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Construction of a metabolism-malnutrition-inflammation prognostic risk score in patients with heart failure with preserved ejection fraction: a machine learning based Lasso-Cox model

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Abstract

Background Metabolic disorder, malnutrition and inflammation are involved and interplayed in the mechanisms of heart failure with preserved ejection fraction (HFpEF). We aimed to construct a Metabolism-malnutrition-inflammation score (MIS) to predict the risk of death in patients with HFpEF.

Methods We included patients diagnosed with HFpEF and without infective or systemic disease. 20 biomarkers were filtered by the Least absolute shrinkage and selection operator (Lasso)-Cox regression. 1000 times bootstrapping datasets were generated to select biomarkers that appeared above 95% frequency in repetitions to construct the MIS.

Results Among 1083 patients diagnosed with HFpEF, 342 patients (31.6%) died during a median follow-up period of 2.5 years. The MIS was finally constructed based on 6 biomarkers, they were albumin (ALB), red blood cell distribution width-standard deviation (RDW-SD), high-sensitivity C-reactive protein (hs-CRP), lymphocytes, triiodothyronine (T3) and uric acid (UA). Incorporating MIS into the basic predictive model significantly increased both discrimination (ΔC-index = 0.034, 95% CI 0.013–0.050) and reclassification (IDI, 6.6%, 95% CI 4.0%-9.5%; NRI, 22.2% 95% CI 14.4%-30.2%) in predicting all-cause mortality. In the time-dependent receiver operating characteristic (ROC) analysis, the mean area under the curve (AUC) for the MIS was 0.778, 0.782 and 0.772 at 1, 3, and 5 years after discharge in the cross-validation sets. The MIS was independently associated with all-cause mortality (hazard ratio: 1.98, 95% CI [1.70–2.31], $P < 0.001$).

Conclusions A risk score derived from 6 commonly used inflammatory, nutritional, thyroid and uric acid metabolic biomarkers can effectively identify high-risk patients with HFpEF, providing potential individualized management strategies for patients with HFpEF.

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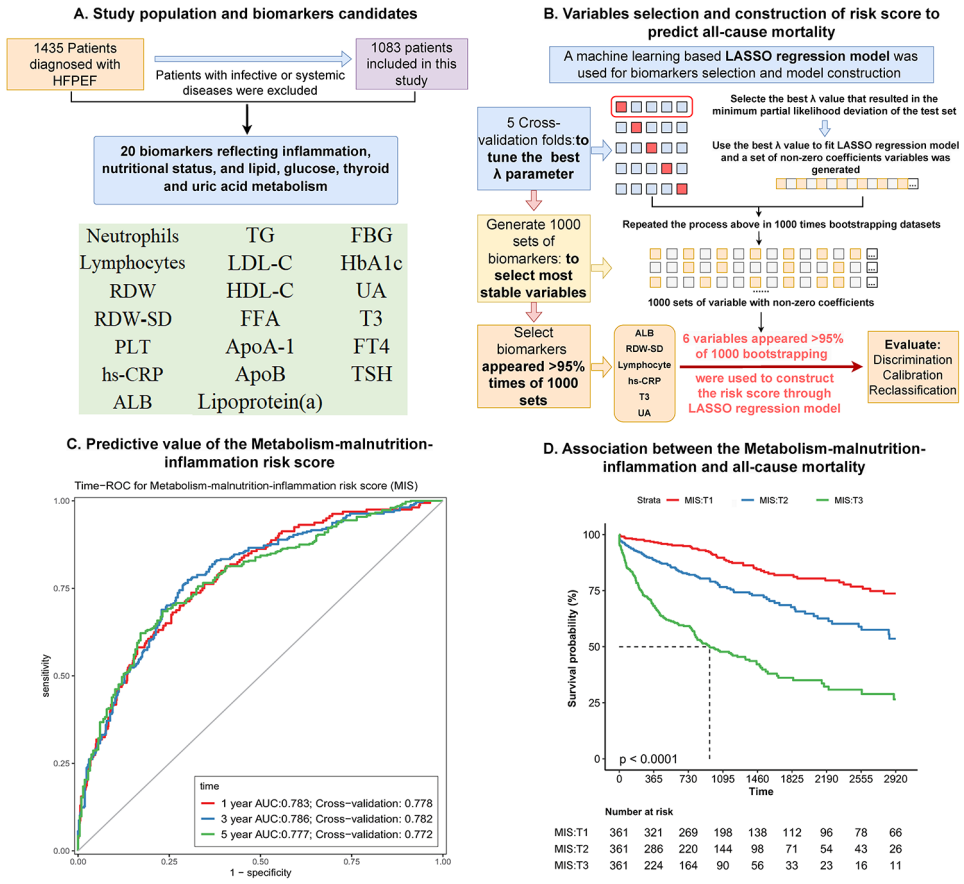
Graphical Abstract



Keywords Heart failure with preserved ejection fraction, Biomarker, Malnutrition-inflammation complex, Machine learning

Introduction

Heart failure (HF) has conventionally been classified based on left ventricular ejection fraction (LVEF) following clinical guidelines. Heart failure with preserved ejection fraction (HFpEF), delineated by LVEF ≥ 50%, comprising at least half of all HF patients [1].The management of HFpEF poses challenges because of its diverse pathophysiology and epidemiological characteristics [2]. Cardiometabolic disorders like obesity, diabetes, and hypertension play a crucial role in the onset and development of HFpEF. These comorbidities are also linked to the severity of HFpEF and personalized treatment approaches [3]. However, several recent studies suggested that, different from that in general population, some conventional cardiovascular risk factors, such as increased serum lipid concentrations or higher blood pressure, are related to lower morbidity and mortality in HF patients. Such an association between cardiometabolic factors and the outcome of HF might be explained by the appearance of the malnutrition-inflammation complex syndrome [4]. HF patients are highly likely to suffer from malnutrition, which can be caused by metabolic derangements and associated with decreased immune function and inflammation [5]. As a result, the activation of the inflammatory response in the metabolic abnormalities and malnutrition of HFpEF might be the key factor in the development and worsening of the condition.

Previous studies have proposed several biomarkers that reflected malnutrition-inflammation burden in patients with cardiovascular disease, such as high-sensitivity C-reactive protein (hs-CRP), albumin, red blood cell distribution width (RDW), neutrophils and lymphocytes [6, 7]. In terms of metabolic factors, previous studies have demonstrated that some parameters from lipid and glucose biomarkers were related to impaired survival in HF patients, such as triglyceride-glucose (TyG) index, Lipoprotein(a), and the apolipoprotein B to apolipoprotein A-1 ratio (apoB/apoA-1) [8–10]. In addition

to lipid and glucose metabolism, recent studies have also revealed that uric acid and thyroid hormone metabolism are also related to the outcome of HF, and chronic inflammation may play a role [11, 12]. However, previous biomarker risk indexes seldom considered adding uric acid and thyroid hormones in the model construction.

In the context of the interplay of multiple mechanisms in HFpEF, we aimed to investigate and select the most predictive indicators from a group of biomarkers reflecting inflammation, nutritional status, and lipid, glucose, thyroid and uric acid metabolism, and construct a Metabolism-malnutrition-inflammation score (MIS) to enhance the risk prediction in HFpEF patients.

Methods

Study population

In this retrospective cohort, we enrolled patients hospitalized for acute decompensated heart failure and diagnosed with HFpEF during the period from 2006 to 2021 at Fuwai Hospital. HFpEF was defined as symptomatic HF with an N-terminal Pro Brain natriuretic peptide (NT-proBNP) level ≥ 200 pg/ml for sinus rhythm or ≥ 600 pg/ml for atrial fibrillation, and with an LVEF ≥ 50%. Patients with the following conditions were excluded in this study: (1) cardiac amyloidosis, (2) acute pulmonary embolism, (3) acute myocarditis, (4) infective endocarditis, (5) malignant tumor, (6) immune disease and (7) blood system disease. The ethics committee of Fuwai hospital has approved the research protocol (2018 − 1041) and this study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Data collection and outcome

We obtained the data about demography, history of the disease, laboratory tests, management, and imaging data from the electronic medical record system. The information about outcomes was obtained through telephone follow-up or outpatient visits. The primary outcome of this study was all-cause mortality. The secondary outcomes included cardiovascular death and non-cardiovascular death.

Biomarkers

Blood samples of hospitalized patients were collected in admission, and the samples were placed in EDTA tubes. In the central laboratory, all biomarkers were tested according to standard protocols. We included 20 biomarkers which reflected inflammation, nutritional status, and lipid, glucose, thyroid and uric acid metabolism in this study, including neutrophils, lymphocytes, red blood cell distribution width (RDW), RDW-SD, platelet (PLT), albumin (ALB), high-sensitivity C-reactive protein (hs-CRP), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), free fatty acid (FFA), apolipoprotein B (ApoB), apolipoprotein A-1 (ApoA-1), lipoprotein(a), fast blood glucose (FBG), glycated haemoglobin A1c (HbA1c), uric acid (UA), triiodothyronine (T3), free thyroxine (FT4), and thyroid stimulating hormone (TSH). We have reported the proportion of dyslipidemia, hyperuricemia and thyroid dysfunction in the baseline characteristics. The definition of dyslipidemia is total cholesterol ≥ 6.22 mmol/L, or TG ≥ 2.26 mmol/L, or LDL-C ≥ 4.14 mmol/L, or HDL-C < 1.04 mmol/L. The definition of hyperuricemia is UA ≥ 6.22 umol/L. The definition of thyroid dysfunction is that the TSH out of 0.45 to 4.5 mIU/L, or FT4 out of 0.7 to 1.7 ng/dL, or T3 out of 0.8 to 1.59 mg/dL.

Statistical analysis

Risk score construction

For biomarker filtration and the MIS construction, we utilized the least absolute shrinkage and selection operator with Cox proportional hazard model (Lasso-Cox) to predict all-cause mortality. Lasso can be utilized for high dimensional data such as biomarker data. It can perform L1 regularization to select variables, to improve the prediction accuracy and interpretation of model. Lasso-Cox model is less variable than other techniques such as the stepwise approach and still yields interpretable models [13]. Firstly, we created 5-fold cross-validation inner loops to determine the parameter λ using the R package "glmnet". Secondly, we generated 1000 times bootstrapping datasets, and use the best λ value tuned from the inner loop to fit the model in each bootstrapping dataset. In order to construct a stable model with the most predictive biomarkers, we chose the biomarkers that were selected above the 95% frequency in 1000 bootstrapping dataset to construct the MIS. All biomarkers were transformed to standard normal distribution (mean = 0, standard deviation = 1) in the selection and model construction. We got the coefficients of each biomarker included in the MIS by inputting them into a new Lasso-Cox model.

Basic prognostic model construction

A Lasso-Cox regression model was also used to construct the basic model, which incorporated age, gender, systolic blood pressure (SBP), body mass index (BMI), New York Heart Association (NYHA) Class III/IV, smoking, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), diabetes mellitus (DM), LVEF, N-terminal Pro Brain natriuretic peptide (NT-proBNP), serum creatine (Scr), therapy with renin-angiotensin system (RAS) inhibitors and beta-blockers.

Performance of risk score

In order to examine the discrimination of the MIS, we assessed the area under the curve (AUC) of time-dependent receiver operating characteristic curves (ROC) over a span of 1 to 5 years. This analysis was conducted utilizing the "timeROC" package in R. To construct a stable model, we further provided the mean and standard deviation of the time-dependent AUC through 100 iterations of 5-fold cross-validation. Additionally, we evaluated the enhancement in Harrel's C-statistic (ΔC-index) resulting from inclusion the MIS into the basic model. The 95% confidence interval for the ΔC-index was determined via 1000 bootstrap samples. Calibration was assessed using the Greenwood-Nam-D'Agostino (GND) test at 3 years, with a significance threshold set at $p>0.05$ indicating a well-calibrated model. Besides, the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were carried out at the 3-year mark to evaluate the reclassification. These metrics were computed using the "survIDINRI" package in R. Finally, Cox regressions were employed to explore the prognostic significance of the MIS and its constituents, adjusting for variables present in the basic model. The performance of MIS was tested in predicting all-cause mortality, cardiovascular death and non-cardiovascular death. The proportional hazard assumption was tested using Schoenfeld residuals via the "coxzph" function in R.

Results

Baseline Characteristics and the results of variable selection

We totally enrolled 1083 patients with HFpEF in this study. The flowchart of the inclusion and exclusion process is shown in Figure S1. The baseline characteristics stratified by the tertile of MIS are shown in Table 1. The median age of the study population was 66 years (55–74), with 487 (45.0%) being female. In terms of the outcomes, 342 patients (31.6%) died from any causes, 216 patients (19.9%) died from cardiovascular causes, and 126 patients (11.6%) died from non-cardiovascular causes. 22 patients (2.0%) died during the hospitalization. The characteristics of patients according to the outcome are shown in Supplementary Table 1.

Through the Lasso-Cox regression in 1000 bootstrapping datasets, ALB, RDW-SD, UA and Lymphocyte appeared 100%, besides, T3 and hs-CRP were selected 99% and 96% times, respectively. Thus, 6 above variables with a frequency>95% were used to construct the MIS in a Lasso-Cox model to predict all-cause mortality, and the formula was: MIS=0.288* RDW-SD -0.24*ALB-0.23*Lymphocyte+0.12*hs-CRP-0.21*T3+0.22*UA (per SD of each biomarker). For each biomarker, the frequency of selection and its median coefficient are shown in Fig. 1.

Predictive performance of the MIS

During a median follow-up duration of 2.5 (1.0-4.1) years, 342 patients (31.6%) experienced all-cause mortality. The AUC of time-dependent ROC for the MIS stood at 0.783 after 1 year, 0.786 after 3 years, and 0.777 after 5 years, in the prediction of all-cause mortality. The cross-validation revealed mean AUC values of 0.778, 0.782, and 0.772 at 1, 3, and 5 years post-discharge, respectively (Fig. 2). When adding the MIS to the basic model, the AUC significantly increased, from 0.760 to 0.807 at 1 year (DeLong test $P<0.001$), from 0.766 to 0.814 at 3 years ($P<0.001$), and from 0.784 to 0.819 at 5 years ($p=0.001$, Fig. 3). The mean AUC of the MIS, basic model, and basic model plus MIS from 1 to 5 years in cross-validation was is in Figure S2. Incorporating the MIS into basic model significantly enhanced the C-index from 0.741 to 0.775, with a ΔC-index of 0.034, 95% CI:0.013–0.050 (Table 2). Furthermore, the MIS showed good calibration, with a P-value of 0.194 for the Greenwood-Nam D'Agostino test (Figure S3). In addition, the model including the MIS significantly improved reclassification when compared to the basic model (IDI, 6.6% [4.0-9.5%], $P<0.001$; NRI, 22.2% [14.4-30.2%], $P<0.001$). Besides, the MIS also demonstrated good discrimination in predicting cardiovascular death (ΔC-index of 0.033, 95% CI: 0.008–0.053) and non-cardiovascular death (ΔC-index of 0.037, 95% CI:0.003–0.062). The discrimination and reclassification of adding the MIS and its components to the basic model in predicting secondary outcomes is shown in Supplementary Table 2.

The independent association between the MIS and the outcome

The Kaplan-Meier curves showed that patients in the highest tertile of the MIS had the worst prognosis (Fig. 4). Besides, the Kaplan-Meier curves of the component biomarkers of MIS are shown in Figure S4. After adjusting for confounding factors (variables included in the basic model), the MIS remained independently associated with the primary outcome (Table 3), the adjusted HR was 1.98 (95% CI 1.70–2.31, $P<0.001$, per 1 score increase). For the association between the component biomarkers and the primary outcome, the adjusted HR was 1.39 (95% CI 1.26–1.54, $P<0.001$) for RDW-SD, 0.74 (95% CI 0.67–0.83, $P<0.001$) for ALB, 1.21 (95% CI 1.09–1.34, $P<0.001$) for UA, 0.75 (95% CI 0.65–0.86, $P<0.001$) for T3, 0.78 (95% CI 0.69–0.88, $P<0.001$) for Lymphocyte, and 1.24 (95% CI 1.12–1.37, $P<0.001$) for hs-CRP. In terms of the secondary outcomes, MIS was also independently associated with both cardiovascular death and non-cardiovascular death (Supplementary Table 3).

Table 1 Baseline characteristics for HFpEF patients according to the tertiles of metabolism-malnutrition-inflammation risk score

	Overall	MIS: T1	MIS: T2	MIS: T3	*P*-Value
N	**1083**	**361**	**361**	**361**	
Clinical characteristics					
Age (years)	66 [55, 74]	62 [52, 71]	67 [56, 75]	69 [59, 76]	< 0.001
Female (%)	487 (45.0)	161 (44.6)	156 (43.2)	170 (47.1)	0.569
Heart rate (b.p.m)	73 [64, 86]	70 [62, 81]	74 [63, 86]	76 [65, 89]	< 0.001
SBP (mmHg)	121.5 [107, 136]	124 [113, 140]	122.1 [106, 136]	118 [102, 131]	< 0.001
DBP (mmHg)	70 [61, 80]	72 [64, 80.5]	70 [62, 80]	66 [58, 78]	< 0.001
BMI (kg/m2)	24.2 [21.8, 26.6]	24.5 [22.5, 26.7]	24.2 [21.9, 26.7]	23.5 [21.2, 26.0]	0.001
CAD (%)	425 (39.2)	155 (42.9)	155 (42.9)	115 (31.9)	0.002
Hypertension (%)	583 (53.8)	196 (54.3)	211 (58.4)	176 (48.8)	0.032
T2DM (%)	302 (27.9)	83 (23.0)	115 (31.9)	104 (28.8)	0.026
COPD (%)	81 (7.5)	11 (3.0)	32 (8.9)	38 (10.5)	< 0.001
Valvular heart disease (%)	219 (20.2)	63 (17.5)	67 (18.6)	89 (24.7)	0.035
AF (%)	527 (48.7)	124 (34.3)	169 (46.8)	234 (64.8)	< 0.001
NYHA Class III/IV (%)	732 (67.6)	175 (48.5)	242 (67.0)	315 (87.3)	< 0.001
Dyslipidemia (%)	590 (56.2)	186 (52.8)	187 (54.5)	217 (61.3)	0.056
Hyperuricemia (%)	507 (47.6)	85 (23.9)	168 (47.6)	254 (71.1)	< 0.001
Thyroid dysfunction (%)	474 (47.1)	102 (30.0)	135 (41.2)	237 (69.9)	< 0.001
Smoking (%)	263 (24.3)	98 (27.1)	88 (24.4)	77 (21.3)	0.19
Drinking (%)	161 (14.9)	64 (17.7)	48 (13.3)	49 (13.6)	0.172
Laboratory Test					
Neutrophil (10^9/L)	4.1 [3.2, 5.5]	4.2 [3.3, 5.3]	4.0 [3.2, 5.3]	4.2 [3.1, 5.9]	0.24
Lymphocyte (10^9/L)	1.5 [1.1, 2.0]	2.0 [1.6, 2.4]	1.6 [1.2, 2.0]	1.0 [0.7, 1.4]	< 0.001
Haemoglobin (g/L)	128.0 [113.0, 143.0]	137.0 [124.0, 148.0]	128.0 [115.8, 142.0]	116.0 [96.0, 134.0]	< 0.001
RDW-SD (fl.)	44.9 [41.9, 49.1]	42.0 [39.8, 43.9]	44.9 [42.4, 47.5]	50.8 [46.2, 55.9]	< 0.001
RDW (%)	13.5 [12.8, 14.9]	12.9 [12.4, 13.4]	13.5 [12.8, 14.3]	14.9 [13.8, 16.7]	< 0.001
Platelet (10^9/L)	179.0 [137.0, 227.5]	195.0 [161.5, 239.0]	179.0 [138.8, 230.0]	155.5 [117.0, 211.2]	< 0.001
ALB (g/L)	39.0 [36.0, 42.0]	41.8 [39.3, 44.2]	38.9 [36.9, 41.3]	35.6 [32.4, 38.8]	< 0.001
FBG (mmol/L)	5.2 [4.7, 6.1]	5.2 [4.8, 6.0]	5.1 [4.7, 6.1]	5.3 [4.6, 6.4]	0.702
HbA1c (%)	6.1 [5.7, 6.8]	6.1 [5.7, 6.9]	6.2 [5.8, 7.0]	6.1 [5.7, 6.7]	0.077
TG (mmol/L)	1.2 [0.9, 1.7]	1.5 [1.1, 2.0]	1.3 [0.9, 1.7]	1.0 [0.7, 1.3]	< 0.001
Lipoprotein(a) (mg/L)	159.1 [78.0, 337.3]	150.2 [78.0, 336.9]	158.7 [79.0, 305.2]	173.7 [77.2, 347.3]	0.645
Apo-A1 (g/L)	1.2 [1.0, 1.4]	1.2 [1.1, 1.4]	1.2 [1.0, 1.4]	1.0 [0.8, 1.2]	< 0.001
ApoB (g/L)	0.8 [0.6, 0.9]	0.8 [0.7, 1.0]	0.8 [0.6, 0.9]	0.7 [0.6, 0.9]	< 0.001
FFA (mmol/L)	0.5 [0.4, 0.7]	0.5 [0.4, 0.7]	0.5 [0.4, 0.6]	0.6 [0.4, 0.8]	< 0.001
LDL_C (mmol/L)	2.3 [1.7, 2.8]	2.4 [1.9, 3.0]	2.4 [1.8, 2.9]	2.0 [1.5, 2.6]	< 0.001
HDL_C (mmol/L)	1.0 [0.8, 1.3]	1.1 [0.9, 1.3]	1.1 [0.8, 1.3]	1.0 [0.8, 1.2]	< 0.001
UA (umol/L)	409.7 [327.7, 532.2]	351.3 [293.9, 414.2]	409.7 [332.2, 496.0]	533.0 [404.7, 666.1]	< 0.001
eGFR	71.6 [51.8, 90.3]	81.4 [65.0, 96.9]	71.6 [53.3, 89.2]	57.4 [40.8, 78.1]	< 0.001
T3 (ng/mL)	0.9 [0.8, 1.1]	1.1 [1.0, 1.3]	0.9 [0.8, 1.1]	0.8 [0.6, 0.9]	< 0.001
FT4 (ng/dL)	1.2 [1.1, 1.4]	1.2 [1.1, 1.3]	1.2 [1.1, 1.4]	1.2 [1.0, 1.4]	0.511
TSH (IU/L)	2.2 [1.1, 3.6]	2.2 [1.3, 3.4]	2.2 [1.2, 3.6]	2.1 [1.1, 4.1]	0.991
Hs-CRP (mg/L)	3.0 [1.3, 8.9]	1.7 [0.8, 3.1]	2.8 [1.3, 7.9]	8.1 [3.0, 12.2]	< 0.001
NT-Pro BNP (pg/ml)	1671.0 [904.6, 2991.9]	1112.2 [675.5, 1931.0]	1565.0 [902.3, 2694.0]	2610.0 [1467.0, 5826.0]	< 0.001
Echocardiography					
LAD (mm)	44 [38, 51]	40.5 [36, 46]	44 [38, 50]	49 [42, 58]	< 0.001
LVEDD (mm)	49 [44, 55]	48 [44, 54]	50 [44, 55]	49 [43, 55]	0.284
LVEF (%)	60 [55, 63]	60 [55, 64]	60 [55, 62]	60 [55, 62]	0.221
RVD (mm)	24 [21, 28]	22 [20, 25]	23 [20, 27]	26 [23, 33]	< 0.001
Therapy					
ACEI/ARB/ARNI (%)	431 (39.8)	182 (50.4)	147 (40.7)	102 (28.3)	< 0.001
β-blocker (%)	765 (70.6)	269 (74.5)	268 (74.2)	228 (63.2)	0.001

Table 1 (continued)

	Overall	MIS: T1	MIS: T2	MIS: T3	*P*-Value
N	**1083**	**361**	**361**	**361**	
MRA (%)	450 (41.6)	124 (34.3)	151 (41.8)	175 (48.5)	0.001
Diuretics (%)	822 (75.9)	273 (75.6)	264 (73.1)	285 (78.9)	0.186
SGLT2 inhibitors (%)	35 (3.2)	9 (2.5)	12 (3.3)	14 (3.9)	0.571

Values are shown as median [interquartile range] or as frequencies [percentage]. Characteristics were compared using a χ2 test for categorical variables and Mann-Whitney U-test for continuous variables

MIS Metabolism-malnutrition-inflammation risk score; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *BMI* body mass index; *CAD* coronary artery disease; *T2DM* Type 2 diabetes mellitus; *COPD* chronic obstructive pulmonary disease; *AF* atrial fibrillation; *NYHA* New York Heart Association; *RDW-SD* red blood cell distribution width-standard deviation; *ALB* albumin; *PLT* platelet; *TG* triglyceride; *LDL-C* low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol; *ApoA-1* apolipoprotein A-1; *ApoB* apolipoprotein B; *FFA* free fatty acid; *FBG* fast blood glucose; *HbA1c* glycated haemoglobin A1c; *UA* Uric acid; *T3* triiodothyronine; *FT4* free thyroxine; *TSH* thyroid stimulating hormone; *hsCRP* high-sensitivity C-reactive protein; *NT-Pro BNP* N-terminal Pro Brain natriuretic peptide; *LAD* left atrial diameter; *LVEDD* left ventricular end-diastolic diameter; *LVEF* left ventricular ejection fraction; *RVD* right ventricular diameter; *ACEI* Angiotensin converting enzyme inhibitor; *ARB* Angiotensin receptor blocker; *ARNI* Angiotensin Receptor-Neprilysin Inhibitor; *MRA* mineralocorticoid receptor antagonists; *SGLT2* Sodium-glucose cotransporter 2

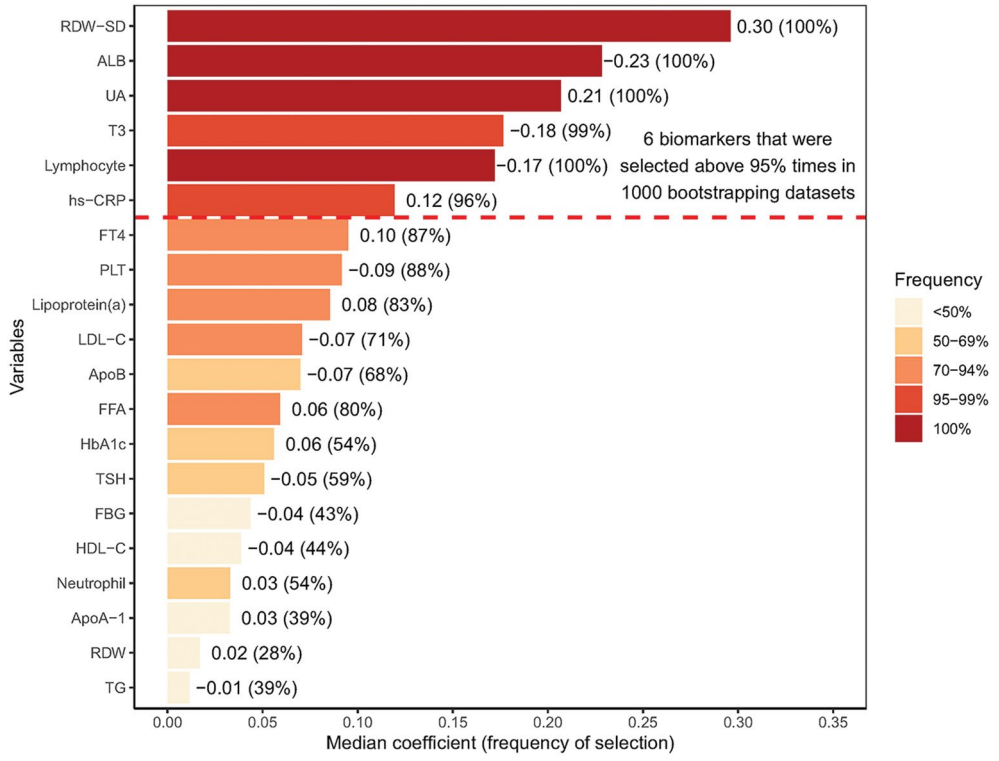


Fig. 1 The frequency of each biomarker selected by Lasso-Cox model and their median coefficients. *RDW-SD* red blood cell distribution width-standard deviation; *ALB* albumin; *UA* Uric acid; *T3* triiodothyronine; *hsCRP* high-sensitivity C-reactive protein; *FT4* free thyroxine; *PLT* platelet; *LDL-C* low-density lipoprotein cholesterol; *ApoB* apolipoprotein B; *FFA* free fatty acid; *HbA1c* glycated haemoglobin A1c; *TSH* thyroid stimulating hormone; *FBG* fast blood glucose; *HDL-C* high-density lipoprotein cholesterol; *ApoA-1* apolipoprotein A-1; *TG* triglyceride

Discussion

Main finding

In this study, we utilized a Lasso-Cox regression to select predictors from a pool of 20 biomarkers representative of metabolism, malnutrition, and inflammation. Subsequently, we developed a risk assessment tool termed MIS, comprising ALB, RDW-SD, Lymphocyte, hs-CRP, UA, and T3. The MIS demonstrated efficacy in the prognostic prediction for HFpEF patients and also exhibited consistent predictive performance across cross-validation iterations. These findings underscore the utility of the MIS in identifying high-risk individuals and facilitating targeted therapeutic interventions.

The role of metabolic inflammation in HFpEF

Systemic proinflammatory states, mostly induced by obesity and metabolic stress, have increasingly been identified as a predominant determinant of HFpEF pathophysiology by recent studies. Metabolic disorders often coincide with disruptions in the immune system. Indeed, there has been a bidirectional effect between metabolic activities and the regulation of immune cells.

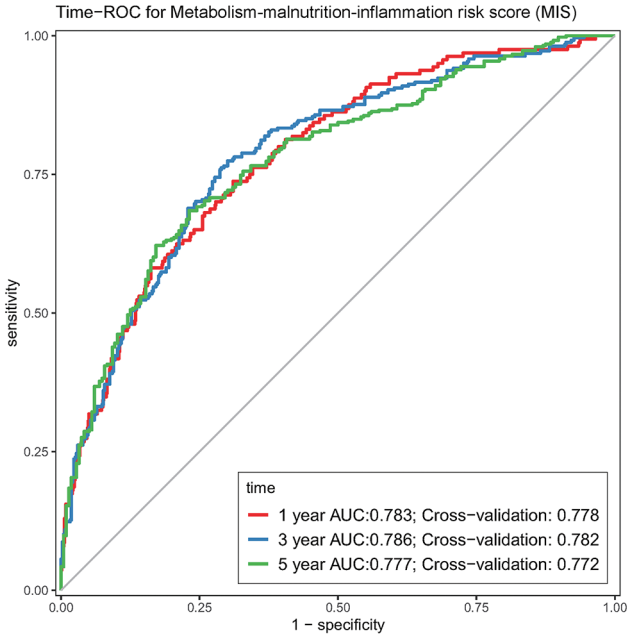


Fig. 2 The time-dependent AUC of the Metabolism-malnutrition-inflammation risk score in predicting primary outcome. The time-dependent AUC in cross-validation was shown as the mean of the AUC in 100 iterations of 5-fold cross-validation at 1, 3, and 5 years after discharge

Table 2 Discrimination and reclassification of adding the MIS and its components to the basic model in predicting primary outcome

	ΔC-index	IDI	*P* for IDI	NRI	*P* for NRI
MIS	**0.034 (0.013–0.050)**	**0.066 (0.040–0.095)**	**< 0.001**	**0.222 (0.144–0.302)**	**< 0.001**
RDW-SD	0.02 (0.004–0.031)	0.034 (0.014–0.059)	< 0.001	0.209 (0.114–0.299)	< 0.001
ALB	0.011 (-0.001-0.021)	0.022 (0.005–0.044)	< 0.001	0.124 (0.033–0.205)	0.020
UA	0.005 (-0.005-0.010)	0.014 (0.002–0.031)	0.020	0.162 (0.034–0.257)	0.033
T3	0.011 (0.001–0.019)	0.018 (0.006–0.038)	< 0.001	0.099 (0.027–0.183)	0.027
Lymphocyte	0.007 (-0.004-0.013)	0.015 (0.002–0.038)	0.007	0.116 (0.040–0.206)	0.007
hs-CRP	0.009 (-0.002-0.017)	0.017 (0.004–0.033)	< 0.001	0.202 (0.083–0.274)	< 0.001

MIS Metabolism-malnutrition-inflammation risk score; *RDW-SD* red blood cell distribution width-standard deviation; *ALB* albumin; *UA* Uric acid; *T3* triiodothyronine; *hsCRP* high-sensitivity C-reactive protein

The basic model was constructed using Lasso-Cox regression incorporating age, gender, *SBP* systolic blood pressure, *BMI* body mass index, *NYHA* New York Heart Association III/IV, smoking, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *AF* atrial fibrillation, *DM* diabetes mellitus, LVEF, *NT-proBNP* N-terminal Pro Brain natriuretic peptide, *Scr* serum creatine, *RAS* therapy with renin-angiotensin system inhibitors and beta-blockers

The 95% confidential interval (CI) of the ΔC-index was calculated in 1000 bootstrap samples. The continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) analyses at 3 years

This reciprocal interaction is increasingly recognized as a pivotal factor in the development of cardiometabolic disorders like HFpEF [3]. In this study, we identified the prognostic role of biomarkers involved in uric acid (UA) and thyroid hormone metabolism, independent of glucose and lipid metabolism. Serum UA is the final product of purine metabolism. Beyond its diagnostic utility for identifying gout, UA levels have been linked to metabolic syndrome and cardiovascular disease [14, 15]. In patients with chronic HF, serum UA has shown significant associations with outcomes across the whole EF phenotypes [11]. While systemic inflammation and endothelial

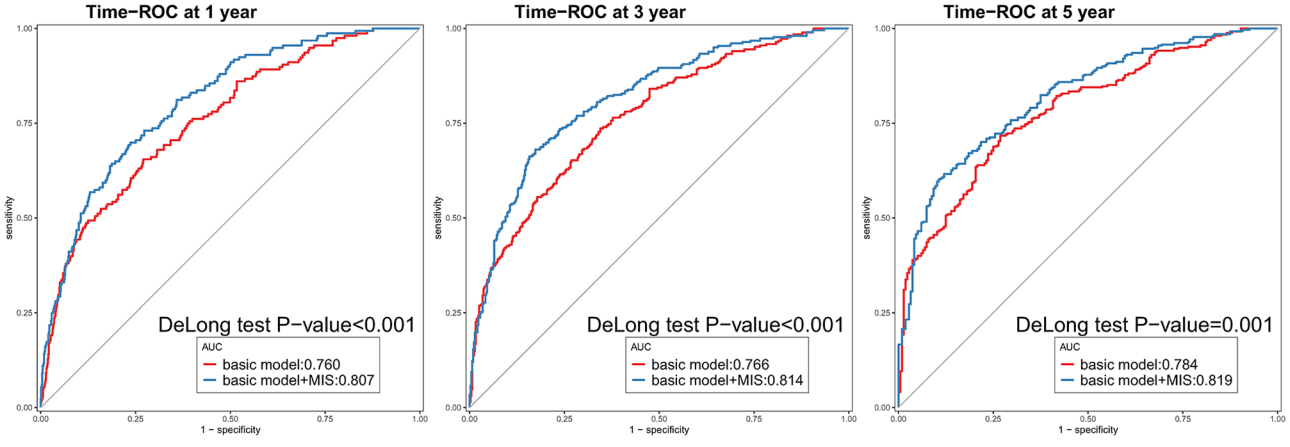


Fig. 3 Comparison of the time-dependent ROC curves between the MIS and MIS plus basic model in predicting primary outcome. The basic model was constructed using Lasso-Cox regression incorporating age, gender, *SBP* systolic blood pressure, *BMI* body mass index, *NYHA* New York Heart Association III/IV, smoking, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *AF* atrial fibrillation, *DM* diabetes mellitus, LVEF, *NT-proBNP* N-terminal Pro Brain natriuretic peptide, *Scr* serum creatine, *RAS* therapy with renin-angiotensin system inhibitors and beta-blockers

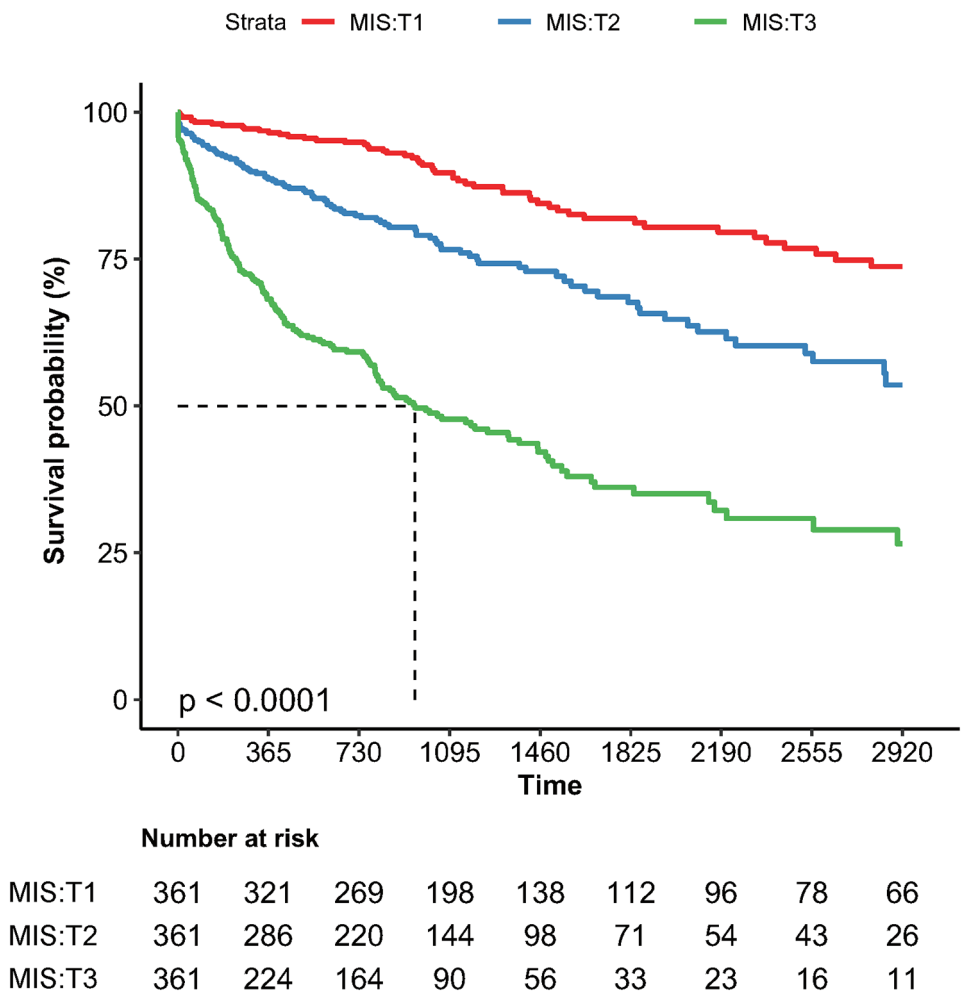


Fig. 4 The Kaplan-Meier curves of patients stratified by the tertiles of the Metabolism-malnutrition-inflammation risk score for primary outcome. *MIS* Metabolism-malnutrition-inflammation risk score

Table 3 The association between the MIS and its components with the primary outcome at univariable and multivariable Cox regression

	Unadjusted HR	Unadjusted *P*-value	Adjusted HR	Adjusted *P*-value
MIS	**2.81 (2.47–3.20)**	**< 0.001**	**1.98 (1.70–2.31)**	**< 0.001**
RDW-SD	1.68 (1.55–1.83)	< 0.001	1.39 (1.26–1.54)	< 0.001
ALB	0.64 (0.58–0.71)	< 0.001	0.74 (0.67–0.83)	< 0.001
UA	1.52 (1.39–1.66)	< 0.001	1.21 (1.09–1.34)	< 0.001
T3	0.53 (0.46–0.61)	< 0.001	0.75 (0.65–0.86)	< 0.001
Lymphocyte	0.58 (0.51–0.65)	< 0.001	0.78 (0.69–0.88)	< 0.001
hs-CRP	1.44 (1.31–1.59)	< 0.001	1.24 (1.12–1.37)	< 0.001

MIS Metabolism-malnutrition-inflammation risk score; *RDW-SD* red blood cell distribution width-standard deviation; *ALB* albumin; *UA* Uric acid; *T3* triiodothyronine; *hs-CRP* high-sensitivity C-reactive protein

The adjusted hazard ratio (HR) and *P*-value were calculated from a multi-variable Cox regression adjusting for the variables in the basic model

dysfunction, potentially linked to UA, are suggested as consequences of HFrEF, they are speculated to act as contributors to HFpEF. Recent research also suggests that elevated serum UA levels correlate with increased cytokine levels and heightened inflammatory responses, which may play a more substantial role in HFpEF than HFrEF [16, 17].

A thyroid hormone directly affects the myocardium, the conduction system, and the peripheral vasculature. Hypothyroidism is associated with hyperlipidemia and ventricular arrhythmias, hyperthyroidism is associated

with atrial arrhythmias, and both are associated with hypertension and HF [18]. Based on our findings, the level of triiodothyronine (T3) was negatively correlated with HFpEF prognosis. According to previous studies, isolated low T3 is associated with more severe HF and an over 2-fold risk of adverse outcomes [19]. In the cardiomyocyte of failure heart, hypoxia and inflammation reduce deiodinase activity. This results in reduced plasma T3 levels and decreased intracellular bioavailability of T3. The effects of thyroid hormones on myocardium include upregulation of myosin heavy chain-α and downregulation of myosin heavy chain-β, regulation of calcium cycling through SERCA2a, and enhancement of adrenergic responsiveness [12]. The activation of the SERCA2a could enhance both systolic and diastolic function, and the latter is an important therapeutic target in HFpEF.

Malnutrition-inflammation complex in HFpEF and related biomarkers

Numerous studies indicate that some of cardiovascular risk factors are associated with elevated risk of adverse outcomes in HF patients, such as a lower BMI, blood pressure and serum cholesterol concentration. These observations are in contrast to that in the general population, which have been referred to as "reverse epidemiology" [4]. The occurrence of the "malnutrition-inflammation complex syndrome" in HF patients offers a potential explanation for the existence of "reverse epidemiology". A reduction in lipoprotein can compromise their endotoxin-scavenging function, making HF patients with malnutrition susceptible to inflammatory endotoxemia [4]. In this study, the Lasso-Cox model finally selected 4 biomarkers, including the RDW-SD, ALB, Lymphocyte and hs-CRP, which can reflect the severity of malnutrition and inflammation within HFpEF patients.

RDW-SD is a metric that quantifies the diversity in the size of circulating red blood cells. A study have proposed that is better to use RDW-SD to eliminate the confounding influence of mean corpuscular volume (MCV) on RDW [20]. Current evidence suggests that RDW is recognized as an indicator of chronic inflammation, exhibiting a notable correlation with inflammatory markers. Additionally, disturbances in iron metabolism, renal dysfunction, and malnutrition have been implicated in the mechanism of elevated RDW levels among HF patients [21]. Our prior studies have established that RDW had an independent association with mortality across diverse ejection fraction categories and etiologies among HF patients [7, 22]. Furthermore, ALB serves as another biomarker reflecting nutritional and inflammatory status. Notably, hypoalbuminemia, defined as an ALB level below 3.4 mg/dl, is observed in approximately 28% of patients with HFpEF [23]. According to Frank-Starling's law, hypoalbuminemia-induced decreases in plasma oncotic pressure facilitate fluid shifts from the blood vessels into the tissues, thereby contributing to cardiogenic pulmonary edema and exacerbating the severity of condition in patients [24].

Prior research has established several nutritional and inflammatory risk scores, incorporating some of the biomarkers investigated in our study and validating their effectiveness. For instance, the geriatric nutritional risk index (GNRI) has been proven to be a reliable screening tool for malnutrition in the elderly, utilizing objective measures such as height, weight, and serum ALB. This index has been linked to the risk of cardiovascular and all-cause mortality in patients with HFpEF [5]. Another study identified CRP, RDW and neutrophil-to-lymphocyte ratio (NLR) as components of an inflammatory prognostic score among 538 acute HF patients [25]. Additionally, the Pan-Immune-Inflammation Value, calculated using biomarkers of complete blood cell counts, has demonstrated superior predictive ability in patients with ST-segment elevation myocardial infarctions [26]. However, these studies have not comprehensively evaluated the discrimination, calibration, and reclassification performance of these scores. Further studies are required to construct a comprehensive index that incorporates biomarkers related to metabolism, malnutrition, and inflammation. Therefore, we specifically focus on HFpEF patients, incorporating 20 biomarkers to develop a risk score that accurately reflects the underlying pathophysiology of HFpEF.

Targeted therapies for metabolic malnutrition and inflammation in HFpEF

Our study has established the prognostic significance of serum UA and hs-CRP, and incorporated them into a comprehensive risk-scoring system. Prior research analyzed the data in the SOCRATES-REDUCED study to explore the influence of vericiguat on hs-CRP and serum UA levels in HFrEF patients. Notably, this study revealed that 12-week treatment with vericiguat was associated with a notable reduction in both hs-CRP and UA levels [27]. These findings suggest a potential anti-inflammatory benefit of vericiguat in HFrEF patients. However, the VITALITY-HFpEF study showed that vericiguat failed to improve the KCCQ compared with placebo [28]. A post-hoc analysis of PARAGON-HF also found that Sacubitril–valsartan can reduce the serum UA level and the initiation of UA-related therapy. While the effect of Sacubitril–valsartan was not significantly modified by serum UA levels, its beneficial effects were more pronounced in terms of renal outcomes [29]. To sum up, these data suggest that UA may be a relevant therapeutic target in HFpEF.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a promising therapeutic option for

patients with both HFrEF and HFpEF [30]. While the precise mechanisms underlying the cardiovascular benefits of SGLT2 inhibition remain unclear, there is speculation that these inhibitors may target metabolic inflammatory pathways. A recent study revealed that patients treated with SGLT2 inhibitors exhibited lower levels of circulating IL-6, serum UA, and fasting insulin compared to those receiving other glucose-lowering drugs [31]. Furthermore, vitro models suggest that SGLT2 inhibitors possess a tangible anti-inflammatory activity, potentially mediated by their ability to reduce UA and insulin concentrations. This effect complements other proposed mechanisms that explain the observed benefits of this drug on cardiovascular and renal endpoints [31]. Given that the components of the Metabolism-malnutrition-inflammation risk score (MIS) have demonstrated potential as therapeutic targets in HFpEF patients, this score may serve as a useful tool in guiding individualized treatment strategies.

Limitations

Firstly, its retrospective nature may have led to selection bias and overlooked potential confounding factors, limiting the comprehensiveness of our analysis. Secondly, while the study focused on 20 easily accessible biomarkers commonly used in clinical settings, it did not include more specialized biomarkers, such as those derived from metabolomics or proteomics. Finally, while the prognostic risk score model established in this study has undergone internal cross-validation, it has not yet been validated by an external cohort. Therefore, we must emphasize the need for further external-validation.

Conclusions

In this study, we created a Metabolism-malnutrition-inflammation risk score (MIS), formulated using six biomarkers: ALB, RDW-SD, Lymphocyte, hs-CRP, UA, and T3. The MIS significantly enhanced the prognostic prediction accuracy for patients with HFpEF, complementing traditional risk factors. The MIS could serve as an effective index in stratifying patients and screening suitable candidates for targeted therapeutic approaches, such as nutritional supplementation or anti-inflammatory treatments.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00856-2.

Supplementary Material 1

Author contributions

FJ designed research, analyzed data and prepared the manuscript; FJ, HL, ZX, LX, XA and WC managed the data, HL, ZX, LX, XA, WC, ZY and ZJ reviewed and edited the manuscript, ZY and ZJ acquired the funding. All authors have read and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The ethics committee of Fuwai hospital has approved the research protocol (2018 – 1041) and informed consent has been obtained from the subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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