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Association between phenotypic age and in-hospital outcomes in patients with acute myocardial infarction: A retrospective observational study

Yajie Gao [a,b], Ke Gao [a,b], Ruijuan Shi [a,b], Xiaorui Huang [a,b], Peizhu Dang [a,b], Hui Liu [c], Xiaopu Zheng [a,b,*], Yanbo Xue [a,b,*]

[a] Department of Cardiology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061 Shaanxi, China
[b] Key Laboratory of Molecular Cardiology of Shaanxi Province, Xi'an 710061 Shaanxi, China
[c] Biobank, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061 Shaanxi, China

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ABSTRACT

Background: Phenotypic age (PhenoAge) has emerged as a superior predictor of age-related morbidity and mortality. This study aimed to assess the associations between PhenoAge and in-hospital outcomes in patients with acute myocardial infarction (AMI).

Methods: 2896 AMI patients admitted to the First Affiliated Hospital of Xi'an Jiaotong University from 2019 to 2022 were analyzed in this retrospective study. PhenoAge was calculated by using the phenotypic age calculator, an equation for chronologic age and 9 clinical biomarkers, and Phenotypic Age Accelerate (PhenoAgeAccel) was measured using the residuals of regression PhenoAge on chronological age. Clinical outcomes were defined as in-hospital major adverse cardiovascular events (MACEs), including cardiogenic shock, malignant arrhythmia, acute heart failure, and mechanical complications.

Results: Overall, patients with high PhenoAge had a higher Gensini score and a higher likelihood of receiving supportive care, as well as worse clinical outcomes. The same results were observed in patients with positive PhenoAgeAccel. Moreover, PhenoAge and PhenoAgeAccel were significantly associated with in-hospital MACEs even after adjusting for multiple traditional risk factors. The area under the curve for PhenoAge was 0.714 ($P < 0.001$), which significantly outperformed chronologic age (AUC: 0.601, $P < 0.001$) and other cardiovascular risk factors. Re-examination of the ROC curves using different combinations of variables, PhenoAge was also able to significantly improve the predictive value of several models.

Conclusions: PhenoAge is significantly associated with clinical outcomes and reliably predicts in-hospital MACEs. Compared with chronological age, PhenoAge is a better complementary biomarker for predicting the risk of in-hospital adverse cardiovascular events in patients with AMI.

1. Background

Over the past two centuries, life expectancy has doubled, making the adverse impacts of an aging population increasingly obvious [1]. Due to an increase in the incidence and prevalence of age-related disorders including cardiovascular disease, societies worldwide are bearing an increasing burden of healthcare consumption and expenditures [2]. Studies predict that there will be a more than 50 % increase in the annual number of cardiovascular disease occurrences between 2010 and 2030 [3–6].

Age is the risk factor for many diseases; however, individuals of the same age, genetic background, lifestyle, and similar risk factors may differ in the incidence and severity of cardiovascular disease or other chronic diseases, as well as in long-term prognosis and life expectancy. It is established that chronological age is only a measure of how long a person has lived and is not a reliable indicator of the biological aging process that occurs in the body, which includes the degree of tissue aging and a person's physical functional reserve [7–11]. Several methods have been developed to determine the biological age of an individual, such as HorvathAge, HannumAge, and GrimAge, which represent the states of DNA methylation [12–14]. Recently, a novel method to evaluate the biological age, Phenotypic Age (PhenoAge), has been proposed.

* Corresponding authors at: Department of Cardiology, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Street, Xi'an 710061, Shaanxi, People's Republic of China.
E-mail addresses: zhengxp001@xjtufh.edu.cn (X. Zheng), xyb001xyb@xjtufh.edu.cn (Y. Xue).

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PhenoAge was calculated using the algorithm developed by Levine et al., which integrates nine clinical biomarkers (albumin, creatinine, glucose, C-reactive protein, lymphocyte percentage, mean corpuscular volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count) with chronological age. These variables are weighted through a Cox proportional hazards model to generate a mortality risk score, which is then transformed into age-equivalent units via Gompertz mortality parameters calibrated to population-level data [15,16]. It is a potent predictor of physical function, cognitive performance metrics, cause-specific mortality, and overall cause-specific mortality [15]. More significantly, research indicates that it is a more accurate predictor of residual life expectancy than chronological age [17,18]. It has also been demonstrated that phenotypic age acceleration (PhenoAgeAccel), the residual of regressing PhenoAge on chronological age, can predict mortality risk by indicating whether an individual's biological age is older (positive value) or younger (negative value) than their chronological age [15].

Even though the calculator may more accurately represent the underlying DNA methylation status in patients with clinical stability, it is still a very decent composite indicator based on common laboratory indicators, and we can use the variables in this phenotypic age calculator to predict disease prognosis. Acute myocardial infarction (AMI) is still a leading cause of cardiovascular mortality and significantly decreases patients' quality of life and life expectancy [19,20]. Thus, the purpose of this research was to investigate the relationships between the calculator (PhenoAge) at admission and in-hospital outcomes in patients suffering from AMI, to develop a new and reliable composite indicator for assessing the severity of illnesses and prognoses.

2. Methods

2.1. Study population

Patients with AMI who were admitted to the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, Shaanxi, China) between January 2019 and October 2022 were enrolled consecutively. Inclusion criteria for the study were: (a) AMI was diagnosed by more than two cardiovascular specialists according to the Fourth Universal Definition of Myocardial Infarction (2018) [21]; (b) age $\geq$ 18 years old; and (c) laboratory tests can be used to calculate the PhenoAge. A total of 2896 patients were finally analyzed. The informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Assessment of PhenoAge and PhenoAgeAccel

PhenoAge was calculated using the algorithm that integrates nine clinical biomarkers (albumin, creatinine, glucose, C-reactive protein, lymphocyte percentage, mean corpuscular volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count) with chronological age. The formula is as follows: [15,16]

$$PhenoAge = 141.50 + \frac{ln[-0.00553 \times ln(1-xb)}{0.09165}$$

$$\begin{aligned} xb = {} & -19.907 - 0.336 \times albumin + 0.0095 \times creatinine + 0.0195 \\ & \times glucose + 0.0954 \times ln(CRP) - 0.0120 \\ & \times lymphocytepercent + 0.0268 \times meancellvolume + 0.3356 \\ & \times redbloodcelldistributionwidth + 0.00188 \\ & \times alkalinephosphatase + 0.0554 \times whitebloodcellcount + 0.0804 \\ & \times chronologicalage \end{aligned}$$

PhenoAgeAccel was measured using the residuals of the regression of PhenoAge on chronological age. These residuals were used to quantify PhenoAge acceleration, with positive values indicating that the individual was physiologically older than their chronological age and negative values indicating that the individual was physically younger than their chronological age. No modifications to the original method were made in our analysis.

2.3. Demographic characteristics and clinical parameters

Demographic data such as age, sex, body mass index (BMI), mean arterial pressure (MAP), alcohol intake, smoking, comorbidities, and oral medication use were gathered. Some laboratory indicators were recorded, such as hemoglobin, leukocyte count, lymphocyte percentage, albumin, creatinine, blood glucose, c-reactive protein, creatine kinase, creatine phosphokinase isoenzyme, and N-terminal pro-brain natriuretic peptide. The estimated glomerular filtration rate (eGFR) was calculated according to the MDRD study equation [22,23]. Fasting blood specimens were collected from all patients within 24 h of admission.

Additionally, we gathered the procedure reports—which included lesion segments, degree of stenosis, and surgical techniques—from patients who had coronary angiography. All of the precise information came from the inpatient medical record system of the First Affiliated Hospital of Xi'an Jiaotong University. At least two senior physicians performed coronary angiography. The Gensini score, which is based on a quantitative conversion of coronary angiography results by assigning different weights to the location of the lesion and the degree of stenosis and then adding them, was used to assess coronary artery severity [24,25]. The higher the Gensini score, the more serious the coronary artery lesions.

The NCDR CathPCI Mortality Risk Prediction model was estimated for assessing *peri*-procedural PCI mortality risk [26]. The predictors in the model included age, cardiogenic shock, prior congestive heart failure, peripheral vascular disease, chronic lung disease, glomerular filtration rate, NYHA, and PCI status (STEMI/NSTEMI). Given that the model was created using a large and representative cohort using modern statistical techniques and has undergone both internal and external validation, it should be the standard option for predicting in-hospital mortality in the United States [27].

2.4. Clinical outcomes

Clinical outcomes were defined as in-hospital major adverse cardiovascular events (MACEs), including cardiogenic shock (requiring medical or mechanical hemodynamic support), malignant cardiac arrhythmias (ventricular tachycardia, ventricular fibrillation, high-degree atrioventricular block, or cardiac arrest), acute heart failure, and mechanical complications resulting from myocardial infarction [28].

2.5. Statistical analysis

Categorical variables were shown as counts and proportions, using the chi-square test or Fisher's precision probability test. Continuous variables conforming to a normal distribution were summarized as mean $\pm$ standard deviation, otherwise by median and interquartile range. One-way ANOVA test or *t*-test was used for normally distributed continuous variables, and the Kruskal-Wallis test was for non-normally distributed continuous variables. Univariate and multivariable logistic regression analyses were also performed to identify clinical predictors of in-hospital MACEs and their components. In the multivariate model, we adjusted for traditional risk factors including gender, BMI, MAP, smoking, drinking, left ventricular ejection fraction (LVEF), low-density lipoprotein (LDL), creatine kinase isoenzyme (CKMB) and Gensini score. Finally, the receiver operating characteristics (ROC) curves were used to clarify the risk prediction of in-hospital MACE by PhenoAge and its predictive role compared with traditional risk biomarkers such as chronological age and others. DeLong's test was used to compare the AUC of each variable (MedCalc version 19.1, Belgium). All statistical

Table 1
Baseline characteristics of study participants.

Variables	T1	T2	T3	*P*-value
All	965	966	965	
Chronological age (years)	51.5 ± 8.4	65.1 ± 6.5 [a]	75.3 ± 8.3[a b]	<0.001
Men, n (%)	847(87.8)	771(79.8) [a]	682(70.7)[a b]	<0.001
Heart rate (times)	78 ± 14.4	77.5 ± 14.9	80.6 ± 18.8[a b]	0.001
SBP (mmHg)	128.1 ± 21	128 ± 21.8	126.8 ± 24.5	0.404
DBP (mmHg)	83.2 ± 14.1	79.8 ± 13.1 [a b]	75.8 ± 13.9[a b]	<0.001
MAP (mmHg)	98.1 ± 15.4	95.9 ± 14.7 [a b]	92.8 ± 15.7[a b]	<0.001
BMI (kg/m^2)	25.79 ± 4.48	24.99 ± 4.01 [a b]	24.02 ± 2.09[a b]	<0.001
Smoking, n (%)	480(63.7)	434(58.3)	314(42.7)[a b]	<0.001
Drinking, n (%)	236(31.3)	194(26.0) [a]	119(16.2)[a b]	<0.001
Comorbidities				
Hypertension, n (%)	425(44.0)	536(55.5) [a]	572(59.3)[a]	<0.001
Diabetes, n (%)	252(26.1)	282(29.2)	341(35.3)[a b]	<0.001
History of PCI, n (%)	89(9.2)	111(11.5)	149(15.4)[a b]	<0.001
Angiographic and procedural characteristics, n (%)				
CAG	900(97.6)	875(94.4)[a]	758(83.6)[a b]	<0.001
Diseased vessels				
One	190(21.1)	108(12.3)[a]	80(10.5)[a b]	<0.001
Two	245(27.2)	227(25.9)	166(21.9)[a b]	<0.001
Three	449(49.9)	534(61.0)[a]	508(66.9)[a]	<0.001
CTO	61(6.8)	83(9.5)	101(13.3)[a b]	<0.001
PCI	786(87.2)	798(89.8)	685(89.8)	0.151
PTCA	223(24.8)	230(25.9)	179(23.5)	0.527
CABG	9(1.0)	31(3.5)[a]	10(1.3)[b]	<0.001
Complete revascularization	569(67.4)	534(62.8)	362(50.4)[a b]	<0.001
IABP	18(2.0)	33(3.6) [a]	88(9.2)[a b]	<0.001
ECMO	1(0.1)	6(0.6)	16(1.8)[a b]	<0.001
Gensini score	69.54 ± 44.21	82.76 ± 46.56 [a]	91.45 ± 47.61[a b]	<0.001
Oral medications, n (%)				
Antiplatelet drugs	947(98.1)	945(97.8)	923(95.6)[a b]	0.001
Statins	947(98.1)	945(97.8)	923(95.6)[a b]	0.001
Beta-blockers	779(80.7)	727(75.3)[a]	657(68.1)[a b]	<0.001
ACEI/ARB	187(19.4)	238(24.6)[a]	227(23.5)[a]	0.014
ARNI	122(12.6)	147(15.2)	164(17.0)[a]	0.026
Diuretics	304(31.5)	487(50.4)[a]	704(73.0)[a b]	<0.001
LVEF (%)	57 ± 10	54 ± 12[a]	50 ± 12[a b]	<0.001
PhenoAge (years)	43.773 ± 7.143	58.777 ± 3.503[a]	76.565 ± 10.901[a b]	<0.001
PhenoAgeAccel (years)	−0.385 ± 0.559	−0.234 ± 0.600[a]	0.576 ± 1.306[a b]	<0.001
Clinical outcomes, n (%)				
In-hospital MACEs	43(4.5)	79(8.2)[a]	199(20.6)[a b]	<0.001
Cardiogenic shock	13(1.3)	35(3.6)[a]	125(13.0)[a b]	<0.001
Malignant arrhythmia	26(2.7)	38(3.9)	77(8.0)[a b]	<0.001
Acute Heart Failure	3(0.3)	4(0.4)	33(3.4)[a b]	<0.001
Mechanical complications	20(2.1)	33(3.4)	69(7.2)[a b]	<0.001

The subjects were divided into three groups according to PhenoAge tertiles. Chi-square test or one-way ANOVA test were used for statistical analysis. Continuous variables are shown as M ± SD or quartiles, and classification variables are shown as percentages. [a]: Compared with tertile 1 group, the difference is statistically significant ($P < 0.05$); [b]: Compared with tertile 2 group, the difference is statistically significant ($P < 0.05$); SBP: Systolic arterial pressure; DBP: Diastolic arterial pressure; MAP: Mean arterial pressure; BMI: Body mass index; CAG: Coronary angiography; CTO: Chronic total occlusion; PCI: Percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; IABP: Intra-aortic balloon pump; ECMO: Extracorporeal Membrane Oxygenation; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin receptor enkephalinase inhibitor; LVEF: Left ventricular ejection fraction; PhenoAge: Phenotypic age; PhenoAgeAccel: Phenotypic age accelerate. MACEs: Major adverse cardiovascular events.

Table 2
Differences between negative and positive groups according to PhenoAgeAccel.

Variables	Negative group (n = 1794)	Positive group (n = 1102)	*P*-value
All	1794	1102	
Chronological age (years)	64.3 ± 11.7	63.4 ± 13.6	0.072
PhenoAge (years)	55.0 ± 12.0	67.3 ± 17.4	<0.001
Gensini score	78.4 ± 46.1	84.6 ± 48.2	0.002
LVEF (%)	56 ± 11	51 ± 12	<0.001
Outcomes			
In-hospital MACEs	91(5.1)	230(20.9)	<0.001
Cardiogenic shock	33(1.8)	140(12.7)	<0.001
Malignant arrhythmia	47(2.6)	94(8.5)	<0.001
Acute Heart Failure	11(0.6)	29 (2.6)	<0.001
Mechanical complications	51(2.8)	71 (6.4)	<0.001

The subjects were divided into two groups based on whether the PhenoAgeAccel was positive or negative. Chi-square test or *t*-test were used for statistical analysis. Continuous variables are shown as M ± SD or quartiles, and classification variables are shown as percentages. LVEF: Left ventricular ejection fraction; MACEs: Major adverse cardiovascular events.

analyses above were performed using SPSS 26.0 (IBM corporation). A two-sided $P < 0.05$ was considered to have statistical significance.

3. Results

3.1. Characteristics of study participants

We divided all the participants into three groups according to the tertiles of PhenoAge, and the characteristics of each subgroups are shown in Table 1. Of the three subgroups, the higher the PhenoAge, the older the chronological age, and the lower the proportion of males. MAP and BMI were lower in the T3 subgroup of patients than in the other two groups. Notably, patients in this group had lower rates of drinking and smoking, most likely as a result of the greater proportion of female patients in this subgroup. Patients in the T3 subgroup have higher rates of diabetes, hypertension, and a history of PCI when it comes to comorbidities ($P < 0.001$). On coronary angiography, we found that patients with an older PhenoAge had more severe vascular lesions and a higher Gensini score, in addition to more life support, such as IABP and ECMO ($P < 0.001$). Patients with higher PhenoAge had worse physical conditions. Compared with the other two groups, more adverse events occurred in the T3 subgroup, suggesting that a higher PhenoAge corresponds with a worse in-hospital outcome ($P < 0.001$).

3.2. Characteristics of PhenoAgeAccel in participants

PhenoAgeAccel was split into two groups based on whether its values were positive or negative. The Gensini score was greater in the positive PhenoAgeAccel subgroup than in the negative subgroup ($P < 0.01$), and patients in the positive subgroup had lower LVEF ($P < 0.001$), which shows that coronary artery disease has progressed in severity and the cardiac function has worsened. As expected, there was a greater incidence of adverse events (20.9 % vs. 5.1 %, $P < 0.001$, Table 2) among patients in the positive group than in the negative group.

3.3. Associations between PhenoAge, PhenoAgeAccel, and clinical outcomes

The associations between chronological age, PhenoAge, PhenoAgeAccel, and clinical outcomes were shown in Table 3. Both

Table 3
Associations between PhenoAge, PhenoAgeAccel, chronological age and clinical outcomes.

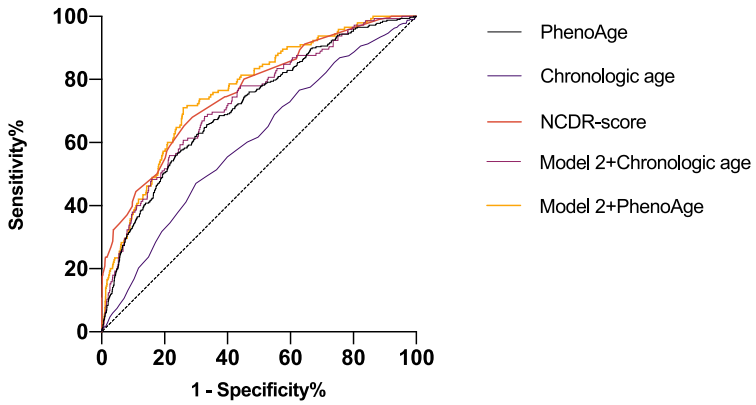
Outcome/variables	Num.	Model 1 OR (95 % CI)	*P*-value	Model 2 OR (95 % CI)	*P*-value	Model 3 OR (95 % CI)	*P*-value
In-hospital MACEs	321						
Chronologic age		1.029(1.019, 1.039)	<0.001	1.016(0.999, 1.032)	0.064	–	–
PhenoAge		1.049(1.041, 1.056)	<0.001	1.043 (1.030, 1.056)	<0.001	1.077(1.054, 1.100)	<0.001
T1	43	Reference		Reference		Reference	
T2	79	1.910(1.302, 2.800)	0.001	1.693(1.044,2.746)	0.033	2.979(1.505, 5.198)	0.001
T3	199	5.570(3.952, 7.852)	<0.001	3.382(2.119, 5.397)	<0.001	7.620(3.553, 16.342)	<0.001
PhenoAgeAccel							
Negative	91	Reference		Reference		Reference	
Positive	230	4.936 (3.821, 6.377)	<0.001	3.084(2.184, 4.357)	<0.001	3.122(2.116, 4.608)	<0.001
Cardiogenic shock	173						
Chronologic age		1.038(1.025, 1.052)	<0.001	1.014(0.989, 1.039)	0.286	–	–
PhenoAge		1.061(1.051, 1.070)	<0.001	1.058 (1.040, 1.076)	<0.001	1.091(1.063, 1.120)	<0.001
T1	13	Reference		Reference		Reference	
T2	35	2.753(1.447, 5.237)	0.002	1.732(0.788, 3.805)	0.171	3.303(1.199, 9.100)	0.021
T3	125	10.897(6.110, 19.437)	<0.001	4.620(2.222, 9.604)	<0.001	16.212(5.036, 52.193)	<0.001
PhenoAgeAccel							
Negative	33	Reference		Reference		Reference	
Positive	140	7.766 (5.272, 11.440)	<0.001	4.519 (2.619, 7.799)	<0.001	4.353(2.308, 8.212)	<0.001
Malignant arrhythmias	141						
Chronologic age		1.018(1.004, 1.032)	0.013	1.020(0.998, 1.042)	0.079	–	–
PhenoAge		1.026 (1.016, 1.037)	<0.001	1.027 (1.011, 1.043)	0.001	1.039(1.013, 1.065)	0.003
T1	26	Reference		Reference		Reference	
T2	38	1.479(0.891, 2.455)	0.130	1.588(0.850, 2.970)	0.147	2.253(1.002, 5.064)	0.049
T3	77	3.132(1.989, 4.931)	<0.001	2.687(1.460, 4.944)	0.001	4.084(1.468, 11.359)	0.007
PhenoAgeAccel							
Negative	47	Reference		Reference		Reference	
Positive	94	3.446 (2.422, 4.961)	<0.001	2.496(1.583, 3.937)	<0.001	2.620(1.561, 4.397)	<0.001
Acute heart failure	40						
Chronologic age		1.037(1.009, 1.065)	0.009	0.998(0.952, 1.047)	0.945	–	–
PhenoAge		1.055(1.039, 1.072)	<0.001	1.043 (1.009, 1.078)	0.014	1.060(1.021, 1.101)	0.003
T1	3	Reference		Reference		Reference	
T2	4	1.333(0.298, 5.973)	0.707	1.222(0.214, 6.975)	0.822	2.719(0.381, 19.392)	0.318
T3	33	11.354(3.470. 37.148)	<0.001	3.116(0.640, 15.158)	0.159	10.140(1.156, 88.938)	0.037
PhenoAgeAccel							
Negative	11	Reference		Reference		Reference	
Positive	29	4.381 (2.179, 8.806)	<0.001	3.203(0.969, 10.583)	0.056	3.204(0.969, 10.592)	0.056
Mechanical complications	122						
Chronologic age		1.028(1.012, 1.044)	<0.001	1.025(1.001, 1.049)	0.042	–	–
PhenoAge		1.027(1.016, 1.038)	<0.001	1.017(0.998, 1.036)	0.072	1.005(0.975, 1.036)	0.751
T1	20	Reference		Reference		Reference	
T2	33	1.671(0.952, 2.934)	0.074	1.192(0.623, 2.297)	0.596	0.964(0.424, 2.194)	0.931
T3	69	3.693(2.194, 6.036)	<0.001	1.152(0.806, 2.949)	0.191	1.098(0.380, 3.170)	0.863
PhenoAgeAccel							
Negative	51	Reference		Reference		Reference	
Positive	71	2.354(1.629, 3.400)	<0.001	1.260 (0.776, 2.046)	0.351	1.109(0.657, 1.872)	0.698

The associations between PhenoAge, PhenoAgeAccel, chronological age and clinical outcomes were analyzed by logistic regression. Chronological age was taken as a continuous variable, PhenoAgeAccel as a categorical variable, and PhenoAge was taken as a continuous variable and a categorical variable after the tripartite grouping for regression analysis. $P < 0.05$ indicated statistically significant. OR: odds ratio; PhenoAge: Phenotypic age; PhenoAgeAccel: Phenotypic age acceleration. Model 1: Unadjusted; Model 2: additionally adjusted sex, body mass index, and mean arterial pressure, smoking, drinking, left ventricular ejection fraction, low-density lipoprotein, creatine kinase isoenzyme, and Gensini score; Model 3: Model 2, additionally adjusted chronological age.

chronological age and PhenoAge were risk factors for in-hospital adverse events. Even after adjusting for conventional risk factors including gender, BMI, drinking, smoking, and others, PhenoAge continued to be an independent predictor of in-hospital MACEs, but chronologic age was no significant. After PhenoAge stratification, compared to the T1 subgroup, the risk of in-hospital MACEs was 1.910 times higher in the T2 subgroup and 5.570 times higher in the T3 subgroup. Similarly adjusting for conventional risk factors, this trend remained constant. Furthermore, whether as a continuous variable or categorical variable, PhenoAge still has predictive value after chronological was adjusted based on model 2. Meanwhile, stratified by chronological age tertiles, PhenoAge consistently predicted adverse events across all subgroups (Supplemental Table S1). In the youngest tertiles of chronological age, for every 1-year increase in PhenoAge, the probability of in-hospital MACEs increased by 4.8 %, and cardiogenic shock increased by 9.0 % in the multivariable model 2. Results were consistent in middle tertile and oldest tertile subgroups. However, the association between chronological age and adverse events was no statistical difference. Additionally, Patients with a positive PhenoAgeAccel tended to have a higher incidence of in-hospital MACEs, even adjusting for other risk factors. Similar results were drawn from additional outcomes.

3.4. ROC curves of PhenoAge

We used ROC curves to clarify the predictive ability of several indicators for in-hospital MACEs, including PhenoAge, chronological age,



Variable	AUC	*P*-value	Z-value	*P* for comparison
Chronological age	0.601	<0.001	reference	reference
PhenoAge	0.714	<0.001	7.322	<0.001
NCDR-score	0.760	<0.001	7.038	<0.001
Model 2	0.720	<0.001	reference	reference
Model 2+ Chronological age	0.728	<0.001	1.330	0.184
Model 2+ PhenoAge	0.763	<0.001	2.691	0.007

Fig. 1. Receiver-operating characteristic curves for In-hospital MACEs. Receiver operating characteristic curve was used to assess the predictive power of the biomarkers and model; PhenoAge: Phenotypic age; Model 2: including sex, body mass index, mean arterial pressure, smoking, drinking, left ventricular ejection fraction, low-density lipoprotein, creatine kinase isoenzyme, and Gensini score; MACEs: major adverse cardiovascular events.

NCDR-score, and various combinations (Fig. 1). PhenoAge considerably outperformed chronologic age (AUC: 0.601) with an AUC of 0.714 ($P < 0.001$), according to ROC curves used to predict in-hospital MACEs. Interestingly, we also discovered that, in contrast to chronological age, PhenoAge might considerably increase the multivariate prediction model's predictive power. At the same time, our findings also showed that the composite model of PhenoAge and traditional risk factors is nearly as effective as the NCDR-score in predicting in-hospital MACEs.

4. Discussion

The rising burden of aging-related cardiovascular diseases necessitates novel tools to stratify risk and personalize care for high-risk populations, such as patients with acute myocardial infarction (AMI). In this study, we demonstrated that PhenoAge and PhenoAgeAccel are more reliable composite indicators for predicting the incidence of adverse cardiovascular events in hospitalized patients with AMI than chronological age.

PhenoAge, which incorporates a composite clinical chemistry biomarker based on the Gompertz mortality model parameterization, has been demonstrated to be effective in identifying individuals at high risk for multiple diseases, making it a useful tool in clinical practice for evaluating intervention efficacy [29,30]. The robust association between elevated PhenoAge and in-hospital MACEs in acute myocardial infarction (AMI) patients underscores its potential as a risk stratification tool. As a composite indicator integrating inflammatory, immunity, liver and kidney function, and metabolic biomarkers, PhenoAge reflects the systemic burden of biological aging. Chronic low-grade inflammation, characterized by innate immune activation and elevated pro-inflammatory cytokines (IL-6, TNF-α), not only drives plaque instability but also synergizes with traditional risk factors (hypertension, obesity) to exacerbate endothelial dysfunction and thrombotic propensity [31,32,33]. Cellular senescence—marked by telomere attrition, mitochondrial oxidative stress, and epigenetic dysregulation—promotes vascular stiffening and plaque vulnerability [34,35].

Liu et al. assert that PhenoAge can differentiate health risks among individuals of the same chronological age and has an independent relationship with all-cause mortality [15]. Another study using data from the National Health and Nutrition Examination Survey (NHANES) showed that cancer survivors with high levels of BA had a higher risk of both all-cause and CVD-specific mortality [36]. Our findings extend prior validations of PhenoAge in diverse populations. In our study, we used PhenoAge to analyze in-hospital MACEs in patients with AMI, and the results showed that the instant PhenoAge at admission was an independent risk factor, demonstrating superior predictive power compared to chronological age after adjusting for traditional risk factors. While PhenoAge correlates with chronological age, our stratified and multivariable analyses demonstrate its ability to resolve aging heterogeneity and predict risk independent of time-lived. Adding PhenoAge to the same predictive model could improve the predictive ability of the model, which chronological age cannot achieve. This confirms that PhenoAge captures aging heterogeneity beyond chronological age, even when chronological age is within a certain interval. To further assess its predictive capability, we also conducted a comparison between the risk model derived from PhenoAge and the NCDR CathPCI mortality risk score, revealing similar predictive performance. The subgroup analysis stratified by chronological age revealed that within a restricted age range, chronological age failed to predict adverse events, whereas PhenoAge retained significant predictive power. These findings suggest that PhenoAge can identify individuals with accelerated biological aging who are at higher risk, thereby addressing the limitations of traditional chronological age stratification in capturing individualized risk disparities. This capability holds clinical relevance by enabling early targeted interventions for high-risk younger populations and optimizing personalized therapeutic strategies for elderly patients based on PhenoAge rather than chronological age alone.

PhenoAgeAccel is a unique and interesting variable. In essence, it is a composite of PhenoAge variables. Elevations of many of variables included in PhenoAge are expected to result in both a positive PhenoAgeAccel value and be associated with worse outcomes [37,38]. For instance, creatinine measurements may indicate worse renal function in individuals who come with CHF or cardiac arrest. Nevertheless, PhenoAgeAccel is still a very useful predictive variable. This study reveals that patients with positive PhenoAgeAccel for AMI patients have a higher risk of in-hospital adverse events, such as cardiogenic shock and malignant arrhythmias. This highlights the importance of early identification of high-risk patients for improving health through PhenoAgeAccel.

While PhenoAge is not an alternative to clinical biomarkers for making medical and health-related decisions, it serves as an effective indicator of an individual's physiological state. Our study still has several limitations. Firstly, it involved retrospective analysis, and only considered the first laboratory test after admission, thus omitting the changes in PhenoAge during hospitalization. Therefore, it is unclear whether PhenoAge or variations in PhenoAge mainly contributed to the adverse events. We only assessed in-hospital MACEs in patients without long-term follow-up, resulting in an unclear long-term prognosis that requires further clinical studies for follow-up. Furthermore, in this research, we exclusively focused on patients with AMI, and additional clinical applicability still requires confirmation. Ultimately, in the future, we hope to evaluate the stable predictive effect of phenotypic age in a more tightly controlled chronological age cohort.

In conclusion, our study shows that PhenoAge is significantly linked to clinical outcomes and predicts in-hospital MACEs with reliability, suggesting that PhenoAge may serve as a valuable composite biomarker for physicians to assess and intervene.

CRediT authorship contribution statement

Yajie Gao: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ke Gao:** Conceptualization. **Ruijuan Shi:** Methodology, Investigation. **Xiaorui Huang:** Methodology. **Peizhu Dang:** Investigation. **Hui Liu:** Data curation. **Xiaopu Zheng:** Writing – review & editing, Funding acquisition, Conceptualization. **Yanbo Xue:** Writing – review & editing, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101670.

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