

Biological age acceleration predicts mortality and heart failure after acute myocardial infarction in older adults

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ABSTRACT

OBJECTIVE To determine whether biological age, estimated using phenotypic age (PhenoAge) and PhenoAge acceleration, predicts in-hospital and intermediate-term outcomes after acute myocardial infarction (AMI) in older adults.

METHODS We conducted a retrospective cohort study of 192 consecutive adults [median age: 71 (62–78) years] admitted with AMI to a national tertiary center in 2022. PhenoAge metrics were derived from routine admission laboratory parameters. Patients were followed until 30 August 2025. Outcomes included in-hospital mortality and two composite endpoints: (1) all-cause mortality, non-fatal myocardial infarction, or revascularization; and (2) the above plus hospitalization for heart failure. Logistic regression models and Cox proportional hazards regression models were adjusted for baseline cardiovascular comorbidities.

RESULTS PhenoAge acceleration was independently associated with in-hospital mortality (OR = 1.051, 95% CI: 1.018–1.084, $P = 0.002$), whereas chronological age was not, and PhenoAge also demonstrated independent association (OR = 1.042, 95% CI: 1.013–1.072, $P = 0.004$). Over a median follow-up of 1285 days, all three aging metrics were independently associated with both composite endpoints and heart failure hospitalization in multivariable analyses. Receiver operating characteristic analyses demonstrated similar discriminative performance across metrics for intermediate-term outcomes [area under the curve (AUC) = 0.63–0.71]. PhenoAge demonstrated significant incremental value over chronological age [net reclassification improvement (NRI) = 0.38–0.43, integrated discrimination improvement (IDI) = 0.059–0.069, $P \leq 0.005$].

CONCLUSIONS PhenoAge acceleration independently predicted in-hospital mortality following AMI, suggesting it captures acute physiological vulnerability not reflected by chronological age. Although PhenoAge acceleration showed comparable intermediate-term discriminatory performance to chronological age, PhenoAge demonstrated significant incremental prognostic value beyond chronological age. Biological aging assessment may help identify biologically vulnerable patients at presentation and support personalized risk stratification in geriatric cardiology. These findings support further prospective evaluation of biological aging metrics in older adults with acute coronary syndromes.

Age is a major determinant of cardiovascular morbidity and mortality; however, chronological age does not fully capture the biological aging of tissues and physiological systems.^[1,2] Biological aging reflects the accumulation of molecular and cellular damage over the lifespan and is influenced by genetic, environmental, and lifestyle factors that affect epigenetic mechanisms including DNA methylation.^[2–6] Consequently, biological age may better reflect physiological reserve and susceptibility to disease than chronological age alone.

Biological aging has been associated with all-cause mortality in the general population and in specific disease states such

as heart failure (HF).^[7–11] It is also linked to a wide range of age-related morbidity, including cardiovascular disease, stroke, and cancer.^[12–17] From a geroscience perspective, individuals of similar chronological age may exhibit markedly different biological aging trajectories driven by variation in inflammation, cellular senescence, and immunosenescence.^[18,19] This variability correlates with frailty and diminished physiological resilience in older adults, suggesting particular relevance in acute cardiovascular syndromes such as acute myocardial infarction (AMI).^[19,20]

Several methods have been developed to estimate biological age. DNA methylation-based clocks are well establish-

ed but remain impractical for routine clinical use.^[3-6] The phenotypic age (PhenoAge) and PhenoAge acceleration are clinically applicable surrogate biomarkers derived from routine laboratory parameters and validated against epigenetic clocks.^[21] PhenoAge predicts cardiovascular outcomes across diverse populations and has been associated with mortality in coronary artery disease and with in-hospital outcomes in AMI.^[21-23] Phenotypic aging indices reflect systemic biological stress processes including inflammaging, metabolic dysfunction, and immune dysregulation, which may be particularly relevant in acute cardiovascular disease.^[18,20,24]

Despite major advances in AMI management, substantial morbidity persists. In a large population study from England, up to one-third of patients developed HF or renal failure after AMI, and 7% experienced recurrent myocardial infarction.^[25] Approximately one-quarter of AMI survivors develop HF within four years.^[26] These observations highlight the ongoing burden of adverse outcomes despite contemporary therapy and underscore the need for improved risk stratification beyond chronological age.

The identification of biological vulnerability beyond chronological age may therefore offer additional prognostic information and could be particularly valuable in the growing population of older, multimorbid AMI patients. In geriatric medicine, concepts such as frailty, diminished physiological reserve, and heterogeneous health trajectories are central to clinical decision-making. Biological aging metrics such as PhenoAge may serve as quantifiable proxies for these geriatric syndromes, capturing systemic dysfunction that influences recovery from an acute stressor like AMI. Consequently, the aim of this study was to investigate whether biological age and biological age acceleration are associated with in-hospital and intermediate-term outcomes after AMI in older adults, and whether these measures provide prognostic information beyond chronological age alone.

METHODS

Study Design and Population

We conducted a retrospective cohort study of all consecutive adults admitted with a diagnosis of AMI to Mater Dei Hospital, Msida, Malta between 1 January 2022 and 31 December 2022. Both ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction were included. The AMI was diagnosed using standard clinical, electrocardiographic, and cardiac biomarker criteria consistent with contemporary international guideline definiti-

ons. Patients were identified through the institutional electronic medical information system. No patients were excluded on the basis of clinical presentation; patients were only excluded if laboratory data required for PhenoAge calculation were incomplete.

Of 265 patients initially screened, 73 patients (27.5%) were excluded due to incomplete admission laboratory data. To assess potential selection bias, available baseline characteristics were compared. Excluded patients were younger [median age: 64 (58–73) years vs. 71 (62–78) years], less frequently female (9.6% vs. 21.9%), and had lower prevalence of prior HF (5.5% vs. 13.5%), prior coronary artery disease (23.3% vs. 32.8%), peripheral vascular disease (1.4% vs. 6.3%), and cerebrovascular disease (1.4% vs. 6.8%), while dyslipidaemia prevalence was similar (28.8% vs. 30.2%). The proportion presenting with ST-segment elevation myocardial infarction was comparable (42.5% vs. 43.2%). These differences suggest the included cohort may be selectively enriched for older, higher-risk patients. Sensitivity analyses using multiple imputation were not performed and represent a methodological limitation.

Data Collection

Demographic characteristics, cardiovascular risk factors, comorbidities, and routine admission laboratory results were retrieved from electronic case summaries and the hospital laboratory database. Laboratory variables required to calculate PhenoAge and PhenoAge acceleration (albumin, creatinine, glucose, C-reactive protein, mean corpuscular volume, red cell distribution width, alkaline phosphatase, white cell count, and lymphocyte percentage) were recorded.^[21] Patients without complete laboratory data required for PhenoAge calculation were excluded. Comorbidities including prior HF, dyslipidemia, and previously documented coronary, cerebrovascular, or peripheral vascular disease were also recorded.

Mater Dei Hospital, Msida, Malta operates a fully integrated electronic health record (EHR) system linking inpatient, outpatient, emergency department, and laboratory data. As the sole national acute hospital in Malta, all acute medical admissions are captured within this system. Non-fatal outcomes including HF hospitalization, reinfarction, and revascularisation were ascertained from electronic discharge summaries and coded diagnoses within the EHR. Outcome events were derived from discharge diagnostic codes and clinical documentation rather than formal adjudication by an independent committee, which is acknowledged as a limitation.



Biological Aging Assessment

PhenoAge and PhenoAge acceleration were calculated as described by Levine, *et al.*^[21] PhenoAge acceleration was defined as the residual from a linear regression of PhenoAge on chronological age, calculated within the study sample, consistent with Liu, *et al.*^[10] and Levine, *et al.*^[21] This residual approach ensures PhenoAge acceleration is independent of chronological age. A positive value indicates the individual is biologically older than expected; a negative value indicates the converse. The cohort regression equation was: $\text{PhenoAge} = 5.44 + 1.07 \times \text{chronological age}$ ($R^2 = 0.47$).^[21] As this metric is internally derived, direct comparison of absolute PhenoAge acceleration values with studies using different derivation cohorts should be interpreted with caution. Chronological age was recorded at admission.

Outcomes

Patients were followed until 30 August 2025 using EHRs and national mortality registry data. Two composite clinical endpoints were evaluated: (1) 3-point composite: all-cause mortality, non-fatal reinfarction, or subsequent revascularization (percutaneous or surgical); and (2) 4-point composite: the above plus hospitalization for HF. Individual components of each composite endpoint were also examined.

Statistical Analysis

Continuous variables are reported as medians (interquartile range), categorical variables are presented as counts (percentages). Logistic regression model was used to evaluate the association between aging metrics and in-hospital mortality. Spearman's rank correlation coefficients assessed relationships between aging parameters and length of hospitalization.

Cox proportional hazards regression models were used to estimate hazard ratios for composite endpoints and their individual components. The proportional hazards assumption was formally assessed using Schoenfeld residuals and log-log survival plots, and was confirmed to be satisfied for all primary outcome analyses. Multivariable models were adjusted for major cardiovascular comorbidities (previous coronary artery disease, peripheral vascular disease, cerebrovascular disease, HF, and dyslipidemia). Chronological age, sex, glycaemia, and renal function were intentionally excluded as covariates because these parameters are components of the PhenoAge algorithm, and their inclusion would introduce multicollinearity.^[21] Smoking status and body mass index

were not systematically available and could not be included, representing a limitation.

To quantify the incremental prognostic value of PhenoAge and PhenoAge acceleration beyond chronological age, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated using logistic regression models with chronological age as the reference, using the PredictABEL package in R statistical software 4.6 (R Foundation for Statistical Computing, Vienna, Austria).

Receiver operating characteristic analyses were performed to compare the prognostic performance of chronological age, PhenoAge, and PhenoAge acceleration. A two-sided P -value < 0.05 was considered statistically significant. Analyses were conducted using SPSS 27.0 (SPSS Inc., IBM, Armonk, NY, USA).

Ethical Approval

Ethical approval was obtained from the University of Malta Research Ethics Committee and Mater Dei Hospital Data Protection Office. This retrospective study utilized anonymized data extracted from EHRs. In accordance with Maltese legislation and ethics approval, the requirement for individual informed consent was waived for this non-interventional study.

RESULTS

Baseline Characteristics

Of 265 patients initially screened, 73 patients were excluded due to incomplete laboratory data, leaving 192 patients for analysis. The median age was 71 (62–78) years and 62% of patients were male. Baseline demographic and clinical characteristics are summarized in Table 1.

In-hospital Outcomes

PhenoAge acceleration was significantly associated with in-hospital mortality on logistic regression analysis (Table 2). Chronological age was not significantly associated with in-hospital mortality. PhenoAge was also significantly associated with in-hospital mortality (OR = 1.042, 95% CI: 1.013–1.072, $P = 0.004$). Length of hospitalization correlated positively with chronological age ($r = 0.27$, $P < 0.001$), PhenoAge ($r = 0.377$, $P < 0.001$), and PhenoAge acceleration ($r = 0.268$, $P < 0.001$).

Composite Cardiovascular Endpoints

During a median follow-up of 1285 days, both the 3-point



Table 1 Baseline characteristics of the study population.

Variable	Value
Female sex	42 (22%)
Chronological age, yrs	71 (62–78)
PhenoAge, yrs	79.1 (66.5–89.3)
PhenoAge acceleration, yrs	7.6 (0.1–17.1)
Previously diagnosed coronary artery disease	63 (32.8%)
Previously diagnosed peripheral vascular disease	12 (6.3%)
Previously diagnosed cerebrovascular disease	13 (6.8%)
Previously diagnosed heart failure	26 (13.5%)
Previously diagnosed dyslipidaemia	58 (30.2%)

Data are presented as *n* (%) or median (interquartile range). PhenoAge: phenotypic age.

Table 2 Logistic regression analysis for in-hospital mortality.

Variable	OR (95% CI)	P-value
PhenoAge	1.042 (1.013–1.072)	0.004
PhenoAge acceleration	1.051 (1.019–1.085)	0.002
Chronological age	1.019 (0.975–1.064)	0.41

PhenoAge: phenotypic age.

nt and 4-point composite endpoints occurred with substantial cumulative incidence. Event rates and follow-up characteristics are summarized in [Tables 3 & 4](#).

On univariate Cox regression analysis, chronological age, PhenoAge, and PhenoAge acceleration were each significantly associated with both composite endpoints. In multivariable analysis adjusting for major cardiovascular comorbidities, all three aging metrics remained independently associated with the 3-point composite endpoint (all-cause mortality, reinfarction, revascularization) and the 4-point composite endpoint (including HF hospitalization) ([Tables 3 & 4](#)).

Among individual outcomes, all-cause mortality and hospitalization for HF were significantly associated with chronological age, PhenoAge, and PhenoAge acceleration. Reinfarction showed a borderline significant association with PhenoAge in unadjusted analysis (HR = 1.022, 95% CI: 1.002–1.043, *P* = 0.033), which attenuated to non-significance after multivariable adjustment. No significant associations were observed for revascularisation in either unadjusted or adjusted analyses.

Predictive Performance

Receiver operating characteristic analyses demonstrated comparable discriminatory performance across aging metrics. For the 3-point composite endpoint, area under the curve (AUCs) (95% CI) were 0.631 (0.552–0.710) for chronological age, 0.706 (0.633–0.780) for PhenoAge, and 0.668 (0.592–0.744) for

PhenoAge acceleration ([Figure 1](#)). For the 4-point composite endpoint, AUCs were 0.643 (0.564–0.722), 0.705 (0.631–0.778), and 0.655 (0.578–0.732), respectively ([Figure 2](#)).

To quantify incremental discrimination, NRI and IDI were calculated with chronological age as the reference model. PhenoAge demonstrated significant incremental value for both composite endpoints: MACE3 NRI = 0.429 (95% CI: 0.159–0.699, *P* = 0.002), IDI = 0.069 (95% CI: 0.035–0.103, *P* < 0.001); MACE4 NRI = 0.384 (95% CI: 0.113–0.655, *P* = 0.005), IDI = 0.059 (95% CI: 0.026–0.093, *P* = 0.001). PhenoAge acceleration did not demonstrate significant incremental reclassification or discrimination improvement over chronological age for either endpoint (all *P* > 0.35).

DISCUSSION

In this retrospective AMI cohort, PhenoAge acceleration was associated with in-hospital mortality, as was PhenoAge (OR = 1.042, 95% CI: 1.013–1.072, *P* = 0.004), whereas chronological age was not. This suggests that accelerated biological aging may reflect reduced physiological reserve during the acute phase of infarction, beyond the information provided by chronological age. Patients whose biological age substantially exceeds their chronological age may have diminished capacity to tolerate the inflammatory and metabolic stress associated with acute myocardial injury, predisposing to early adverse events.^[18–23]



Table 3 Unadjusted Cox proportional hazards for composite and individual outcomes.

Outcome	HR (95% CI)	P-value
3-point endpoint		
PhenoAge	1.026 (1.015–1.037)	< 0.001
PhenoAge acceleration	1.026 (1.014–1.038)	< 0.001
Chronological age	1.024 (1.007–1.042)	0.006
4-point endpoint		
PhenoAge	1.025 (1.015–1.036)	0.001
PhenoAge acceleration	1.025 (1.013–1.037)	< 0.001
Chronological age	1.026 (1.009–1.044)	0.002
All-cause mortality		
PhenoAge	1.041 (1.028–1.055)	< 0.001
PhenoAge acceleration	1.037 (1.022–1.051)	< 0.001
Chronological age	1.043 (1.020–1.067)	< 0.001
Hospitalization for heart failure		
PhenoAge	1.036 (1.018–1.055)	0.01
PhenoAge acceleration	1.034 (1.015–1.055)	< 0.001
Chronological age	1.033 (1.003–1.065)	0.03
Non-fatal infarction		
PhenoAge	1.022 (1.002–1.043)	0.033
PhenoAge acceleration	1.023 (0.999–1.048)	0.06
Chronological age	1.020 (0.987–1.053)	0.239
Need for revascularization		
PhenoAge	1.010 (0.991–1.030)	0.289
PhenoAge acceleration	1.003 (0.977–1.031)	0.813
Chronological age	1.007 (0.978–1.036)	0.641

PhenoAge: phenotypic age.

Table 4 Adjusted Cox proportional hazards for composite and individual outcomes*.

Outcome	HR (95% CI)	P-value
3-point endpoint		
PhenoAge	1.024 (1.012–1.036)	< 0.001
PhenoAge acceleration	1.02 (1.01–1.04)	0.002
Chronological age	1.02 (1.00–1.04)	0.039
4-point endpoint		
PhenoAge	1.024 (1.012–1.036)	< 0.001
PhenoAge acceleration	1.02 (1.01–1.04)	0.003
Chronological age	1.02 (1.00–1.04)	0.015
All-cause mortality		
PhenoAge	1.037 (1.021–1.053)	< 0.001
PhenoAge acceleration	1.027 (1.010–1.044)	0.002
Chronological age	1.036 (1.012–1.061)	0.004
Hospitalization for heart failure		
PhenoAge	1.028 (1.007–1.048)	0.008
PhenoAge acceleration	1.022 (0.999–1.045)	0.060
Chronological age	1.025 (0.992–1.059)	0.136

Continued

Outcome	HR (95% CI)	P-value
Non-fatal infarction		
PhenoAge	1.02 (0.99–1.04)	0.15
PhenoAge acceleration	1.02 (0.99–1.05)	0.28
Chronological age	1.02 (0.98–1.05)	0.35
Need for revascularization		
PhenoAge	1.02 (0.99–1.04)	0.16
PhenoAge acceleration	1.01 (0.98–1.04)	0.47
Chronological age	1.01 (0.98–1.04)	0.54

*Refers to adjust for previously diagnosed coronary artery disease, peripheral vascular disease, cerebrovascular disease, heart failure, and dyslipidemia. PhenoAge: phenotypic age.

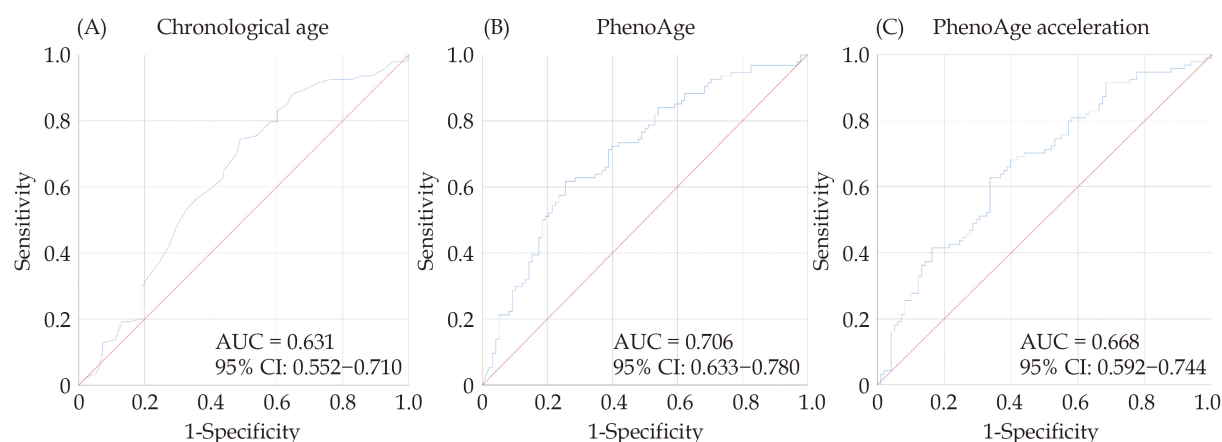


Figure 1 Receiver operating characteristic curves for prediction of 3-point major adverse cardiovascular events using chronological age (A), PhenoAge (B), and PhenoAge acceleration (C). AUC: area under the curve; PhenoAge: phenotypic age.

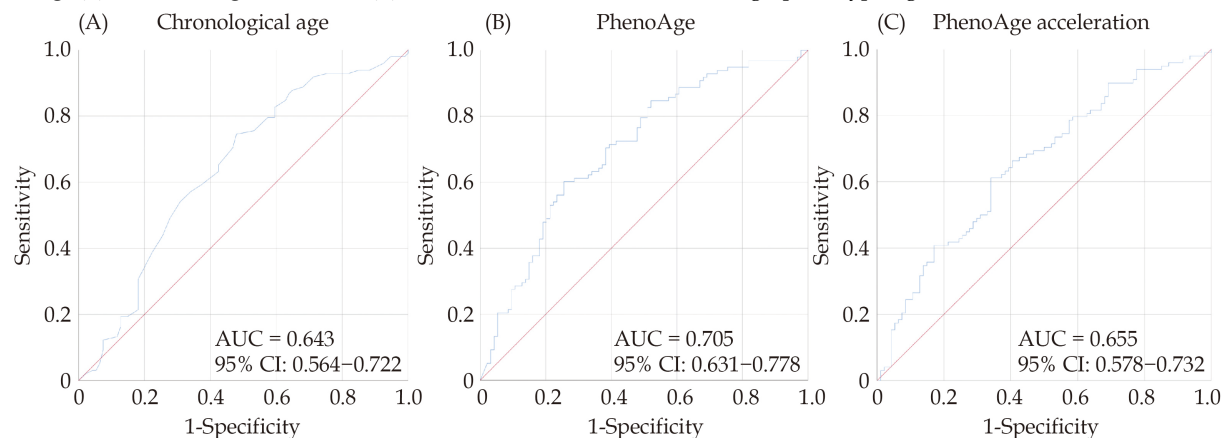


Figure 2 Receiver operating characteristic curves showing the discriminative performance of chronological age (A), PhenoAge (B), and PhenoAge acceleration (C) for prediction of the 4-point major adverse cardiovascular event composite endpoint. AUC: area under the curve; PhenoAge: phenotypic age.

Biological aging incorporates laboratory indices related to inflammatory activity, metabolic status, and tissue repair. Several components of the PhenoAge algorithm, C-reactive protein, albumin, lymphocyte proportion, and red cell distribution width, have recognized associations with systemic inflammation and immune dysregulation.^[21] Inflammation and im-

paired metabolic homeostasis contribute to plaque instability, myocardial injury, and subsequent deterioration, and may be particularly relevant during acute presentation.^[27–29] This may explain the independent associations of both PhenoAge and PhenoAge acceleration with in-hospital mortality observed in our cohort.



We also found that PhenoAge and PhenoAge acceleration were associated with intermediate-term outcomes, including both composite cardiovascular endpoints, all-cause mortality, and hospitalization for HF. PhenoAge demonstrated higher discriminatory performance (AUC = 0.706 for MACE3 and AUC = 0.705 for MACE4) compared with chronological age (AUC = 0.631 for MACE3 and AUC = 0.643 for MACE4). PhenoAge provided significant incremental reclassification and discrimination improvement over chronological age (NRI = 0.38–0.43, IDI = 0.059–0.069, all $P \leq 0.005$), whereas PhenoAge acceleration did not. These findings suggest that absolute biological age carries more discriminatory information than the acceleration residual for intermediate-term outcomes, while the acceleration metric retains particular value for predicting in-hospital mortality. It is plausible that secondary prevention strategies, including lipid-lowering therapy, renin-angiotensin system inhibition, antiplatelet therapy, and newer cardiometabolic agents, attenuate biological vulnerability over time, thereby reducing the differential prognostic separation between biological and chronological aging.^[30–36]

Notably, hospitalization for HF demonstrated the strongest association with biological aging metrics. HF is closely linked to inflammation, endothelial dysfunction, sarcopenia, and frailty, and biological aging measures may therefore be particularly relevant to this outcome subset.^[36–40] PhenoAge acceleration likely reflects cumulative systemic vulnerability and may help identify patients at heightened risk of subsequent HF and functional decline following AMI. In the adjusted analysis, chronological age was no longer significantly associated with HF hospitalization (HR = 1.025, 95% CI: 0.992–1.059, $P = 0.136$), whereas PhenoAge remained independently associated (HR = 1.028, 95% CI: 1.007–1.048, $P = 0.008$), suggesting that biological age captures HF risk that chronological age alone does not after adjustment for cardiovascular comorbidities.

The absence of DNA methylation-based biological aging clocks represents a limitation. Although these clocks directly reflect epigenetic change, PhenoAge was originally developed and validated against methylation-derived aging measures and has demonstrated comparable predictive capacity for morbidity and mortality across multiple populations.^[21] The routine availability of its laboratory components makes PhenoAge clinically practical in real-world settings. Nevertheless, future studies should evaluate whether combining phenotypic and methylation-based metrics enhances risk prediction in AMI.

Lifestyle-related and environmental factors including diet, physical activity, adiposity, and pollutant exposure have been associated with accelerated biological aging.^[41–50] Whether modifying biological aging through lifestyle or pharmacological intervention translates into improved cardiovascular resilience remains uncertain and warrants prospective investigation. Mechanistic pathways linking biological aging to cardiovascular pathology, particularly during acute illness, also warrant further exploration.

In summary, biological aging, particularly biological age acceleration, was associated with adverse outcomes after AMI, with the strongest influence observed during the acute phase. While PhenoAge acceleration showed comparable long-term discriminatory performance to chronological age, PhenoAge demonstrated significant incremental prognostic value beyond chronological age for intermediate-term composite endpoints. Hence, biological aging assessment may help identify patients who are biologically vulnerable at presentation and who may benefit from closer monitoring and personalized risk stratification. These findings support further investigation of biological aging metrics in cardiovascular disease and raise the possibility that modifiable aging processes could represent future therapeutic targets.

STRENGTHS AND LIMITATIONS

A strength of this study is the use of comprehensive real-world clinical and laboratory data from the contemporary AMI population, with complete mortality follow-up facilitated by linkage to the national mortality registry. Several limitations must be acknowledged. Firstly, the retrospective single-center design limits generalizability, and the absence of external validation in an independent cohort is an important constraint; prospective multicenter studies are required to confirm these findings. Secondly, 73 patients (27.5%) were excluded due to incomplete admission laboratory data; excluded patients were younger with lower comorbidity burden, and findings should be interpreted in this context. Sensitivity analyses using multiple imputation were not performed and represent a further limitation. Thirdly, nonfatal outcomes were ascertained from EHR discharge codes rather than formal independent event adjudication. Fourthly, DNA methylation-based clocks were not available for comparison. Last but not least, smoking status and body mass index were not systematically available. Prospective multicenter studies incorporating molecular aging markers and formal event adjudication are required to confirm these observations.



CONCLUSIONS

In this retrospective AMI cohort, biological aging, including both PhenoAge and PhenoAge acceleration, was associated with in-hospital mortality and adverse intermediate-term clinical outcomes. Although PhenoAge acceleration showed comparable discriminatory ability to chronological age, PhenoAge demonstrated significant incremental prognostic value beyond chronological age. Further studies are warranted to validate these findings and to determine whether biological aging assessment can contribute to personalized cardiovascular risk stratification following AMI.

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REFERENCES

- [1] López-Otín C, Blasco MA, Partridge L, *et al.* The hallmarks of aging. *Cell* 2013; 153: 1194–1217.
- [2] Li A, Koch Z, Ideker T. Epigenetic aging: biological age prediction and informing a mechanistic theory of aging. *J Intern Med* 2022; 292: 733–744.
- [3] Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol* 2013; 14: R115.
- [4] Hannum G, Guinney J, Zhao L, *et al.* Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell* 2013; 49: 359–367.
- [5] Horvath S, Oshima J, Martin GM, *et al.* Epigenetic clock for skin and blood cells applied to Hutchinson Gilford Progeria Syndrome and *ex vivo* studies. *Aging (Albany NY)* 2018; 10: 1758–1775.
- [6] Lu AT, Quach A, Wilson JG, *et al.* DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging (Albany NY)* 2019; 11: 303–327.
- [7] Zou Y, Huang J, Tang X, *et al.* Associations between five indicators of epigenetic age acceleration and all-cause and cause-specific mortality among US adults aged 50 years and older. *Clin Epigenetics* 2025; 17: 66.
- [8] Wang K, Gao J, Liu Y, *et al.* Biological age construction for prediction of mortality in the Chinese population. *Geroscience* 2025; 47: 5869–5880.
- [9] Cribb L, Hodge AM, Yu C, *et al.* Inflammation and epigenetic aging are largely independent markers of biological aging and mortality. *J Gerontol A Biol Sci Med Sci* 2022; 77: 2378–2386.
- [10] Liu Z, Kuo PL, Horvath S, *et al.* A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: a cohort study. *PLoS Med* 2018; 15: e1002718.
- [11] Xu X, Xu Z. Association between phenotypic age and the risk of mortality in patients with heart failure: a retrospective cohort study. *Clin Cardiol* 2024; 47: e24321.
- [12] Mutambudzi M, Brown MT, Chen NW. Association of epigenetic age and everyday discrimination with longitudinal trajectories of chronic health conditions in older adults. *J Gerontol A Biol Sci Med Sci* 2024; 79: glae005.
- [13] Zhang F, Deng S, Zhang J, *et al.* Causality between heart failure and epigenetic age: a bidirectional Mendelian randomization study. *ESC Heart Fail* 2023; 10: 2903–2913.
- [14] Zhao W, Wang Z, Mi C, *et al.* PhenoAge and PhenoAgeAccel in the context of dyslipidemia: association with stroke and potential as a new predictor in the US general population. *Postgrad Med J* 2024; 101: 17–28.
- [15] Faul JD, Kim JK, Levine ME, *et al.* Epigenetic-based age acceleration in a representative sample of older Americans: associations with aging-related morbidity and mortality. *Proc Natl Acad Sci U S A* 2023; 120: e2215840120.
- [16] Bian L, Ma Z, Fu X, *et al.* Associations of combined phenotypic aging and genetic risk with incident cancer: a prospective cohort study. *Elife* 2024; 13: RP91101.
- [17] Xie Q, Qu H, Xie S, *et al.* Associations of biological aging with the morbidity and all-cause mortality of patients with lung cancer. *Sci Rep* 2025; 15: 17880.
- [18] Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018; 15: 505–522.
- [19] Hamczyk MR, Nevado RM, Baretino A, *et al.* Biological versus chronological aging: JACC Focus Seminar. *J Am Coll Cardiol* 2020; 75: 919–930.
- [20] Fougère B, Boulanger E, Nourhashémi F, *et al.* Chronic inflammation: accelerator of biological aging. *J Gerontol A Biol Sci Med Sci* 2017; 72: 1218–1225.
- [21] Levine ME, Lu AT, Quach A, *et al.* An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY)* 2018; 10: 573–591.
- [22] Ma Q, Li BL, Yang L, *et al.* Association between phenotypic age and mortality in patients with multivessel coronary artery disease. *Dis Markers* 2022; 2022: 4524032.
- [23] Gao Y, Gao K, Shi R, *et al.* Association between phenotypic age and in-hospital outcomes in patients with acute myocardial infarction: a retrospective observational study. *Int J Cardiol Heart Vasc* 2025; 58: 101670.
- [24] Zhu X, Chen Z, Shen W, *et al.* Inflammation, epigenetics, and metabolism converge to cell senescence and ageing: the regulation and intervention. *Signal Transduct Target Ther* 2021; 6: 245.
- [25] Hall M, Smith L, Wu J, *et al.* Health outcomes after myocardial infarction: a population study of 56 million people in England. *PLoS Med* 2024; 21: e1004343.
- [26] Gho JMIH, Schmidt AF, Pasea L, *et al.* An electronic health records cohort study on heart failure following myocardial infarction in England: incidence and predictors. *BMJ Open* 2018; 8: e018331.
- [27] Liu C, Yang F, Hu Y, *et al.* The relationships between inflammatory biomarkers, plaque characteristics, and macrophage clusters in coronary plaque: a quantitative assessment of macrophages based on optical coherence tomography. *Front Cardiovasc Med* 2025; 12: 1625239.
- [28] Katamine M, Minami Y, Nagata T, *et al.* High-sensitivity C-reactive protein, plaque vulnerability and adverse events in patient with stable coronary disease: an optical coherence tomography study. *Int J Cardiol* 2025; 421: 132924.
- [29] Fröbert O, Stone GW, Larsen AI, *et al.* Relationships of hs-



- CRP to high-risk vulnerable plaque after NSTEMI: insights from the PROSPECT II Trial. *JACC Cardiovasc Interv* 2025; 18: 1217–1228.
- [30] Zivkovic S, Maric G, Cvetinovic N, *et al*. Anti-inflammatory effects of lipid-lowering drugs and supplements: a narrative review. *Nutrients* 2023; 15: 1517.
- [31] Lee SA, Riella LV. Narrative review of immunomodulatory and anti-inflammatory effects of sodium-glucose cotransporter 2 inhibitors: unveiling novel therapeutic frontiers. *Kidney Int Rep* 2024; 9: 1601–1613.
- [32] Rykova EY, Klimontov VV, Shmakova E, *et al*. Anti-inflammatory effects of SGLT2 inhibitors: focus on macrophages. *Int J Mol Sci* 2025; 26: 1670.
- [33] Cyrus T, Sung S, Zhao L, *et al*. Effect of low-dose aspirin on vascular inflammation, plaque stability, and atherogenesis in low-density lipoprotein receptor-deficient mice. *Circulation* 2002; 106: 1282–1287.
- [34] Awad K, Zaki MM, Mohammed M, *et al*. Effect of the renin-angiotensin system inhibitors on inflammatory markers: a systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc* 2022; 97: 1808–1823.
- [35] Mehdi SF, Pusapati S, Anwar MS, *et al*. Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. *Front Immunol* 2023; 14: 1148209.
- [36] Allara E, Shi W, Bolton T, *et al*. Burden of cardiovascular diseases in England (2020–2024): a national cohort using electronic health records data. *Lancet Public Health* 2025; 10: e943–e954.
- [37] Solomon SD, Dobson J, Pocock S, *et al*. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007; 116: 1482–1487.
- [38] Lewis EF, Lamas GA, O'Meara E, *et al*. Characterization of health-related quality of life in heart failure patients with preserved versus low ejection fraction in CHARM. *Eur J Heart Fail* 2007; 9: 83–91.
- [39] Reina-Couto M, Pereira-Terra P, Quelhas-Santos J, *et al*. Inflammation in human heart failure: major mediators and therapeutic targets. *Front Physiol* 2021; 12: 746494.
- [40] Mollar A, Bonanad C, Diez-Villanueva P, *et al*. Frailty and hospitalization burden in patients with chronic heart failure. *Am J Cardiol* 2022; 183: 48–54.
- [41] Chen XL, Zhao QQ, Lin SR, *et al*. Epigenetic clocks as mediators of health behaviors and mortality in middle-aged and older adults. *J Nutr Health Aging* 2025; 29: 100602.
- [42] Liu Y, Kang M, Wei W, *et al*. Dietary diversity score and the acceleration of biological aging: a population-based study of 88, 039 participants. *J Nutr Health Aging* 2024; 28: 100271.
- [43] Zhang C, Han RF, Yin S, *et al*. Differential associations of dietary inflammatory potential, antioxidant capacity, and Mediterranean diet adherence with biological aging: a UK Biobank study. *J Nutr Health Aging* 2025; 29: 100638.
- [44] Ammous F, Peterson MD, Mitchell C, *et al*. Physical activity is associated with decreased epigenetic aging: findings from the Health and Retirement Study. *J Cachexia Sarcopenia Muscle* 2025; 16: e13873.
- [45] Ryan J, Wrigglesworth J, Loong J, *et al*. A systematic review and meta-analysis of environmental, lifestyle, and health factors associated with DNA methylation age. *J Gerontol A Biol Sci Med Sci* 2020; 75: 481–494.
- [46] Ni W, Nikolaou N, Ward-Caviness CK, *et al*. Associations between medium- and long-term exposure to air temperature and epigenetic age acceleration. *Environ Int* 2023; 178: 108109.
- [47] Wen Y, Chen Y, Ma Y, *et al*. Long-term BMI trajectories and epigenetic age acceleration: the role of genetic risk for obesity. *BMC Med* 2025; 23: 589.
- [48] Duan S, Wu Y, Zhu J, *et al*. Associations of polycyclic aromatic hydrocarbons mixtures with cardiovascular diseases mortality and all-cause mortality and the mediation role of phenotypic ageing: a time-to-event analysis. *Environ Int* 2024; 186: 108616.
- [49] Shi X, Wang Y, Yang F, *et al*. Associations of exposure to volatile organic compounds with biological aging: a cross-sectional study. *BMC Public Health* 2025; 25: 1476.
- [50] Mi P, Cao X, Feng H, *et al*. Association of blood cadmium levels with epigenetic age acceleration in U. S. adults aged > 50 years. *Front Public Health* 2025; 13: 1504830.

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