Cardiovascular Innovations and Applications

Vol. 9 (2024) 15
ISSN 2009-8618
DOI 10.15212/CVIA.2023.0091

RESEARCH ARTICLE

Association between Biological Age and Contrast-Associated Acute Kidney Injury in Patients Undergoing Coronary Angiography: A Cross-Sectional Study

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Received: 4 October 2023; Revised: 8 November 2023; Accepted: 30 November 2023

Abstract

Background: Biological age is a reliable indicator reflecting the real physiological state and aging status of individuals. This study was aimed at exploring the association between biological age and contrast-associated acute kidney injury (CA-AKI).

Methods: This retrospective study was conducted on 4078 patients with coronary artery disease (CAD) undergoing coronary angiography (CAG). Biological age was calculated according to chronological age and blood biomarkers, and the "age gap," reflecting retardation or acceleration of biological aging, was further determined. Logistic regression analysis was used to examine the association of the biological age and age gap with CA-AKI. Receiver operating characteristic (ROC) analysis and subgroup analysis were also conducted.

Results: Among the 4078 patients (68.00 [61.00, 74.00] years, 2680 (65.7%) men), 725 CA-AKI cases were identified. Older biological age (≥79.3 *vs.* <79.3 years, OR [95% CI] = 3.319 [2.714 to 4.059]) and greater age gap (≥1.12 *vs.* <1.12, OR [95% CI] = 2.700 [2.240 to 3.256]) were independent risk factors for CA-AKI (both P <0.001). ROC analysis indicated that biological age (AUC = 0.672) and age gap (AUC = 0.672) had better predictive ability for CA-AKI than chronological age (AUC = 0.583). Subgroup analysis also indicated similar findings (all P <0.001).

Conclusion: Biological age was found to be an independent risk factor for CA-AKI after CAG, with better predictive value than chronological age.

Keywords: Contrast-associated acute kidney injury; Biological age; Aging; Coronary angiography; Coronary artery disease

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Introduction

Science and medicine have made substantial advances in controlling diseases, thus increasing human life expectancy and increasing the proportion of older people globally [1]. Consequently, the proportions of older and very old people are growing. To date, advanced age is the strongest risk factor for cardiovascular diseases [2]. Furthermore, the kidney is one of the most vulnerable organs to aging. With aging, the kidney undergoes irreversible functional and structural degeneration [3]. Therefore, older patients with coronary artery disease (CAD) who must undergo coronary angiography (CAG) have elevated risk of contrast-associated acute kidney injury (CA-AKI) [4]. According to statistics, the overall incidence of CA-AKI accounts for nearly one-third of all AKI cases and is considered a serious risk to global public health. Aging is correlated with the incidence of CA-AKI and is an independent predictor of CA-AKI [5].

A currently underestimated challenge is that assessment of risk for age-associated diseases solely on the basis of advancing chronological age can be influenced by a variety of factors, such as lifestyle, environment, and diet [6]. Therefore, the concept of "biological age" has recently been proposed to represent a particular individual's aging status [7]. The potential biological mechanism of aging may be central to the elevated incidence of, and susceptibility to, age-associated diseases [8]. Currently, telomere length, a relatively well-studied biomarker reflecting biological age, incorporates the combined burden of heritable and environmental factors [9]. In addition, recent clinical studies have identified blood biomarkers that can also be used to effectively calculate biological age and reflect biological aging, and are also the most convenient index to determine [10, 11]. Clinical research has indicated that biological age is associated with all-cause mortality in patients with CAD [12]. However, the extent to which biological age is associated with the risk of CA-AKI has not been extensively examined.

Consequently, this study used several plasma biomarkers at baseline to calculate biological age. The aim of this study was to explore the association between biological age and the risk of CA-AKI after CAG in patients with CAD, and to compare the power of biological age and chronological age in predicting CA-AKI incidence.

Methods

Study Design and Participants

This retrospective study was aimed at exploring the relationships between biological age and CA-AKI. Participants were examined at Sir Run Run Shaw Hospital between December 2006 and December 2019. The study protocol was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines as well as the principles of the Declaration of Helsinki, and local laws and regulations. Ethical clearance was obtained from the Sir Run Run Shaw Hospital (No. 20220228-30). The requirement for informed consent was waived, because this was a retrospective study.

Eligible participants were patients with CAD who underwent CAG. The detailed inclusion criteria were as follows: biological age associated biomarkers assessed at baseline; serum creatinine (SCr) assessed multiple times, involving baseline measurement and postoperative measurement (≤72 hours); and available data on demographics, CAG procedures, laboratory examination findings, and medications. The criteria for exclusion comprised repeated contrast agent injection, acute infectious diseases, AKI (e.g., glomerular nephritis or nephrotic syndrome), history of malignancy, and baseline estimated glomerular filtration rate (eGFR) below 15 mL/(min × 1.73 m^2).

Primary Endpoint

The primary endpoint was CA-AKI. According to the guidelines of the European Society of Urogenital Radiology, CA-AKI was diagnosed when (1) SCr elevation exceeded 0.5 mg/dL (44.2 μmol/L) or 25% of baseline, within 72 hours after CAG or PCI, or (2) no alternative etiology was identified [13, 14].

Definition of Biological Age

The definition of the biological age was adapted from Morgan et al. (2018) [11]. Ten variables (chronological age and nine blood biomarkers) were combined to calculate biological age (in years). The detailed calculation formula was as follows:

$$Biological\ age = 141.5022 + \frac{\ln\left[-0.00553 \times \ln\left(\exp\left(\frac{-1.51714 \times \exp\left(MortalityScore\right)}{0.0076927}\right)\right)\right]}{0.09165}$$

where MortalityScore = −19.907 − 0.0336 × albumin (g/L) + 0.0095 × SCr (μmol/L) + 0.1953 × fasting blood glucose (FBG, mmol/L) + 0.0954 × ln [C-reactive protein (CRP, mg/L)] − 0.0120 × lymphocyte percentage (%) + 0.0268 × mean red blood cell volume (MCV, fL) + 0.3306 × red blood cell distribution width (RDW, %) + 0.00188 × alkaline phosphatase (U/L) + 0.0554 × white blood cell count (WBC, $\times 10^9$/L) + 0.0804 × chronological age (years).

Furthermore, we propose an "age gap" concept to further reflect the retardation or acceleration of biological aging, as calculated as the biological age divided by the chronological age. A ratio >1.00 indicated accelerating aging, whereas a ratio <1.00 indicated decelerating aging.

Data Collection

Data were extracted from the Hospital Information System, and all baseline data involving demographic data (chronological age, sex, body mass index (BMI), history of smoking, history of drinking, heart failure, diabetes, hypertension, systolic blood pressure (SBP), and diastolic blood pressure (DBP)), laboratory data (SCr elevation percentage, platelets, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), cardiac troponin I (cTnI), left ventricular ejection fraction (LVEF), eGFR, albumin, RDW, lymphocyte percentage, WBC, MCV, FBG, alkaline phosphatase, and CRP), CAG/PCI procedure data (types of contrast agent, lesions location, and multivessel PCI), and medication data (angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACEIs/ARBs), beta blockers, calcium channel blockers (CCBs), diuretics, and statins) were collected at admission. Fasting blood samples were collected to detect routine blood and biochemistry parameters. Diabetes was defined by FBG ≥ 126 mg/dL, glycated hemoglobin ≥ 6.5%, or use of antidiabetic medication [15]. Hypertension was defined by SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of anti-hypertension medication [16]. BMI was calculated as the weight in kilograms divided by the square of the height in meters. CAG and PCI procedures followed standard practice and were performed by at least two experienced operators.

Statistical Analysis

Variables in the study included categorical and continuous variables. The Kolmogorov–Smirnov test was applied to determine whether continuous variables followed a normal distribution. Mean ± standard deviation were used for normally distributed continuous variables, and medians with IQR were used for abnormally distributed variables. Counts (percentages) were used for categorical variables. Continuous variables were compared with the Student t-test or Mann-Whitney U test, and categorical variables were compared with the chi-square test or Fisher exact test, respectively.

Spearman correlative analysis for exploring the correlation between biological age and variables was performed with a correlation matrix. The optimal cutoff values of biological age and age gap were calculated according to the receiver operator characteristic (ROC) curves (Figure S1). According to the cutoff values (biological age: 79.3 years; age gap: 1.12) and four ordered categories (biological age: <60.0, 60.0–74.9, 75.0–89.9, and ≥90.00, years; age gap: <1.00, 1.00–1.09, 1.10–1.19, and ≥1.20), the biological age and age gap were converted into categorical variables. Furthermore, logistic regression analysis was performed to identify whether biological age and age gap were

associated with CA-AKI risk. Three models were constructed for adjusting for potential confounders identified in previous studies: in model 1, no covariates were adjusted for; in model 2, sex, congestive heart failure, history of diabetes, hypertension, and SBP were adjusted for; and in model 3: eGFR, LVEF, administration of diuretic, ACEI/ARB were additionally adjusted for. Sample size was evaluated with the events per variable rule. More than 20 events per variable (total events = 725) were achieved in regression analyses, thus indicating the reliability of the results. Restricted cubic splines were then used to determine the potential non-linear association between these two variables and CA-AKI. Additionally, ROC analysis was conducted to identify whether the predictive performance of biological age and age gap for CA-AKI was better than that of chronological age. Finally, subgroup analyses were conducted according to chronological age (≥65 vs. <65, years), sex (male vs. female), diabetes (yes vs. no), hypertension (yes vs. no), and congestive heart failure (yes vs. no), with multivariable logistic regression, and the results were presented in forest plots.

A two-tailed P value <0.05 indicated statistically significant differences. SPSS version 22.0 (SPSS Inc, Chicago, USA) and R version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Result

Baseline Characteristics

Figure 1 displays the flowchart with details of this study. The baseline characteristics of 4078 patients are presented in Table 1. In total, the median [IQR] age was 68.00 [61.00, 74.00] years, and the number of men was 2680 (65.7%). Compared with patients without CA-AKI, more patients with CA-AKI had a history of heart failure (431 (59.4%) *vs.* 1179 (35.2%), P < 0.001) and diabetes (204 (28.1%) *vs.* 783 (23.4), P = 0.007). However, no significant difference was observed in the history of smoking (107 (14.8%) *vs.* 579 (17.3%), P = 0.113) or hypertension (469 (64.7%) *vs.* 2120 (63.2%), P = 0.484). In terms of medication history, the patients with

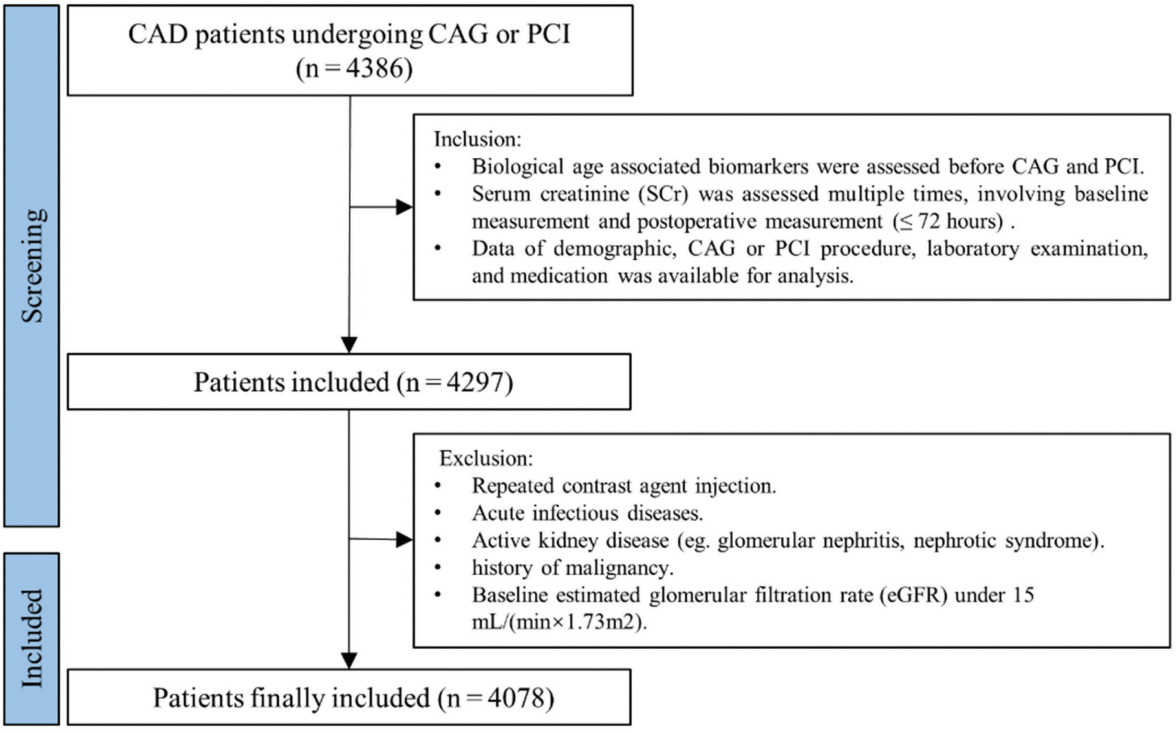

Figure 1 Study Flowchart.
CAG, coronary angiography; PCI, percutaneous coronary intervention; SCr, serum creatinine; eGFR, estimated glomerular filtration rate.

Table 1 Baseline Characteristics.

Characteristics		CA-AKI		P value
	Overall (n = 4078)	No (n = 3353)	Yes (n = 725)	
Demographic data				
Chronological age, years	68.00 [61.00, 74.00]	68.00 [61.00, 73.00]	70.00 [64.00, 77.00]	<0.001*
Biological age, years	73.07 [63.76, 84.54]	71.62 [62.69, 82.21]	81.98 [70.63, 94.66]	<0.001*
Age gap	1.08 [0.99, 1.19]	1.06 [0.99, 1.16]	1.16 [1.06, 1.30]	<0.001*
Male, n (%)	2680 (65.7)	2248 (67.0)	432 (59.6)	<0.001*
BMI, kg/m^2	24.04 [20.76, 27.51]	23.95 [20.67, 27.46]	24.68 [21.16, 28.00]	0.025*
Smoking, n (%)	686 (16.8)	579 (17.3)	107 (14.8)	0.113
Drinking, n (%)	621 (15.2)	531 (15.8)	90 (12.4)	0.023*
Heart failure, n (%)	1610 (39.5)	1179 (35.2)	431 (59.4)	<0.001*
Diabetes, n (%)	987 (24.2)	783 (23.4)	204 (28.1)	0.007*
Hypertension, n (%)	2589 (63.5)	2120 (63.2)	469 (64.7)	0.484
SBP, mmHg	122.50 [113.43, 132.56]	123.19 [114.03, 132.73]	119.92 [110.00, 130.22]	<0.001*
DBP, mmHg	69.42 [63.96, 75.13]	69.90 [64.71, 75.63]	66.54 [61.43, 72.76]	<0.001*
Laboratory data				
SCr elevation percentage, %	5.10 [−3.90, 17.70]	1.90 [−5.80, 9.90]	43.80 [32.60, 68.80]	<0.001*
Platelets, ×10^9	174.00 [139.50, 216.50]	174.00 [140.00, 215.00]	173.50 [139.00, 225.00]	0.878
LDL-C, mmol/L	2.08 [1.58, 2.71]	2.08 [1.59, 2.71]	2.08 [1.54, 2.72]	0.346
HDL-C, mmol/L	0.98 [0.82, 1.16]	0.98 [0.83, 1.17]	0.94 [0.75, 1.12]	<0.001*
TC, mmol/L	3.96 [3.28, 4.73]	3.96 [3.32, 4.76]	3.95 [3.11, 4.62]	0.003*
cTnI, μg/L	0.00 [0.00, 0.18]	0.00 [0.00, 0.09]	0.08 [0.00, 1.03]	<0.001*
LVEF, %	61.40 [53.82, 68.70]	62.20 [55.00, 69.00]	59.00 [48.00, 65.40]	<0.001*
eGFR, mL/(min × 1.73 m^2)	84.39 [65.88, 94.60]	84.63 [67.14, 94.43]	83.20 [57.56, 95.03]	0.037*
CAG/PCI procedure data				
Type of contrast agent, n (%)				0.997
Isotonic	1308 (32.1)	1076 (32.1)	232 (32.0)	
Hypotonic	2770 (67.9)	2277 (67.9)	493 (68.0)	
Lesion location, n (%)				
LM	126 (11.1)	105 (11.1)	21 (11.5)	0.973
LAD	877 (64.2)	711 (63.0)	166 (70.3)	0.038*
LCX	324 (26.4)	269 (26.3)	55 (27.1)	0.888
RCA	451 (36.4)	371 (35.9)	80 (38.5)	0.543
Multivessel PCI (%)	76 (7.1)	63 (7.1)	13 (7.3)	1
Medication data, n (%)				
ACEI/ARB	1806 (44.3)	1517 (45.2)	289 (39.9)	0.009*
Beta blocker	2057 (50.4)	1667 (49.7)	390 (53.8)	0.051
CCB	1154 (28.3)	955 (28.5)	199 (27.4)	0.607
Diuretic	1315 (32.2)	921 (27.5)	394 (54.3)	<0.001*
Statin	3396 (83.3)	2842 (84.8)	554 (76.4)	<0.001*

CA-AKI, contrast-associated acute kidney injury; BMI, body mass index; Scr, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C; high-density lipoprotein cholesterol; TC, total cholesterol; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; LM, left main coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CAG, coronary angiography; PCI, percutaneous coronary intervention; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. *P <0.05.

CA-AKI had a statistically significantly lower percentage of ACEI/ARB (289 (39.9%) *vs.* 1517 (45.2%), P = 0.009) and statin (554 (76.4%) *vs.* 2842 (84.8%), P < 0.001) use, but a higher percentage of diuretic (394 (54.3%) *vs.* 921 (27.5%), P < 0.001) use. Use of other cardiovascular medications (beta blocker and CCB) did not differ between groups (both P > 0.05).

Table 2 displays the baseline characteristics of biological age and related laboratory data. Significant differences in biological age and the age gap were observed between the CA-AKI group and non-CA-AKI group (both P < 0.001). The biological age of patients with CA-AKI was 81.98 [70.63, 94.66] years, whereas that of patients without CA-AKI was 71.62 [62.69, 82.21] years. The age gap was 1.16 [1.06, 1.30] in patients with CA-AKI, and 1.06 [0.99, 1.16] in patients without CA-AKI. All biological age-associated parameters, including SCr, albumin, RDW, lymphocyte percentage, WBC, MCV, FBG, alkaline phosphatase, and CRP, significantly differed between groups (all P < 0.05).

Biological Age is Associated with Most Blood Biochemical Parameters

To determine the correlation between biological age and relative blood biochemical parameters, we performed Spearman correlation analysis. Biological age was most associated with chronological age (r = 0.73) (Figure 2). Biological age and age gap were positively associated with most blood biochemical parameters but negatively associated with albumin and lymphocyte percentage. Both biological age (r = 0.20) and age gap (r = 0.23) were positively correlated with the SCr elevation proportion.

Older Biological Age and Greater Age Gap are Independent Risk Factors for CA-AKI

Subsequently, logistic regression analysis was conducted to determine the relationships of the biological age (Table 3) or age gap (Table 4) with CA-AKI incidence, according to the three models.

Higher biological age at baseline was significantly associated with greater risk of CA-AKI after CAG or PCI (≥79.3 *vs.* <79.3 years, OR = 3.015, 95% CI [2.558 to 3.554], P < 0.001) (Table 3). This association remained significant even after adjustment for sex, congestive heart failure, history of diabetes, hypertension, and SBP (model 2: ≥79.3 *vs.* <79.3 years, OR = 2.722, 95% CI [2.285 to 3.243], P < 0.001), as well as after additional adjustment for eGFR, LVEF, diuretic use, ACEI use, or ARB use (model 3: ≥79.3 *vs.* <79.3 years, OR = 3.319, 95% CI [2.714 to 4.059], P < 0.001). Compared with that in the younger biological age group (<60.0 years), the CA-AKI risk was almost tenfold higher (model

Table 2 Baseline Characteristics of Biological Age Associated Variables.

Characteristics	Overall (n = 4078)	CA-AKI		P value
		No (n = 3353)	Yes (n = 725)	
Chronological age, years	68.00 [61.00, 74.00]	68.00 [61.00, 73.00]	70.00 [64.00, 77.00]	<0.001*
Biological age, years	73.07 [63.76, 84.54]	71.62 [62.69, 82.21]	81.98 [70.63, 94.66]	<0.001*
Age gap	1.08 [0.99, 1.19]	1.06 [0.99, 1.16]	1.16 [1.06, 1.30]	<0.001*
SCr, μmol/L	77.00 [65.00, 95.00]	76.00 [65.00, 93.00]	79.00 [63.00, 110.00]	0.002*
Albumin, g/L	39.70 [36.80, 42.60]	40.00 [37.20, 42.80]	38.30 [34.70, 41.10]	<0.001*
RDW, %	13.60 [13.07, 14.40]	13.50 [13.00, 14.30]	13.90 [13.30, 14.90]	<0.001*
Lymphocyte percentage, %	21.90 [15.61, 28.50]	22.50 [16.60, 29.00]	18.00 [11.80, 26.00]	<0.001*
WBC, $\times 10^9$	6.60 [5.30, 8.30]	6.50 [5.30, 8.10]	7.30 [5.50, 9.70]	<0.001*
MCV, fL	91.70 [88.60, 94.70]	91.70 [88.73, 94.70]	91.35 [88.20, 94.25]	0.043*
FBG, mmol/L	5.90 [5.08, 7.52]	5.84 [5.07, 7.35]	6.30 [5.16, 8.75]	<0.001*
Alkaline phosphatase, U/L	82.00 [68.00, 101.00]	81.00 [67.00, 100.00]	86.00 [70.00, 106.00]	0.001*
CRP, mg/L	2.30 [0.90, 7.90]	2.00 [0.80, 6.50]	4.40 [1.40, 15.70]	<0.001*

CA-AKI, contrast-associated acute kidney injury; Scr, serum creatinine; RDW, red blood cell distribution width; WBC, white blood cell count; MCV, mean (red) cell volume; FBG, fasting blood glucose; CRP, C-reactive protein. *P <0.05.

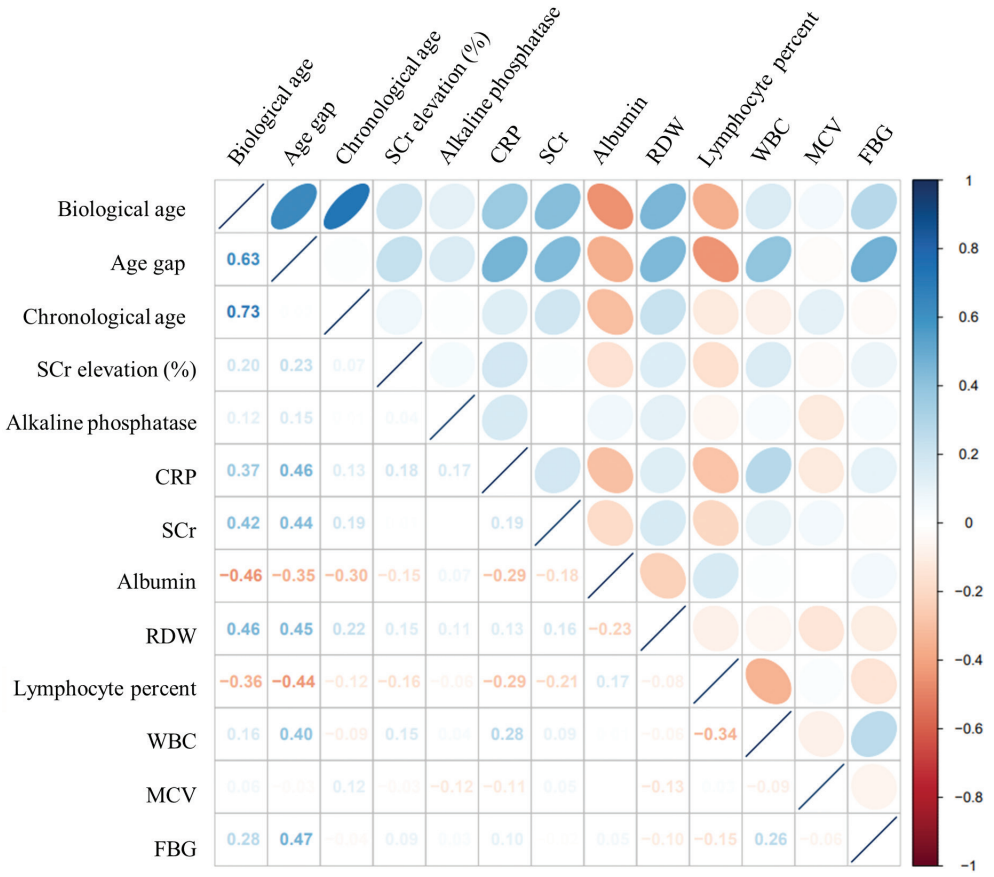

Figure 2 Correlation Matrix.
Pearson correlations are displayed at the bottom left of the matrix plot. A higher correlation is represented by lower transparency and narrower ellipses. Blue indicates positive correlation, and red indicates negative correlation. SCr, serum creatinine; CRP, C-reactive protein; RDW, red blood cell distribution width; WBC, white blood cell count; MCV, mean red blood cell volume; FBG, fasting blood glucose.

3: OR = 9.669, 95% CI [6.630 to 14.101], P < 0.001) in patients with older biological age (≥90.0 years).

Similarly, CA-AKI incidence increased with increasing age gap (Table 4). A greater age gap was an important risk factor for CA-AKI (≥1.12 *vs.* <1.12, OR = 2.979, 95% CI [2.526 to 3.513], P < 0.001). We further stratified the age gap into four distinct categories (predefined cut points: <1.00, 1.00–1.09, 1.10–1.19, and ≥1.20) and observed a significant association between the age gap and CA-AKI (≥1.12 *vs.* <1.00, OR = 5.025, 95% CI [3.879 to 6.510], P for trend <0.001). After multivariable adjustment, identical results to those in the univariate analyses were obtained (model 2 and model 3). Furthermore, in restricted cubic spline analyses (Figure 3), significant nonlinear associations were observed between the biological age (P for nonlinearity = 0.011) or age gap and CA-AKI risk (P for nonlinearity <0.001).

Biological Age and Age Gap Have Better Predictive Ability for CA-AKI than Chronological Age

To assess performance in predicting CA-AKI, we performed ROC curve analysis. Both biological age (AUC [95% CI] = 0.672 [0.650 to 0.694]) and age gap (AUC [95% CI] = 0.672 [0.651 to 0.694]) predicted the incidence of CA-AKI, and had better predictive power than chronological age (AUC [95% CI] = 0.583 [0.559 to 0.606]) (Figure 4).

The Association between Biological Age/Age Gap and CA-AKI Incidence is Similar Across Subgroups

In addition, to investigate whether the results were stable across subgroups, we conducted multivariable logistic regression among chronological age

Table 3 Logistic Regression Analysis of the Association between Biological Age and CA-AKI.

Biological age	Cases/overall (%)	Model 1		Model 2		Model 3	
		Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value
Biological age, dichotomous							
<79.3	308/2622 (11.7)	1 [Reference]		1 [Reference]		1 [Reference]	
≥79.3	417/1456 (28.6)	3.015 [2.558 to 3.554]	<0.001	2.722 [2.285 to 3.243]	<0.001	3.319 [2.714 to 4.059]	<0.001
Biological age, four ordered categories							
<60	57/686 (8.3)	1 [Reference]		1 [Reference]		1 [Reference]	
60–74.9	199/1552 (12.8)	1.623 [1.191 to 2.211]	<0.001	1.564 [1.142 to 2.140]	<0.001	1.776 [1.290 to 2.446]	<0.001
75–89.9	220/1161 (18.9)	2.580 [1.895 to 3.512]	<0.001	2.369 [1.724 to 3.255]	<0.001	3.057 [2.189 to 4.270]	<0.001
≥90	249/679 (36.7)	6.390 [4.674 to 8.737]	<0.001	5.479 [3.943 to 7.612]	<0.001	9.669 [6.630 to 14.101]	<0.001
P for trend			<0.001		<0.001		<0.001

Model 1 was not adjusted.
Model 2 was adjusted for sex, congestive heart failure, history of diabetes, hypertension, and SBP.
Model 3 was adjusted as in model 2 plus eGFR, ejection fraction, administration of diuretic, ACEI or ARB.
The abbreviations refer to Table 1. *P <0.05.

Table 4 Logistic Regression Analysis of the Association between Age Gap and CA-AKI.

Age gap	Cases/overall (%)	Model 1		Model 2		Model 3	
		Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value
Age gap, dichotomous							
<1.12	290/2520 (11.5)	1 [Reference]		1 [Reference]		1 [Reference]	
≥1.12	435/1558 (27.9)	2.979 [2.526 to 3.513]	<0.001	2.672 [2.233 to 3.198]	<0.001	2.700 [2.240 to 3.256]	<0.001
Age gap, four ordered categories							
<1.0	87/1080 (8.1)	1 [Reference]		1 [Reference]		1 [Reference]	
1.00–1.09	169/1219 (13.9)	1.837 [1.398 to 2.413]	<0.001	1.852 [1.401 to 2.449]	<0.001	1.830 [1.378 to 2.429]	<0.001
1.10–1.19	178/827 (21.5)	3.130 [2.378 to 4.121]	<0.001	3.076 [2.307 to 4.103]	<0.001	3.068 [2.287 to 4.117]	<0.001
≥1.20	291/952 (30.6)	5.025 [3.879 to 6.510]	<0.001	4.586 [3.459 to 6.080]	<0.001	4.765 [3.552 to 6.394]	<0.001
P for trend			<0.001		<0.001		<0.001

Model 1, model 2, and model 3 were constructed similarly to the description on Table 3.
The abbreviations refer to Table 1. *P <0.05.

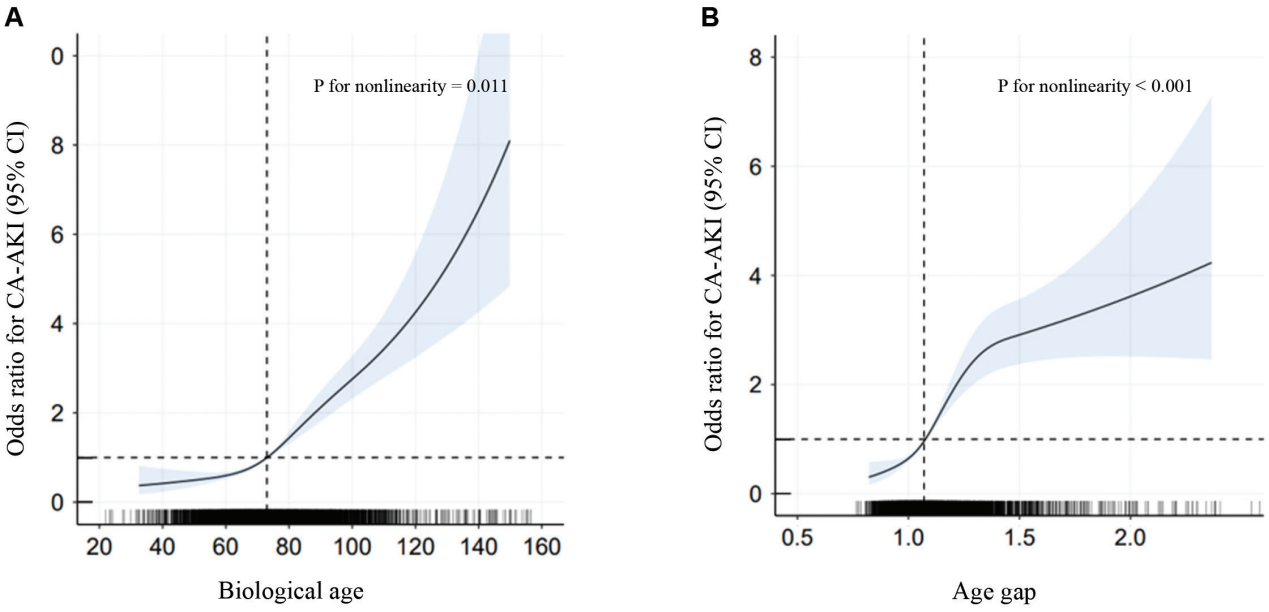

Figure 3 Restricted Cubic Spline Curve Analysis of the Non-Linear Associations of Biological Age (A) and Age Gap (B) with CI-AKI.
The solid line indicates the adjusted odds ratio of biological age/age gap for CI-AKI, and the shaded area around the solid line indicates the 95% confidence interval of the curve.

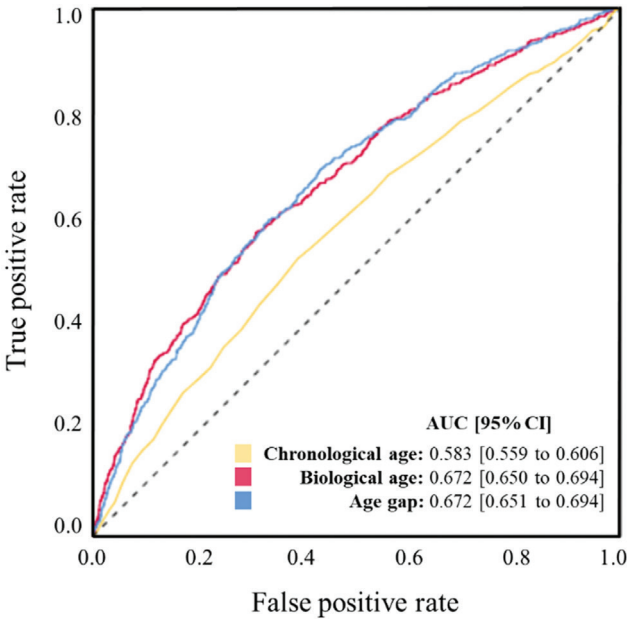

Figure 4 Receiver Operating Characteristic (ROC) Analysis Depicting the Performance of Three Age-Associated Parameters.
Yellow solid line, chronological age; pink solid line, biological age; blue solid line, age gap. ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

(≥65 *vs.* <65, years), sex (male *vs.* female), diabetes (yes *vs.* no), hypertension (yes *vs.* no), and congestive heart failure (yes *vs.* no) subgroups. The findings were similar to the main results across different subgroups (all P for trend <0.05) (Figure S2 and Figure S3).

Discussion

The current study confirmed an association between biological age and the incidence of CA-AKI in patients with CAD who underwent CAG. Furthermore, we proposed the age gap concept (the ratio between biological age and chronological age) to explore the retardation and acceleration of biological aging. Both biological age and the age gap were found to be independent risk factors for CA-AKI and to have better predictive ability than chronological age. Gaining insight into how to decrease biological age could potentially guide successful interventions to slow or stop CA-AKI.

Aging is an irreversible physiological process directly or indirectly affected by a variety of factors [17]. However, owing to the interindividual variability of aging, chronological age itself is not a reliable indicator of disease burden [18]. Because individuals age at different rates, the concept of biological age was proposed. In contrast to the chronological age which, is based on only the passage of time, biological age reflects

the true structural and functional decline with age [7]. Researchers have reported that the basic biology of aging plays crucial roles in cardiovascular diseases, nephropathy, and their complications [19, 20]. Aging is considered a driving force of acute and chronic renal injury [20]. Hollenberg et al. have observed decreased eGFR with advancing age and have reported the effects of aging on renal function decline [21]. Fabbian et al. and Chao et al. have also reported that older patients have significantly higher risk of AKI and more severe prognoses than younger patients [22, 23].

Because advanced age is known to be an important risk factor for CA-AKI, we hypothesized that a close link might exist between biological age and CA-AKI [5]. As hypothesized, the results indicated that the incidence of CA-AKI increased with biological age. Specifically, the CA-AKI risk was almost tenfold higher in patients with an older biological age of ≥90.0 years than a biological age <60.0 years. Calculating the biological age preoperatively might aid in early detection and diagnosis of CA-AKI in patients undergoing CAG.

The field of geroscience has shown that biological age can be identified by nine hallmarks: telomere attrition, epigenetic alterations, genomic instability, cellular senescence, stem cell exhaustion, altered intercellular communication, mitochondrial dysfunction, loss of proteostasis, and dysregulated nutrient sensing [24]. However, these indicators are difficult to determine in general clinical settings. In clinical practice, finding a convenient and rapid indicator of biological aging will be key to understanding the relationship between aging and diseases. Herein, we measured biological aging on the basis of several hematological indicators and known chronological age, and assessed its association with CA-AKI. This composite indicator of biological age combined multiple systems throughout the body, such as inflammation (e.g., CRP and lymphocyte percentage), nutrition (e.g., albumin and glucose), and organ function (e.g., SCr) [11]. Aging, inflammation, malnutrition, and CKD itself are known risk factors for CA-AKI [5]. Evidence has suggested that increased biological age might contribute to CA-AKI incidence. Therefore, we quantified biological age in vivo with several blood biomarkers, in contrast to previous methods. We confirmed that biological age is an independent risk factor for CA-AKI. Compared with chronological age, biological age had better ability in predicting CA-AKI. The findings of this study provide a reasonable basis for developing a new set of therapies targeting the biological mechanisms of aging and the CA-AKI process. Age itself may become a modifiable risk factor for CA-AKI in the near future.

In addition, the pace of aging is currently receiving greater attention [25, 26]. Herein, we proposed the age gap as a means of quantifying the degree of accelerated aging, according to the difference between predictive age and chronological age. For example, the brain age gap and retinal age gap have been extensively studied and shown to be associated with disease prognosis [27]. Therefore, our proposed age gap, defined as the ratio between biological age and chronological age, can be used to further identify the relative advancement or retardation in biological aging. Multivariate logistic regression analysis demonstrated that a higher age gap was independently associated with the incidence of CA-AKI. Identifying the relationship between the age gap (the pace of biological aging) and diseases is currently a growing concern in medical practice.

How biological aging contributes to CA-AKI pathogenesis remains unclear; nonetheless, several potential mechanisms may be considered. Aging is accompanied by a chronic inflammatory state, which is not associated with infection [28]. The chronic inflammatory response decreases immune function, which inevitably causes systemic organ dysfunction involving kidney injury [29, 30]. On the basis of phylogenomic evidence, immunity related gene expression is increased in the aging kidney, and inflammatory indicators are elevated accordingly [31]. In this study, biological age was positively correlated with SCr elevation, CRP, and WBC, indicating that aging is accompanied by the renal injury and the pro-inflammatory state. In contrast, an increase in large artery stiffness with age contributes to renal microvascular damage and renal injury [32]. A pilot exploratory study has verified that arterial stiffness predicts AKI

after coronary artery bypass graft surgery [33]. Furthermore, the neuroendocrine changes during the aging process can also cause abnormal blood pressure responses, thus leading to renal hypoperfusion and increasing the risk of AKI [34]. In general, biological aging is among the most important mechanisms in CA-AKI onset. Therefore, patients with greater biological age have higher risk of CA-AKI and require close monitoring. Patients undergoing PCI should be assessed for their biological age to prevent CA-AKI. Perioperative interventions such as appropriate nutritional and anti-inflammatory therapy may aid in delaying biological age. Additional studies in clinical settings are required to further investigate the association between biological age and long-term outcomes in patients with CA-AKI.

Several limitations of this work should be acknowledged. The first limitation was the retrospective study design, thus potentially leading to retrospective bias in the statistics. The second limitation was that, among the diverse definitions of CA-AKI, we used only the European Society of Urogenital Radiology definition. The third limitation was that, owing to a lack of data on epigenetic biomarkers such as telomere length, we could not directly compare our results with the ideal measurement method of biological age. Further studies are needed to identify whether biological age assessed through other measurement methods might be associated with CA-AKI risk. The fourth limitation was that, although all patients received standard hydration treatment in the perioperative period for CAG, each patient's specific amount of oral hydration was difficult to determine and might have affected the incidence of CA-AKI. Given the current study's limitations, the results of this study must be interpreted with caution, and further large prospective studies are needed.

Conclusion

This study revealed that biological age is an independent risk factor of CA-AKI and has better predictive power than chronological age in patients with CAD undergoing CAG. Better understanding the effects of biological age on CA-AKI incidence will help guide more personalized medicine treatment.

Declarations

Data Availability Statement

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

Ethics Statement

The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University (20220228-30). Informed consent was waived because this study was retrospective.

Author Contributions

WB Z conceived and designed the study. HP J organized the data and drafted the manuscript with the help of ZZ C, P W, DB L, and YC T. HP J and ZZ C analyzed the data. XL H and XL J constructed the figures. WB Z and SD X detected errors in the entire process. All authors have read and approved the manuscript for submission.

Funding

This work was supported by grants from the Zhejiang Provincial Health Department (2018KY460) and Traditional Chinese Medicine Science and Technology Project of Zhejiang Province (2021ZB172).

Competing Interests

The authors declare that they have no competing interests.

Supplementary Material

Supplementary Materials for this paper are available at the following link https://cvia-journal.org/wp-content/uploads/2024/01/SUPPLEMENTAL_MATERIAL-1.pdf.

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