Prediction of biological age and all-cause mortality by 12-lead electrocardiogram in patients without structural heart disease

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Abstract

Background:
The 12-lead electrocardiogram (ECG) is affected by not only the cardiovascular but also the non-cardiovascular status. Whether ECG can be the determinant of biological age (BA) and the gap between chronological age (CA) and ECG-predicted BA reflect differences in prognosis are unclear.

Methods:
In the Shinken Database 2010 – 2017 (n = 19170), 12-lead ECG was analyzed in 13005 patients excluding those with structural heart disease or having pacing beats, atrial or ventricular tachyarrhythmia, and indeterminate axis (R axis > 180˚) on index ECG. The prediction model of BA was developed by principal component analysis with 438 ECG parameters. The gap between ECG-predicted BA and CA was calculated (AgeDiff = ECG-predicted BA − CA).

Results:
The ECG-predicted BA was significantly correlated with CA (r = 0.967). Patients with a positively wide AgeDiff had a higher incidence of all-cause mortality compared to those with a narrow AgeDiff or those with negative AgeDiff. The risk of AgeDiff > 0 for all-cause mortality compared with AgeDiff ≤ 0 was 1.78 (95%CI: 1.00 – 3.16), which increased according to the aging and became the highest in patients with CA of 71 – 80 years.

Conclusion:
Our data suggested that 12-lead ECG can be a tool to estimate BA. The gap between ECG-predicted BA and CA allowed estimation of increased risk of all-cause mortality in patients without structural heart disease.

Background

Aging is one of the strongest predictors of mortality. However, chronological age (CA) itself might not be a reliable indicator of the functional deterioration because aging is thought to have heterogeneity which are reliant upon a balance between exposure to damaging properties and resiliency.1, 2 To simply represent the actual status of individual aging, the concept of biological age (BA) have been developed. BA is estimated as a single variable which merged the complex equations for estimating age using multiple biomarkers. For the estimation, various biomarkers are used including physical, physiological, or biochemical parameters which would represent individual health status. 2-4

ECG has been widely recorded to detect or evaluate the risk of cardiac diseases. ECG parameters can be affected by age, gender, and individual physical conditions5, 6 which are mainly related to the circulatory and the respiratory system. The possible mechanisms underlying these effects have been considered to include changing topography of the heart in relation to the thorax and diaphragm, modification of the constituents of the volume conductor (skin, subcutaneous fat, lung parenchyma), or alterations of cardiac configuration and intracardiac conduction.5, 7

Aging is one of the most important factors underlying these electrophysiological and electroanatomical changes.5, 6, 8 There have been several studies that challenged to predict BA or “heart age” using ECG.9–11 Moreover, it has been reported that there is a discrepancy between BA estimated by ECG and the actual CA,9 which could be related to individual physical conditions and also various cardiovascular diseases. This concept could be utilized to the simple
method of screening for the patient health status, but for actual clinical use, we may have to consider the racial
difference in the performance for the prediction models of BA.\textsuperscript{11} Moreover, so far, most of the models have developed
with only several representative ECG parameters by linear regression model,\textsuperscript{10,12} and in only one report, artificial
intelligence modeling was applied.\textsuperscript{9} In the present study, we developed a prediction model for BA with hundreds of
automatically measured ECG parameters by principal component analysis (PCA) algorithm\textsuperscript{4} using a single-center cohort
in a Japanese cardiovascular hospital.

\section*{Methods}

\subsection*{Study population}

The Shinken Database includes all patients newly visiting the Cardiovascular Institute, Tokyo, Japan, excluding foreign
travelers and patients with active cancer. This single hospital-based database was established in June 2004. Details of
this database have been described elsewhere.\textsuperscript{13}

In the present study, computerized database of ECG was used, which was available since February 2010. Therefore, out
of total 32570 patients in the Shinken Database, 19170 patients registered between February 2010 and March 2018 were
extracted. After excluding patients with structural heart diseases (n = 4915), patients with age under 20 years or over 90
years (<20 or >90 years; n = 168), and patients with index ECG showing indeterminate axis (R axis >180˚) (n = 76), pacing
beats (n = 102), or atrial or ventricular tachyarrhythmia (n = 1763), the remaining 12837 patients were the target
population in the present study.

\subsection*{Definition of structural heart disease}

The definitions of structural heart diseases were as follows: valvular heart disease, moderate or severe stenosis or
regurgitation on echocardiography; coronary artery disease, diagnosed on angiography or scintigraphy; and hypertrophic
and dilated cardiomyopathy, diagnosed on echocardiography or magnetic resonance imaging [MRI]. Heart failure was
diagnosed when the patients had symptoms of New York Heart Association (NYHA) class $\geq 2$.

\subsection*{Patient follow-up}

The health status and the incidences of cardiovascular events and mortality were maintained in the database by being
linked to the medical records of the hospital, and by study documents of prognosis sent once per year to those who
stopped hospital visits or who were referred to other hospitals. In the present study, we included the follow-up data until
March 2019, and excluded follow-up data of > 3 years after the initial visit to avoid imbalance of follow-up period among
patients due to the different registration years (between 2010 and 2018).

\subsection*{Parameters obtained from ECG}

The 12-lead ECG was recorded for 10 s in the supine position, using a GE ECG machine (GE CardioSoft V6.71 and MAC
5500 HD; GE Healthcare, Chicago, IL) at a sampling rate of 500 Hz, and stored using the MUSE data management
system.

In the database of the computerized raw data of electrocardiogram with GE system, measurement of 639 parameters
was automatically performed. Of these, 201 parameters (9 not lead-specific and 192 [16 × 12 leads] lead-specific) were
temporally stored data, including the relative coordinate points (i.e., the start point of P-wave) and calculated values
much the same to the original parameters (i.e., among QTc parameters, QTc Calculation [QTc Bazett] was used and QTc
Framingham and QTc Fridericia were excluded). After excluding them, remaining 438 parameters (6 not lead-specific and
432 [36 × 12 leads] lead-specific) were used in the analysis (Table 1).
Evaluation and Statistical analysis

Statistical analyses were carried out using SPSS version 26.0 (IBM, Chicago, IL). In all analyses, \( P < 0.05 \) was taken to indicate statistical significance. Categorical and consecutive data are presented as number (%) and mean ± SD.

(1) Modeling of biological age (BA) using ECG parameters: BA was modeled using ECG parameters following two steps according to the PCA algorithm.\(^4\) [Step 1] Pre-BA

\[
\text{Pre-BA} = \left( \sum_{i=1}^{m} \sum_{j=1}^{n} \beta_{ij} \frac{x_{ij} - \bar{x}_i}{sd(x)} \right) p_i
\]

was calculated. In the equation, \( m \) indicates the number of principal components, and \( i \) indicates their individual orders; \( n \) indicates the number of ECG parameters, and \( j \) indicates their individual orders; \( \beta \) indicates the coefficient in the PCA; \( x \) indicates each ECG parameter; and \( sd(x) \) indicate the average value and the standard deviation of each ECG parameter. The \( p_i \) was calculated as following formula; \( p_i = \frac{R^2_{i}}{\text{sum of } R^2_{i}} \)

[Step 2] BA was calculated by the following formula: \( BA = \text{pre-BA} \times \text{(CA)} + \text{+(CA - )} \times (1 - B) \). In the equation, \( \text{(CA)} \) and \( \text{indicate the standard deviation and the average value of CA, and B} \) indicates the standardized coefficient in the univariable linear regression analysis where pre-BA and CA were the dependent and the independent variable, respectively.

(2) AgeDiff (gap between BA and CA) and its effect on mortality: AgeDiff was individually calculated as the gap between BA and CA (AgeDiff = BA - CA). Patients were categorized by 3-year ranges of AgeDiff (\( \leq 0, 0< \text{to} \leq 3, 3< \text{to} \leq 6, 6< \text{to} \leq 9, \) and >9 years), and the cumulative incidence of total mortality by the AgeDiff categories were plot by the Kaplan-Meyer method. Additionally, patients were categorized by AgeDiff >0 and AgeDiff \( \leq 0 \), and the hazard ratio of AgeDiff >0 for mortality in reference to AgeDiff \( \leq 0 \) was evaluated by Cox regression analysis with univariable and multivariable models.

Results

Patient characteristics

The characteristics of 12837 patients are shown in Table 2. The study patients included 6897 males (53.7%) and the mean age was 55.5 ± 15.0 years.

Prediction models for BA by ECG parameters

Using the 438 ECG parameters, the PCA model for CA was constructed, which consisted of 81 unrotated principal components with corresponding eigen values of \( \geq 1.0 \). About 85.9% of total variance was explained by the 81 principal components.

The individual BA was significantly correlated with CA (\( r = 0.967, p <0.001 \), Figure 1A). When separated by age categories, the coefficient correlation was 0.805 (\( p <0.001 \)) in patients under 40 years and 0.508 (\( p <0.001 \)) in patients over 81 years. The dispersion of AgeDiff was smaller in younger patients and larger in elderly patients (Figure 1B). The number of the deceased patients and their AgeDiff with respect to individual CA were displayed in Table 3. The AgeDiff in total population was higher in the deceased patients; 1.97 ± 7.09 in deceased patients and -0.01 ± 5.81 in alive patients (\( p = 0.012, \text{Table 3} \)).

Prediction of all-cause mortality using BA
Distribution of deceased or alive patients according to gender and subgroups of AgeDiff were shown in Table 4. During the median follow-up period of 284.2 days, all-cause death occurred in 17, 12, 10, 7, and 9 patients in the AgeDiff categories of $\leq 0$, $0 < \text{ to } \leq 3$, $3 < \text{ to } \leq 6$, $6 < \text{ to } \leq 9$, and $> 9$ years. All-cause mortality in the AgeDiff categories of $\leq 0$, $0 < \text{ to } \leq 3$, $3 < \text{ to } \leq 6$, $6 < \text{ to } \leq 9$, and $> 9$ years were 0.4%, 0.5%, 0.5%, 0.5%, 0.6%, 0.1% at 1 year, and 0.8%, 1.4%, 1.5%, 2.0%, and 2.5% at 3 year, respectively (Figure 2).

The hazard ratio of AgeDiff >0 for the mortality in reference to AgeDiff $\leq 0$ according to individual CA are shown in Table 5. The incident risk of all-cause mortality in patients with AgeDiff >0 increased according to the aging, and the risk of any death was the highest in CA of 71–80 years.

Discussion

Major findings

In this study, we developed a prediction model for BA using 438 ECG parameters. The BA using ECG was significantly correlated with CA ($r = 0.967$). The AgeDiff (= BA- CA) in total population was higher in the deceased patients ($1.97 \pm 7.09$) compared with alive patients (-0.01 $\pm 5.81$). Patients with a positively wide AgeDiff had a higher incidence of all-cause mortality compared with those with a positively narrow AgeDiff or negative AgeDiff (2.5% at 3 year in AgeDiff $> 9$ years compared with 0.8% at 3 year in AgeDiff $\leq 0$ years, respectively). The incident risk of all-cause mortality in patients with AgeDiff >0 increased according to the aging, and the risk of all-cause death was the highest in CA of 71–80 years.

Clinical implication of gap between ECG-predicted BA and CA

There have been a number of recent investigations regarding the prediction of BA using medical records, vital signs and laboratory data, or epigenetic changes. These investigations indicated a gap between predicted BA and actual CA, and the gap was deemed to represent epigenetic age acceleration, because it was shown to be associated with higher risks of all-cause mortality, cardiovascular disease, and cross-sectionally with obesity, earlier menopause, and frailty.

ECG, which can be performed readily and repeatedly, and can be analyzed instantly, could be a candidate of a tool for predicting BA, because ECG parameters would vary according to individual age and gender. Although ECG is mainly responsible for the circulatory and the respiratory system, several analyses have revealed that ECG can be affected by various extracardiac diseases: ventricular repolarization was altered by hemodialysis; prolonged QTc was observed in end-stage liver disease and non-alcoholic fatty liver disease; ST segment and T wave can be altered in acute cholecystitis; ST depression, left ventricular hypertrophy, prolonged QTc, and T wave inversion were observed in patients with intracranial hemorrhage and other ECG abnormalities were represented in patients with brain injury and stroke; higher heart rate, prolonged QTc, and low voltage appeared in patients with thyroid dysfunction. The possible common mechanisms which connects the various systemic health status and ECG would be vascular status and autonomic nerve system, which would possibly be the key pathogenesis that accords aging.

In the present study, we developed a model for predicting BA using hundreds of ECG parameters and found that the predicted BA in our model could primarily predict CA well ($r = 0.967$). This result is in line with previous reports that predicted the heart age with several ECG parameters. Moreover, a relatively large AgeDiff suggested an increased mortality rate, and the risk of all-cause mortality in patients with AgeDiff >0 increased according to the aging. This result
is in accordance with previous reports that demonstrated the association between AgeDiff (gap between BA and CA) and mortality.\textsuperscript{11} Our data confirmed these results with hundreds of automatically measured ECG parameters in Japanese patients without structural heart diseases. Also, our data suggested that AgeDiff with the method we employed could be one of the promising markers for predicting mortality.

\textbf{Limitations}

There were several limitations in this study. First, all of the participants were patients who visited a cardiovascular hospital in an urban area. Although the study subjects were patients without constructive heart diseases, it will be necessary to validate the results of this study in larger populations of healthy subjects. Second, we used the parameters measured with a GE-ECG machine. The approach or algorithms to measure the waves may be slightly different between ECG machines from various manufacturers, and revalidation with other ECG machines may be necessary. Third, patient characteristics, such as cardiac anatomical information, comorbidities, concomitant medications, and frailty, were not included in our models.

\textbf{Conclusion}

We developed a prediction model for BA using 12-lead electrocardiogram parameters in patients without structural heart diseases. This ECG-predicted BA and AgeDiff could be used for prediction of all-cause mortality.

\textbf{Declarations}

\textbf{Ethics and informed consent}

This study was performed in accordance with the ethical norms based on the Declaration of Helsinki (revised in 2013) and Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare, Japan, issued in 2017). Written informed consent was obtained from all participants. The study protocol was reviewed by the Institutional Review Board of the Cardiovascular Institute.

\textbf{Consent for publication}

Not applicable.

\textbf{Availability of data and materials}

Data cannot be shared publicly because of a lack of such description in the study protocol and informed consent. Data are available from the Ethics Review Committee at the Cardiovascular Institute for researchers who meet the criteria for access to confidential data. (contact via the corresponding author).

\textbf{Competing interests}

Dr. Suzuki received research funding from Mitsubishi Tanabe Pharm, and Daiichi Sankyo. Dr. Yamashita has received research funds and/or lecture fees from Daiichi Sankyo, Bayer Yakuhin, Bristol-Myers Squibb, Pfizer, Nippon Boehringer
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**Author's contributions**

NH, SS, and TY conceives the study concept and study design. NH and SS analyzed the data. All authors collected the data and draft the manuscript. TY checked the analyzed data and the manuscript. All authors approved the final version.

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### Tables

**Table 1. List of ECG parameters used in this study.**

| Parameters available in MUSE database system: 639 parameters |
|-------------------------------------------------------------|
| Parameters used for analysis: 438 parameters |
| (1) Not lead-specific parameters: 6 parameters |
| P-R Interval, P axis, QRS Duration, QTc Calculation (QTc Bazett), R axis, T axis |
| (2) Lead-specific parameters: 432 [36 × 12 leads] parameters |
| ST at J Point, P Area, P' Area, P Area (Full), P Peak Time, P' Peak Time, P Peak Amplitude, P' Peak Amplitude, P Duration, P' Duration, QRS Area, Q Area, Q Peak Amplitude, Q Duration, R Area, R Area, R Peak Time, R Duration, R' Duration, S Area, S' Area, S Peak Time, S Duration, S' Duration, T Area, T' Area, T Area (Full), T Peak Time, T Peak Amplitude, T' Peak Amplitude, T Duration, T' Duration, Minimum ST level, Max R Amplitude, Maximum ST level, Max S Amplitude |
| Parameters excluded: 201 parameters |
| (1) Not lead-specific parameters: 9 parameters |
| P Onset, P Offset, QRS Count, QTc Framingham, QTc Fridericia, Q-T Interval, Q Onset, Q Offset, T Offset |
| (2) Lead-specific parameters: 192 [16 × 12 leads] parameters |
| P Onset Amplitude, QRS Balance, QRS Deflection, QRS Intrinsicoid, Q Peak Time, R' Peak Time, R Peak Amplitude, R' Peak Amplitude, S' Peak Time, S Peak Amplitude, S' Peak Amplitude, T' Peak Time, T End, ST at End ST, ST at Mid ST, Special T |
P', R', S', and T' indicated the second components of P, R, S and T wave, respectively, which could be positive or negative polarity.

**Table 2. Patient characteristics**

|                       | Total (n = 12837) | Male (n = 6897) | Alive (n = 6863) | Deceased (n = 34) | Female (n = 5940) | Alive (n = 5919) | Deceased (n = 21) |
|-----------------------|-------------------|-----------------|-----------------|------------------|-------------------|-----------------|------------------|
| Age                   | 55.5 ± 15.0       | 54.2 ± 14.4     | 54.1 ± 14.4     | 70.9 ± 12.1      | 57.0 ± 15.6       | 56.9 ± 15.6     | 70.1 ± 14.1      |
| Male                  | 6897 (53.7)       | 6897 (53.7)     | 6863 (53.7)     | 34 (0.3)         | 0.0 (0.0)         | 0.0 (0.0)       | 0.0 (0.0)        |
| BMI                   | 23.4 ± 27.0       | 24.2 ± 4.5      | 24.2 ± 4.5      | 23.3 ± 4.1       | 22.5 ± 39.3       | 22.5 ± 39.4     | 22.5 ± 3.5       |
| SBP                   | 125.8 ± 18.5      | 127.5 ± 16.7    | 127.5 ± 16.7    | 125.0 ± 16.9     | 124.0 ± 20.2      | 124.0 ± 20.2    | 131.3 ± 22.0     |
| DBP                   | 75.3 ± 13.8       | 77.1 ± 11.5     | 77.1 ± 11.5     | 71.0 ± 14.0      | 73.2 ± 15.8       | 73.2 ± 15.8     | 74.3 ± 10.3      |
| Heart rate            | 71.1 ± 12.9       | 71.2 ± 13.5     | 71.2 ± 13.4     | 73.8 ± 17.8      | 71.0 ± 12.3       | 71.0 ± 12.3     | 74.3 ± 17.0      |
| eGFR                  | 74.9 ± 17.7       | 74.3 ± 17.0     | 74.5 ± 16.9     | 57.6 ± 23.0      | 75.5 ± 18.5       | 75.6 ± 18.4     | 62.7 ± 29.2      |
| LVEF                  | 67.8 ± 6.8        | 66.3 ± 6.6      | 66.3 ± 6.6      | 62.8 ± 13.6      | 69.5 ± 6.5        | 69.5 ± 6.5      | 66.1 ± 8.4       |
| Hypertension          | 4484 (34.9)       | 2628 (20.5)     | 2607 (20.3)     | 21 (0.2)         | 1856 (14.5)       | 1845 (14.4)     | 11 (0.1)         |
| Dyslipidemia          | 2855 (22.2)       | 1497 (11.7)     | 1488 (11.6)     | 9 (0.1)          | 1358 (10.6)       | 1353 (10.5)     | 5 (0.0)          |
| Diabetes              | 923 (7.2)         | 640 (5.0)       | 631 (4.9)       | 9 (0.1)          | 283 (2.2)         | 278 (2.2)       | 5 (0.0)          |
| Hyperuricemia         | 1362 (10.6)       | 1160 (9.0)      | 1149 (9.0)      | 11 (0.1)         | 202 (1.6)         | 199 (1.6)       | 3 (0.0)          |
| CKD                   | 1100 (8.6)        | 617 (4.8)       | 603 (4.7)       | 14 (0.1)         | 483 (3.8)         | 475 (3.7)       | 8 (0.1)          |
| Anemia (Hb <11 g/dL)  | 186 (1.4)         | 55 (0.4)        | 46 (0.4)        | 9 (0.1)          | 131 (1.0)         | 127 (1.0)       | 4 (0.0)          |
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, systolic blood pressure; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease; Hb, hemoglobin.

Table 3. The number of deceased subjects and their AgeDiff with respect to individual CA
| CA       | Total   | Male       | Female     | AgeDiff N       | Male       | Female     | AgeDiff N       |
|---------|---------|------------|------------|-----------------|------------|------------|-----------------|
| Alive   | 12782   | 6863       | 5919       | -0.01 ± 5.81    | 0.40 ± 5.61| -0.48 ± 6.00|
| ≤40 years | 2352   | 1319       | 1033       | -4.66 ± 4.88    | -3.01 ± 4.81| -6.78 ± 4.10|
| 41-50 years | 2468 | 1444       | 1024       | -2.27 ± 4.76    | -1.49 ± 4.96| -3.38 ± 4.23|
| 51-60 years | 2828 | 1656       | 1172       | -0.08 ± 4.75    | 0.21 ± 4.85| -0.48 ± 4.57|
| 61-70 years | 2928 | 1519       | 1409       | 2.26 ± 4.99     | 2.69 ± 5.16| 1.80 ± 4.76|
| 71-80 years | 1721 | 740        | 981        | 4.18 ± 5.01     | 4.45 ± 5.19| 3.98 ± 4.87|
| ≥81 years | 485    | 185        | 300        | 5.99 ± 5.35     | 6.05 ± 4.96| 5.95 ± 5.58|
| All-cause death | 55  | 34         | 21         | 1.97 ± 7.09     | 3.39 ± 5.16| -0.33 ± 9.10|
| ≤40 years |       |            |            |                 |            |            |                 |
| 41-50 years | 4    | 2          | 2          | -4.58 ± 3.90    | -1.28 ± 1.28| -7.88 ± 0.62|
| 51-60 years | 9    | 6          | 3          | -2.62 ± 5.99    | -0.81 ± 6.06| -6.25 ± 4.68|
| 61-70 years | 14   | 8          | 6          | 1.38 ± 6.73     | 2.21 ± 4.05| 0.26 ± 9.60|
| 71-80 years | 12   | 10         | 2          | 4.78 ± 4.56     | 4.13 ± 3.88| 8.07 ± 8.22|
| ≥81 years | 16    | 8          | 8          | 4.60 ± 8.14     | 7.96 ± 3.99| 1.24 ± 10.02|
| CV death  | Total  | 23         | 15         | 0.80 ± 8.64     | 1.77 ± 5.79| -1.03 ± 12.71|
| ≤40 years |       |            |            |                 |            |            |                 |
| 41-50 years | 2    | 1          | 1          | -3.91 ± 5.00    | -0.37 ± 5.00| -7.45 |
| Age Group | Deaths | AgeDiff Mean ± Standard Deviation |
|-----------|--------|----------------------------------|
| 51-60 years | 6 | -4.08 ± 6.25 |
| 4 | -2.11 ± 6.43 |
| 2 | -8.03 ± 4.96 |
| 61-70 years | 3 | 4.94 ± 8.76 |
| 4 | -0.12 ± 0.34 |
| 2 | 15.05 |
| 71-80 years | 7 | 3.51 ± 5.10 |
| 4 | 1.78 ± 2.47 |
| 6 | 13.88 |
| ≥81 years | 5 | 2.26 ± 14.23 |
| 2 | 12.49 ± 3.55 |
| 1 | -4.56 ± 14.98 |
| Non-CV death Total | 32 | 2.81 ± 5.74 |
| 19 | 4.67 ± 4.35 |
| 13 | 0.10 ± 6.58 |
| ≤40 years | 2 | -5.25 ± 4.34 |
| 1 | -2.19 |
| 1 | -8.32 |
| 41-50 years | 3 | 0.31 ± 5.13 |
| 2 | 1.80 ± 6.27 |
| 1 | -2.67 |
| 51-60 years | 11 | 0.40 ± 6.22 |
| 6 | 2.99 ± 4.48 |
| 5 | -2.70 ± 7.04 |
| 61-70 years | 5 | 6.57 ± 3.38 |
| 4 | 7.65 ± 2.73 |
| 1 | 2.26 |
| 71-80 years | 11 | 5.66 ± 3.80 |
| 6 | 6.45 ± 2.97 |
| 5 | 4.72 ± 4.80 |

Table 4. Distribution of deceased or alive subjects according to gender and subgroups of AgeDiff
| AgeDiff (years) | Alive          | Deceased | p-value |
|-----------------|----------------|----------|---------|
| **Total**       |                |          |         |
| ≤0              | 6435(99.7)     | 17(0.3)  | 0.004   |
| 0<, ≤3          | 2570(99.5)     | 12(0.5)  |         |
| 3<, ≤6          | 1951(99.5)     | 10(0.5)  |         |
| 6<, ≤9          | 1052(99.3)     | 7(0.7)   |         |
| 9<              | 774(98.9)      | 9(1.1)   |         |
| ≤0              | 6435(99.7)     | 17(0.3)  | 0.005   |
| 0<              | 6347(99.4)     | 38(0.6)  |         |
| **Male**        |                |          |         |
| ≤0              | 3268(99.8)     | 8(0.2)   | 0.006   |
| 0<, ≤3          | 1463(99.5)     | 7(0.5)   |         |
| 3<, ≤6          | 1118(99.4)     | 7(0.6)   |         |
| 6<, ≤9          | 571(99.0)      | 6(1.0)   |         |
| 9<              | 443(98.7)      | 6(1.3)   |         |
| ≤0              | 3268(99.8)     | 8(0.2)   | 0.005   |
| 0<              | 3595(99.3)     | 26(0.7)  |         |
| **Female**      |                |          |         |
| 0≤              | 3167(99.7)     | 9(0.3)   | 0.428   |
| 0<, ≤3          | 1107(99.6)     | 5(0.4)   |         |
| 3<, ≤6          | 833(99.6)      | 3(0.4)   |         |
| 6<, ≤9          | 481(99.8)      | 1(0.2)   |         |
| 9<              | 331(99.1)      | 3(0.9)   |         |
|               | All cause death | CV death    | Non-CV death |
|---------------|-----------------|-------------|--------------|
| Total         | 1.78 (1.00−3.16)| 1.32 (0.57−3.05)| 2.28 (1.03−5.09) |
| ≤40 years     |                 |             |              |
| 41−50 years   | 0.03 (0.00−227.84)| 0.03 (0.00−9961.22)| 0.03 (0.00−8998.6) |
| 51−60 years   | 0.49 (0.12−1.95) | 0.50 (0.09−2.70) | 0.47 (0.04−5.23) |
| 61−70 years   | 1.18 (0.37−3.75) | 0.95 (0.09−10.45) | 1.25 (0.33−4.72) |
| 71−80 years   | 2.53 (0.33−19.6) | 1.38 (0.17−11.46) | 27.69 (0.00−448543.09) |
| ≥81 years     | 1.08 (0.25−4.75) | 0.60 (0.07−5.39) | 1.56 (0.20−12.19) |

Table 5. Hazard ratio for mortality in total subjects according to individual CA for subjects with AgeDiff >0 compared for those with AgeDiff ≤0

Abbreviations: CI, confidence interval;

Figures
Association between individual BA or AgeDiff and chronological age (A) The individual BA was significantly correlated with CA ($r = 0.967, p < 0.001$). (B) The dispersion of AgeDiff was smaller in younger patients and larger in elderly patients. BA indicates biological age; CA, chronological age; AgeDiff is defined as ECG-predicted BA − CA.

Figure 1
Figure 2

All-cause mortality by the AgeDiff categories