RESEARCH ARTICLE

Is elabela/toddler a poor prognostic marker in heart failure patients?

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Abstract

Background: Elabela/toddler (ELA-32) is a recently identified endogenous apelin receptor ligand. ELA levels are known to rise in heart failure (HF) patients. However, the association between elevated ELA levels and prognosis in these patients remains unknown. We aimed to investigate whether ELA plasma levels are correlated with prognosis in heart failure patients with reduced ejection fraction (HFrEF).

Methods: This case-control cross-sectional study enrolled 150 patients, including 73 HFrEF patients and 77 age- and gender-matched healthy volunteers. We collected a blood sample at hospital admission to measure ELA-32 levels. The study endpoint was cardiovascular mortality or HF-related hospitalization. We followed up all patients in the study for a mean of 7.48 ± 2.73 months.

Results: In patients with HFrEF, ELA-32 levels were higher than those in controls. The levels of ELA-32 showed a significant increase at advanced New York Heart Association stages. In the receiver operating characteristics curve analysis, a cut-off value of the serum ELA-32 level of 8.25 ng/mL showed a sensitivity of 76 % and specificity of 82 % for predicting the study endpoint [area under the curve: 0.84; 95 % confidence interval (CI): 0.72–0.98; p <0.001]. Cardiovascular mortality (p =0.042) and HF-related hospitalization (p <0.001) were statistically more significant in patients with ELA-32 levels greater than 8.25. Age [Hazard ratio (HR) =1.023; 95 % CI: 0.964-1.230, p =0.039], N-terminal pro-brain natriuretic peptide (HR =1.300; 95 % CI: 1.017-1.874, p =0.017), left ventricular end-diastolic volume (HR =1.142; 95 % CI 1.022-1.547, p =0.028), and ELA-32 ≥8.25 (HR =2.556; 95 % CI: 1.078-3.941, p <0.001) remained independently associated with the risk of study endpoint.

Conclusion: For the first time, HF-related hospitalizations and cardiovascular mortality are independently associated with increased ELA-32 levels in patients with HFrEF. HIPPOKRATIA 2023, 27 (4):126-131.

Keywords: Elabela, heart failure, mortality, hospitalization, N-terminal pro-brain natriuretic peptide, NT-proBNP

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Introduction

Heart failure (HF) is a clinical syndrome in which cardiac output fails to meet metabolic needs and is clinically characterized by shortness of breath, fatigue, and fluid retention[1]. Understanding the pathophysiology of HF is essential in initiating alternative treatment options for each patient and minimizing cardiovascular risk factors to reduce HF risk[2]. In HF patients, many systems, such as renin-angiotensin-aldosterone (RAA) and natriuretic peptide system, play an active role in increasing the initial clinical status and cardiac output. These systems are interrelated to maintain cardiac status and are the target site of drugs used to diagnose and treat HF[3,4].

Apelin peptide and apelin receptor (APJ) play a crucial role in the heart and blood vessels and have cardioprotective effects[5,6]. The effects of apelin and Elabela (ELA) are directed against the RAA system, which increases myocardial vascularity, decreases remodeling, and increases cardiac output in patients with HF[7-10]. Comparatively to apelin, few human studies with ELA exist in the literature, even though apelin and ELA are known to prevent cardiac diseases and slow the disease progression in patients with HF. ELA levels have not been compared with HF prognosis in any study.

In light of all this information, the relationship between ELA-32 and the prognosis of HF with reduced ejection fraction (HFrEF) is unclear. We aim to investigate the association between ELA-32 levels and poor prognosis in patients with HFrEF.

Methods and materials

This study is a cross-sectional case-control study conducted at a tertiary health center between December 2021 and October 2022. We screened 110 consecutive patients with HFrEF admitted to the HF clinic. Thirty-seven patients with HFrEF were excluded from the study for not meeting the inclusion criteria. Finally, 73 patients with HFrEF and 77 age- and sex-matched healthy volunteers were enrolled. Patients with HFrEF had a left ventricular ejection fraction (LVEF) below 40 % and were treated

according to the New York Heart Association (NYHA) class. Healthy volunteers were randomly selected adults with LVEF >50 %, no modifiable cardiovascular risk factors, and no active disease. We followed up all patients for a mean of 7.48 ± 2.73 months. The study followed the ethical guidelines outlined in the Declaration of Helsinki. The local Ethics Committee approved this study (decision No 2011-KAEK-27/2021-2100099791), and informed consent was obtained both verbally and in writing.

Patients excluded from the study were those with newly diagnosed acute coronary syndrome, chronic or acute liver diseases, renal impairment (estimated glomerular filtration rate <30 ml/kg/1.73m^2), hepatitis B or C, moderate to severe valvular heart disease, collagen tissue disease (such as systemic lupus erythematosus), pulmonary hypertension, portal hypertension, inflammatory disease (such as rheumatoid arthritis and inflammatory bowel disease), autoimmune disease, hematologic disease (such as hemophilia and leukemia), active thyroid disease, cancer, suspected pregnancy, regular alcohol consumption (>20 g/day), impaired renal function during follow-up (a 25 % decrease in creatinine clearance), lack of regular clinical monitoring, individuals under the age of 18, and those who declined to participate in the study.

We conducted echocardiographic measurements using the Vivid 7 Pro device (GE, Vingmed, Horten, Norway) with patients positioned in the left lateral position. Two experienced cardiologists, blinded to the study, assessed LVEF, left atrium (LA), diastolic (LVEDV), and systolic (LVESV) volumes of the ventricle, left atrial volume index (LAVi), and other echocardiographic measurements. The LA's endocardium was traced using the apical 4-chamber (A) and apical 2-chamber (B) views at the end of ventricular systole. We measured LA length (L) between the back wall and the hinge points of the mitral valve and calculated LA volume by using the distance between these points [(0.85) x (AxB/L)]. LAVi is obtained by dividing the LA volume by the body surface area (BSA)[11]. LVEF was calculated using the modified Simpson method[12].

Blood drawn from the antecubital vein was used for simultaneous measurements of blood tests. We used commercial kits (Sunred Biological Technology, Shanghai, China) to measure serum Ela-32 levels, which were assessed utilizing a sandwich enzyme-linked immunosorbent assay using double antibodies. According to the manufacturer, around 12 % of variation occurs between assays, and 10 % occurs within assays. Blood samples for all the tests mentioned above were collected within 24 hours of admission.

The study endpoint was cardiovascular mortality or HF-related hospitalization. The term "in-hospital cardiovascular mortality" refers to cardiovascular death (including cardiac arrest, pulmonary edema, and cardiogenic shock). Patients with HF that require 40 mg intravenous furosemide within two hours of admission and a hospital stay of more than three days were considered to have HF-related hospitalization. Study investigators adjudicated all events.

Statistical analysis

We used G*Power software version 3.1.9.6 for power analysis. The minimum sample size was determined to be 118 individuals with an 85 % test power at the 5 % alpha level. The data were analyzed using the IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). We assessed normal distribution conformity of continuous variables using the Kolmogorov-Smirnov test. Results are presented as means ± standard deviation for continuous variables or as median (interquartile range) values, while categorical variables are presented as numbers and percentages. We used the Student's t-test to compare variables exhibiting normal distributions and the Mann-Whitney U-test for variables without normal distributions. We employed the Fisher's Exact test or Chi-squared test to compare probability ratios of categorical variables and the Pearson and Spearman tests for correlation analysis. We performed receiver operating characteristic (ROC) analysis to determine the optimal cut-off value of ELA-32 for the prediction of study endpoints, with point sensitivity and specificity determined according to the Youden J index. This univariate analysis included possible confounding variables such as age, sex, LVEF, LVEDV, LAVi, hemoglobin, sodium, uric acid, N-terminal pro-brain natriuretic peptide (NT-proBNP), cardiac troponin (Tn), and ELA-32 to estimate study endpoints. The variable with a non-adjusted p-value of 0.1 was considered a potential risk factor and included in the multivariate analysis. We conducted a multivariate Cox proportional hazards regression to determine the independent predictors of study endpoints. A p-value of <0.05 was deemed statistically significant.

Results

In total, the study consisted of 150 patients, comprising 73 individuals with HFrEF (54 males, 19 females) and 77 in the control group (47 males, 30 females). In the HFrEF group, the mean age was 66.82 ± 11.95 years; in the control group, it was 64.23 ± 12.34 years. HFrEF patients had higher levels of ELA-32 than controls (9.89 ± 3.22 vs 1.84 ± 1.13, p <0.001) (Table 1). However, ELA-32 levels were statistically different between groups according to NYHA classification. Patients' ELA-32 levels increased with increasing NYHA class levels (Table 2) (Figure 1).

ELA-32 was correlated with cardiac Tn, NT-proBNP, LVEF, LVEDV, LVESV, left ventricular end diastolic dimension (LVEDD) diameter, left ventricular end systolic dimension (LVESD) diameter, LA diameter, and LAVi (Table 3).

ROC curve analysis confirmed the predictive value of ELA-32 for study endpoint. The cut-off value of the ELA-32 was 8.25 (area under the curve: 0.84; 95 % confidence interval (CI): 0.72–0.98; p <0.001; sensitivity, 76 %, specificity, 82 %) (Figure 2).

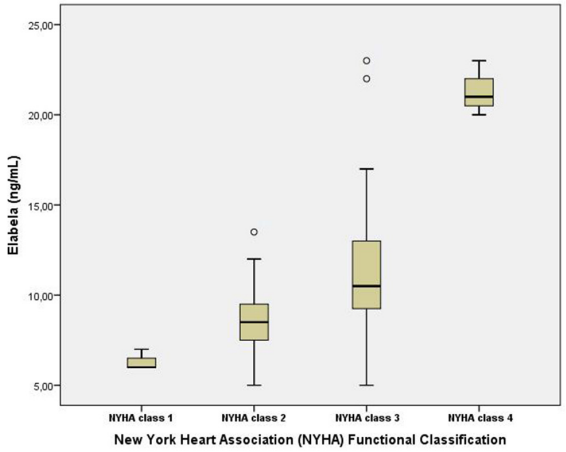

Figure 1: Comparison of Elabela levels according to the New York Heart Association class in heart failure patients with reduced ejection fraction.

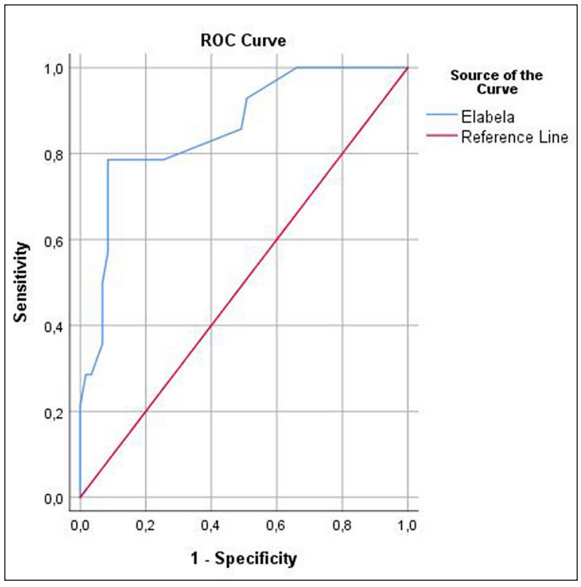

Figure 2: Receiver operating characteristic analyses for Elabela levels to predicting study endpoints**.**
ROC: Receiver operating characteristic.

The effect of variables on study endpoints was tested using Cox regression analysis. Age [Hazard ratio (HR) =1.023; 95 % CI: 0.964-1.230, p =0.039], NT-proBNP (HR =1.300; 95 % CI: 1.017-1.874, p =0.017), LVEDV (HR =1.142; 95 % CI: 1.022-1.547, p =0.028), and ELA-32 ≥8.25 (HR =2.556; 95 % CI: 1.078-3.941, p <0.001) were statistically significant (Table 4).

During the 7.48 ± 2.73 months of follow-up, cardiovascular mortality, hospital stay duration, and HF-related hospitalization were statistically more significant in patients with an ELA-32 level greater than 8.25 (Table 5).

Reproducibility

Twenty patients were randomly selected, and the measurements were repeated under identical baseline conditions. The reproducibility of the echocardiographic imaging parameters obtained through transthoracic echocardiography was evaluated using the coefficient of variation between measurements. The intra- and inter-assay coefficients of variation were 5 % and 3 %, respectively.

Discussion

The important findings of our study were as follows: i) serum ELA-32 levels increased in HF patients compared to healthy subjects; ii) ELA-32 levels increased with increasing NYHA class level in HFrEF patients; iii) ELA-32 was strongly correlated with LVEF and LVEDV; iv) ELA-32 was an independent predictor of cardiovascular mortality and HF-related hospitalization in HFrEF patients.

HF is the leading cause of mortality and morbidity in developed countries with a predominantly elderly population[13]. New clinical markers and therapies are needed to address this clinical situation. Apelin-APJ interaction has favorable effects on HF[14]. ELA (Elabela, also known as Apela/Toddler) is a new endogenous ligand of APJ[15]. Studies on ELA have shown *in vivo* that ELA is positively correlated with a parameter indicating cardiac contractility (left ventricular fractional shortening)[8,16]. In a study conducted in rats, ELA-32 was shown to cause an increase in LV and right ventricular ejection fraction[8]. As reported in another rat study, the ELA-APJ system suppresses angiotensin-converting enzyme (ACE) expression and may prevent undesirable pathophysiological processes such as cardiac hypertrophy, fibrosis, and impaired contractility that the angiotensin II signaling pathway may cause[17].

LV diameter can be used for risk classification of cardiac death independent of LVEF[19]. Cardiovascular events are independently predicted by LV enlargement in patients with HFrEF[19]. LVEDV and ELA levels were positively correlated in this study. LA diameter has been found to predict HFrEF, and to be associated with disease severity[20]. A weak correlation was found between LAD diameters and ELA levels in our study. However, we found a strong correlation between LAVi and ELA levels.

NT-proBNP is a prominent HF biomarker both for risk assessment and monitoring treatment response[21,22]. NT-proBNP levels are a prognostic biomarker for patients with acute decompensated heart failure (ADHF) and *de novo* heart failure (DNHF), and patients with ADHF who have the same NT-proBNP levels have an increased mortality risk for a year than those with DNHF[23]. NT-proBNP and ELA showed a strong correlation in our study. As a result, patients with HFrEF may benefit from ELA for risk stratification. There is strong evidence that HF contributes to the pathophysiology of myocardial damage and that cardiac Tn-I is frequently used in clinical practice as it is highly sensitive and specific[24]. The HFrEF group showed higher levels of ELA and Tn-I than the control group, with a correlation between ELA and Tn-I.

HF causes pathological hypertrophy in myocytes, and

Table 1: Baseline clinical characteristics, laboratory, and echocardiographic parameters of a group including 73 heart failure patients with reduced ejection fraction and a group including 77 age- and gender-matched healthy volunteers.

	HFrEF group (n =73)	Control group (n =77)	p
Age (years)	66.8 ± 11.9	64.2 ± 12.3	0.194
Gender (M/F)	54/19	47/30	0.091
BMI (kg/m^2)	25.1 ± 1.0	24.96 ± 0.9	0.152
Family history of CAD, n (%)	15 (20.5)	-	-
Current smoker, n (%)	23 (31.5)	-	-
Hypertension, n (%)	15 (20.5)	-	-
Diabetes mellitus, n (%)	5 (6.8)	-	-
Hyperlipidemia, n (%)	16 (21.9)	-	-
SBP (mmHg)	111.8 ± 13.3	113.3 ± 13.7	0.502
DBP (mmHg)	71.3 ± 7.4	72.5 ± 9.3	0.377
Heart rate (beats/min)	81.7 ± 11.5	78.7 ± 12.6	0.131
Laboratory data			
Glucose (mg/dl)	103.6 ± 18.2	99.4 ± 12.6	0.108
Creatinine (mg/dl)	0.81 ± 0.22	0.75 ± 0.18	0.099
Uric acid (mg/dl)	6.3 ± 1.6	5.9 ± 2.3	0.278
Sodium (mmol/L)	137.2 ± 3.2	137.8 ± 3.9	0.313
Potassium (mmol/L)	3.88 ± 0.58	4.07 ± 0.75	0.084
AST (U/L)	24.7 ± 18.5	26.7 ± 11.2	0.452
ALT (U/L)	24.9 ± 8.0	23.6 ± 11.3	0.408
TSH (uIU/mL)	1.6 ± 0.80	1.8 ± 1.2	0.365
Hemoglobin (g/dl)	11.3 ± 1.9	14.1 ± 1.4	<0.001
Hemotocrit (%)	32.7 ± 6.3	39.3 ± 5.2	<0.001
WBC count 10^9/ L	11.7 ± 2.8	11.0 ± 2.4	0.075
Platelet count, 10^9/ L	328 ± 89.6	341.2 ± 47.8	0.299
LDL-cholesterol	97.6 ± 22.0	98.5 ± 27.8	0.826
HDL-cholesterol	52.1 ± 13.6	55.4 ± 11.2	0.106
Cardiac Tn (ng/L)	55 (104.5)	-	-
NT-proBNP (pg/mL)	4385 (3112)	55 (34)	<0.001
Elabela-32 (ng/mL)	9.89 ± 3.22	1.84 ± 1.13	<0.001
Echocardiographic data			
LVEF (%)	25.5 ± 5.0	60.2 ± 4.1	<0.001
LVEDV (ml)	141.05 ± 6.79	86.23 ± 4.54	<0.001
LVESV (ml)	97.71 ± 5.07	36.53 ± 4.95	<0.001
LVEDD dimension (mm)	51.2 ± 3.6	40.4 ± 1.1	<0.001
LVESD dimension (mm)	34.8 ± 4.8	28.0 ± 1.8	<0.001
LA (mm)	37.8 ± 4.7	33.7 ± 3.6	<0.001
LAVi (ml/m^2)	38.9 ± 2.9	30.2 ± 1.7	<0.001
IVS (mm)	10.1 ± 1.1	9.8 ± 1.0	0.093
PW (mm)	8.4 ± 1.2	7.9 ± 0.7	0.004
Medical therapy before admission, n			
ARNI, n	11		
ACEI/ARB, n	57		
Beta-bloker, n	36		
Ivabradin, n	8		
Diuretic, n	39		
Spironolactone, n	17		

Values are presented as means ± standard deviation, medians with the interquartile range values in brackets. HfrEF: heart failure patients with reduced ejection fraction, ACEI: angiotensinogen converting enzyme inhibitor, ALT: alanine aminotransferase, ARB: angiotensin receptor blocker, ARNI: angiotensin receptor-neprilysin inhibitor, AST: aspartate transaminase, BMI: body mass index, CAD: coronary artery disease, DBP: diastolic blood pressure, HDL: high-density lipoprotein, HFrEF: heart failure with reduced ejection fraction, IVS: interventricular septum, LA: left atrium, LAVi: left atrial volume index, LDL: low-density lipoprotein, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, n: number, NT-proBNP: N-terminal pro-brain natriuretic peptide, p: statistical significance, PW:posterior wall, SBP: systolic blood pressure, TSH: thyroid-stimulating hormone, Tn: troponin, WBC: white blood cell.

Table 2: Pairwise comparisons of Elabela values according to the New York Heart Association classification of heart failure with reduced ejection fraction patients.

NYHA classifacation	Elabela (ng/mL)	Pairwise comparisons	p [Elabela (ng/mL)]
NYHA class 1 (n=12)	6.25±0.75	Class 1 - Class 2	0.025
NYHA class 2 (n=27)	8.64±1.30	Class 1 - Class 3	<0.001
NYHA class 3 (n=24)	10.58±1.59	Class 1 - Class 4	<0.001
NYHA class 4 (n=10)	15.95±3.22	Class 2 - Class 3	0.024
		Class 2 - Class 4	<0.001
		Class 3 - Class 4	0.034

NYHA: New York Heart Association.

remodeling of the ventricular wall. The ELA-APJ pathway in an animal model[17,25] can suppress pathological hypertrophy and remodeling. In rat models of myocardial infarction, the effects of ELA on cardiac fibrosis were observed in invasive catheter measurements, and LV systolic and end-diastolic pressures were improved following ELA treatment[26]. Biological studies on ELA are rare, and comprehensive studies are needed. Several pathways within the apelin/ELA APJ system have been discussed in detail, and therapeutic strategies have been suggested for those with cardiovascular diseases[27]. As seen in the current study, increased ELA levels were associated with natriuretic peptide levels in HFrEF patients, suggesting that different systems may be active simultaneously in the pathogenesis of HF.

Table 3: The correlation between Elabela and various variables.

	r-value	p
Age	0.115	0.161
BMI	0.121	0.140
Cardiac Tn	0.257	0.001
NT-proBNP	0.869	<0.001
LVEF	-0.849	<0.001
LVEDV	0.832	<0.001
LVESV	0.691	<0.001
LVEDD dimension	0.811	<0.001
LVESD dimension	0.568	<0.001
LA	0.337	<0.001
LAVi	0.736	<0.001

BMI: body mass index, Tn: troponin, NT-proBNP: N-terminal pro-brain natriuretic peptide, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, LA: left atrium, LAVi: left atrial volume index.

One limitation of our study is its single-center design and limited number of cases. We performed a one-time measurement of ELA-32 levels in HFrEF patients. However, we have not obtained any information about the effect of different drug combinations or dose increases on ELA-32 blood levels over time. Although ELA-32 levels were only measured once, considering the relationship between ELA-32 levels and NYHA, biochemical, and echocardiographic parameters, our study may guide prospective studies for the therapeutic use of ELA and derivatives. The kit we used in the study is reasonably priced; however, the cost of the review and cost-effectiveness analyses is not included herein.

In conclusion, for the first time in the literature, the relationship between ELA levels and cardiovascular mortality and HF-related hospitalization in patients with HFrEF was evaluated. ELA-32 levels increased in parallel with the NYHA stage in HFrEF patients. ELA-32 levels are independent predictors of cardiovascular mortality and HF-related hospitalization in HFrEF patients.

Conflict of interest

Authors declare no conflicts of interest.

Table 4: Univariate and multivariate Cox regression analysis for predicting study endpoints. The variable with a non-adjusted p-value of 0.1 was considered a potential risk factor and included in the multivariate analysis.

Variables	Univariate analysis			Multivariate analysis		
	HR	95 % CI	p	HR	95 % CI	p
Age	1.052	1.000-1.101	0.041	1.023	0.964-1.230	0.039
Gender	0.963	0.332-2.764	0.941			
LVEF	0.924	0.853-0.991	0.032	0.756	0.632-1.018	0.465
LVEDV	1.215	0.742-1.627	0.023	1.142	1.022-1.547	0.028
LAVi	0.686	0.492-0.822	0.078			
Hemoglobin	0.944	0.873-1.025	0.154			
Sodium	1.011	0.952-1.080	0.610			
Uric acid	1.078	0.910-1.261	0.378			
NT-proBNP	1.187	1.091-1.579	0.011	1.300	1.017-1.874	0.017
Cardiac Tn	1.000	0.998-1.002	0.948			
ELA-32	1.395	1.123-1.716	0.002	1.501	1.112-2.480	0.008
ELA-32 ≥8.25	2.264	1.197-4715	0.001	2.556	1.078-3.941	<0.001

HR: hazard ratio, CI: confidence interval, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LAVi: left atrial volume index, NT-proBNP: N-terminal pro-brain natriuretic peptide, Tn: troponin, ELA: Elabela.

Table 5: Clinical outcomes depending on whether the Elabela (ELA-32) value is equal to or greater than 8.25, or less than 8.25.

	All (n =73)	ELA-32 ≥8.25 (n =42)	ELA-32 <8.25 (n =31)	p
Cardiovascular mortality	9 (12.3)	8 (19)	1 (3.2)	0.042
HF-related hospitalization	29 (39.7)	26 (61.9)	3 (9.7)	<0.001
Hospital stay duration (days)	7.65 ± 4.08	9.35 ± 4.47	5.35 ± 1.78	<0.001

Values are presented as means ± standard deviation, medians with the interquartile range values in brackets. HF: heart failure, ELA: Elabela.

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