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Original Research Article

Proenkephalin for early post–MI risk stratification: comparative prognostic performance versus NT-proBNP and GRACE

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ABSTRACT

Background: Accurate post–myocardial infarction (MI) risk stratification is essential, yet clinical scores and natriuretic peptides incompletely capture early cardiorenal stress. Proenkephalin (PENK), a stable endogenous opioid precursor, reflects early glomerular dysfunction and neurohormonal activation. This study evaluated PENK for mortality prediction after MI compared with NT-proBNP and the GRACE risk score and identified optimal cutoffs.
Methods: In this prospective observational cohort, 50 consecutive MI patients enrolled between December 2024 and July 2025 at a tertiary center were studied. Clinical variables, lifestyle factors, comorbidities, hemodynamics, Killip class, MI type and biomarkers (Troponin-I, serum creatinine, NT-proBNP and Proenkephalin) were measured at presentation and Day 28. GRACE scores were calculated at baseline. The primary outcome was all-cause mortality. Cox proportional hazards models assessed independent prognostic value and ROC analysis compared discrimination and derived cutoffs.
Results: Mean age was 62.25±15.19 years; 68% were male, 66% smokers, 46% diabetics and 48% hypertensive. STEMI constituted 62%. Killip class I–IV: 42%, 28%, 8% and 22%. Troponin-I declined from 5,925±11,262 to 784±1,431 pg/ml (p=0.005). NT-proBNP remained elevated (4,019±4,096 to 3,880±3,695 pg/ml, p=0.001). PENK decreased from 138±35 to 89.7±28.5 pg/ml (p=0.003). Mean GRACE score was 133.6±38.1, mortality was 6%. PENK (HR 1.004, p=0.011), NT-proBNP (HR 1.001, p=0.048) and GRACE (HR 1.015, p=0.002) independently predicted mortality. ROC AUCs were 0.78 (PENK), 0.74 (NT-proBNP) and 0.69 (GRACE).
Conclusions: Proenkephalin provided the strongest mortality discrimination after MI with high negative predictive value, complementing NT-proBNP and GRACE for refined post-MI risk stratification.

Keywords: Cardiorenal syndrome, Grace score, Myocardial infarction, NT-proBNP, Proenkephalin

INTRODUCTION

Approximately 64.3 million people globally are afflicted with heart failure. Heart failure (HF) is increasingly acknowledged as a significant clinical and public health concern worldwide. The prevalence of diagnosed heart failure cases is projected to be 1% to 2% of the adult population in affluent nations, with an anticipated increase of 46% by 2030 in the United States.[1] In recent decades, biomarkers have received considerable study attention in the everyday treatment and management of heart failure patients. Circulating cardiac biomarkers are crucial for the diagnosis, management and prognosis of cardiac conditions, especially heart failure. The now sanctioned biomarkers for heart failure include natriuretic peptides, specifically B-type natriuretic peptide (BNP) and the N-terminal portion of its prohormone (NT-proBNP). Additionally, a novel biomarker, proenkephalin (PENK), has been examined both alone and in conjunction with other factors in relation to heart failure; yet, there has been no significant enhancement in cardiovascular mortality.[2]

Risk stratification and prognostication are crucial steps in the therapy of acute myocardial infarction (AMI).

The Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) risk scores exhibit commendable discriminatory efficacy, even within Asian demographics.[3] Additional indicators, such as diminished left ventricular ejection fraction (LVEF) and inadequate recovery of LVEF following AMI, have long been acknowledged in the risk categorisation of AMI patients. N-terminal pro brain natriuretic peptide [NT-proBNP] is a recognised biomarker for diagnosing heart failure. Nonetheless, its use in risk classification for acute myocardial infarction remains contentious.[4] The 2020 European Society of Cardiology guideline on acute coronary syndrome (ACS) care recommends considering the measurement of BNP or NT-proBNP plasma concentrations for prognostic assessment (class IIa, level of evidence B).[5]

Novel kidney biomarkers provide enhanced prediction of renal and cardiovascular outcomes. Circulating PENK, a stable endogenous polypeptide with no known protein binding or cleavage, has emerged as an early indicator of glomerular dysfunction and tubular injury according to numerous preclinical and clinical studies. Prior research indicates that elevated PENK predicts negative renal outcomes, detrimental cardiovascular events and increased all-cause mortality across several critically ill patient cohorts, underscoring its potential utility in risk stratification for patients with ACS6. The rapid elevation in PENK plasma levels following renal stress (within 2-6 hours) and their superior connection with the assessed glomerular filtration rate, in contrast to serum creatinine and cystatin C, may assist in identifying patients predisposed to acute kidney injury (AKI). Consequently, the incorporation of this innovative biomarker may enhance the precision of personalised and prompt treatment approaches in severely unwell patient groups, including those with ACS. Acute kidney damage is a prevalent consequence of ACS, resulting from diminished cardiac output, renal congestion or a combination of both factors. Furthermore, the significant comorbidity burden and the use of contrast agents render patients with ACS especially vulnerable to AKI.[7] Approximately 5%-15% of patients with ACS experience AKI during their initial hospitalisation, with up to 30% of these instances deemed avoidable by the prompt implementation of appropriate supportive interventions.

While the endogenous opioid systems (enkephalins, endorphins and dynorphins) are well-documented in analgesia, emerging data indicates their involvement in cardiovascular control.[8] The distribution of preproenkephalin A and PENK is extensive, encompassing the neurological system, adrenal medulla and immune system, with enkephalins co-released from nerve terminals with catecholamines. Enkephalins are released by both myocytes and nonmyocytes in the heart, potentially exerting autocrine/paracrine effects primarily on delta receptors.[9] The activation of opioid receptors [OPRs] primarily induces a depressor effect, resulting in hypotension and bradycardia, through central and peripheral mu and delta receptors, alongside the suppression of norepinephrine release and sympathetic vasoconstriction. The activation of OPR diminishes the positive inotropic impact mediated by beta-adrenergic receptors and the elevation of cyclic adenosine monophosphate, while also exerting an independent, direct negative inotropic effect. The administration of a delta OPR antagonist in dogs with experimental heart failure (HF) elevated blood pressure, cardiac output and renal, cardiac, splanchnic and skeletal muscle blood flow.[10] The density of delta and other OPRs, while broadly dispersed, is most concentrated in the kidney. In contrast, delta receptors have been associated with ischaemic preconditioning, however the effects may vary based on dosage and duration of ischaemia.[11]

Met-enkephalin serves as a ligand for the ubiquitously expressed opioid growth (or zeta) receptor, which exerts a continuous inhibitory influence on cellular proliferation through cyclin-dependent inhibitory kinase (p16, p21) pathways and can impede ventricular deoxyribonucleic acid formation. Modulation of PENK levels may influence apoptosis, as PENK interacts with histone deacetylase within a transcriptional repression complex that regulates pro-apoptotic processes. Acute stress, exemplified by AMI, activates various neurohormones, including the PENK and vasopressin systems.[12] Previous investigations on met- enkephalin in AMI indicated no variation over four days; however, interpretation may have been hindered by the short half-life of met-enkephalin. A novel assay for stable PENK has been developed and we have examined the efficacy of this marker in comparison to established risk stratification methods (NT-proBNP and risk scores) in AMI.[13] Biomarkers such NT-proBNP exhibit the strongest correlation with mortality and heart failure following AMI, although they are less effective in forecasting the occurrence of readmission due to recurrent AMI, highlighting the necessity for enhanced prediction of this outcome.

In canines with induced HF, the administration of a delta OPR antagonist elevated blood pressure, cardiac output and perfusion to the kidneys, heart, splanchnic region and skeletal muscle.[14] Although widely distributed, the concentration of delta and other OPRs is greatest in the kidney. Delta receptors are also associated with ischaemic pre-conditioning, however the effects may differ according on the intensity and duration of the ischaemia. Met-enkephalin serves as a ligand for the ubiquitously expressed opioid growth (or zeta) receptor, which diminishes ventricular DNA synthesis and maintains a tonic inhibitory influence on cell proliferation through cyclin-dependent inhibitory kinase (p16, p21) pathways.[15,16] A transcriptional repression complex of PENK and histone deacetylase modulates pro-apoptotic activity and modifications in PENK levels may influence this mechanism.

METHODS

Study design and setting

This prospective observational cohort study was conducted at Subharti Medical College, a tertiary care center in Meerut, Uttar Pradesh, India, from December 2024 to July 2025. Adult patients presenting with myocardial infarction (MI), including ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), were consecutively enrolled based on established clinical, electrocardiographic and biochemical diagnostic criteria.

Study population

50 consecutive adult patients (aged 18 years or older) diagnosed with STEMI or NSTEMI were included. Exclusion criteria were advanced chronic kidney disease (stage 5), active inflammatory or infectious diseases or refusal to provide informed consent.

Data collection

Baseline demographic data (age, sex, body mass index (BMI)), lifestyle factors (smoking status, alcohol consumption, physical activity categorized as active or sedentary) and comorbidities (hypertension, type 2 diabetes mellitus) were recorded. Hemodynamic parameters, namely systolic and diastolic blood pressure and heart rate, were measured at presentation. Clinical severity was assessed using the Killip classification system and type of MI (STEMI versus NSTEMI) was documented.

The Global Registry of Acute Coronary Events (GRACE) risk score was calculated at baseline using age, heart rate, systolic blood pressure, serum creatinine, Killip class, presence of cardiac arrest at admission, ST- segment deviation on ECG and cardiac biomarkers.

Biomarker measurements

Blood samples were collected at presentation and on day 28 to measure: High-sensitivity Troponin-I, Serum creatinine, N-terminal pro-B-type natriuretic peptide (NT proBNP) and Proenkephalin (PENK).

Outcome assessment

The primary outcome was all-cause mortality assessed during hospitalization and early post discharge follow-up up to Day 28. Mortality status was verified through hospital records and direct patient contact; three patients in the cohort expired during this period.

Statistical analysis

Continuous variables are presented as mean±standard deviation (SD) and categorical variables as counts and percentages. Comparative analyses utilized chi-square or Fisher's exact tests for categorical variables and Student's t-test or Mann-Whitney U-test for continuous variables as appropriate. Paired analyses of biomarkers between baseline and Day 28 were conducted using paired t-tests or Wilcoxon signed-rank tests depending on normality.

Cox proportional hazards regression modeled the independent association of age, sex, BMI, Proenkephalin, NT-proBNP and GRACE score with mortality. Hazard ratios (HR), 95% confidence intervals (CI) and p- values were reported.

Receiver operating characteristic (ROC) analyses evaluated the discriminative power of biomarkers and risk scores for mortality prediction. Area under the curve (AUC), optimal cut offs, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy metrics were calculated.

RESULTS

A total of 50 patients diagnosed with myocardial infarction (MI) were enrolled. The mean age of the cohort was 62.25±15.19 years, with the largest proportion (32%) falling in the 60-70 year age group, followed by 24% aged over 70 years. Males comprised 68% of the study population, while females accounted for 32%.

The mean body mass index (BMI) was 24.31±3.49 kg/m^2; 38% of patients met criteria for Obese Class I and 24% were overweight. Regarding lifestyle habits, 66% were current smokers and 52% reported alcohol use, with half of the cohort (50%) describing themselves as physically active and the remainder as sedentary.

The most common comorbidities were type 2 diabetes mellitus (46%) and hypertension (48%). At presentation, the mean systolic blood pressure (SBP) was 117.4±15.3 mmHg and the mean diastolic blood pressure (DBP) was 76.6±13.3 mmHg. Mean heart rate was 94.1±18.7 bpm, with heart rate showing a statistically significant association with outcomes (p=0.001), whereas SBP and DBP were not significant.

ST-segment elevation myocardial infarction (STEMI) was more prevalent (62%) than non-ST-segment elevation myocardial infarction (NSTEMI; 38%). Killip class distribution at baseline was: Class I in 42%, Class II in 28%, Class III in 8% and Class IV in 22%, indicating that almost one-third (30%) presented in advanced heart failure (Killip III-IV) (p=0.0077).

The mean GRACE score at baseline was 133.6±38.1. Risk category distribution was: low risk (score 0-87) in 6%, intermediate risk (88-128) in 50%, high risk (129-180) in 32% and very high risk (181-225) in 12%, with a significant overall distribution difference (p=0.0011).

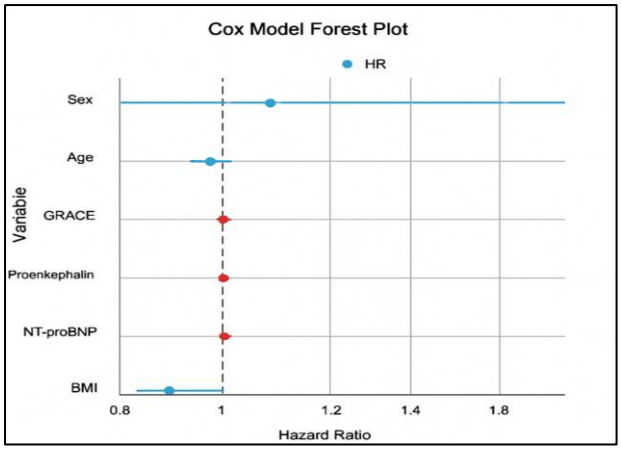

Figure 1: Cox model forest plot showing hazard ratios (HR) and 95% confidence intervals for six variables in a cox proportional hazards model-sex, age, GRACE, proenkephalin, NT-proBNP and BMI. The vertical dashed line represents HR=1 (null value). Blue markers indicate non-significant hazard ratios, while red markers denote statistically significant hazard ratios (p<0.05).

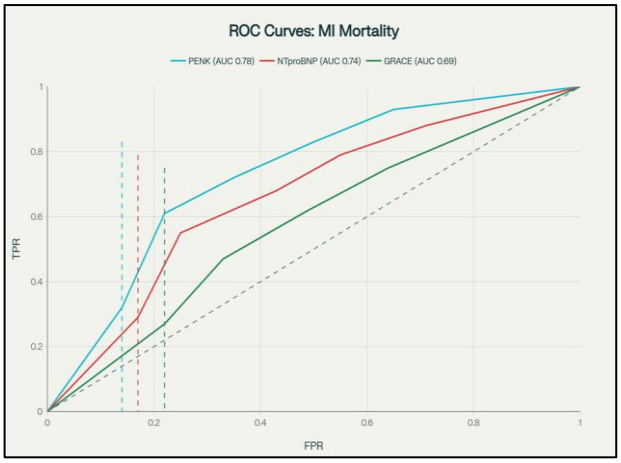

Figure 2: NT-proBNP demonstrated an AUC of 0.74 with an optimal threshold of 5,800 pg/ml (sensitivity 79%, specificity 70%, accuracy 0.75, PPV 0.53, NPV 0.89). The GRACE score had an AUC of 0.69 with a cut-off of 115 (sensitivity 75%, specificity 65%, accuracy 0.70, PPV 0.48, NPV 0.86).

Table 1: Changes in cardiorenal biomarkers between presentation and day 28 in post-myocardial infarction patients.

Biomarker	Unit	At presentation (Mean±SD)	At Day 28 (Mean±SD)	P value	Interpretation
Troponin-I	pg/ml	5925.38±11262.20	784.12±1430.75	0.005	Large, significant decline indicating resolution of acute myocardial injury.
Serum creatinine	mg/dl	1.28±0.85	0.96±0.42	0.014	Significant improvement in renal function during recovery.
NT-proBNP	pg/ml	4019.42±4096.17	3879.85±3694.87	0.001	Modest but significant reduction, consistent with partial relief of ventricular stress.
Proenkephalin	pg/ml	138.00±35.20	89.70±28.50	0.003	Significant decline suggesting attenuation of early cardiorenal and neurohormonal stress.

Values are expressed as mean±standard deviation (SD). Statistical significance determined by paired-sample comparison.

Table 2: Clinical outcome distribution among post-myocardial infarction patients.

Outcome	Frequency (N)	(%)	P value
Survived	47	94.0	0.003
Did Not Survive	3	6.0	—
Total	50	100.0	—

Statistical significance (p=0.003) indicates a significant difference in survival outcome distribution.

Serial biomarker analyses from presentation to Day28 demonstrated significant changes. Mean high-sensitivity Troponin-I decreased from 5,925±11,262 pg/ml at presentation to 784±1,431 pg/ml at Day28 (p=0.005), consistent with resolution of acute myocardial injury. Serum creatinine declined from 1.28±0.85 mg/dl to 0.96±0.42mg/dl (p=0.014), suggesting recovery or optimization of renal function after the acute phase. NT-proBNP levels remained elevated across the cohort but fell modestly from 4,019±4,096 pg/ml to 3,880±3,695 pg/ml (p=0.001), indicative of persistent ventricular stress in a subset of patients.

Proenkephalin levels decreased notably from 138±35 pg/ml to 89.7±28.5 pg/ml (p=0.003), reflecting attenuation of early cardiorenal stress and neurohormonal activation over the 28-day period. Biomarker Trajectories are shown in (Table 1).

Outcomes

During the follow-up period (in-hospital and up to 28days post-MI), all-cause mortality occurred in three patients (6%), while 94% of patients survived (p=0.003 for distribution) shown in (Table 2).

Prognostic modelling

In multivariable cox proportional hazards regression analysis, proenkephalin, NT-proBNP and GRACE score each emerged as significant independent predictors of mortality. Proenkephalin had a hazard ratio (HR) of

1.004 per pg/ml (95% confidence interval [CI] 1.001-1.008; p=0.011), NT-proBNP had an HR of 1.001 per pg/ml (95%CI 1.000-1.002; p=0.048) and GRACE score had an HR of 1.015 per point (95%CI 1.005-1.026; p=0.002). Age, sex and BMI were not statistically significant predictors shown in (Figure 1).

Discrimination and optimal cut-offs

Receiver operating characteristic (ROC) curve analysis demonstrated that Proenkephalin achieved the highest discrimination for mortality with an area under the curve (AUC) of 0.78. The optimal cut-off was 145.5 pg/ml, yielding sensitivity of 83%, specificity of 72%, accuracy of 0.78, positive predictive value (PPV) of 0.56 and negative predictive value (NPV) of 0.91 shown in (Figure 2).

DISCUSSION

The discussion presented here evaluates the clinical and biomarker characteristics of a cohort of 50 patients diagnosed with acute myocardial infarction (AMI), contextualizing findings in relation to existing literature while underscoring the prognostic utility of emerging biomarkers, particularly Proenkephalin (PENK).

The mean age of 62.25±15.19 years observed in this study aligns well with major cohorts that highlight the predominance of AMI among older adults, typically those aged 60-70 years and above. This demographic consistency is supported by studies such as Ng et al, Siranart et al and Wenzl et al, establishing age as a critical risk factor for morbidity and mortality following AMI.[17-19]

Gender distribution showed a male predominance (68%), consistent with known epidemiological trends in coronary artery disease where men present earlier and more frequently with AMI. Though the gender difference did not reach statistical significance, this finding parallels reports by Ng et al and Wenzl et al.[17,19] Behavioral risk factors like smoking and alcohol consumption, more prevalent in males, likely contribute to this pattern. Notably, Leong et al, remind clinicians that women may experience worse outcomes, emphasizing the need for heightened awareness of sex-specific differences in presentation and management.[20]

Body mass index (BMI) distribution centered around overweight to mildly obese categories, echoing findings from Ng et al and Siranart et al, who linked elevated BMI to adverse cardiac outcomes and biomarker elevations.[17,18] However, conflicting evidence from Tan et al, highlights the potential influence of metabolic comorbidities in modulating these associations.[21,22]

Lifestyle factors such as smoking (66%) and alcohol use (52%) were highly prevalent in this cohort, reinforcing their role as modifiable cardiovascular risk factors. Consistent findings by Siranart et al, Wenzl et al and Emmens et al, reveal smoking's contribution to neurohormonal activation and cardiac-renal risk, while alcohol, though less directly correlated with Proenkephalin levels, may impact subclinical cardiac and renal dysfunction.[18,19,21]

Hypertension and diabetes, present in 48% and 46% of patients respectively, reaffirm their established roles as major contributors to AMI risk and outcomes. Literature corroborates these findings, indicating elevated Proenkephalin and biomarker levels in these populations, with hypertension and diabetes exacerbating cardio-renal complications and mortality risk.[18,21]

Hemodynamic parameters demonstrated that heart rate, but not systolic or diastolic blood pressure, significantly correlated with outcomes, aligning with the predictive strength assigned to heart rate in the GRACE risk model and corroborated by Ng et al and Wenzl et al.[17,18] Elevated heart rate remains a crucial prognostic marker in acute coronary syndromes and heart failure cohorts.[18,22]

AMI subtype distribution favoured STEMI (62%), consistent with epidemiological data from Kawamura et al, Tan et al and Leong et al, highlighting the predominance of STEMI presentations in acute care settings.[20,22,23]

Killip classification in this cohort predominantly included ClassI patients (42%), indicative of lower heart failure burden at presentation. This distribution mirrors findings from Ng et al and Kawamura et al, supporting Killip class as a robust early risk stratified impacting short-term outcomes.[17-19,23,24]

Biomarker trends demonstrated significant reductions in Troponin-I, NT-proBNP and proenkephalin levels from presentation to Day 28, reflecting successful reperfusion and myocardial recovery. These findings reinforce Troponin-I's value as an injury marker, NT-proBNP's association with myocardial stress and prognosis and position Proenkephalin as a sensitive marker of neurohumoral activation and cardio-renal status.[17-20,22-25] The relative superiority of Proenkephalin's sensitivity, specificity and negative predictive value suggests its

potential to complement or surpass traditional markers and scoring systems like NT-proBNP and GRACE.

The GRACE score in this population demonstrated a moderate-to-high-risk distribution consistent with reported studies, validating its role in risk stratification when combined with biomarker data.[19,22-24]

Mortality at 6% in this cohort was relatively low, potentially reflecting timely intervention and optimized care and aligning with improved outcomes reported elsewhere.[17,23] Elevated baseline Proenkephalin, NT-proBNP and GRACE scores were associated with mortality, highlighting their prognostic significance and reinforcing the value of integrating novel biomarkers in clinical risk assessment.

ROC analysis revealed proenkephalin as the most accurate predictor of mortality, outperforming NT-proBNP and the GRACE score, with the highest area under the curve and favorable sensitivity and specificity metrics. This underscores Proenkephalin's promise for enhanced clinical utility in identifying high-risk post-MI patients and guiding tailored interventions to improve outcomes.[17,18,25]

In summary, this study corroborates established demographic and clinical profiles of AMI patients while emphasizing the emerging prognostic value of Proenkephalin. Combining Proenkephalin with NT-proBNP and established risk scores such as GRACE may facilitate superior risk stratification for mortality and adverse cardio-renal outcomes, supporting its integration into routine clinical practice for optimized post-MI management. Further larger multicenter studies are warranted to validate these findings and explore the utility of Proenkephalin-guided therapeutic strategies.

This study has several limitations. The small sample size (n=50) and low mortality rate (6%) limit statistical power, restrict generalizability and may overestimate effect sizes in multivariable and ROC analyses. Being a single-center observational study, results are subject to selection and referral bias and may not reflect variations in management across different settings. Biomarker assessment was limited to baseline and Day 28, precluding detailed evaluation of early and intermediate temporal dynamics. Residual confounding cannot be excluded, as important variables such as infarct size, left ventricular ejection fraction, revascularization details, medication adherence and detailed renal parameters were not fully accounted for. Additionally, cost-effectiveness, assay availability and real-world feasibility of Proenkephalin testing were not assessed. Larger multi-center studies with longer follow-up are needed to validate these findings and define the clinical role of Proenkephalin-guided risk stratification.

CONCLUSION

This study demonstrates that Proenkephalin is a promising novel prognostic biomarker in patients with acute myocardial infarction (AMI), showing a significant association with clinical outcomes and outperforming traditional markers such as NT-proBNP and GRACE scores in predictive accuracy. The significant decline in Proenkephalin levels from baseline to Day 28 and its strong correlation with adverse outcomes in Cox regression analysis reinforce its utility in risk stratification. NT-proBNP and GRACE score also maintained prognostic relevance but with slightly lower predictive values. The diagnostic accuracy analysis further confirmed Proenkephalin's superior sensitivity (83%) and negative predictive value (91%), highlighting its potential in clinical decision-making. These findings support the integration of Proenkephalin as an adjunctive biomarker in post-MI prognostic assessment to guide personalized treatment and improve patient outcomes. Future large-scale, multi-centric studies are warranted to validate these results and facilitate its adoption in routine cardiology practice.

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REFERENCES

1. James SL, Abate D, Abate KH. Global, regional and national incidence, prevalence and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study. 2017. Lancet. 2018;392:1789-858.
2. Groenewegen A, Rutten FH, Mosterd A. Epidemiology of heart failure. Eur J Heart Fail. 2020;22:1342-56.
3. Heidenreich PA, Albert NM, Allen LA. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6:606-19.
4. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med. 2003472130.
5. Kanagala P, Squire IB, Jones DJ. Proenkephalin and prognosis in heart failure with preserved ejection fraction: a GREAT network study. Clin Res Cardiol. 2019;108:940-9.
6. Pepe S, van den Brink OW, Lakatta EG, Xiao RP. Cross-talk of opioid peptide receptor and beta-adrenergic receptor signalling in the heart. Cardiovasc Res. 2004;63:414-22.
7. Imai N, Kashiki M, Woolf PD, Liang CS. Comparison of cardiovascular effects of mu- and delta-opioid receptor antagonists in dogs with congestive heart failure. Am J Physiol. 19942673;2:912-7.
8. Denning GM, Ackermann LW, Barna TJ. Proenkephalin expression and enkephalin release are

widely observed in non-neuronal tissues. Peptides. 2008;29:83-92.
9. Schultz JE, Hsu AK, Gross GJ. Ischemic preconditioning in the intact rat heart is mediated by delta1- but not mu- or kappa-opioid receptors. Circulation. 1998;97:1282-9.
10. Felker GM, Anstrom KJ, Adams KF. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2017;318:713-20.
11. Ng LL, Squire IB, Jones DJ. Proenkephalin, renal dysfunction and prognosis in patients with acute heart failure: a GREAT Network study. J Am Coll Cardiol. 2017;69:56-69.
12. Proenkephalin, Renal Dysfunction and Prognosis in Patients with Acute Heart Failure: A GREAT Network Study. J. Am. Coll. Cardiol. 2017;69:56-69.
13. Arbit B, Marston N, Shah K. Prognostic usefulness of proenkephalin in stable ambulatory patients with heart failure. Am J Cardiol. 2016;117:1310-4.
14. Matsue Y, Ter Maaten JM, Struck J. Clinical correlates and prognostic value of proenkephalin in acute and chronic heart failure. J Card Fail. 2017;23:231-9.
15. Emmens JE, Ter Maaten JM, Damman K. Proenkephalin, an opioid system surrogate, as a novel comprehensive renal marker in heart failure. Circ Heart Fail. 2019;12:005544.
16. Ng LL, Sandhu JK, Narayan H. Proenkephalin and prognosis after acute myocardial infarction. J Am Coll Cardiol. 2014;63:280-9.
17. Siranart N, Laohasurayotin K, Chokesuwattanaskul R. Proenkephalin as a novel prognostic marker in heart failure patients: a meta-analysis. Eur Heart J. 2022;43:544-908.
18. Wenzl FA, Wang P, Arrigo M. Proenkephalin improves cardio-renal risk prediction in acute coronary syndromes: the KID-ACS score. Eur Heart J. 2025;46:38-54.
19. Leong DP, Joseph PG, McKee M. Reducing the global burden of cardiovascular disease, part 2: prevention and treatment of cardiovascular disease. Circulation. 2022;146:1215-30.
20. Emmens JE, Ter Maaten JM, Brouwers FP. Proenkephalin and the risk of new-onset heart failure: data from prevention of renal and vascular end-stage disease. Clin Cardiol. 2021;44:1662=72.
21. Tan R, Chokesuwattanaskul R, Laohasurayotin K. Prognostic accuracy of proenkephalin in acute myocardial infarction: a systematic review and meta-analysis. Front Cardiovasc Med. 2023;10:1162632.
22. Kawamura Y, Yoshimachi F, Murotani N. Comparison of mortality prediction by the GRACE score, multiple biomarkers and their combination in all-comer patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. Intern Med. 2023;62:503-10.
23. Yao Y, Shao C, Li X. A novel biomarker scoring system alone or in combination with the GRACE score for the prognostic assessment in non-ST-elevation myocardial infarction. Clin Epidemiol. 2022;14:911-23.
24. Siranart N, Laohasurayotin K, Phanthong T. Proenkephalin as a novel prognostic marker in heart failure patients: a systematic review and meta-analysis. Int J Mol Sci. 2023;24:4887.
25. Bradshaw PJ, Ko DT, Newman AM, Donovan LR, Tu JV. Validity of the GRACE (Global Registry of Acute Coronary Events) acute coronary syndrome prediction model for six month post-discharge death in an independent data set. Heart. 2006;92:905-9.

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