integrity, leading to exercise intolerance and physical debilitation.^{7,11} Nevertheless, accumulating data have shown that SA is a better indicator of lean muscle mass and estimator of protein reserve than body adiposity and may exert beneficial effects in obese patients with HFpEF resulting from dysregulated metabolic disorders.^{9,10} Consequently, worse nutritional status in HFpEF accompanied by lower BMI may indicate a more deleterious, highly catabolic condition termed 'cardiac cachexia' and serves as a particularly potent predictor of all-cause mortality. Likewise, our findings also suggest that albumin-based circulating nutritional surrogates may serve to discriminate overweight or obese patients as 'nutritional healthy' or 'nutritional unhealthy' (Figure 3A–C),^{16,36} whether mediated partly by a coupled BMI-to-nutritional relationship or equilibrated muscle-protein patients remained to be determined. Considering the mixture of a more prevalent 'sarcopenic obesity' phenotype and a characteristic lean HFpEF phenotype in Asians^{37,38} and the potential deleterious cardiovascular effects associated with higher BMI,^{3–5,39} it is likely that baseline physical nutrition may play a more crucial role in determining long-term survival and HF recurrence in Asian patients with HFpEF after discharge.³¹ Despite this, we still observed the 'Obesity Paradox' in our HFpEF cohort after discharge. As protein is the main component of lean mass, which may more accurately reflect protein storage, our finding of a linear relationship between SA and BMI in HFpEF survivors only (Figure 1A) may be explained by the fact that, for patients presenting with a benign HF course, a larger BMI was due to greater muscle mass rather than fat; thus, with more protein and better nutritional reserves, these patients might have better functional capacity and better outcomes.^{9,10}

Study limitations

We acknowledge that there are several limitations to the present study. First, this was a retrospective, single-centre study. Extrapolation of our findings and their generalizability may need further investigation, including any potential background disparities among different races. Second, we realized that relating outcome measures simply by circulating nutritional markers and BMI in the absence of more advanced HF biomarkers (e.g. atrial natriuretic peptide), skeletal muscle

mass, body fat composition, muscle strength, or physical performance (e.g. 6 min walk distance) may lead to some biased interpretations and to a limited understanding of the pathological role and prognostic significance of sarcopenic obesity in HFpEF. Further, we also may not be able to define 'cardiac cachexia' more specifically due to the lack of longitudinal information about body weight changes. Information integrating skeletal muscle mass may better characterize true percentage of fat depots and may better explain exercise or functional capacity and clinical endpoints. However, as blood sampling for albumin, lipids, and lymphocytes was more readily available on a daily basis for this study, implementation of the cut-offs for nutritional markers used here and their prognostic implications may allow for broader use in clinical settings across different ethnic groups or regions.

Conclusions

In summary, body mass in terms of BMI was small, and malnutrition was common in post-discharge, ethnically Asian patients with HFpEF. Incorporation of a variety of circulating biological markers, especially those with albumin-based nutritional indices, may provide additive and independent prognostic values beyond BMI measurements after discharge. In aggregate, these findings represent the complex interactions between body mass and nutritional markers, reflecting true physical health and highlighting the need to intensify nutritional support as part of multidisciplinary teamwork in patients with HFpEF after discharge, especially in Asians. Our data also underscore the clinical significance and potential viability of using BMI and nutritional surrogates synergistically for risk stratification in HFpEF. Furthermore, these data may provide an opportunity in identifying pathway-specific subgroups that may benefit from targeted nutritional therapeutics to improve practice.

Clinical perspectives

Clinical competencies

Assessments of a variety of circulating nutritional markers provide implementable and complementary prognostic value, which aid in risk stratification in HFpEF. The presence of malnutrition is a warning sign of intrinsic reservoir loss and heightened systemic inflammation, leading to unfavourable outcomes. Thus, nutritional status may improve the identification of a certain higher risk group of 'nutritionally unhealthy obese' known as sarcopenic obesity and provide additional predictive values in discharged patients with HFpEF beyond BMI information. This highlights an unmet need for better definition and characterization in evaluating true 'physical health' in HF.

Translational outlook

The demonstration that better nutritional status and BMI improve survival highlights the biological significance of nutrition as an alternative dimension in the care of patients with HF and supports a putative role of systemic inflammatory cascade in patients with HFpEF presenting with poor nutrition. These findings potentially point to preventable or signal-specific therapeutic targets in HFpEF. Whether adequate dietary modification and consolidation, body fitness, or active nutritional supplementation could improve clinical outcomes in HFpEF deserves further research.

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The contributions of the clinical coordinators are duly acknowledged.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Mortality and HF Re-hospitalization According to Serum Albumin, Prognostic Nutritional Index, Controlling Nutritional Status Score and Geriatric Nutritional Risk Index.

Table S2. Associations of TLC and clinical outcomes of all-cause death and HF re-hospitalization.

Table S3. Multivariate Analysis of Nutritional Status and BMI Predicting Mortality in Patients with HFpEF.

Figure S1. Kaplan-Meier survival plot of all-cause mortality and heart failure rehospitalization according to low and high nutritional indexes. (A) serum albumin concentration (C) total lymphocyte count (E) prognostic nutritional index according to low and high (B) serum albumin concentration (D) total lymphocyte count (F) prognostic nutritional index.

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