Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Comparative Prognostic Value of Phenotypic and Chronological Age for Post-STEMI Mortality and Cardiovascular Events

Fatma Can
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi
Utku Ulukoksal
utkuulukoksal@gmail.com
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi
Furkan Fatih Yucedag
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi
Elif Ozoguz
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi
Oktay Seker
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi
Sahin Yilmaz
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi
Can Yucel Karabay
Dr. Siyami Ersek Göğüs Kalp Ve Damar Cerrahisi Eğitim Ve Araştırma Hastanesi

Research Article

Keywords: Phenotypic Age, Biological Age, Myocardial Infarction, Risk Stratification, Biological Markers

Posted Date: March 8th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8912127/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

The global population aged ≥ 65 years is increasing and is expected to outnumber those under 18 by 2080. Aging is a key risk factor for cardiovascular mortality, and many acute coronary syndrome cases occur in individuals > 75 years. Chronological age may not fully reflect physiological aging; thus, biological age metrics such as phenotypic age (PhenoAge) may offer superior prognostic insight.

Objectives

To evaluate the prognostic value of PhenoAge and phenotypic age acceleration(PhenoAccel) in patients with STEMI, and compare their predictive capacity to chronological age.

Methods

This retrospective, single-center study included 358 STEMI patients treated between 2021 and 2024. PhenoAge was calculated using a validated model incorporating nine clinical biomarkers. Primary outcomes included in-hospital mortality, all-cause mortality, recurrent myocardial infarction, and heart failure hospitalization over a median follow-up of 28 months. Associations between age metrics and outcomes were assessed using multivariable logistic and Cox regression models. Kaplan-Meier and log-rank tests were used for survival analysis.

Results

Median chronological age was 59 years; PhenoAge, 71.4 years; and PhenoAccel, 12.9 years. In-hospital mortality was 5.3%, all-cause mortality 13.4%, recurrent MI 7.3%, and heart failure hospitalization 11%. PhenoAge (OR: 1.057; p = 0.005) and PhenoAccel (OR: 1.086; p = 0.002) independently predicted in-hospital mortality. Both metrics also predicted long-term mortality, whereas chronological age was only marginally significant (p = 0.07). Chronological age best predicted heart failure hospitalization.

Conclusions

PhenoAge and PhenoAccel are independent predictors of short- and long-term mortality in STEMI patients. Their incorporation into clinical practice may improve risk stratification and support personalized treatment strategies.

Introduction

The population aged 65 and older is increasing at a faster rate than all other age groups, and by 2080, it is projected to outnumber individuals under the age of 18.[1] Aging remains a major risk factor for cardiovascular mortality, and approximately 30–40% of hospital admissions related to acute coronary syndromes occur in individuals over 75 years of age.[2,3] Moreover, the progression of cardiovascular diseases accelerates aging-related cellular processes, contributing to a decline in quality of life among older adults.[2] In light of this significant demographic shift and its expected impact on global cardiovascular disease burden, there is a growing need to reconsider how age is defined. Classifying individuals solely based on chronological age may be insufficient in capturing the complexity of the aging process.

Chronological age remains a fundamental parameter in clinical decision-making; however, it does not always reflect a patient's true biological condition. Biological age is a more complex and comprehensive concept that encompasses the functional effects of physiological and pathophysiological processes accumulated over time.[4] Environmental, metabolic, and genetic factors can influence the aging process in highly individual ways.[5] Initially introduced through frailty scoring systems in geriatric medicine, the concept of biological age has gained increasing relevance across various clinical settings. For example, individuals with genetic disorders such as Werner syndrome may appear young chronologically but exhibit signs of accelerated biological aging and are at higher risk for age-related diseases, including myocardial infarction, cancer, and diabetes.

Various molecular, cellular, and imaging-based models have been developed to estimate biological age. Among these, methods based on telomere shortening and DNA methylation levels at CpG sites—such as the Horvath, Hannum, Li, Grim, and Pheno clocks—have been identified as important predictors of both cellular aging and cardiovascular outcomes.[6–10] In addition, early markers of vascular and biological aging, including large artery stiffness, endothelial dysfunction, specific circulating biomarkers, and composite indices derived from these parameters, can also be used to estimate biological age—even in the absence of overt disease or conventional risk factors.[11–13]

In this study, we aimed to evaluate the prognostic value of phenotypic age and phenotypic age acceleration (defined as the difference between phenotypic and chronological age) in a real-world cohort of 358 patients presenting with STEMI. We hypothesized that these age-related metrics may demonstrate varying predictive capacities for key clinical outcomes, including recurrent myocardial infarction, hospitalization for heart failure, in-hospital mortality, and long-term all-cause mortality. The assessment of phenotypic age was intended to enhance risk stratification and to support the development of more individualized treatment strategies in patients with STEMI.

Methods

Study Design and Patient Population

This study was designed as a single-center, retrospective, observational analysis. A total of 1,541 patients aged 18 years or older who presented to the emergency department with a preliminary diagnosis of STEMI and underwent primary percutaneous intervention between 2021 and 2024 were initially considered for inclusion. Patients who died before receiving an angiographic diagnosis, those referred for coronary artery bypass grafting (CABG) after imaging, and those with missing laboratory data required for phenotypic age calculation were excluded. Following these criteria, data from 358 eligible patients were retrospectively retrieved using the hospital electronic medical record system and the national medical information database. The study protocol was reviewed and approved by an independent ethics committee and conducted in accordance with the principles of the Declaration of Helsinki.[14]

PhenoAge Formulation

In this study, phenotypic age was calculated using the formula developed by Liu et al..[15] This formulation is based on analyses conducted using data from the NHANES-III cohort (n = 9,926), in which the association between 42 clinical biomarkers and mortality was assessed using Cox proportional hazards regression. To avoid overfitting, an elastic net regression model was applied, resulting in the selection of 9 biomarkers; albumin, serum creatinine, glucose, log-transformed CRP, lymphocyte percentage, mean corpuscular volume [MCV], red cell distribution width [RDW], alkaline phosphatase [ALP], and white blood cell count [WBC].[15] Two separate Gompertz proportional hazard models were constructed: one incorporating the 9 selected biomarkers and chronological age ($h_1(t)$), and the other including only chronological age ($h_2(t)$). The aim was to determine the age in the $h_2(t)$ model that corresponds to the same mortality risk calculated by $h_1(t)$, based on an individual's biomarker profile. For example, if a 50-year-old individual has a 5% mortality risk according to the $h_1(t)$ model, and this same level of risk is observed at age 60 in the $h_2(t)$ model, the individual's phenotypic age is considered to be 60.

$$\text{Model 1}: h_1(t) = \alpha_{j1} \cdot \exp(\gamma_1 t), \text{ where } \alpha_{j1} = \exp(\beta_0 + \beta_1 x_{1,j} + \beta_2 x_{2,j} + \cdots + \beta_m x_{m,j})$$

$$\text{Model 2}: h_2(t) = \alpha_{j2} \cdot \exp(\gamma_2 t), \text{ where } \alpha_{j2} = \exp(\beta_0' + \beta_{Age}' \, age_j)$$

To estimate phenotypic age, the 1-year mortality risk from the biomarker model $h_1(t)$ is matched to the corresponding risk in the age-only model $h_2(t)$, where t=1

$$t = 1 \quad h_1(t) = h_2(t) > \text{for individual j} >$$

$$\exp(\beta_0 + \beta_1 x_{1,j} + \beta_2 x_{2,j} + \cdots + \beta_m x_{m,j}) \cdot \exp(\gamma_1 t) = \exp(\beta_0' + \beta_{age}' \text{PhenoAge}_j) \cdot \exp(\gamma_2 t)$$

The equation is then solved for PhenoAge_j representing the phenotypic age estimate for individual j;

$$\text{Phenotypic Age} = 141.50 + \frac{\ln[-0.00553 \times \ln(1 - xb)]}{0.09165}$$

xb=19.907+0.0336·Albumin+0.0095·Creatinine+0.0195·Glucose+0.0954·ln(CRP)+0.0120·Lymphocyte %+0.0268·Mean Corpuscular Volume (MCV)+0.3356·Re
Phosphatase (ALP)+0.0554·White Blood Cell (WBC) count+0.0804·Chronological Age

Data Collection and Evaluation

Demographic characteristics, medical history, electrocardiographic (ECG) and echocardiographic findings, laboratory values, medications, angiographic images, hospitalizations, and mortality data throughout follow-up were analyzed. Phenotypic age was calculated using the PhenoAge model, and the difference between chronological age and phenotypic age was defined as "PhenoAcceleration (PhenoAccel)," serving as an indicator of accelerated biological aging.[15] Myocardial infarction (MI) types were categorized based on ECG characteristics and angiographic localization of the infarction. TIMI flow was assessed according to the degree of distal blood flow visualized during coronary angiography and graded on the TIMI scale from 0 to 3: TIMI 0–1 indicated poor flow, TIMI 2 indicated partial perfusion, and TIMI 3 indicated complete perfusion.[16]

Statistical Analysis

Baseline characteristics and demographic data were summarized using descriptive statistics. Continuous variables were expressed as median and interquartile range (IQR), whereas categorical variables were presented as frequencies and percentages. Age-related variables were stratified into tertiles defined by the 25th and 75th percentiles relative to the median values.

The prognostic effects of phenotypic age, chronological age, and age acceleration on clinical outcomes were assessed. The primary clinical endpoints included in-hospital mortality, all-cause mortality over a 28-month follow-up period, recurrent myocardial infarction (MI), and hospitalization due to heart

failure.

Multivariate logistic regression analysis was conducted to evaluate the independent impact of variables on in-hospital mortality. A baseline model was constructed initially with eight clinical covariates: sex, smoking status, hypertension, diabetes, hyperlipidemia, post-procedural final TIMI flow, no-reflow phenomenon during the procedure, and family history of myocardial infarction. Each age-related variable (chronological age, PhenoAge, and PhenoAccel) was subsequently added individually to this baseline model to assess their independent predictive values. Variables included in the regression models were selected based on clinical experience and previously demonstrated risk factors in the literature.

The associations between each age-related variable and outcomes during follow-up, including all-cause mortality, recurrent myocardial infarction, and hospitalization for heart failure, were evaluated using Cox regression analysis adjusted by the baseline covariates.

For survival analysis, Kaplan–Meier curves were constructed after stratifying phenotypic and chronological age variables into three tertiles based on their median values: lower, middle, and upper age groups. Accordingly, patients were classified as <53, 53–64, and >64 years for chronological age, and <65, 65–79, and >79 years for phenotypic age. This grouping enabled the evaluation of discrepancies between biological and chronological aging and their associations with long-term cardiovascular outcomes. Differences in survival among tertiles were compared using the Log-rank test.

Results were presented as odds ratios (OR) or hazard ratios (HR), Nagelkerke's R^2, 95% confidence intervals (CI), and p-values. A two-tailed p-value <0.05 was considered statistically significant. All analyses were performed using R statistical software (Institute for Statistics and Mathematics, Vienna, Austria).

Results

A total of 358 patients meeting inclusion criteria were analyzed in this study (median chronological age: 59 [IQR: 51–68] years; median PhenoAge: 71.4 [IQR: 61.7–83.6] years; median PhenoAccel: 12.9 [IQR: 7.1–18.2] years; 76.8% male). Despite the notable median age difference, a strong correlation was observed between chronological and phenotypic age (Pearson correlation coefficient: 0.8, 95% CI 0.77–0.84, $p < 0.01$) (Fig. 1). Baseline demographic and clinical characteristics are provided in Table 1.

During the median 28-month follow-up, in-hospital mortality occurred in 19 patients (5.3%), with a mean duration of 3.3 days from admission to death. Additionally, during the entire follow-up period, 48 patients (13.4%) experienced all-cause mortality, with a median time to death of 2.1 months. Recurrent myocardial infarction (MI) occurred in 26 patients (7.3%; median 11 months), and hospitalization due to heart failure was recorded in 33 patients (11%; median 3 months).

Angiographic characteristics of our cohort highlighted additional complexities influencing STEMI outcomes. While 69% of patients achieved TIMI grade 3 flow post-PCI, 8.9% experienced no-reflow, and 6.4% had persistent TIMI grade 0 flow—both well-established predictors of adverse prognosis.

Primary clinical outcomes and related statistical analyses are presented in Table 2. Regarding predictors of in-hospital mortality, chronological age (OR: 1.023, 95% CI: 0.975–1.073; $p < 0.001$), PhenoAge (OR: 1.057, 95% CI: 1.017–1.098; $p = 0.005$), and PhenoAccel (OR: 1.086, 95% CI: 1.031–1.144; $p = 0.002$) were significant. Phenotypic age acceleration (PhenoAccel) was the strongest predictor of in-hospital mortality. Furthermore, PhenoAge demonstrated a significantly stronger predictive ability compared to chronological age alone.

Throughout the 28-month follow-up, all-cause mortality was predicted by chronological age (HR: 1.027, 95% CI: 0.998–1.058; $p = 0.07$), PhenoAge (HR: 1.039, 95% CI: 1.016–1.062; $p < 0.001$), and PhenoAccel (HR: 1.050, 95% CI: 1.018–1.082; $p = 0.002$). PhenoAccel consistently demonstrated the highest predictive value for both in-hospital and all-cause mortality. Chronological age was the strongest predictor (HR: 1.066) of hospitalization for heart failure, with lower hazard ratios observed for PhenoAge (HR: 1.039) and PhenoAccel (HR: 1.008), reflecting a reduced predictive strength of these biological aging metrics for this specific outcome. No significant differences among the age-related metrics were found regarding recurrent MI during the follow-up period ($HR \approx 0.98$; $p > 0.2$).

Discussion

As interest in biological age increases, several models have been developed to more accurately reflect the physiological aging process than chronological age alone. Frailty index (FI) assessments represent a robust method for estimating biological age. These indices quantify the cumulative burden of health deficits by evaluating a set of 20 to 100 health-related variables over an individual's lifespan. FI-based models have gained considerable clinical importance over time. On average, FI scores increase by 2–3% with each additional year of chronological age, underscoring their close association with the aging process.[17] Furthermore, the ability of frailty indices to predict parental longevity—differentiating individuals whose parents lived long lives from those whose parents had shorter lifespans—highlights the genetic underpinnings of frailty.[17] Importantly, the FI34 index, which incorporates 34 health variables, has demonstrated superior mortality prediction compared to both chronological age and DNA methylation–based biological age estimators.[18]

Although biomarker-based biological age estimation methods are relatively easy to apply, determining which markers to include and the appropriate weight of each within the predictive equation has taken researchers in the field considerable time and effort (Voitenko and Tokar, 1983; relationship between lymphocyte blast formation and biological age). To be included in a biological age prediction model, a biomarker is generally expected to meet several criteria: (a) It should reflect the outcomes of multiple physiological pathways in a manner that correlates with aging and provide more accurate estimates than chronological age; (b) It should be able to predict remaining life expectancy at an age when approximately 90% of the population is still alive, and this prediction should apply across a wide range of diseases within the studied population; (c) The measurement of the biomarker itself should not alter life expectancy or affect the results of other age-sensitive tests.[19] The Levine BioAge model estimates biological age by integrating ten biomarkers—CRP, serum

creatinine, HbA1c, systolic blood pressure, serum albumin, total cholesterol, cytomegalovirus (CMV) seropositivity, ALP, forced expiratory volume (FEV), and blood urea nitrogen (BUN)—with chronological age using the Klemera–Doubal algorithm. It is currently regarded as one of the most accurate models in the literature for predicting the relationship between biological age and mortality.[15, 20] The Klemera–Doubal algorithm does not aim to directly predict mortality; rather, it models an individual's health status based on biomarkers and derives a biological age estimate anchored to chronological age. [21] However, the inclusion of parameters such as CMV serostatus and FEV, represents a limitation of the Levine BioAge model in terms of its broad applicability. The PhenoAge model used in our study estimates biological age—referred to by the original authors as "Phenotypic Age"—by incorporating nine biomarkers (albumin, serum creatinine, glucose, log-transformed CRP, lymphocyte percentage,, RDW, ALP and WBC) together with chronological age, fitted into two Gompertz proportional hazards models.[15] The data used in this model were derived from the NHANES-III population, similar to the Levine BioAge model, but PhenoAge was additionally validated in the NHANES-IV cohort (n = 11,432). PhenoAge has been shown to outperform Levine BioAge in predicting mortality within healthy populations. In terms of cardiovascular mortality, the hazard ratio for BioAge was calculated as 1.14 (95% CI: 1.10–1.17), whereas for PhenoAge it was 1.10 (95% CI: 1.07–1.13).[15, 20] Another study conducted within the NHANES cohort demonstrated that PhenoAge was associated with increased all-cause mortality in patients with heart failure (HR: 1.05; 95% CI: 1.04–1.05).[22] Moreover, mortality prediction based on PhenoAge has been shown to remain valid across various subgroups stratified by age, number of comorbidities, health behaviors, and cause of death.[23]

In recent years, the use of artificial intelligence (AI)–based deep learning algorithms has enabled the estimation of “heart age” from electrocardiogram (ECG) data, and this estimated age has been proposed as a novel cardiovascular risk marker.[24] Notably, AI-predicted age derived from ECG was shown to outperform chronological age in predicting cardiovascular events, particularly in individuals under the age of 60 (Chronological Age vs. AI-Age AUC: 0.642 vs. 0.700; p = 0.003).[24] Similarly, imaging modalities such as echocardiography have been utilized for biological heart age estimation. For instance, a deep learning model trained on 160,508 echocardiographic videos was able to predict patients’ ages with a mean absolute error of approximately 6.7 years, and higher predicted age was significantly associated with increased future risk of coronary artery disease and heart failure.[25] In addition, cardiac magnetic resonance (CMR) imaging analyzed via AI has been used to detect aging-related structural and functional patterns of the heart in three dimensions, allowing for estimation of the heart’s "apparent" biological age.[26] These AI-based cardiac aging metrics hold substantial promise for improving cardiovascular risk stratification, enabling earlier identification of high-risk individuals, and guiding targeted preventive interventions.

Building on these advances in biological age estimation, it is important to explore how such models perform in high-risk clinical settings. ST-segment elevation myocardial infarction (STEMI) remains one of the leading causes of morbidity and mortality worldwide.[27] While the introduction of primary percutaneous coronary interventions (PCI), advancements in stent technologies, and the optimization of medical therapies have substantially reduced acute-phase mortality, long-term outcomes following STEMI continue to pose a significant clinical challenge.[28] Although several risk scoring systems (e.g., GRACE) are currently in use, most were developed in earlier eras and are primarily focused on acute-phase outcomes.[29] Furthermore, no single clinical or demographic parameter offers sufficient predictive power for long-term events. As a result, the search for novel, integrative risk markers has intensified, particularly those that can capture an individual’s overall physiological vulnerability rather than relying solely on conventional factors.

In this context, our study focused on the role of phenotypic age and its potential divergence from chronological age in predicting adverse outcomes. We aimed to determine whether phenotypic age offers incremental prognostic value over traditional risk stratification methods in the acute STEMI setting and throughout long-term follow-up.

Our findings demonstrate that both phenotypic age and phenotypic age acceleration are independent predictors of in-hospital and long-term mortality, even after adjusting for chronological age and sex. Each 1-year increase in phenotypic age was associated with a significant increase in risk for both early and total mortality. Importantly, phenotypic age acceleration showed the strongest association with in-hospital mortality, highlighting its robust predictive performance.

Heart failure hospitalization was significantly associated with chronological age and phenotypic age but not with phenotypic age acceleration. This finding suggests that while biological age is a relevant predictor of heart failure risk, the acceleration metric may not independently contribute to this outcome. However, this result should be interpreted with caution, as the lack of statistical significance may be related to the relatively small number of heart failure hospitalizations in the cohort, potentially limiting the power to detect such associations.

Notably, chronological age was not significantly associated with long-term mortality in our cohort, whereas biological age markers retained statistical significance. This finding supports the hypothesis that b phenotypic age may better reflect accumulated physiological damage — including systemic inflammation, vascular dysfunction, and metabolic derangements — all of which contribute to adverse cardiovascular outcomes. Heart failure hospitalization was also significantly associated with phenotypic age and chronological age, but not with phenotypic age acceleration, suggesting that cumulative biological burden, rather than aging acceleration per se, may drive heart failure risk post-STEMI.

Kaplan–Meier survival curves derived from our study revealed notable differences in survival times across the examined groups (Fig. 2). In both the PhenoAge and chronological age stratifications, a marked decline in survival was observed in the higher age tertiles. Notably, in the survival analysis based on PhenoAge and PhenoAccel, increased early mortality was particularly evident in the middle tertile, which is of special interest. This finding suggests that phenotypic age may more sensitively reflect biological aging and comorbidity burden than chronological age, even among individuals with similar chronological age. Individuals with elevated phenotypic age in the middle tertile may be at a disadvantage in terms of early mortality due to latent metabolic, inflammatory, or cardiovascular risk factors. On the other hand, methodological factors; such as sample size, the number of events, and how the group boundaries were defined, may also have influenced these results, underscoring the need for further validation in future studies.

Strengths and Limitations

A key strength of our study is its use of a validated and reproducible biological age metric in a well-characterized STEMI cohort, allowing real-world applicability. The phenotypic age model relies on readily available clinical biomarkers, enhancing its clinical feasibility. To the best of our knowledge, this study represents the first application of phenotypic age metrics specifically within a STEMI population. Additionally, our study extends previous findings on biological aging by applying them to an acute, high-risk cardiovascular population with long-term follow-up. Our findings suggest that integrating phenotypic age metrics into current clinical workflows may enhance long-term risk prediction in STEMI patients, potentially improving follow-up strategies and therapeutic decisions.

However, some limitations should be acknowledged. The study's observational design limits causal inference, and the moderate sample size, along with underrepresentation of women (23%), may affect generalizability. Nonetheless, these factors do not diminish the internal consistency of our findings or the demonstrated associations between biological age and clinical outcomes.

Conclusion

Phenotypic age and phenotypic age acceleration are independent predictors of both in-hospital and long-term mortality in STEMI patients. These findings support the clinical utility of biological aging models in cardiovascular risk stratification, beyond traditional measures such as chronological age.

Incorporating phenotypic age into routine risk assessments may help identify high-risk patients who could benefit from more intensive monitoring and personalized therapeutic strategies.

Lastly, only 23% of the patients were women, which may limit generalizability of findings across sexes and warrants caution in interpretation. The underrepresentation of women is a known limitation in cardiovascular research and highlights the need for more inclusive studies.

Abbreviations

ALP, alkaline phosphatase; BioAge, biological age; CABG, coronary artery bypass grafting; CI, confidence interval; CMR, cardiac magnetic resonance; CMV, cytomegalovirus; CRP, C-reactive protein; ECG, electrocardiogram; FEV, forced expiratory volume; FI, frailty index; FI34, 34-item frailty index; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; IQR, interquartile range; MCV, mean corpuscular volume; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; PCI, percutaneous coronary intervention; PhenoAccel, phenotypic age acceleration; PhenoAge, phenotypic age; RDW, red cell distribution width; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; WBC, white blood cell.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital. Due to the retrospective observational design of the study, the requirement for informed consent to participate was waived by the ethics committee, and clinical trial registration was not required.

Consent for publication

Not applicable, as this study did not include any identifiable individual data.

Availability of data and materials

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

Conflict of Interest Statement

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Funding

No funding was received for this study.

Authors' contributions

F.C. and U.U. wrote the main manuscript text. F.F.Y. and E.O. were responsible for data collection and analysis. O.S. and S.Y. contributed to the literature review and interpretation of the results. C.Y.K. supervised the study, critically revised the manuscript for important intellectual content, and approved the final version. All authors reviewed the manuscript.

References

1. Aging. 2023, United Nations.
2. Damluji, A.A., et al., Management of Acute Coronary Syndrome in the Older Adult Population: A Scientific Statement From the American Heart Association. Circulation, 2023. 147(3): p. e32-e62.
3. D'Agostino, R.B., Sr., et al., General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 2008. 117(6): p. 743-53.
4. Damluji, A.A., et al., Chronological vs Biological Age in Interventional Cardiology: A Comprehensive Approach to Care for Older Adults: JACC Family Series. JACC Cardiovasc Interv, 2024. 17(8): p. 961-978.
5. Wu, J.W., et al., Biological age in healthy elderly predicts aging-related diseases including dementia. Sci Rep, 2021. 11(1): p. 15929.
6. Jylhava, J., N.L. Pedersen, and S. Hagg, Biological Age Predictors. EBioMedicine, 2017. 21: p. 29-36.
7. Si, J., et al., DNA Methylation Age Mediates Effect of Metabolic Profile on Cardiovascular and General Aging. Circ Res, 2024. 135(9): p. 954-966.
8. Blackburn, E.H., E.S. Epel, and J. Lin, Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. Science, 2015. 350(6265): p. 1193-8.
9. Horvath, S. and K. Raj, DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet, 2018. 19(6): p. 371-384.
10. Pavanello, S., et al., Longer Leukocytes Telomere Length Predicts a Significant Survival Advantage in the Elderly TRELONG Cohort, with Short Physical Performance Battery Score and Years of Education as Main Determinants for Telomere Elongation. J Clin Med, 2021. 10(16).
11. Newman, A.B., et al., Trajectories of function and biomarkers with age: the CHS All Stars Study. Int J Epidemiol, 2016. 45(4): p. 1135-1145.
12. Ferrucci, L. and E. Fabbri, Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol, 2018. 15(9): p. 505-522.
13. Lakatta, E.G., M. Wang, and S.S. Najjar, Arterial aging and subclinical arterial disease are fundamentally intertwined at macroscopic and molecular levels. Med Clin North Am, 2009. 93(3): p. 583-604, Table of Contents.
14. World Medical, A., World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. JAMA, 2025. 333(1): p. 71-74.
15. Liu, Z., et al., A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: A cohort study. PLoS Med, 2018. 15(12): p. e1002718.
16. Braunwald, E. and M.S. Sabatine, The Thrombolysis in Myocardial Infarction (TIMI) Study Group experience. J Thorac Cardiovasc Surg, 2012. 144(4): p. 762-70.
17. Kim, S., et al., Association of healthy aging with parental longevity. Age (Dordr), 2013. 35(5): p. 1975-82.
18. Kim, S., et al., The frailty index outperforms DNA methylation age and its derivatives as an indicator of biological age. Geroscience, 2017. 39(1): p. 83-92.
19. Butler, R.N., et al., Biomarkers of aging: from primitive organisms to humans. J Gerontol A Biol Sci Med Sci, 2004. 59(6): p. B560-7.
20. Levine, M.E., Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? J Gerontol A Biol Sci Med Sci, 2013. 68(6): p. 667-74.
21. Klemera, P. and S. Doubal, A new approach to the concept and computation of biological age. Mech Ageing Dev, 2006. 127(3): p. 240-8.
22. Xu, X. and Z. Xu, Association Between Phenotypic Age and the Risk of Mortality in Patients With Heart Failure: A Retrospective Cohort Study. Clin Cardiol, 2024. 47(8): p. e24321.
23. Chen, L., et al., Exploring multi-omics and clinical characteristics linked to accelerated biological aging in Asian women of reproductive age: insights from the S-PRESTO study. Genome Med, 2024. 16(1): p. 128.
24. Hirota, N., et al., Cardiovascular events and artificial intelligence-predicted age using 12-lead electrocardiograms. Int J Cardiol Heart Vasc, 2023. 44: p. 101172.
25. Rawlani, M., et al., Artificial Intelligence Prediction of Age from Echocardiography as a Marker for Cardiovascular Disease. medRxiv, 2025.
26. Shah, M., et al., Environmental and genetic predictors of human cardiovascular ageing. Nat Commun, 2023. 14(1): p. 4941.
27. Mensah, G.A., et al., Global Burden of Cardiovascular Diseases and Risks, 1990-2022. J Am Coll Cardiol, 2023. 82(25): p. 2350-2473.
28. Thrane, P.G., et al., Mortality Trends After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol, 2023. 82(10): p. 999-1010.
29. Chen, X., et al., The prognostic utility of GRACE risk score in predictive adverse cardiovascular outcomes in patients with NSTEMI and multivessel disease. BMC Cardiovasc Disord, 2022. 22(1): p. 568.

Tables

Table-1: Baseline clinicial characteristics

Characteristic	(n, IQR, %)
Chronological Age (median [IQR])	59 [51–68]
PhenoAge (median [IQR])	71.4 [61.7–83.6]
PhenoAccel (median [IQR])	12.9 [7.1–18.2]
Gender (Female)	83 (23.2%)
Family History (yes)	99 (27.7%)
Hypertension (yes)	173 (48.3%)
Previous Myocardial infarction (yes)	70 (19.6%)
Dyslipidemia (yes)	35 (9.8%)
Smoking (yes)	183 (51.1%)
Diabetes Mellitus (yes)	94 (26.3%)
Atrial Fibrillation (yes)	6(1.6%)
In-Hospital EF %	45[38–55]
MI localization	
Anterior	145(40.6%)
Inferior	77(21.7%)
Lateral	16(4.5%)
Inferior+Right	78(21.7%)
Inferio+Posterior	29(8.2%)
Posterior	13(3.7%)
KAG result	
Noreflow	32 (8.9%)
Final TIMI flow 0	23 (6.4%)
Final TIMI flow 1	27 (7.5%)
Final TIMI flow 2	60 (16.8%)
Final TIMI flow 3	248 (69.3%)
Hmg (g/dL)	13.8 [12.5–14.9]
Kreatinin (mg/dL)	0.84 [0.75-1.05]
LDL (mg/dL)	111 [87-137]

Table-2: Primary Outcomes

		HR/OR*[%95 C.I]	-2log likelihood	R^2	p
Inhospital mortality n:19 (%5.3)	Chronological Age	1.023 [0.97-1.073]*	125.64	0.18	<0.05
	PhenoAge	1.057 [1.017-1.098]*	117.92	0.24	<0.05
	PhenoAccel	1.086 [1.031-1.144]*	116.38	0.47	<0.05
All-cause mortality n:48 (%13.4)	Chronological Age	1.027 [0.99-1.058]	494.14		0.07
	PhenoAge	1.039 [1.16-1.062]	485.97		<0.05
	PhenoAccel	1.050 [1.018-1.082]	488.54		<0.05
Hospitalization for Heart Failure n:33(%11)	Chronological Age	1.066[1.027-1.107]	305.52		<0.05
	PhenoAge	1.039[1.012-1.067]	309.35		<0.05
	PhenoAccel	1.008[0.97-1.047]	317.2		0.68
Recurrent Myocardial Infarction n:26 (%7.3)	Chronological Age	0.988[0.94-1.021]	262.38		0.33
	PhenoAge	0.98[0.95-1.014]	262.10		0.27
	PhenoAccel	0.98[0.93-1.036]	263.01		0.58

Figures

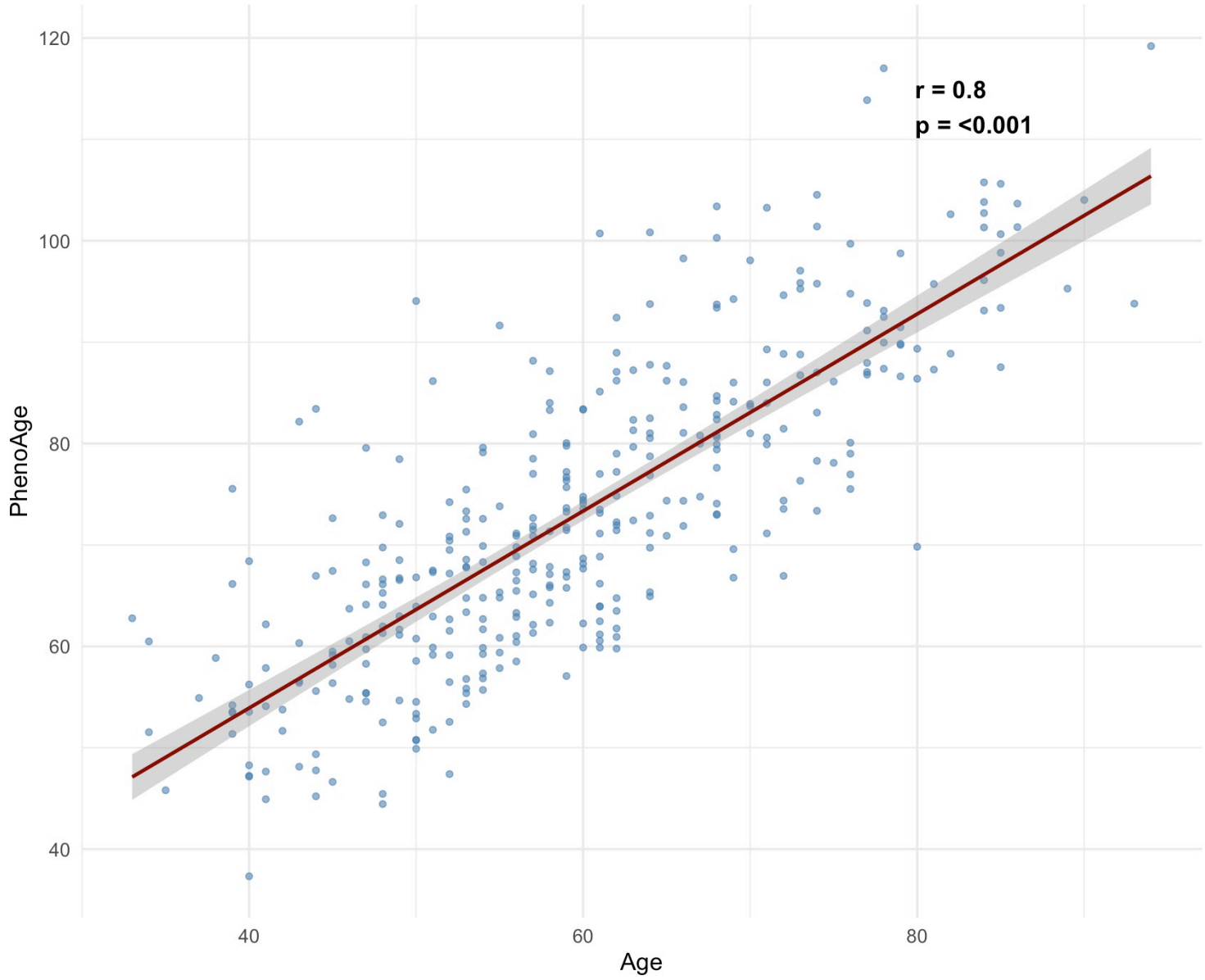


Figure 1

Correlation Between Chronological Age and PhenoAge. Scatter plot illustrating the linear relationship between chronological age (x-axis) and phenotypic age (y-axis) in the study population (n = 358). A strong positive correlation was observed (Pearson's r = 0.80, 95% CI 0.77-0.84, p < 0.001), indicating that phenotypic age increases in parallel with chronological age. The red line represents the linear regression fit with 95% confidence interval (shaded area).

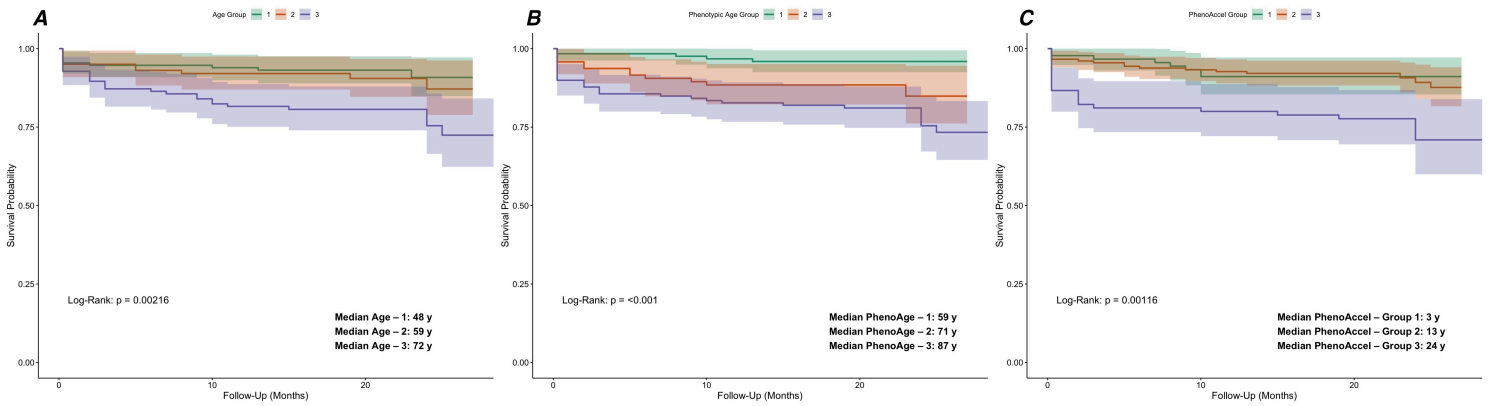


Figure 2

Kaplan–Meier survival curves stratified by chronological age, phenotypic age, and phenotypic age acceleration tertiles.
(A) Survival probabilities according to chronological age tertiles (median ages: 48, 59, and 72 years).
(B) Survival probabilities based on phenotypic age tertiles (median PhenoAge values: 59, 71, and 87 years).
(C) Survival probabilities stratified by phenotypic age acceleration tertiles (median PhenoAccel values: 3, 13, and 24 years).
Log-rank tests demonstrated statistically significant differences in survival across all stratifications, with phenotypic age and phenotypic age acceleration showing more pronounced early mortality separation, particularly in middle tertiles. Shaded areas indicate 95% confidence intervals.