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Review Article

Circulating Elabela for severity assessment and prognosis of human diseases: clinical evidence and translational limitations

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Abstract: Elabela (ELA) is an endogenous ligand that is of critical importance in the modulation of the cardiovascular, renal, and placental physiology. Clinical studies have pointed to an association of circulating levels of ELA with some pathophysiologic conditions, such as coronary artery disease, heart failure, chronic kidney impairment, preeclampsia, and microvascular complications of the diabetes. However, its correlation with the degree of the disease and short-term prognosis is not always consistent; it could dependon: the stage of the disease, timing of the sample collection, renal status, type of specimen, different peptide variants, and the analytical method. Current evidence is mainly from cross-sectional studies with a small sample size and a lack of any standard assay protocol. Research on the prognosis of heart failure is still scarce and gives contradictory findings. In this review, we discuss the biological basis and the clinical correlations of ELA, assesses its limitations by the detection methods and the sample handling, and outline the future directions. In the future, prospective multicenter studies with proven detection methods, prespecified clinical endpoints, and external validation are needed to clarify the clinical benefits of ELA beyond existing biomarkers.

Keywords: Elabela, apelin receptor, biomarker, heart failure, chronic kidney disease, preeclampsia

Introduction

Elabela (ELA), also called apela or toddler, is an endogenous bioactive peptide. It is encoded by the APELA gene, called apelin receptor early endogenous ligand (APELA), on human chromosome 4. By proteolytic processing, the precursor of 54 amino acids is processed to ELA-32, a peptide that contains 32 amino acid (QRPVNLTMRRKLRKHNCLQRRCMPLHSRVPFP). It also exists as shorter biologically active fragments: ELA-21 and ELA-11. The peptide segments have a conserved C-terminal domain that is involved in the activation of the receptor [1].

ELA is present in different tissues during embryonic development and also in adulthood, in the heart, vascular system, kidneys, placenta, etc. The biological effects of ELA are mainly mediated by the interaction with the apelin receptor (APLNR, formerly called APJ), but it also binds to apelin [2]. ELA activates G protein as well as the β-arrestin-mediated response and subsequent signaling through the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) cascades [3, 4].

Experimental studies have shown that the ELA-APLNR signaling pathway is involved in embryonic development [5], cardiovascular homeostasis [6], renal protection [7] and placental adaptation (**Figure 1**) [8]. However, it remains uncertain whether tissue expression can predict the concentration of the full-length circulating peptide.

Therefore, clinical studies have examined circulating ELA in heart failure (HF) [9], hypertension [10], chronic kidney disease (CKD) [11], and preeclampsia (PE) [12-14]. The results of the studies vary depending on the disease phenotypes and sampling conditions (**Table 1**).

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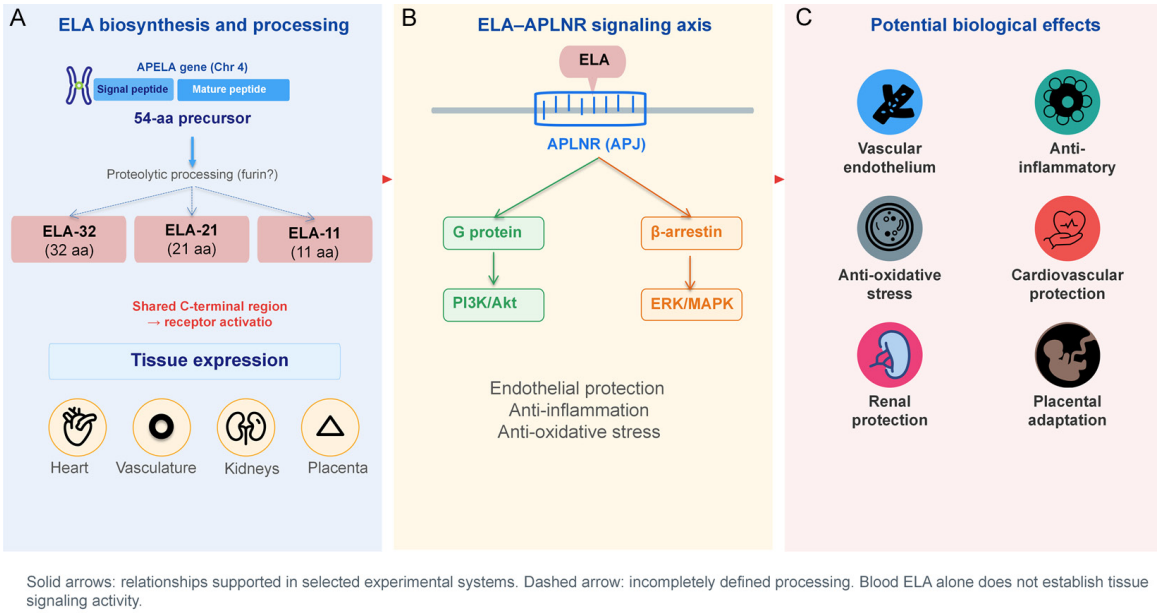


Figure 1. ELA processing, APLNR signaling, and potential biological effects. ELA-32, ELA-21 and ELA-11 are shown jointly as bioactive forms capable of APLNR activation. G protein signaling and β-arrestin recruitment are context dependent; PI3K/Akt and ERK/MAPK participate in experimental protective responses. Solid arrows indicate relationships supported in selected experimental systems; the dashed processing arrow indicates incompletely defined tissue-specific maturation. Experimental effects on inflammation and cardiorenal injury are not evidence of clinical biomarker utility. Circulating concentration also reflects production, degradation, uptake, clearance, and the measurement method, and does not establish tissue signaling activity. Figure abbreviations: ELA, Elabela; APLNR, apelin receptor; aa, amino acid; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; Other clinical abbreviations are defined in **Table 1**.

The reported changes in ELA vary depending on the disease, and sometimes even within the same condition. Depending on the phase of the disease, when the sample was obtained, the status of the kidney function, the type of matrix of the specimen, the specific peptide isoform, and the analytical techniques used, all of these could play a role (**Figure 2**). In the observed track, there is an initial compensatory rise and then a second fall; but this is still only a theory, because there is not yet any longitudinal human evidence to support it. In this article we discuss the basic biologic mechanisms, the clinical associations, the limits of measurement, and the steps of validation we need to conduct rigorous validation studies to demonstrate its clinical utility relative to existing biomarkers.

Biological characteristics and signaling mechanisms

Biosynthesis, proteolytic processing, and biological stability

ELA is expressed in cardiovascular, renal, and placental tissues. Some studies have suggested that the endothelial cells of cardiac microvessels might be the source of ELA in the heart [15]; in addition, there are reports indicating that its expression is also present in cardiomyocytes, renal cells, and placental trophoblasts [7, 8, 16]. Under physiologic and pathologic circumstances, the relative contributions of various cells to circulating ELA are not clear. ELA is described as a 54-amino-acid precursor, which is then processed into shorter bioactive peptides, such as ELA-32, ELA-21, and ELA-11 [17]. Additionally, furin has been proposed as a processing enzyme, but the exact intracellular cleavage pathway and its tissue specificity remain to be fully established.

The kidneys may be involved in the uptake and degradation of ELA. However, the relative roles of filtration and local proteolysis are not yet clearly defined [7, 18]. In experimental systems, ELA shows relative resistance to angiotensin-converting enzyme, angiotensin-converting enzyme 2, and neprilysin under selected assay conditions [19]. This observation does not establish stability in clinical blood samples.

Table 1A. Clinical studies of circulating ELA and limits of inference

Study/context	Population and design	Specimen and assay	Concentration or main estimate	Interpretation and limitation
STEMI [30]	74 STEMI; 74 angiography-negative controls; cross-sectional	Serum in methods; Sunred ELISA; early sampling	0.68 ± 0.68 vs 1.34 ± 0.88 ng/mL; P < 0.001; inverse SYNTAX association	No outcome follow-up; abstract/methods differ on matrix; timing inconsistently reported
ACS [31]	175 ACS; 26 angiography-negative controls; cross-sectional	EDTA plasma; Peninsula S-1508.0001; morning after admission	95.04 ± 18.66 vs 71.90 ± 8.93 ng/mL; P < 0.01; nonlinear SYNTAX association	Restricted-range association; no validated cutoff or outcome prediction
Mixed CAD [32]	238 CAD; 86 controls; cross-sectional	EDTA/aprotinin plasma; Phoenix EIA; collected before angiography	1.55 ± 0.23 vs 1.40 ± 0.15 ng/mL; P < 0.05; no significant SYNTAX correlation	Cross-sectional; source gives inconsistent control concentrations in its overall and subgroup reporting; no outcome follow-up
HF with hypertension [9]	134 hypertensive HF; 134 hypertensive non-HF; 40 controls; 180-day HF follow-up	Extracted plasma; Peninsula S-1508 EIA	Adjusted MACE HR 0.75 (95% CI 0.61-0.99), P = 0.048; continuous ELA in the reported Cox model[a]	Lower ELA associated with MACE (death or HF readmission); signal mainly from readmission; mortality difference nonsignificant
HFrEF [34]	73 HFrEF; 77 controls; case-control comparison with mean follow-up 7.48 ± 2.73 months	Serum ELA-32; Sunred sandwich ELISA	9.89 ± 3.22 vs 1.84 ± 1.13 ng/mL, P < 0.001; higher ELA-32 associated with CV death/HF hospitalization; endpoint AUC 0.84 (0.72-0.98)	Opposite outcome direction to [9]; sample-derived threshold; regression reporting contains inconsistencies; no external validation
HF diagnosis [46]	216 HF; 119 non-HF; single-center diagnostic comparison	Extracted plasma; Peninsula S-1508 EIA; samples within 24 h of admission	7.3 ± 3.9 vs 13.7 ± 3.0 ng/mL; P < 0.001; diagnostic AUC 0.835 (95% CI 0.790-0.873)	Diagnostic comparison of existing HF; HFpEF predominated; no validation of prospective-event prediction

Concentrations are mean ± SD unless identified as medians. Values retain the units of each source and are not interchangeable reference intervals. [a]HR is reported for continuous ELA; the unit increment is not explicitly stated in the article text. No risk reduction per unit is inferred here.

Table 1B. Clinical studies of circulating ELA and limits of inference continued

Study/context	Population and design	Specimen and assay	Concentration or main estimate	Interpretation and limitation
Hypertension/carotid IMT [37]	104 hypertensive participants; cross-sectional	Peptide extraction followed by ELISA; matrix and kit not specified in abstract[b]	ELA vs carotid IMT: r = -0.213, P = 0.030; lower ELA with increased IMT	Vascular phenotype association; no incident-event prediction
CKD [11]	20 each: controls, CKD1, CKD3, CKD5; cross-sectional	Reported serum; EDTA/acetic-acid tubes described; Peninsula EIA	Controls 6.14 ± 1.03; CKD1 5.39 ± 1.91; CKD3 3.81 ± 1.12; CKD5 2.67 ± 1.01 ng/mL; overall P < 0.001	Matrix reporting inconsistent; no longitudinal renal endpoint
T2D/albuminuria [38]	80 T2D; four ACR/creatinine strata, n = 20 each; cross-sectional	Serum; Peninsula human ELA EIA	ELA vs ACR: r = -0.561, P < 0.001; ELA vs eGFR: r = 0.318, P = 0.004	Association with existing albuminuria; no kidney-progression follow-up
Early- and late-onset PE [13]	Early PE 54/controls 56; late PE 52/controls 52; cross-sectional comparison	Plasma; Peninsula EIA; sensitivity 0.088 ng/mL	Late PE median 8.43 vs 3.95 ng/mL, P < 0.001; early PE comparison P = 0.319	No validated pre-onset prediction or added value over sFlt-1/PlGF
Late-onset PE [41]	60 PE; 60 controls; clinical comparison and assay development	Serum; Phoenix [pGlu1]-ELA-32 immunoassay	12.57 ± 7.77 vs 36.99 ± 23.58 ng/mL; lower in PE	Lower ELA, opposite to [13]; disease-status comparison; assay development does not establish pre-onset prediction
Diabetic retinopathy [43]	20 each: controls, no DR, NPDR, PDR; cross-sectional	Serum; Fine Biotech EH4533 sandwich ELISA	Controls/no DR/NPDR/PDR: 216.49 ± 58.85/217.19 ± 97.54/221.76 ± 93.12/302.35 ± 146.17 pg/mL; overall P = 0.123	Numerical PDR increase was not significant; no validated severity gradient

[b]The available abstract reports peptide extraction and ELISA but does not specify the specimen matrix or kit. Matrix descriptions in [11] and [30] are internally inconsistent and remain explicit. AUCs for diagnosis and for follow-up endpoints must not be compared as the same intended use. Abbreviations: ELA, Elabela; ACS, acute coronary syndrome; CAD, coronary artery disease; STEMI, ST-segment elevation myocardial infarction; HF, heart failure; HFrEF/HFpEF, HF with reduced/preserved ejection fraction; CKD, chronic kidney disease; T2D, type 2 diabetes; PE, preeclampsia; DR, diabetic retinopathy; NPDR/PDR, nonproliferative/proliferative DR; IMT, intima-media thickness; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve; MACE, major adverse cardiac events; CV, cardiovascular; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; EDTA, ethylene diamine tetraacetic acid; sFlt-1/PlGF, soluble fms-like tyrosine kinase-1/placental growth factor.

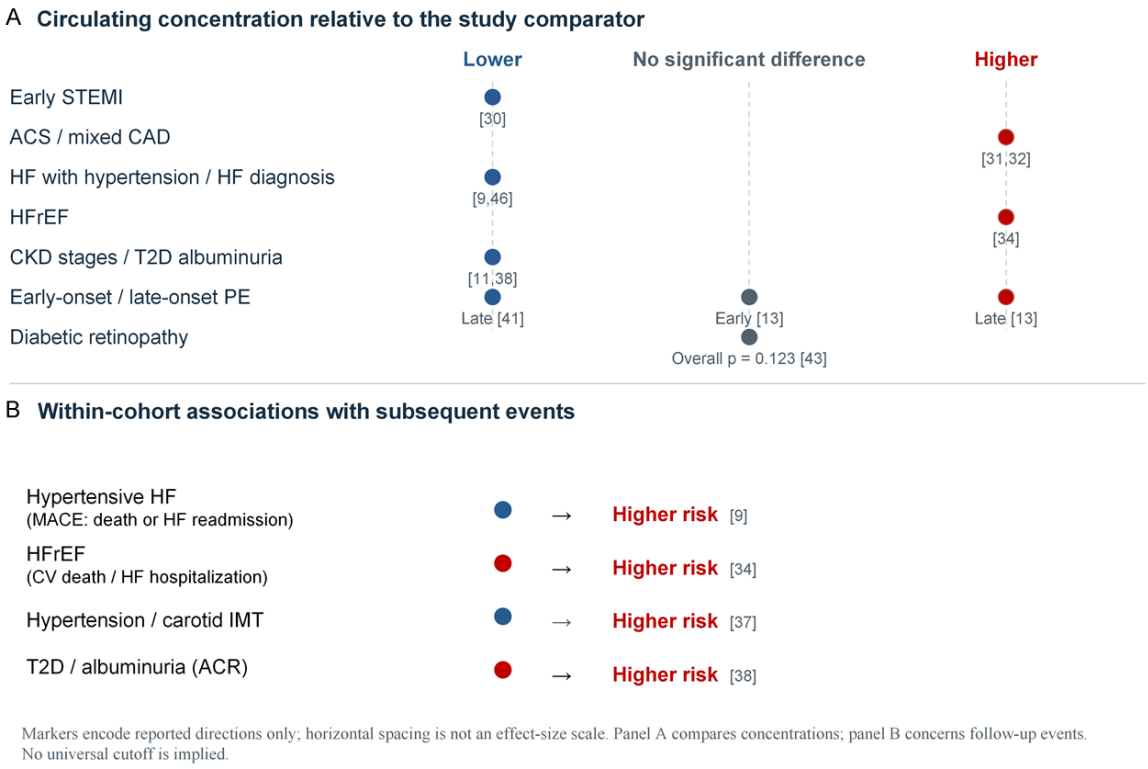


Figure 2. Study-specific ELA patterns and heart failure outcomes. A. Maps reported concentration differences against each study comparator. Marker positions encode direction or statistical non-significance, and their spacing has no effect-size meaning. Late-onset PE and HF studies reported opposing directions; the numerical increase in proliferative diabetic retinopathy was not significant in the overall comparison. B. Distinguishes within-cohort associations with subsequent events from between-group concentration differences. The hypertensive HF and HFrEF studies reported discordant outcome associations. No pooled effect, causal relation or transferable cutoff was implied. Figure abbreviations: ELA, Elabela; STEMI, ST-segment elevation myocardial infarction; ACS, acute coronary syndrome; CAD, coronary artery disease; HF, heart failure; HFrEF, HF with reduced ejection fraction; CKD, chronic kidney disease; T2D, type 2 diabetes; PE, preeclampsia; MACE, major adverse cardiac events; CV, cardiovascular; IMT, intima-media thickness; ACR, albumin-to-creatinine ratio.

ELA-32 has a reported *in vitro* half-life of about 47 minutes in human plasma and about 44 seconds in kidney homogenate [18]. Modified peptides, like PEGylated and acylated analogues [20] and an Fc-fusion construct [21], have been developed to extend exposure. Their pharmacology cannot be assumed to match that of endogenous circulating ELA. The kidney-homogenate result should not be interpreted as a whole-blood half-life. Gene delivery has also been investigated to sustain ELA expression in hypertensive rats [22].

ELA-APLNR signaling

ELA is an endogenous agonist of APLNR and activates multiple intracellular pathways [23]. PI3K/Akt and ERK/MAPK signaling have been experimentally linked to endothelial survival and resistance to oxidative injury [4, 23]. APLNR can recruit β-arrestin, which affects receptor trafficking and downstream responses [24].

The ELA-21 and ELA-11 retain the conserved C-terminal region of ELA-32, but the peptide length and membrane interaction might affect their biological activity [1]. Clinical assays that recognize this shared region might detect more than one molecular form; thus, isoform-specific concentrations require analytical confirmation.

ELA shares the same receptor of apelin, but it behaves differently because of differences in the ligand structure, ligand concentration, and cellular environment that can modulate the G protein coupling, and the recruitment and dynamics of receptor trafficking [24]. Even if these differences could lead to different bio-

logical outcome, circulating ELA as a biomarker is of uncertain clinical importance.

Circulating ELA levels and physiologic determinants

Previous reports have indicated that the concentrations of ELA-21 and ELA-11 in human serum can reach picograms per milliliter levels [25]. There is large variation in the level of ELA in peripheral blood reported by different previous studies, and a reference interval for the healthy individuals is not yet defined [18]. Such variations may be due to a combination of biological variability and to technical reasons, as for example, variations in the sample matrices, analytical techniques, antibody specificity and calibration. Commercial immunoassays may also have different sensitivities to the different ELA isoforms and peptide fragments. In any case, any comparison of the absolute concentration values in the different studies should take in account the analytical methods used.

Multiple physiologic and clinical factors may affect the level of ELA in the circulation, such as renal function and pregnancy status [12, 26, 27]. Age and gender also need to be taken into account [16, 22]. Among these variables, renal function is of particular clinical significance, as the kidneys play a dual role in both the metabolism and systemic clearance of ELA [11]. Therefore, impaired renal function may independently alter the level of ELA in the circulation. In clinical research on ELA, renal indicators - especially the estimated glomerular filtration rate (eGFR) - should be considered as preset covariates. The state of pregnancy also needs to be separately considered, as gestational age, placental function, body mass index, and the presence of pregnancy-related complications may all affect its concentration in the circulation.

The ELA present in the circulation cannot be considered a reflection of tissue expression or APLNR signal transduction. Its concentration is determined by generation, release, degradation, intake, and clear decision process. A single blood test cannot distinguish between these processes [7, 18].

ELA levels associated with pathologic conditions are not uniform. For example, a reduced circulating concentration has been observed in some cohorts of heart failure patients and in some stages of chronic kidney disease [9, 11]. The research done on preeclampsia and acute coronary syndromes gives findings that are either not consistent or directly opposed [12, 26]. Such variations do not support the idea of a global drop in ELA in all disease states. Rather, the levels of circulating ELA seem to change depending on the kind of disease, its severity and the stage of its progression and of the sampling time. The presence of such heterogeneity and the differences among populations make it very difficult to define a common reference range or to find clinically useful cutoffs.

Cardiovascular disease: associations with disease severity and clinical outcomes

Coronary artery disease and acute coronary syndromes

Experimental studies indicate that ELA might modulate endothelial function, oxidative stress, inflammation, and vascular remodeling [23, 28, 29]. Nevertheless, clinical studies on the circulating ELA levels in patients with coronary artery disease (CAD) and acute coronary syndrome (ACS) have yielded heterogeneous results. The association between ELA and the burden of angiographic diseases is not fixed; it varies according to clinical presentation, the time of sampling, and the analytical method employed.

In a study of 74 patients with early ST-segment elevation myocardial infarction (STEMI) who had primary percutaneous coronary intervention, the circulating ELA was lower than controls, and it was inversely related to the SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score [30]. Although the title and abstract mention the first 24 hours, the methods and conclusion describe earlier sampling. The methods described in the abstract do not specify the plasma, but rather the serum. These reporting inconsistencies hinder the ability to compare with other studies. This finding indicates a correlation between the presence of lower ELA in acute ST-elevation myocardial infarction and the anatomic complexity of coronary lesions. The cross-sectional design cannot determine the order of myocardial injury.

In another separate study involving 175 ACS patients and 26 angiography-negative controls,

the plasma ELA levels of the ACS patients were higher (95.04 ± 18.66 ng/mL compared to 71.90 ± 8.93 ng/mL) [31]. Its relationship with SYNTAX score was non-linear, and a positive correlation was reported when the ELA range was 63.47-85.49 ng/mL [31]. In a mixed CAD cohort consisting of 238 CAD patients and 86 controls, the patients' ELA levels were also higher, but there was no significant association with SYNTAX score [32]. Therefore, higher ELA concentrations in CAD patients do not always indicate more severe angiographic lesions.

The direction of ELA varies across various clinical stages of CAD, and this remains unclear. Some studies have found that in ACS [31], the ELA concentrations are increased. On the contrary, other studies have described that during the early phase of STEMI [30], the ELA concentrations were lower. These findings seem conflicting, but they might be due to differences in the interval between symptom onset and blood collection, the timing of reperfusion, the size of the infarct, the renal function, the control-group selection, the sample matrix, and the assay characteristics. But, comparing these studies cannot determine how ELA changes during an acute coronary event. Serial measurements are necessary to determine whether the observed differences are due to changes over time or differences between study populations and methods.

More specific experimental evidence indicates that ELA may slow down the progression of atherosclerosis by regulating vascular inflammation and macrophage polarization [33]. These mechanism studies have provided biologic evidence for the protective effect of the ELA-APLNR axis, but this should not be misinterpreted as meaning that the circulating ELA is a recognized diagnostic marker or therapeutic target in coronary artery disease.

Serial sampling is anchored to the onset of symptoms and reperfusion is necessary to determine whether ELA changes during acute ischemia and recovery. Comparisons should differentiate between STEMI and other ACS presentations, and also account for the specimen matrix and renal function.

Heart failure

Circulating ELA has also been investigated as a potential marker of disease severity and prognosis in heart failure (HF). In a single-center study of hypertensive patients with heart failure, major adverse cardiac events (MACE) were defined as all-cause death or heart failure readmission during 180 days of follow-up [9]. The association with lower ELA was driven mainly by readmission; mortality did not differ significantly between the low- and high-ELA groups.

Lower baseline plasma ELA was associated with more adverse cardiac events in patients with hypertension and heart failure [9, 16]. In multivariable Cox proportional hazards analysis, the association persisted after adjustment for established prognostic variables [9]. These observations raise the possibility that ELA provides prognostic information complementary to conventional measures of cardiac function, but incremental predictive performance has not been established. However, a small study on HF with reduced ejection fraction (HFrEF) reported an association between higher serum ELA-32 concentrations and adverse outcomes [34]. This finding requires confirmation and limits its generalization of the association between lower ELA concentrations and poorer prognosis to other HF populations.

The discordant findings cannot establish a common prognostic direction across HF populations. Differences in HF phenotype, clinical stability, renal function, and serum versus plasma measurement limit direct comparison. Repeated sampling during decompensation and stabilization would help distinguish transient responses from persistent associations with cardiac dysfunction.

Hypertension and vascular dysfunction

Experimental evidence suggests that ELA participates in blood pressure regulation and may protect against hypertension-associated vascular and renal injury [35, 36]. In the deoxycorticosterone acetate/salt-induced hypertension model, renal ELA expression was reduced, whereas ELA overexpression attenuated hypertension, renal structural injury, oxidative stress, and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation [36]. Some protective effects persisted after disruption of APLNR signaling in this experimental model, suggesting that additional mechanisms may be involved. Independent mechanistic confirmation is needed.

Limited clinical evidence also supports an association between circulating ELA and vascular dysfunction. In a small cross-sectional study of patients with essential hypertension, plasma ELA concentrations were lower than those in age-matched normotensive controls [10]. Lower ELA was also associated with impaired brachial artery flow-mediated dilation and increased brachial-ankle pulse wave velocity, suggesting potential relationships with endothelial dysfunction and arterial stiffness [10]. Another clinical study found an association between circulating ELA and hypertension-related subclinical atherosclerosis [37].

These findings indicate that the reduction of circulating ELA may be associated with vascular dysfunction in essential hypertension. But the available clinical studies are small, and mostly cross-sectional, so we cannot make conclusions about causality, temporal sequence, or prognostic value. It is also uncertain whether reduced ELA contributes to hypertension, is a consequence of vascular or renal injury, and is affected by antihypertensive treatment and renal clearance.

Longitudinal assessment before and after blood pressure control could determine whether ELA tracks vascular dysfunction independently of antihypertensive treatment and renal function.

Kidney disease: circulating ELA and renal phenotypes

Chronic kidney disease

The kidney expresses ELA and may also participate in its clearance and degradation [7, 18]. A cross-sectional study of 60 patients with CKD and 20 controls reported different serum ELA concentrations across CKD stages, with associations involving eGFR, serum creatinine, and blood urea nitrogen [11]. These findings suggest that kidney function must be considered both as a disease phenotype and as a determinant of measured circulating ELA. They do not distinguish changes in peptide synthesis from altered clearance or proteolysis. Reduced clearance alone would not explain lower circulating ELA; reduced production or altered proteolysis may also contribute, but their relative effects have not been established.

Diabetic kidney disease and evidence gaps

Serum ELA was associated with albuminuria among patients with type 2 diabetes [38]. Neither this study nor the CKD stage comparison established that ELA predicts subsequent loss of kidney function. A five-year apelinergic-system study reported longitudinal renal associations for apelin [39]; these findings do not establish the prognostic value of ELA. Future renal studies should measure both peptides in the same samples, adjust for eGFR and albuminuria, and evaluate prespecified longitudinal kidney endpoints.

Pregnancy-related and metabolic microvascular disorders

Hypertensive disorders of pregnancy and preeclampsia

Circulating ELA has been studied extensively in hypertensive disorders of pregnancy, particularly preeclampsia, but the available experimental and clinical evidence is not fully concordant. In mice, APELA deficiency produced hypertension, proteinuria, glomerular endothelial proliferation, impaired placental angiogenesis, and fetal growth restriction, whereas exogenous ELA partially reversed the preeclampsia-like phenotype [40]. These experimental findings support a role for the ELA-APLNR axis in placental development and maternal cardiovascular adaptation. However, the extent to which this knockout model reproduces the heterogeneous pathophysiology of human preeclampsia remains uncertain.

Human findings are less consistent. In one study, maternal plasma ELA concentrations in early-onset preeclampsia did not differ significantly from those in gestational-age-matched uncomplicated pregnancies, whereas concentrations were higher in late-onset preeclampsia [13]. Moreover, when ELA was evaluated together with soluble Fas (sFas), and not as a single marker, a stronger correlation with the late-onset preeclampsia was found [13]. Such observations show that the relation is for some phenotypes only, and not for a consistent, universal deficit in the ELA.

However, the increase in the ELA levels described by Para et al. [13] is not entirely reproduced in cases of late onset preeclampsia. In

fact, another investigation provided evidence to the contrary: women affected had serum ELA concentrations that were less than in the control groups [41]. A systematic review also pointed out the great heterogeneity all in the human studies [14]. Although the differences in the gestational age, mother's body mass index, disease severity, specimen matrix, and assay methodology could in part explain these differences, the effect of each variable was not defined. So, circulating ELA does not appear to be suitable as an independent diagnostic biomarker for preeclampsia. To discriminate between predictive association and response of the already established pathology, it is necessary to have samples in some specific gestational stage before the clinical manifestation. The early onset and the late onset phenotypes have to be separately evaluated.

Diabetes and microvascular complications

Diabetic retinopathy represents a predominant small-vessel disorder associated with diabetes mellitus. Experimental and mechanistic evidence suggest that the ELA-APLNR system may influence endothelial survival, oxidative stress, inflammation, and microvascular homeostasis in diabetes [42]. However, direct evidence supporting a protective effect of ELA in the human retina remains limited, and findings from other diabetic complications should not be extrapolated automatically to diabetic retinopathy.

Clinical evidence is restricted to a small number of exploratory studies. A pilot cross-sectional study, with 20 participants in each diabetic subgroup and 20 controls, reported mean serum ELA concentrations of approximately 217.19 pg/mL in patients without diabetic retinopathy, 221.76 pg/mL in those with nonproliferative diabetic retinopathy, and 302.35 pg/mL in those with proliferative diabetic retinopathy [43]. The between-group comparison was not statistically significant in the study table; the numerical difference therefore should not be interpreted as a validated severity gradient. A compensatory response remains a hypothesis that cross-sectional data cannot test.

These findings do not establish a relationship between circulating ELA and retinopathy severity. Interpretation was limited by the small sample size, the lack of a statistically robust between-group difference or external validation, and possible confounding by diabetes duration, glycemic control, renal function, body mass index, and treatment. Intraocular ELA was not measured and could not be inferred from the serum findings.

Studies using standardized retinopathy grading should distinguish circulating from intraocular ELA and determine whether either measurement relates to subsequent retinal progression. The current pilot findings do not establish ELA as a marker of retinopathy severity.

Clinical and translational value of circulating ELA

Relationship with established clinical indicators and potential incremental value

The clinical relevance of circulating ELA depends on whether it adds information beyond established diagnostic and prognostic indicators. In one heart failure cohort, lower plasma ELA was associated with higher B-type natriuretic peptide (BNP), worse New York Heart Association functional class, and lower left ventricular systolic function [9]. ELA concentrations also differed among ejection-fraction phenotypes [9]. These associations require confirmation in other populations and do not by themselves establish incremental predictive value.

The inverse association with BNP measured in the hypertensive heart failure cohort and the positive association with left ventricular ejection fraction (LVEF) are consistent with lower ELA accompanying worse cardiac function in that cohort. However, the opposite findings in the HFrEF cohort limit this interpretation across heart failure populations. Neither relationship establishes that ELA improves prediction beyond natriuretic peptides and clinical variables.

In CAD and ACS, associations between ELA and the SYNTAX score have varied across studies. ELA was inversely associated with the SYNTAX score during the early phase of STEMI [30], showed a concentration-dependent nonlinear association in another ACS cohort [31], and was unrelated to the score in a mixed population with stable angina, unstable angina, and acute myocardial infarction [32]. These inconsistent results indicate that ELA cannot cur-

rently be regarded as a stable surrogate for anatomical coronary disease burden.

To establish incremental clinical value, future studies should compare models with and without ELA and report changes in discrimination and calibration. Appropriate analyses may include changes in the C-statistic, calibration plots or slopes, likelihood-based model comparison, and decision curve analysis. Reclassification measures should be used cautiously and only with clinically meaningful risk categories. At present, evidence that ELA improves clinical decision-making beyond BNP, N-terminal pro-B-type natriuretic peptide (NT-proBNP), LVEF, or established coronary risk scores is insufficient. In CKD, the corresponding comparison should include eGFR and albuminuria; in preeclampsia, it should include clinical assessment and the soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio.

Evidence from longitudinal clinical outcomes

Longitudinal evidence for the prognostic value of ELA remains limited and is concentrated mainly in heart failure. In a prospective, single-center study, 134 hypertensive patients with heart failure were followed for 180 days [9]. Higher plasma ELA was associated with better readmission-free and major adverse cardiac event (MACE)-free survival; the reported adjusted hazard ratio for MACE was 0.75 (95% confidence interval 0.61-0.99; P = 0.048) [9]. This preliminary association should be interpreted cautiously in view of the short follow-up, restricted population, and borderline statistical significance. An association with all-cause mortality was not demonstrated in this cohort, and long-term survival prognostic value remains unconfirmed.

In a separate study of 73 patients with HFrEF followed for a mean of 7.48 ± 2.73 months, higher serum ELA-32 was associated with cardiovascular death or HF-related hospitalization [34]. This opposite direction limits extrapolation across HF populations and requires independent confirmation.

Evidence in kidney disease is primarily cross-sectional rather than prognostic. Serum ELA concentrations differed across CKD stages and were associated with indices of renal function, including estimated glomerular filtration rate, serum creatinine, and blood urea nitrogen [11]. The cited study did not assess renal survival or progression to kidney failure during follow-up. It supports an association with CKD severity but cannot establish prediction of subsequent renal outcomes.

Similarly, in type 2 diabetes, serum ELA was associated with the urinary albumin-to-creatinine ratio and albuminuria severity [38]. This cross-sectional analysis could not establish whether ELA predicts the onset or progression of diabetic kidney disease. Prospective studies with repeated measurements and prespecified renal endpoints, such as sustained eGFR decline or kidney failure, are required.

Evidence in pregnancy should also be distinguished from true prognostic validation. Maternal ELA was higher in late-onset preeclampsia but not significantly different in early-onset disease in one study [13]. Measurements obtained after disease onset assess an association with existing disease and cannot establish prediction before clinical presentation.

Outcome evidence is therefore concentrated in small HF studies with discordant findings, while prospective prognostic value in the other disease settings remains unestablished.

Comparison with apelin

ELA and apelin are endogenous APLNR ligands whose circulating concentrations, molecular forms, processing, and receptor responses may differ (**Table 2**) [44, 45]. Both of these biomarkers have been investigated in the context of cardiovascular disease, but existing research is characterized by heterogeneity in the study populations, in sample collection protocols, and in analytical techniques. These differences limit indirect comparisons of their clinical performance; direct head-to-head studies in the same samples are needed.

Since certain molecular forms of ELA are relatively tolerant to specific enzymes under certain experimental conditions, it is considered to be a potentially more stable or more informative biomarker. However, at the moment the existing clinical data have not been able to show that ELA has more reliable prognostic value than apelin. Indeed, the levels of ELA reported change according to the particular pathology, disease stage, time of collection of the sample and the detection used. Moreover, the

Table 2. ELA and apelin as APLNR ligands and candidate biomarkers

Feature	ELA	Apelin	Interpretation
Precursor	APELA	APLN	Distinct peptide precursors
Receptor	APLNR	APLNR	Shared receptor does not imply identical responses
Molecular forms	ELA-32, ELA-21, ELA-11	Multiple apelin isoforms	Specify molecular species and antibody recognition
Experimental stability	Relative resistance to selected enzymes in experimental conditions [19]	Susceptibility depends on peptide form and enzyme [19]	No established superiority for clinical sample stability
Direct HF comparison	Higher diagnostic AUC than apelin in one cohort [46]	Lower diagnostic AUC in the same cohort [46]	Existing HF classification; no proven prognostic superiority
Outcome evidence	Small HF cohorts with opposite directions [9, 34]	Longitudinal renal association in a separate study [39]	Different populations and endpoints prevent indirect ranking
Analytical validity	Epitope, extraction and matrix effects [18, 47]	Isoform recognition and assay heterogeneity [24, 44]	Measure both peptides in the same samples with validated assays

Direct analytical and clinical comparisons require the same population, sampling window, specimen matrix and intended outcome. Cross-sectional diagnostic discrimination does not establish prospective prognostic utility or clinical benefit. Abbreviations: ELA, Elabela; APELA, apelin receptor early endogenous ligand; APLN, Apelin; APLNR, apelin receptor; HF, heart failure; AUC, area under the receiver operating characteristic curve.

Table 3. Minimum reporting and validation framework for circulating ELA

Domain	Required reporting or evaluation	Purpose
Clinical question	Intended population, decision and comparator model	Avoid an undefined claim of biomarker utility
Biological context	Phenotype, stage, treatment, eGFR; gestational age and PE subtype where relevant	Separate biological and disease-related variation
Specimen handling	Matrix, tube/anticoagulant, collection-to-processing time, temperature, storage duration and freeze-thaw cycles	Make preanalytical variation assessable
Assay validation	Peptide species, kit/lot, extraction and recovery, LLOQ, precision, dilutional parallelism, matrix effects and cross-reactivity	Establish what is measured and with what uncertainty
Statistical analysis	Continuous ELA, prespecified covariates, below-LLOQ handling and nonlinear modeling when justified	Avoid information loss and unstable data-derived thresholds
Predictive assessment	Pre-determined endpoints; discrimination and calibration; optimism correction; independent external validation	Separate the correlational study from the reproducible prediction
Clinical value	Clinical model versus model plus ELA; disease-specific established biomarkers; net benefit and prospective impact	Determine whether the test can improve decision-making

The proposed sample processing protocol and clinical thresholds need to be verified for ELA specificity. This framework outlines the requirements for future research, but it does not imply that the current detection methods or cohorts have met these requirements. Abbreviations: ELA, Elabela; LLOQ, lower limit of quantification.

type of associations seem to vary in conditions like in heart failure, in coronary artery disease, in chronic kidney disease, in preeclampsia, and in complications of diabetes.

A few studies have simultaneously measured ELA and apelin in the same population, including patients with CKD [11]. In a 2024 study on heart failure, the area under the receiver operating characteristic curve (AUC) of ELA for the test subjects was higher than that of apelin [46]. However, this comparison was made for patients who had already been diagnosed with heart failure, and it did not confirm that ELA has a better predictive ability for subsequent events, nor did it prove that it had additional value compared to clinical models.

Technical and methodologic considerations

Analytical methods and assay comparability

Most clinical studies have done the following: they used commercially available enzyme-linked immunosorbent assays (ELISAs) to quantify circulating ELA. On the other hand, the liquid chromatography-tandem mass spectrometry (LC-MS/MS) is mainly used for experiments in the field of peptide identification, metabolic processes, and stability studies [18]. These two analytical approaches measure different aspects of the ELA system, and they should not be considered interchangeable.

The reasons for the common use of ELISA are the easiness of operations, the high throughput, and the possibility to investigate large clinical cohort. However, the accuracy of this assay is affected by many variables, as the specificity of the antibodies used, the efficiency of the recognition of the epitopes, the protocols of the sample extraction, the application of the calibration standard, the matrix interference, and the cross reactivity with ELA fragments or other structurally similar peptides. While commercial ELISA kits may detect full-length ELA-32, truncated variants, or shared peptide epitopes, they often lack the discriminatory power required to reliably differentiate biologically distinct ELA isoforms. So, a reported "total ELA" concentration might represent different molecular species across various assays.

Sample extraction is another source of variation. The variability of the results can also come from the sample extraction procedure. Some studies compared commercial with custom assays. They showed that the manner of extraction is a crucial point to determine the precise quantification of ELA [47]. If the samples are tested directly, without separation of the serum or the plasma, the results can be affected by problems such as non-specific binding, interference of high abundance of plasma proteins, or the low recovery of the target peptide. It is therefore important for those doing the studies to specify whether samples were extracted or concentrated before the analysis, and to give data on the extraction recovery. Absent such information, cross-study comparisons of absolute ELA concentrations obtained using different commercial assay kits lack analytical validity and cannot be considered reliable.

LC-MS/MS gives more molecular specificity, and may differentiate between intact ELA and its proteolytic fragments. But endogenous ELA is technically hard to quantify because it has low abundance, is susceptible to oxidation, undergoes extensive proteolytic processing, adsorbs to laboratory surfaces or plasma proteins, and has suboptimal chromatographic behavior [18]. Of note, one of the LC-MS/MS *in vitro* investigations was able to characterize the synthetic ELA metabolites in the human plasma and in the homogenates of the kidney, but the quantification of the endogenous ELA peptides in human tissues was still not reliably possible even after antibody-based enrichment [18]. This is a large difference: the immunoassays can report ELA in the specimen in which the mass spectrometry is not able to check the presence of the corresponding endogenous peptide forms.

So far, there is no gold standard for the measurement of circulating ELA, and both ELISA and LC-MS/MS are not yet in that position. For a robust assay validation in future studies, the criteria are: analytical sensitivity, the lower limit of quantification, the linearity, as well as the intra- and inter-assay precision. Other factors to note include dilutional parallelism, spike-and-recovery, matrix effect, and stability in appropriate storage. It is also important to characterize the antibody epitopes and to look at the cross-reactivity against different apelin isoforms (ELA-32, ELA-21 and ELA-11). Where feasible, immunological assay results should be corroborated using orthogonal analytical methods.

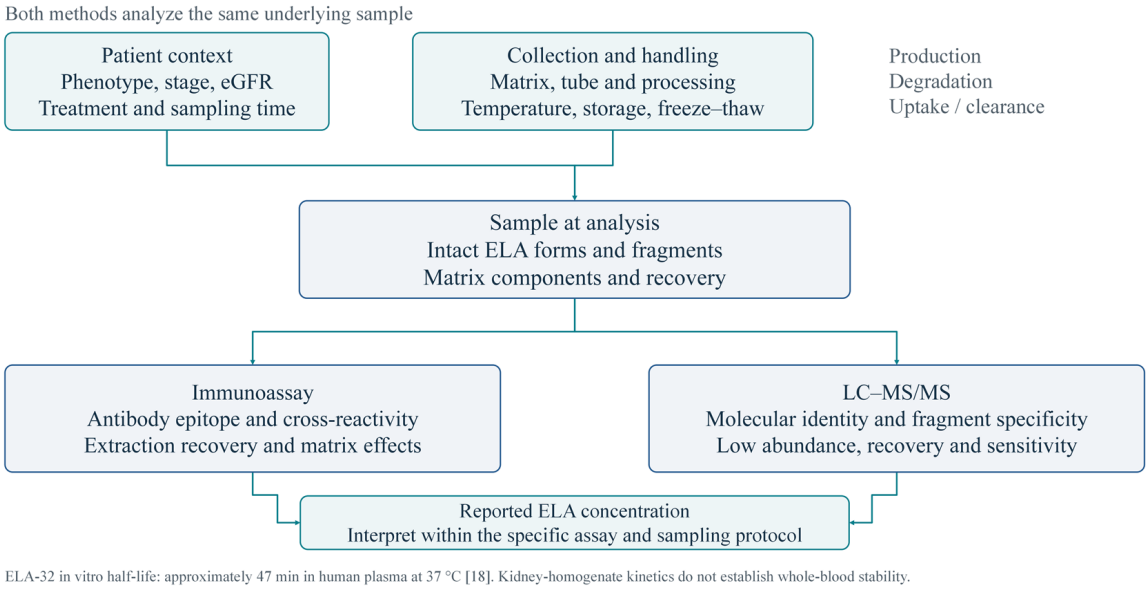


Figure 3. Sources of variation in measured circulating ELA. Biological context and specimen handling determine the intact peptide forms, proteolytic fragments, and matrix components presented to both immunoassay and LC-MS/MS. Immunoassays rely on epitope recognition and more than one molecular species will be detected. LC-MS/MS exhibits distinct specificity and recovery rate requirements and its sensitivity may be insufficient for the reliable quantification of endogenous peptides. Reported values need to be interpreted in conjunction with the analysis and sampling protocols. The half-life of approximately 47 minutes is applicable to the in vitro situation of ELA-32 in human plasma at 37 °C; kidney-homogenate kinetics do not establish whole-blood stability. Figure abbreviations: ELA, Elabela; eGFR, estimated glomerular filtration rate; LC-MS/MS, Liquid chromatography-tandem mass spectrometry.

Clinical reports should include the test reagent manufacturer, catalog and batch numbers, the sample matrix, the extraction method, the calibration range, the percent of the values under the detection limit, the coefficient of variation, and the quality control protocols. Such information is important in order to ensure the reproducibility and to determine whether the variations that were observed among the studies were because of the biology or because of differences in analysis.

Influence of sample collection and processing on the ELA detection results

ELA-32 may degrade in biological samples. Therefore, the conditions for sample collection and processing can affect the measurement results. Existing clinical studies use different samples such as serum and EDTA plasma, but often lack a basis for selection or direct comparison. The coagulation process, type of anticoagulant, antibody binding, and extraction efficiency may all affect the recovery rate of peptides. Therefore, it is not advisable to combine or compare directly the test results of different sample types. At present, the evidence comparing serum with plasma for ELA remains limited.

The time interval from blood collection to processing and the temperature are particularly important. It was reported that the *in vitro* half-life of ELA-32 at 37°C is approximately 47.2 ± 5.7 minutes, and it degrades more rapidly in renal homogenates [18]. Delayed processing may lead to a reduction in complete ELA-32 and the accumulation of shorter fragments. Due to the different epitopes recognized by various antibodies, ELISA detection values may decrease, remain unchanged, or even increase.

Before the ELA dedicated pre-analysis process is verified, the sample types within the cohort should be unified, the temperature should be controlled and processed as soon as possible, and stored at -80°C to minimize repeated freezing and thawing. One should record and report the time from sampling to centrifugation, processing temperature, type of anticoagulant, storage duration and freeze-thaw cycles. The above measures still need to be verified for ELA and are not yet established standards (**Figure 3**).

Statistical analysis and clinical validation

Several recurring statistical limitations affect the interpretation of ELA studies. First, the concentrations of circulating peptides are usually right-skewed, and they might have values below the assay's lower limit of quantification. So, before doing analysis, one should examine the distributional assumptions. Appropriate approaches might involve logarithmic transformation or the use of nonparametric methods, depending on the nature of the data. The proportion of values below the quantification limit and the method used to handle them should be reported explicitly, since simple substitution mayt introduce bias.

ELA is usually divided into high-concentration and low-concentration groups, by taking the sample median or selecting a cutoff from the same dataset. Such categorization removes information and may increase the risk of overfitting. In particular, selecting a Youden-index cutoff and evaluating its performance in the same cohort can give optimistic estimates [9]. Primary analyses should keep ELA as a continuous variable, and use flexible models for potential nonlinear associations when the sample size allows.

Most of the available studies measured ELA only once, and there was no independent validation. Future studies should include repeated measurements when necessary and assess whether ELA provides additional information beyond established biomarkers and established clinical models. Diagnostic and prognostic performance should be evaluated by assessing discrimination and calibration, and using decision curve analysis to evaluate potential clinical net benefit. Before proposing a clinically applicable ELA cutoff, we need to perform internal validation through bootstrapping or cross-validation, and then conduct external validation independent cohorts (**Table 3**).

Research gaps and future directions

Longitudinal and prognostic validation

The association between ELA and specific diseases should first be clarified as to whether it can be repeatedly verified in different research centers and populations. To this end, it is necessary to unify the sample collection and analysis process, adopt consistent definitions of clinical phenotypes and study endpoints, and verify them in independent cohorts. The research objective should be to discover stable and reproducible disease correlations rather than to establish a uniform ELA threshold applicable to all diseases.

Multicenter and multi-disease validation

Clinical evidence is unevenly distributed among disease areas, and there are many studies on CKD, diabetic kidney disease, and metabolic disorders, which are small and cross-sectional, with few repeated measurements or long-term outcomes. It is unclear whether changes in circulating ELA in kidney disease indicate altered synthesis, degradation, tissue uptake, or clearance [11]. Future multicenter studies need to include detailed renal phenotyping and a variety of populations, with consistent disease severity and clinical outcome definitions. It is also necessary to have the same sampling and analytical protocol in all the sites of the trials and to have at the same moment an external validation for the correlation with the disease.

Emerging cardiometabolic applications

Although experimental studies indicate that ELA plays a role ininsulin sensitivity and cardiometabolic injury, there is limited human evidence for metabolic syndrome, obesity, and metabolic dysfunction-associated steatotic liver disease [48]. Conducting research on these diseases may help clarify whether ELA can reflect the interrelationships among metabolic dysfunction, endothelial injury, inflammation, or cardiovascular risk.

Future prospective studies, after adjusting for known risk factors, can be conducted to evaluate the association between ELA levels and new-onset diabetes, the progression of metabolic dysfunction, and atherosclerotic cardiovascular events. Such studies should be based on clear biological evidence, adopt standardized sample collection and analysis procedures, and be repeatedly validated by independent cohorts before using the value of ELA in diagnosis or prognosis determination (**Figure 4**).

Conclusion

Circulating ELA has been associated with disease severity and vascular or organ dysfunc-

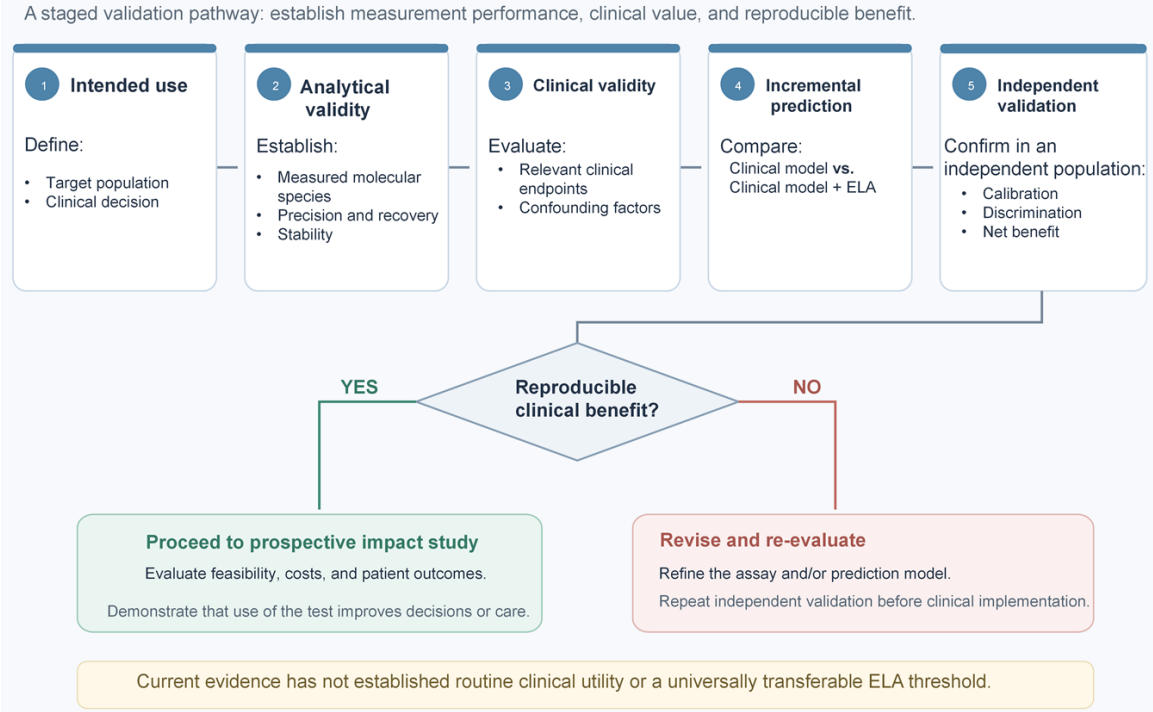


Figure 4. Validation pathway from ELA measurement to clinical use. A defined intended use precedes evaluation of analytical validity, clinical validity, incremental prediction, and independent validation. The comparative framework should include also the biomarkers known to be specific of the disease under discussion, and how ELA affects the choice of the clinical, practical use, economic impact, and patient result by means of prospective investigations. Failure to establish a benefit prompts revision of the assay, intended use, or model and repeat independent evaluation. The proposed sequence does not imply that ELA has completed clinical validation. Figure abbreviations: ELA, Elabela.

tion in several cardiovascular, renal, metabolic, and pregnancy-related conditions. However, this is not always the case. The strength of these associations can depend on the variations in the stage of the disease, the time of the sample collection, the renal performance, the type of the sample matrix, and the analytical technique. In small heart failure studies, associations with subsequent events have been reported, but the direction is inconsistent, and evidence for other diseases is mostly cross-sectional.

Therefore, ELA seems to be at present a possible research biomarker, not a clinically useful, already validated diagnostic test. Future studies will obviously need to address a number of important points: the standardization of the way the measurements are done, the reproducibility of the results, the adjustment of the disease related confounding factors, and the external validation of the results of the studies. It is important to know whether ELA has clinical utility in addition to the other markers and whether different molecular forms of ELA have different diagnostic and prognostic implications.

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Disclosure of conflict of interest

None.

Abbreviations

ELA, Elabela; APELA, apelin receptor early endogenous ligand; APLNR, Apelin receptor; CKD, Chronic kidney disease; BNP, B-type natriuretic peptide; PI3K, Phosphoinositide 3-kinase; Akt, Protein kinase B; ERK, Extracellular signal-regulated kinase; MAPK, Mitogen-activated protein kinase; HF, Heart failure; CAD, Coronary artery disease; ACS, Acute coronary syndrome; ELISA, Enzyme-linked immunosorbent assay; EDTA, Ethylene diamine tetraacetic acid; LC-MS/MS, Liquid chromatography-tandem mass spectrometry; PE, Preeclampsia; STEMI, ST-segment elevation myocardial infarction; SYNTAX, SYNergy between PCI with TAXUS and Cardiac Surgery; MACE, Major adverse cardiac events; LVEF, Left ventricular ejection fraction; NLRP3, NOD-like receptor family, pyrin domain containing 3; eGFR, Estimated glomerular filtration rate; RNA, Ribonucleic acid; sFas, soluble Fas; sFlt-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; LLOQ, Lower limit of quantification.

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References

[1] Huang SK, Shin K, Sarker M and Rainey JK. Apela exhibits isoform- and headgroup-dependent modulation of micelle binding, peptide conformation and dynamics. Biochim Biophys Acta Biomembr 2017; 1859: 767-778.

[2] Wang Z, Yu D, Wang M, Wang Q, Kouznetsova J, Yang R, Qian K, Wu W, Shuldiner A, Sztalryd C, Zou M, Zheng W and Gong DW. Elabela-apelin receptor signaling pathway is functional in mammalian systems. Sci Rep 2015; 5: 8170.

[3] Respekta N, Pich K, Dawid M, Mlyczyńska E, Kurowska P and Rak A. The apelinergic system: Apelin, ELABELA, and APJ action on cell apoptosis: anti-apoptotic or pro-apoptotic effect? Cells 2022; 12: 150.

[4] Wang X, Zhang L, Feng M, Xu Z, Cheng Z and Qian L. ELA-11 protects the heart against oxidative stress injury induced apoptosis through ERK/MAPK and PI3K/AKT signaling pathways. Front Pharmacol 2022; 13: 873614.

[5] Stock J, Kazmar T, Schlumm F, Hannezo E and Pauli A. A self-generated Toddler gradient guides mesodermal cell migration. Sci Adv 2022; 8: eadd2488.

[6] Rossin D, Vanni R, Lo Iacono M, Cristallini C, Giachino C and Rastaldo R. APJ as promising therapeutic target of peptide analogues in myocardial infarction- and hypertension-induced heart failure. Pharmaceutics 2023; 15: 1408.

[7] Liu Y, Jiang M, Li Y, Chen P and Chen X. Advances in the study of ELABELA in renal physiological functions and related diseases. Front Pharmacol 2023; 14: 1276488.

[8] Pécheux O, Correia-Branco A, Cohen M and Martinez de Tejada B. The apelinergic system in pregnancy. Int J Mol Sci 2023; 24: 8014.

[9] Ma Z, Zhao L, Martin S, Zhang Y, Dong Y, Zhong JC and Yang XC. Lower plasma Elabela levels in hypertensive patients with heart failure predict the occurrence of major adverse cardiac events: a preliminary study. Front Cardiovasc Med 2021; 8: 638468.

[10] Li Y, Yang X, Ouyang S, He J, Yu B, Lin X, Zhang Q and Tao J. Declined circulating Elabela levels in patients with essential hypertension and its association with impaired vascular function: a preliminary study. Clin Exp Hypertens 2020; 42: 239-243.

[11] Lu X, Liu S, Luan R, Cui W, Chen Y, Zhang Y, Lu Y, Zhang H, Shi L, Miao L and Xu F. Serum elabela and apelin levels during different stages of chronic kidney disease. Ren Fail 2020; 42: 667-672.

[12] Huang R, Zhu J, Zhang L, Hua X, Ye W, Chen C, Sun K, Wang W, Feng L and Zhang J; Shanghai Birth Cohort study. Is ELABELA a reliable biomarker for hypertensive disorders of pregnancy? Pregnancy Hypertens 2019; 17: 226-232.

[13] Para R, Romero R, Gomez-Lopez N, Tarca AL, Panaitescu B, Done B, Hsu R, Pacora P and Hsu CD. Maternal circulating concentrations of soluble Fas and Elabela in early- and late-onset preeclampsia. J Matern Fetal Neonatal Med 2022; 35: 316-329.

[14] Georgiadou D, Afink GB and van Dijk M. The apelinergic-axis in human preeclamptic preg-

nancies: a systematic review. Pregnancy Hypertens 2019; 17: 148-157.
[15] Sato T, Sato C, Kadowaki A, Watanabe H, Ho L, Ishida J, Yamaguchi T, Kimura A, Fukamizu A, Penninger JM, Reversade B, Ito H, Imai Y and Kuba K. ELABELA-APJ axis protects from pressure overload heart failure and angiotensin II-induced cardiac damage. Cardiovasc Res 2017; 113: 760-769.
[16] Yang P, Read C, Kuc RE, Buonincontri G, Southwood M, Torella R, Upton PD, Crosby A, Sawiak SJ, Carpenter TA, Glen RC, Morrell NW, Maguire JJ and Davenport AP. Elabela/toddler is an endogenous agonist of the apelin APJ receptor in the adult cardiovascular system, and exogenous administration of the peptide compensates for the downregulation of its expression in pulmonary arterial hypertension. Circulation 2017; 135: 1160-1173.
[17] Liet B, Nys N and Siegfried G. Elabela/toddler: new peptide with a promising future in cancer diagnostic and therapy. Biochim Biophys Acta Mol Cell Res 2021; 1868: 119065.
[18] Nyimanu D, Kay RG, Kuc RE, Brown AJH, Gribble FM, Maguire JJ and Davenport AP. In vitro metabolism of synthetic Elabela/Toddler (ELA-32) peptide in human plasma and kidney homogenates analyzed with mass spectrometry and validation of endogenous peptide quantification in tissues by ELISA. Peptides 2021; 145: 170642.
[19] Sainsily X, Coquerel D, Giguère H, Dumont L, Tran K, Noll C, Ionescu AL, Côté J, Longpré JM, Carpentier A, Marsault É, Lesur O, Sarret P and Auger-Messier M. Elabela protects spontaneously hypertensive rats from hypertension and cardiorenal dysfunctions exacerbated by dietary high-salt intake. Front Pharmacol 2021; 12: 709467.
[20] Wang C, Xiong M, Yang C, Yang D, Zheng J, Fan Y, Wang S, Gai Y, Lan X, Chen H, Zheng L and Huang K. PEGylated and acylated Elabela analogues show enhanced receptor binding, prolonged stability, and remedy of acute kidney injury. J Med Chem 2020; 63: 16028-16042.
[21] Xi Y, Yu D, Yang R, Zhao Q, Wang J, Zhang H, Qian K, Shi Z, Wang W, Brown R, Li Y, Tian Z and Gong DW. Recombinant Fc-Elabela fusion protein has extended plasma half-life andmitigates post-infarct heart dysfunction in rats. Int J Cardiol 2019; 292: 180-187.
[22] Schreiber CA, Holditch SJ, Generous A and Ikeda Y. Sustained ELABELA gene therapy in high-salt diet-induced hypertensive rats. Curr Gene Ther 2017; 16: 349-360.
[23] Wang X, Liang G, Guo Q, Cai W, Zhang X, Ni J, Tao Y, Niu X and Chen S. ELABELA improves endothelial cell function via the ELA-APJ axis by activating the PI3K/Akt signalling pathway in HUVECs and EA.hy926 cells. Clin Exp Pharmacol Physiol 2020; 47: 1953-1964.
[24] Davenport AP, Williams TL, Nyimanu D, Macrae RGC, Kuc RE, Chapman FA, Yang P, Dhaun N and Maguire JJ. International Union of Basic and Clinical Pharmacology. CXXI. Apelin receptor pharmacology in the human cardiovascular system and emerging clinical applications. Pharmacol Rev 2026; 78: 100130.
[25] Al-Rubaye AAH, Jasim WE and Mohsin AA. Circulating Elabela-21 and Elabela-11 levels as predictive biomarkers in individuals with recently developed type 2 diabetes. Afr Health Sci 2025; 25: 136-144.
[26] Guo YY, Li T, Liu H, Tang L, Li YC, Hu HT, Su YF, Lin Y, Wang YY, Li C, Huang HF, Jin L and Liu XM. Circulating levels of Elabela and Apelin in the second and third trimesters of pregnancies with gestational diabetes mellitus. Gynecol Endocrinol 2020; 36: 890-894.
[27] Dawid M, Mlyczyńska E, Jurek M, Respekta N, Pich K, Kurowska P, Gieras W, Milewicz T, Kotula-Balak M and Rak A. Apelin, APJ, and ELABELA: role in placental function, pregnancy, and foetal development-an overview. Cells 2021; 11: 99.
[28] Qi RQ, Chen YF, Cheng J, Song JW, Chen YH, Wang SY, Liu Y, Yan KX, Liu XY, Li J and Zhong JC. Elabela alleviates cuproptosis and vascular calcification in vitaminD3- overloaded mice via regulation of the PPAR-γ/FDX1 signaling. Mol Med 2024; 30: 223.
[29] Ye C, Geng Z, Zhang LL, Zheng F, Zhou YB, Zhu GQ and Xiong XQ. Chronic infusion of ELABELA alleviates vascular remodeling in spontaneously hypertensive rats via anti-inflammatory, anti-oxidative and anti-proliferative effects. Acta Pharmacol Sin 2022; 43: 2573-2584.
[30] Erkan REC and Adiyaman MS. Decreased Elabela level in the first 24 hours of ST elevation myocardial infarction patients. Int J Med Biochem 2024; 7: 150-155.
[31] DU SL, Yang XC, Zhong JC, Wang LF and Fan YF. Plasma levels of Elabela are associated with coronary angiographic severity in patients with acute coronary syndrome. J Geriatr Cardiol 2020; 17: 674-679.
[32] Tian QP, Liu ML, Zhang YR, Ji DR, Liu SM, Zhao J and Qi YF. Plasma level of Elabela in patients with coronary heart disease and its correlation with the disease classification. Int Heart J 2021; 62: 752-755.
[33] Tang L, Yi X, Tan W, Yang H, Song S, Xiong J, Liu C, Zhang Y, Wang M, Zhu M, Zheng L, Yu J and Xu C. ELABELA ameliorates atherosclerosis through restoring the M1/M2 macrophage balance in ApoE(-/-) mice. J Am Heart Assoc 2025; 14: e041261.
[34] Küçük U, Kırılmaz B, Kaya H, Akşit E and Arslan K. Is elabela/toddler a poor prognostic marker

in heart failure patients? Hippokratia 2023; 27: 126-131.
[35] Xu C, Wang F, Chen Y, Xie S, Sng D, Reversade B and Yang T. ELABELA antagonizes intrarenal renin-angiotensin system to lower blood pressure and protects against renal injury. Am J Physiol Renal Physiol 2020; 318: F1122-F1135.
[36] Chen Z, Wu C, Liu Y, Li H, Zhu Y, Huang C, Lin H, Qiao Q, Huang M, Zhu Q and Wang L. ELABELA attenuates deoxycorticosterone acetate/salt-induced hypertension and renal injury by inhibition of NADPH oxidase/ROS/NLRP3 inflammasome pathway. Cell Death Dis 2020; 11: 698.
[37] Hendrianus, Adiarto S, Prakoso R, Firdaus I, Indriani S, Rudiktyo E, Widyantoro B, Taofan, Ambari AM and Sukmawan R. A novel peptide Elabela is associated with hypertension-related subclinical atherosclerosis. High Blood Press Cardiovasc Prev 2023; 30: 37-44.
[38] Zhang H, Gong D, Ni L, Shi L, Xu W, Shi M, Chen J, Ai Y and Zhang X. Serum Elabela/Toddler levels are associated with albuminuria in patients with type 2 diabetes. Cell Physiol Biochem 2018; 48: 1347-1354.
[39] Nyimanu D, Chapman FA, Gallacher PJ, Kuc RE, Williams TL, Newby DE, Maguire JJ, Davenport AP and Dhaun N. Apelin is expressed throughout the human kidney, is elevated in chronic kidney disease & associates independently with decline in kidney function. Br J Clin Pharmacol 2022; 88: 5295-5306.
[40] Ho L, van Dijk M, Chye STJ, Messerschmidt DM, Chng SC, Ong S, Yi LK, Boussata S, Goh GH, Afink GB, Lim CY, Dunn NR, Solter D, Knowles BB and Reversade B. ELABELA deficiency promotes preeclampsia and cardiovascular malformations in mice. Science 2017; 357: 707-713.
[41] Yang N, Liu K, Zhang W, Li Y, Shen S, Lu C, Xu K, Peng W, Deng C, Chen M, Yang L and Lai S. Predicting late-onset preeclampsia by detecting ELABELA content using an immunochromatographic colloidal gold test strip: blood ELABELA content predicts the risk of pre-eclampsia. J Clin Hypertens (Greenwich) 2023; 25: 932-942.
[42] Han Z, Zhang J, Shi M, Chen J, Li A, Ye Y and Zhang H. Context-dependent duality of the apelin/elabela-APJ system in diabetes and its complications (Review). Int J Mol Med 2026; 57: 161.
[43] Seyithanoğlu M, Meşen S, Comez A, Meşen A, Beyoğlu A, Baykişi Y and Alkan Baylan F. The potential of serum elabela levels as a marker of diabetic retinopathy: results from a pilot cross-sectional study. PeerJ 2025; 13: e18841.
[44] Chapman FA, Maguire JJ, Newby DE, Davenport AP and Dhaun N. Targeting the apelin system for the treatment of cardiovascular diseases. Cardiovasc Res 2023; 119: 2683-2696.
[45] Parlati ALM, Madaudo C, Nuzzi V, Manca P, Gentile P, Di Lisi D, Jordán-Ríos A, Shamsi A, Manzoni M, Sadler M, Godino C, Corrado E, Paolillo S, Novo G, Tuttolomondo A, Galassi AR, Filardi PP, Bromage D and Cannata A. Biomarkers for congestion in heart failure: state-of-the-art and future directions. Card Fail Rev 2025; 11: e01.
[46] Liu C, Xiong J, Yi X, Song S, Yang H, Tan W, Yang X, Zheng L, Yu J and Xu C. Decreased plasma ELABELA level as a novel screening indicator for heart failure: a cohort and observational study. Sci Rep 2024; 14: 11333.
[47] Georgiadou D, Boussata S and van Dijk M. ELABELA measurements by commercial ELISA kits require sample extraction. Am J Physiol Endocrinol Metab 2019; 317: E1218-E1219.
[48] Chęcińska-Maciejewska Z, Pruszyńska-Oszmałek E, Kołodziejski P, Ciborek A and Krauss H. Elabela in lipid-related cardiometabolic dysfunction: a critical narrative review. Metabolites 2026; 16: 408.