

LETTER TO THE JOURNAL

Plasma metabolites in patients of the REDINSCOR III registry hospitalised for de novo heart failure with preserved ejection fraction: Prognostic implications of linoleamide and 2-trans,4-cisdecadienoylcarnitine levels

Dear Editor

Heart failure with preserved ejection fraction (HFpEF) constitutes approximately 50% of all heart failure (HF) diagnoses. Despite its prevalence, effective therapies are limited given the incomplete understanding of its pathogenesis and pathophysiology.¹ Taking into account these considerations, in this multicentre cohort of new-onset HFpEF hospitalised patients, we described a comprehensive untargeted metabolomic study to determine endogenous metabolites that were associated with the risk of suffering an event of death or readmission for cardiovascular causes.

A total of 126 plasma samples were analysed (Figure S1), including those from 105 patients with new-onset HFpEF. At enrolment, the median age of these patients was 75 ± 10 years, 51% were male, and in the previous year mostly were pauci-symptomatic (81% NYHA class I-II). At the last evaluation, 18 patients suffered an event (all-cause mortality or cardiovascular readmission), while 82 patients did not. Table 1 summarises the demographic and clinical characteristics of HFpEF patients by event status at the end of the follow-up. Both groups were similar regarding variables except for haemoglobin, creatinine and NT-proBNP values prior to discharge. Additionally, the 20 healthy controls (CNT) individuals had a mean age of 66 ± 5 years, and 60% were male.

Metabolic differences between CNT and HFpEF patients groups were assessed after data preprocessing in both positive and negative ESI modes (Figure S2). As shown in Table S1, we identified 24 metabolites that showed statistically significant differences between HFpEF patients and the CNT group, with a fold change threshold of $|FC| \geq 2$. Regarding this finding, we performed an analysis between the HFpEF patients who experienced an event with those who did not to discover if there were

metabolomic changes. As a result, seven metabolites exhibited significant differences, being linoleamide levels the ones that were most altered in this comparison (Table S1). Then, we focused on linoleamide, an endogenous lipid which is structurally related to sphingosine and sphiganine and closely related with sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) activity,^{2,3} whose levels were higher in patients who were rehospitalised for an event ($p < .0001$) (Figure S3A). Previously, Tarazón et al.⁴ determined through untargeted metabolomics that circulating sphingosine-1-phosphate (S1P), a metabolite also closely related with SERCA, could be a novel approach to detect cardiac rejection. In addition, significant alterations in the main components of the sphingolipid metabolism pathways and an accumulation of S1P was observed in HF patients.⁵ Collectively, these findings highlight the potential role of linoleamide in HFpEF patients who experienced an event. Furthermore, it is widely known that the heart is a mitochondrion-rich tissue, and at the molecular level, impaired mitochondrial function has been suggested to contribute to HFpEF development.⁶ Circulating plasma acylcarnitines, which are intermediates of mitochondrial β -oxidation of fatty acids, are an emerging molecular signature of HF and are thought to reflect mitochondrial dysfunction.⁷ Considering that it is well-established that alterations in acylcarnitines levels are associated with HF risk,^{8,9} we wanted to investigate the influence of 2-trans,4-cis-decadienoylcarnitine, a medium-chain acylcarnitine, whose levels were also higher in patients who experienced an event ($p < .01$) (Figure S3B). Previously, Zhang and Zhang¹⁰ reported that the inactivity of mitochondrial relevant NADP-dependent enzymes provoked elevated plasma 2-trans,4-cis-decadienoylcarnitine levels. Here, we observed an upregulation of 2-trans,4-cis-decadienoylcarnitine as in previous studies, suggesting

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TABLE 1 Baseline characteristics of enrolled HFpEF patients.

	Overall (<i>n</i> = 105)	No event (<i>n</i> = 82)	Event (<i>n</i> = 18)	<i>p</i> Value
Demographic data				
Age (years)	75±10	75 ± 10	76 ± 11	.691
Male sex (%)	51	52	50	1.000
Body mass index (kg/m ²)	31±7.9	30 ± 6.6	34 ± 11	.267
Current smoker (%)	15	15	17	.713
Previous year NYHA classification (%)				
I	39	40	35	.792
II	42	41	47	.788
III	17	19	12	.729
IV	1.9	1.2	5.9	.318
Comorbidities				
Hypertension (%)	70	68	83	.260
Diabetes mellitus (%)	28	27	39	.762
Dyslipidemia (%)	50	56	39	.204
Paroxysmal atrial fibrillation (%)	16	17	17	1.000
Permanent atrial fibrillation (%)	19	18	17	1.000
Previous ischemic heart disease (%)	8.6	7.3	11	.632
Echo-Doppler study				
Ejection fraction (%)	59 ± 6.8	59 ± 7.2	61 ± 4.5	.112
Valve disease (moderate or severe) (%)	13	12	22	.261
Laboratory data				
Haemoglobin (g/dL)	129 ± 20	130 ± 18	118 ± 25	.016
Creatinine (mg/dL)	1.2 ± 0.5	1.1 ± 0.4	1.6 ± 0.8	.012
NT-proBNP prior to discharge (pg/mL)	1144 (430–2101)	914 (366–1705)	1770 (1058–4159)	.008
NT-proBNP at admission (pg/mL)	2525 (1554–4523)	2342 (1546–4142)	3383 (1566–4777)	.309

Note: *p* Value is the comparison between patients who suffered an event of death or readmission for cardiovascular causes and patients who did not.

Abbreviations: HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal fragment of B-type natriuretic peptide; NYHA, New York Heart Association.

its involvement in mitochondrial dysfunction in HFpEF patients.

ROC curves were performed to analyse the capability of linoleamide and 2-trans,4-cis-decadienoylcarnitine for predicting an event. After adjusting by age and gender, we obtained an AUC value of 0.726 ($p < .01$) for linoleamide and 0.710 ($p < .01$) for 2-trans,4-cis-decadienoylcarnitine. The combination of both metabolites was associated with improved predictive accuracy, with an AUC value of 0.785 ($p < .0001$), which was higher than the AUC values for each metabolite alone (Figure 1 and Table S2).

Further, the relationship between metabolites and event risk was assessed using COX proportional hazard regression. Firstly, univariate tests were made to detect differences between patients with and without an event of death or readmission for cardiovascular causes, obtaining a significant influence of linoleamide, 2-trans,4-cis-decadienoylcarnitine and NT-proBNP prior to discharge (Table S3). Next, a univariate study using COX regression was proposed given that it detects the influence of

linoleamide, 2-trans,4-cis-decadienoylcarnitine and NT-proBNP prior to discharge, independently, on the time until the event. Here we obtained that only both metabolites were significantly associated with the risk of suffering an event (Table 2), NT-proBNP did not demonstrate a significant effect ($p = .43$). Considering these univariate results, a multivariate COX regression model was proposed, obtaining better AIC and C-statistic values, suggesting enhanced prognostic value for predicting the event in HFpEF patients (Table 2).

Then, from the multivariate model, a time-dependent ROC curve was constructed to evaluate its performance in the adjusted observations. We took 3, 6 and 10 months to study the performance of the multivariate model, obtaining for 3 months an AUC = 0.761, for 6 months an AUC = 0.800 and for 10 months an AUC = 0.794 (Figure 2A and Table S4). Furthermore, a Kaplan–Meier survival model was performed stratifying patients in different groups depending on the metabolites respective median values. Significant differences were found between the sur-

TABLE 2 Association between metabolites and the risk of suffering an event.

Metabolites	Univariate analysis			Multivariate analysis		
	Hazard ratio [95% CI]	C-statistics [95% CI]	AIC	Hazard ratio [95% CI]	C-statistics [95% CI]	p-Value
Linoleamide	1.25 [1.11–1.41]	0.75 [0.62–0.87]	154	1.22 [1.08–1.37]	0.77 [0.65–0.88]	<.01
2-trans,4-cis-decadienoylcarnitine	2.35 [1.30–4.23]	0.67 [0.54–0.79]	156	2.12 [1.13–3.97]		<.05

Abbreviation: AIC, Akaike information criterion.

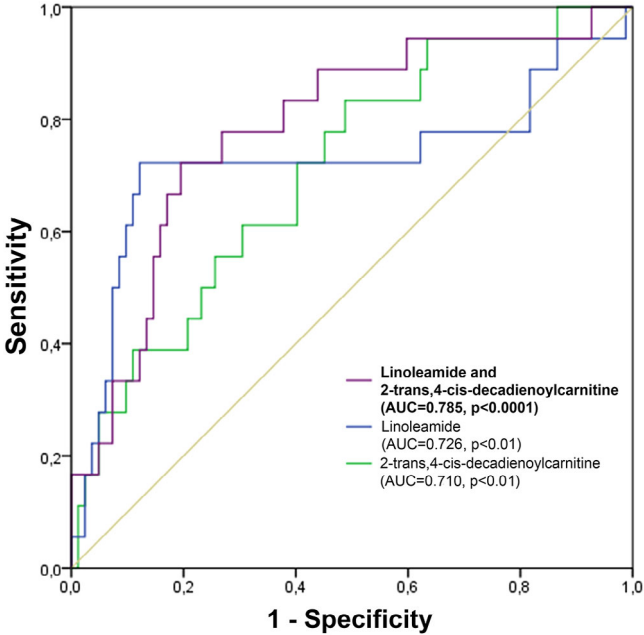


FIGURE 1 Circulating linoleamide, 2-trans,4-cis-decadienoylcarnitine, and combined receiver-operating characteristic curves for the prediction of an event of death or readmission for cardiovascular causes within 12 months of follow-up, adjusted by age and gender. AUC, area under the curve; ROC, receiver-operating characteristic.

vival curves ($p < .01$), in particular; between the curves of group 1 and group 4 ($p < .05$) (Figure 2B). Patients in group 4, which had levels of both metabolites above their respective medians, suffered poorer clinical outcomes than patients in group 1, who had both metabolites levels below their respective median. This finding is in line with our premise given that both metabolites were associated with an increased risk of suffering an event of death or readmission for cardiovascular causes, and both showed higher levels in patients who suffered an event compared with patients who did not.

Our study is limited on several points. The small number of clinical events may increase the risk of overfitting in the multivariate model, which should be taken into account when interpreting the results. Furthermore, although this study benefits from a multicentre design, which enhances the diversity and generalisability of the sample, it lacks validation in an entirely independent external cohort. Future research should focus on validating these biomarkers in separate patient cohorts to strengthen their clinical utility.

In conclusion, a combination of linoleamide and 2-trans,4-cis-decadienoylcarnitine plasma levels could be a novel approach to determine HFpEF prognosis. This discovery contributes to progress in the knowledge of HFpEF pathophysiology, raises questions about the role of these

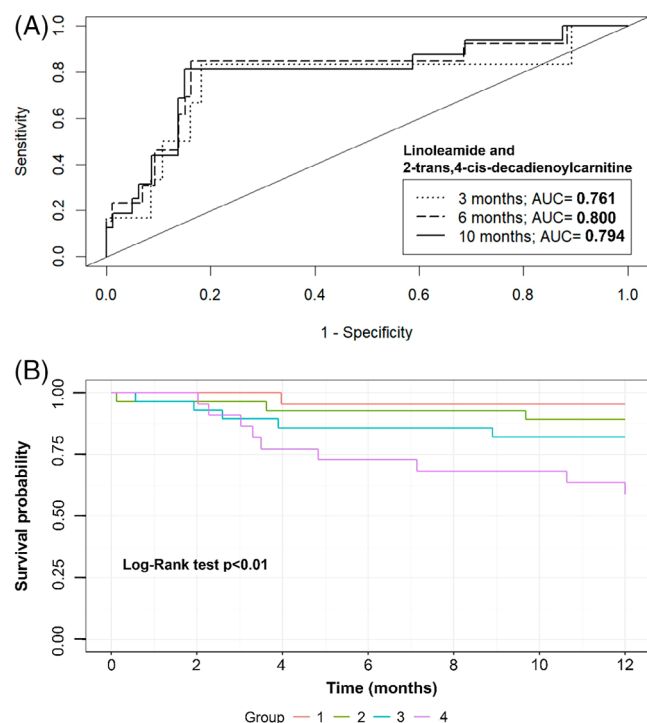


FIGURE 2 Prognostic evaluation of the multivariate model and survival analysis based on metabolite levels in HFpEF patients. Combined metabolites for time-dependent ROC curve (A) and Kaplan–Meier curve (B). Group 1 consisted of patients with levels of both metabolites below their respective median values; group 2 included patients with 2-trans,4-cis-decadienoylcarnitine levels above its median and linoleamide levels below its median; group 3 comprised patients with linoleamide levels above its median and 2-trans,4-cis-decadienoylcarnitine levels below its median; and group 4 consisted of patients with levels of both metabolites above their respective medians. AUC, area under the curve; ROC, receiver-operating characteristic.

metabolites in its diagnosis and prognosis, and opens the way for future studies of potential therapeutic targets.

AUTHOR CONTRIBUTIONS

MDA, ERL, and LMD: designing the study, acquiring and analysing the data, contributing to data interpretation, writing the manuscript. MDGC, MMS, JMG, SV, JPV, AC, LMB, AGT, MGCL, and JFD: acquiring data and contributing to the critical review.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

ETHICS STATEMENT

The study complied with the Declaration of Helsinki and was approved by the participating centres’ medical ethics committees. Prior to sample collection, signed informed consent was obtained from each patient.

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