

The Predicted Value of Kidney Injury Molecule-1 (KIM-1) in Healthy People

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Purpose: Recent studies have focused on whether kidney injury molecule-1 (KIM-1) might serve as a marker of acute kidney tubular injury. Our study analyzed the levels of KIM-1 in the healthy population of different ages to explore the correlation between KIM-1 and age. Moreover, we constructed a model to predict kidney age.

Methods: A cross-sectional study was conducted by Huashan Hospital, Shanghai, China, between April 2020 and December 2020. KIM-1 and other kidney biomarkers were measured in 176 healthy individuals ranging from 26 to 91 years old. Statistical correlated analyses for urinary KIM-1, creatinine (uCREA), potassium (K), sodium (Na) and chlorine (Cl), plasmic renin, angiotensin-2 (AngII) and aldosterone (ALD), and serum microalbuminuria (MALB), β 2-microglobulin (B2MG), cystatin C (CYSC), urea nitrogen (BUN), creatinine (CREA), and glucose (GLU) were performed to assess the correlation between age and kidney biomarkers. All variables were selected as independent variables for the prediction of age by multiple linear regression.

Results: KIM-1 positively correlated with age in kidney healthy people ($r = 0.41$, $p < 0.05$), whether among females ($r = 0.51$, $p < 0.05$) or males ($r = 0.27$, $p < 0.05$). It was much related to K ($r = 0.34$), B2MG ($r = 0.28$), and CL ($r = 0.23$). The predicted model was constructed with eGFR, Cl, ALD, CYSC, KIM-1, BUN, GLU and AngII, reaching an adjusted R^2 of 69.5% and a standard error of the estimated 7.84 years.

Conclusion: The level of urinary KIM-1 increases with age in healthy people. The model constructed by KIM-1 and the other 7 biomarkers can predict kidney age in healthy people.

Keywords: aging, kidney biomarkers, KIM-1, healthy

Introduction

The aging people in the general population is steadily increasing worldwide, which causes socioeconomic problems, especially health issues. Chronic kidney disease (CKD) is an important problem characterized by poor health outcomes and high health-care costs. Moreover, it often occurs with diabetes, hypertension, heart disease and stroke.¹ Hence, it cannot be ignored for health management anymore. More promising biomarkers are necessary to implement into clinical practice for early diagnosis.² The kidney injury molecule-1 (KIM-1), also known as T-cell immunoglobulin and mucin-domain-containing molecule-1 (TIM-1), was first proposed to have a role in restoration after a kidney injury almost two decades ago and became a novel therapeutic target for kidney injury at various stages.^{3,4} It is a type 1 transmembrane protein, with an immunoglobulin and mucin domain. Recent studies were carried out to evaluate whether KIM-1 is present in human acute kidney failure and might serve as a urinary marker of acute kidney tubular injury.^{5,6} In the first human study, high urinary KIM-1 levels and extensive expression of this protein were detected in biopsies from the proximal tubule of patients with acute tubular necrosis.⁷ A follow-up study of 16.6 years showed that p-KIM-1 predicts the future decline of eGFR and risk of CKD in healthy middle-aged participants.⁸ A study suggested the possibility of serum KIM-1, NGAL, and NAG as clinical indicators for evaluating the condition of patients with fracture traumatic shock and the possibility of a combined test of serum KIM-1, NGAL, and NAG for diagnosing the condition.⁹ The

studies of KIM-1 mainly involved early preeclampsia,¹⁰ HIV-positive persons,¹¹ urinary obstruction¹², and many other diseases, but very few on healthy kidneys. To evaluate the prognostic value of KIM-1 in kidney aging, we measured the levels of KIM-1 in the healthy population with different ages to explore whether the KIM-1 is correlated with age. Moreover, we constructed a model to evaluate kidney age with other age-related biomarkers.

Materials and Methods

Study Design

This cross-sectional study of healthy Chinese was conducted by Huashan Hospital, Shanghai, China, between April 2020 and December 2020. All participants gave informed consents. Healthy residents of Youyi Road Community Health Service Centre in Baoshan District were enrolled if they were healthy according to our inclusion criteria, which included: (1) The participants are not diagnosed with kidney-related diseases, such as hypertension, diabetes mellitus, or kidney diseases. (2) The laboratory tests and physical examinations of participants were qualified, estimated Glomerular Filtration Rate (eGFR) >60 mL/min/1.73m², fasting blood glucose (GLU) <7.0 mmol/L, glycated hemoglobin (HBA1C) $<6.5\%$, systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg, albumin creatinine ratio (ACR) <30 mg/g (Figure 1).

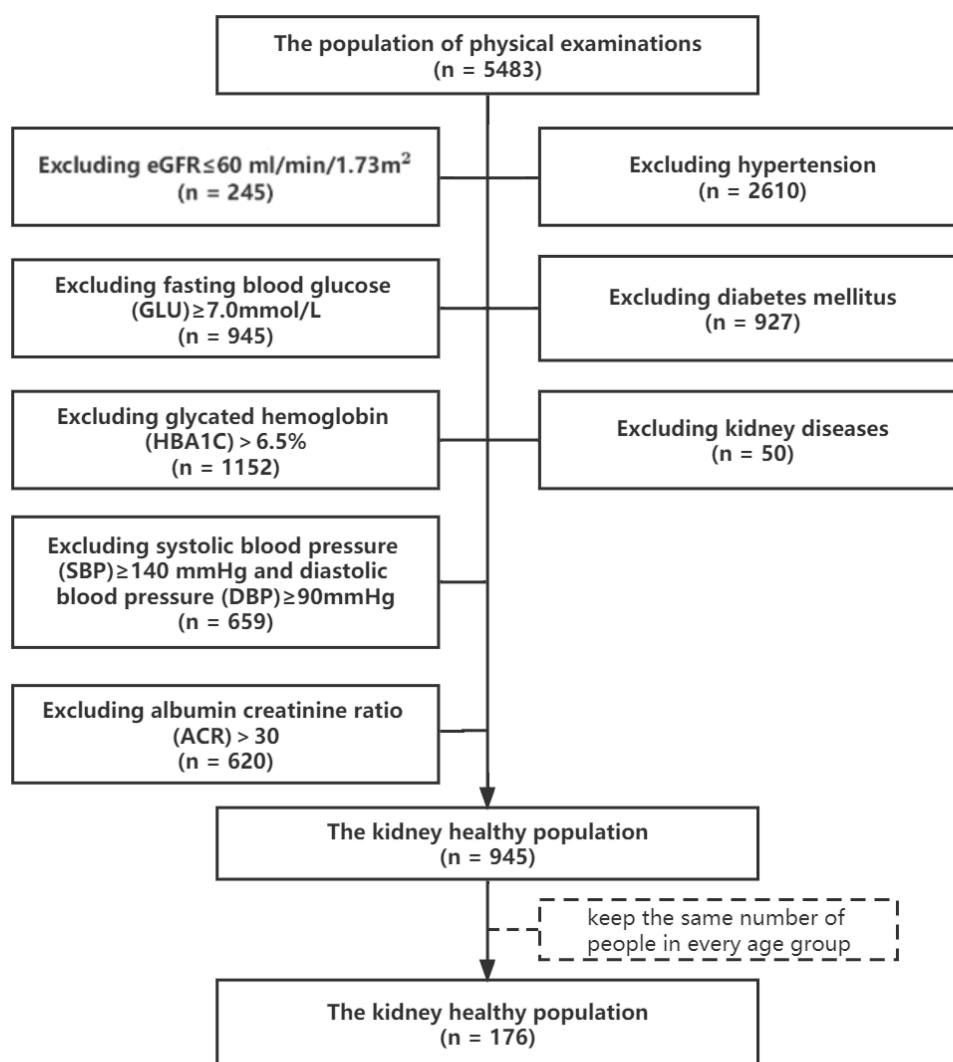


Figure 1 Flow diagram of screening participants.

Sample Collection and Lab Assessment

First-morning urine and blood samples were obtained from each participant into sterile containers. All the specimens were stored at 2–8°C until centrifugation. The urine and blood samples were centrifuged at 4000 rpm for 10 minutes at 4°C and 2500 rpm for 5 min at 4°C, respectively. The supernatant was stored at –80°C until detection by an authenticated medical laboratory. The urine samples were analyzed for KIM-1 and uCREA, K, Na and Cl in urine. The plasma samples were analyzed for Renin, AngII and ALD. The serum samples were analyzed for MALB, B2MG, CYSC, CREA, and BUN. KIM-1 was assessed using Enzyme-Linked Immunosorbent Assay (ELISA) kits (ELISA, R&D Systems®, Minneapolis, USA). Renin, AngII and ALD were detected with reagents from AutoLumo A2000 (Zhengzhou, China). The others were detected with reagents from Roche Diagnostics (Rotkreuz, Switzerland) on a Cobas e 601 instrument (Roche Diagnostics, Rotkreuz, Switzerland). eGFR was calculated using the CKD Epidemiological Collaboration equation, CKD-EPI-Asia equation chronic kidney disease epidemiology collaboration equations in Asian (CKD-EPI-Asian)¹³ as follows:

$$\begin{aligned} \text{if female and CREA} \leq 0.7, \text{eGFR (mL/min/1.73 m}^2\text{)} &= 151 \times (\text{CREA}/0.7)^{-0.328} \times (0.993)^{\text{Age}} \\ \text{if female and CREA} > 0.7, \text{eGFR (mL/min/1.73 m}^2\text{)} &= 151 \times (\text{CREA}/0.7)^{-1.210} \times (0.993)^{\text{Age}} \\ \text{if male and CREA} \leq 0.9, \text{eGFR (mL/min/1.73 m}^2\text{)} &= 149 \times (\text{CREA}/0.9)^{-0.415} \times (0.993)^{\text{Age}} \\ \text{if male and CREA} > 0.9, \text{eGFR (mL/min/1.73 m}^2\text{)} &= 149 \times (\text{CREA}/0.9)^{-1.210} \times (0.993)^{\text{Age}} \end{aligned}$$

Statistical Analysis

The normality of data was tested with the Shapiro–Wilk test. The continuous variables of participants were presented as mean $\pm$ standard deviation for normal distribution and as median (interquartile range, IQR) for skewed distribution. Categorical variables were presented as a number. The levels of urinary markers were normalized to the urinary CREA (uCREA) concentration. The Spearman correlation test was performed to assess the correlation between age and urinary biomarkers. Linear regression analyses were performed to determine factors associated with age. The Bland-Altman graph described the precision of the predicted model. The Bland-Altman method was applied for calculating the difference between age and predicted age. All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA), and GraphPad Prism 8.3.0 (GraphPad Software, San Diego, CA, USA). A *p*-value of <0.05 was considered statistically significant.

Results

In total 945 participants, 176 were selected for our investigation for baseline measurements (Figure 1). The age ranged from 26 to 91 years old with 115 (65%) females and 61 (35%) males. We divided them into 6 groups with 10 years old intervals. According to previous research and findings, variables correlated to kidney functions have been selected in our study. After log transforming the ratio of KIM-1, K, Na, and Cl to uCREA, we normalized urinary biomarkers (Table 1).

Spearman correlation test was performed that KIM-1 positively correlation with age in kidney health people ($r=0.41$, $p<0.05$), whether among females ($r=0.51$, $p<0.05$) or males ($r=0.27$, $p<0.05$). Moreover, there is no difference among groups. $\log_{10}\text{KIM-1/uCREA}$ shows a slow increase with age, both females and males (Figure 2).

Besides $\log_{10}\text{KIM-1/uCREA}$, other biomarkers also presented correlation to age. Meanwhile, $\log_{10}\text{KIM-1/uCREA}$ correlated to them (Figure 3). From top to end they were, $\log_{10}\text{K/uCREA}$ ($r=0.34$, $p<0.05$), B2MG ($r=0.28$, $p<0.05$), $\log_{10}\text{Cl/uCREA}$ ($r=0.23$, $p<0.05$), CYSC ($r=0.21$, $p<0.05$), AngII ($r=0.21$, $p<0.05$), eGFR ($r=-0.21$, $p<0.05$), MALB ($r=-0.20$, $p<0.05$), Renin ($r=-0.17$, $p<0.05$).

We constructed a mathematical model for predicting the kidney age with biomarkers correlating with age. The Multiple linear regression analysis was performed age as a dependent variable and 15 biomarkers related to the kidney function as independent variables. They were, eGFR ($r=-0.64$, $p<0.05$), B2MG ($r=0.59$, $p<0.05$), CYSC ($r=0.57$, $p<0.05$), CREA ($r=0.48$, $p<0.05$), AngII ($r=0.47$, $p<0.05$), ALD ($r=0.45$, $p<0.05$), $\log_{10}\text{KIM-1/uCREA}$ ($r=0.41$, $p<0.05$), MALB ($r=-0.38$, $p<0.05$), $\log_{10}\text{K/uCREA}$ ($r=0.37$, $p<0.05$), $\log_{10}\text{Cl/uCREA}$ ($r=0.35$, $p<0.05$), BUN ($r=0.35$, $p<0.05$), $\log_{10}\text{Na/uCREA}$ ($r=0.29$, $p<0.05$), Renin ($r=-0.23$, $p<0.05$), GLU ($r=0.16$, $p<0.05$), $\log_{10}\text{Mg/uCREA}$ ($r=0.16$, $p<0.05$). In the collinearity statistics, the VIF appeared over 5, which means these biomarkers affected each other too

Table 1 Characteristics of the Participants in Different Groups

	<40	40–49	50–59	60–69	70–79	≥80
Age (years)	34±4	45(42,48)	55(52,58)	64±3	74(72,77)	83±3
Gender						
Male	5(33%)	4(11%)	15(37%)	18(49%)	11(37%)	8(50%)
BUN (mmol/L)	4.73±0.82	4.66±1.04	5.52±1.10	5.63±1.25	5.88±1.12	5.55±1.25
CREA (umol/L)	58.40±13.67	52.00(48.50,59.00)	62.27±10.85	70.05±12.51	68.73±12.31	77.19±14.49
eGFR (mL/ (min*1.73m2))	139.80±27.32	132.70±19.94	117.10±18.35	101.20±15.54	96.00(84.75,108.80)	87.56±21.42
MALB (mg/L)	9.20(4.20,15.50)	7.71±3.44	7.00(4.35,12.50)	4.10(2.40,7.00)	5.70(3.33,7.93)	2.90(1.98,3.88)
ACR (mg/L)	7.99±4.47	6.40(4.45,8.40)	6.00(4.90,11.45)	4.50(3.40,7.25)	6.70(3.95,13.50)	7.39±3.57
GLU (mmol/L)	5.50±0.64	5.48±0.51	5.75±0.56	5.79±0.47	5.63±0.35	5.74±0.44
HbA1c (%)	5.79±0.20	5.67±0.31	5.88±0.25	5.90(5.60,6.20)	5.75(5.68,5.93)	5.92±0.37
SBP (mmHg)	123.30±9.47	122.30±10.67	120.10±9.90	122.80±9.10	130.00(123.50,130.00)	127.00(120.50,129.50)
DBP (mmHg)	82.00(78.00,84.00)	75.97±6.97	73.61±7.73	73.73±6.07	76.00(71.50,80.00)	75.50±4.71
B2MG (mg/L)	1.38±0.22	1.42±0.26	1.56±0.18	1.64(1.53,1.86)	1.84±0.31	2.24±0.51
CYSC (mg/L)	0.80±0.11	0.78(0.72,0.87)	0.86±0.09	0.92±0.13	0.98±0.14	1.18±0.17
Renin (pg/mL)	28.34±16.10	16.27(11.17,24.10)	10.59(7.04,17.45)	9.72(5.99,19.75)	9.61(6.36,14.43)	15.97(6.38,24.13)
AngII (pg/mL)	81.90±9.19	79.51(70.57,89.80)	88.18(78.38,93.54)	92.00±16.74	102.80(91.00,120.40)	96.72(85.30,119.20)
ALD (pg/mL)	116.00±34.18	119.20±37.70	105.60(89.51,127.70)	136.40(104.20,187.40)	235.00±82.63	167.70±67.67
KIM-1 (ng/mL)	1.01±0.69	0.96(0.62,1.63)	0.93(0.65,1.37)	0.88(0.58,1.38)	0.99(0.68,1.47)	0.63(0.46,1.06)
log ₁₀ KIM-1/uCREA (ug/umol)	−4.16±0.27	−4.00±0.24	−3.96±0.20	−3.94±0.17	−3.80±0.20	−3.79(−3.87, −3.61)
uCREA (umol/L)	11,765±5591	10,753(7520,13,349)	10,330(5979,12,796)	8637±4397	5976(4013,8319)	3860(2344,7776)
log ₁₀ K/uCREA (mmol/umol)	−2.64±0.18	−2.52±0.15	−2.48±0.17	−2.45±0.26	−2.39±0.19	−2.32(−2.52, −2.13)
log ₁₀ Na/uCREA (mmol/umol)	−1.92±0.27	−1.87±0.22	−1.86±0.21	−1.79±0.25	−1.80±0.21	−1.56(−1.78, −1.33)
log ₁₀ Cl/uCREA (mmol/umol)	−2.01±0.24	−1.91±0.22	−1.89±0.20	−1.83±0.24	−1.82±0.21	−1.60(−1.86, −1.38)
log ₁₀ Ca/uCREA (mmol/umol)	−3.43(−3.63, −3.32)	−3.48±0.29	−3.45±0.26	−3.43±0.34	−3.48±0.38	−3.30(−3.53, −3.19)
log ₁₀ Mg/uCREA (mmol/umol)	−3.56±0.26	−3.41±0.23	−3.46±0.18	−3.37±0.25	−3.40±0.23	−3.33(−3.46, −3.08)
log ₁₀ P/uCREA (mmol/umol)	−2.69(−2.79, −2.57)	−2.64±0.17	−2.64(−2.77, −2.55)	−2.67±0.27	−2.68±0.15	−2.66(−2.78, −2.57)

Note: Data are expressed as number (%), mean ± standard deviation, or median (interquartile range).

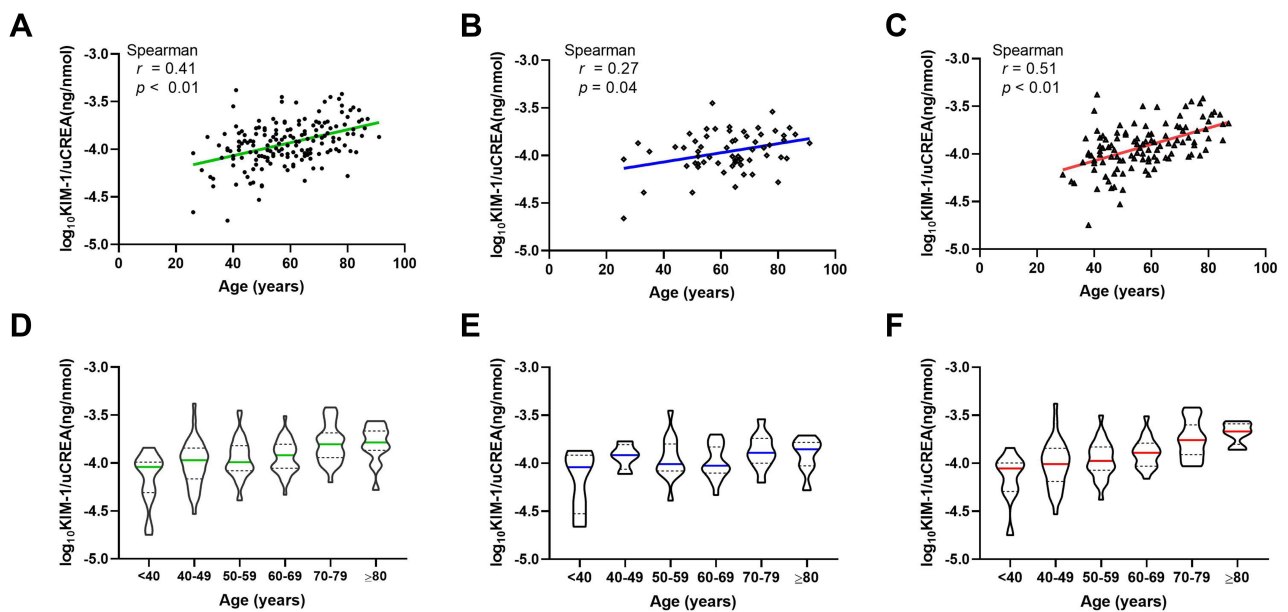


Figure 2 The distribution of KIM-1 after normalizing by uCREA concentration with age.

Notes: (A) The whole healthy study population. (B) The male healthy study population. (C) The female healthy study population. (D) The whole healthy study population in different age groups. (E) The male healthy study population in different groups. (F) The female healthy study population in different age groups.

much. Hence, we adopted a stepwise regression method to eliminate redundant biomarkers. The selection of variables procedure is summarized in Table 2. Finally, eGFR, $\log_{10} \text{Cl/uCREA}$, ALD, CYSC, $\log_{10} \text{KIM-1/uCREA}$, BUN, GLU and AngII stood out to be an equation for predicting the age with an adjusted R^2 of 69.5% and the standard error of the estimate of 7.84 years.

Then we analysed the coincidence between age and predicted age. Figure 4 illustrates the difference in age and predicted age following Bland-Altman analysis and 95% CIs were plotted as shaded areas. The results reached an Adjusted R^2 of 69.5%, a bias of -0.016 , and a standard deviation of 7.84 years.

Discussion

In this cross-sectional study, we examined urinary KIM-1 in healthy people with different ages to verify whether it can be used as a potential biomarker predicting kidney health. We found its correlation with age in both females and males and constructed a model for predicting the kidney age, together with other age-related biomarkers.

KIM-1 Correlated to the Age in Healthy People

To our knowledge, KIM-1 is a new and potential biomarker of proximal tubular injury.⁴ Most studies examined KIM-1 in different diseases and acquired many positive results for early diagnosing of kidney injury. However, very few studies focused on the prediction of KIM-1 in kidney healthy people. It is useful to explore aging and health evaluation with disease biomarkers. Some researchers established reference intervals in particular sections or populations in recent years.^{14,15} In our research, including KIM-1, biomarkers of 176 participants' age distributed evenly and considered healthily were detected for correlation analysis with age. It had a moderate correlation with age ($r=0.41$), independent with gender, suggesting it is a common phenomenon in the population. A biomarker derived from a healthy population is more convenient and acceptable in clinical application. Because it not only gives a simple result to help doctors make a quick medical decision, it also provides an intuitive reference to help health consultants offer advice.

KIM-1 Was a Good Tubule Biomarker Than the Glomerulus

As a biomarker of the kidney, KIM-1 showed a correlation with other biomarkers. In our study, KIM-1 was much related to K ($r=0.34$, $p<0.05$), B2MG ($r=0.28$, $p<0.05$), CL ($r=0.23$, $p<0.05$). The kidney tubular function is essential for volume

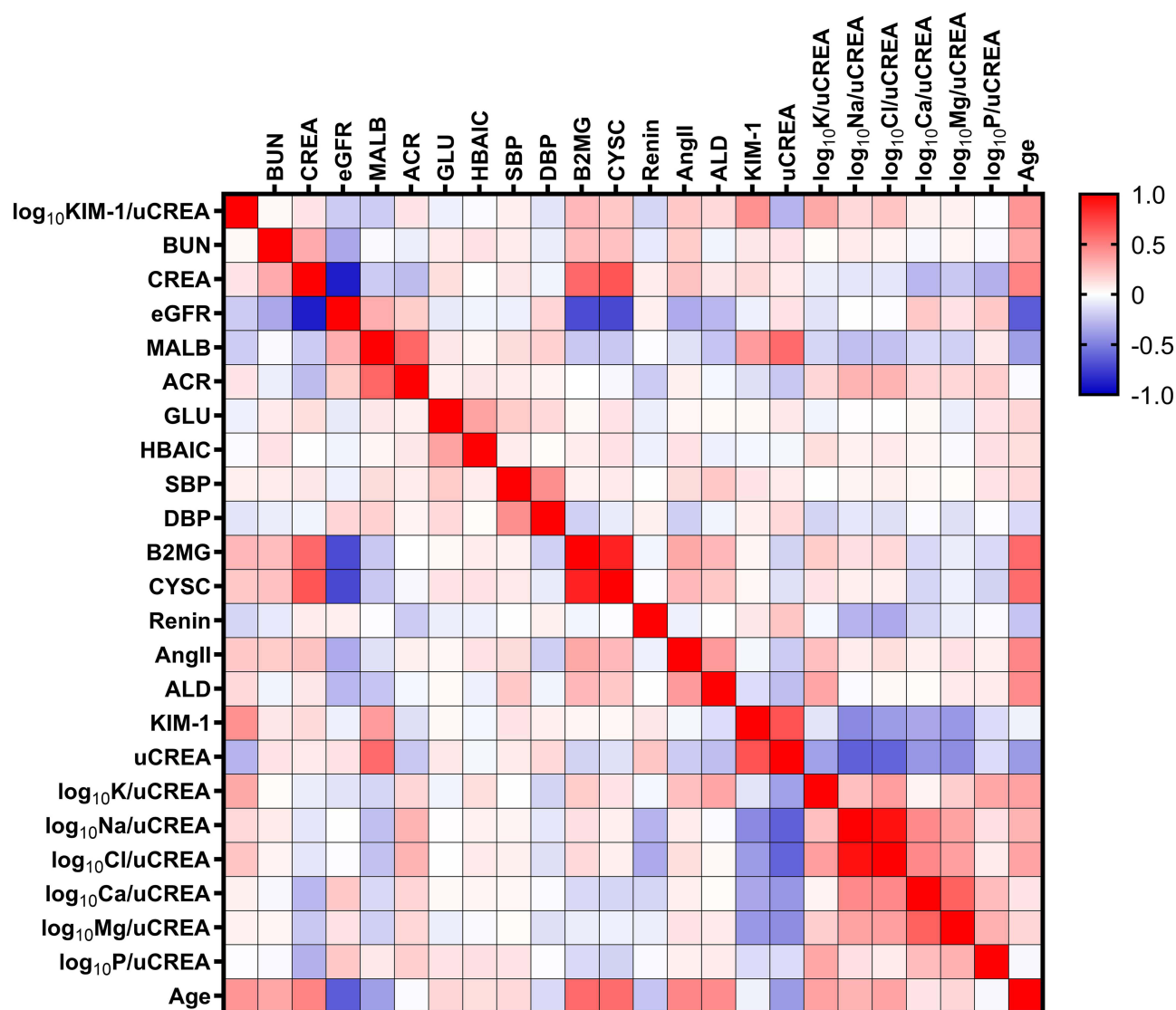


Figure 3 Spearman correlation between urinary biomarkers and age.

Abbreviations: log₁₀KIM-1/uCREA, urinary KIM-1 normalized by uCREA concentration; BUN, urea nitrogen; CREA, creatinine; eGFR, estimated Glomerular Filtration Rate; MALB, urinary microalbumin; ACR, urinary albumin/creatinine ratio; GLU, blood glucose; HBAIC, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; B2MG, beta2 microglobulin; CYSC, cystatin C; AngII, aldosterone; ALD, angiotensin-2; KIM-1, kidney injury molecule-1; uCREA, urinary creatinine; log₁₀K/uCREA, urinary potassium normalized by uCREA concentration; log₁₀Na/uCREA, urinary sodium normalized by uCREA concentration; log₁₀Cl/uCREA, urinary chlorine normalized by uCREA concentration; log₁₀Ca/uCREA, urinary calcium normalized by uCREA concentration; log₁₀Mg/uCREA, urinary magnesium normalized by uCREA concentration; log₁₀P/uCREA, urinary phosphorus normalized by uCREA concentration.

status regulation, acid-base homeostasis, mineral metabolism, and hormone production.¹⁶ It is poorly quantified by traditional measures of kidney health, including eGFR and albuminuria.¹⁷ The pathology of tubulointerstitial damage and fibrosis were visible to the clinician until biopsies.¹⁸ As a polypeptide existed on the surface of most cells with a nucleus, B2MG is filtered by glomerular filtration and resorbed and decomposed in the proximal tubules.¹⁹ However, KIM-1 was uncorrelated to serum CREA. CREA is a common biomarker that is filtered by the glomerulus but is not absorbed by proximal tubules. In other words, it is a typical laboratory sign of glomerulus dysfunction. KIM-1 can be partly considered a good biomarker because it can distinguish where the dysfunction is probably in the tubule rather than the glomerulus. KIM-1 also had a relationship with kidney hormones, AngII ($r=0.47$, $p<0.05$), ALD ($r=0.45$, $p<0.05$). In general, KIM-1 is a good biomarker of kidney tubules and has extensive bonds with other biomarkers of kidney functions.

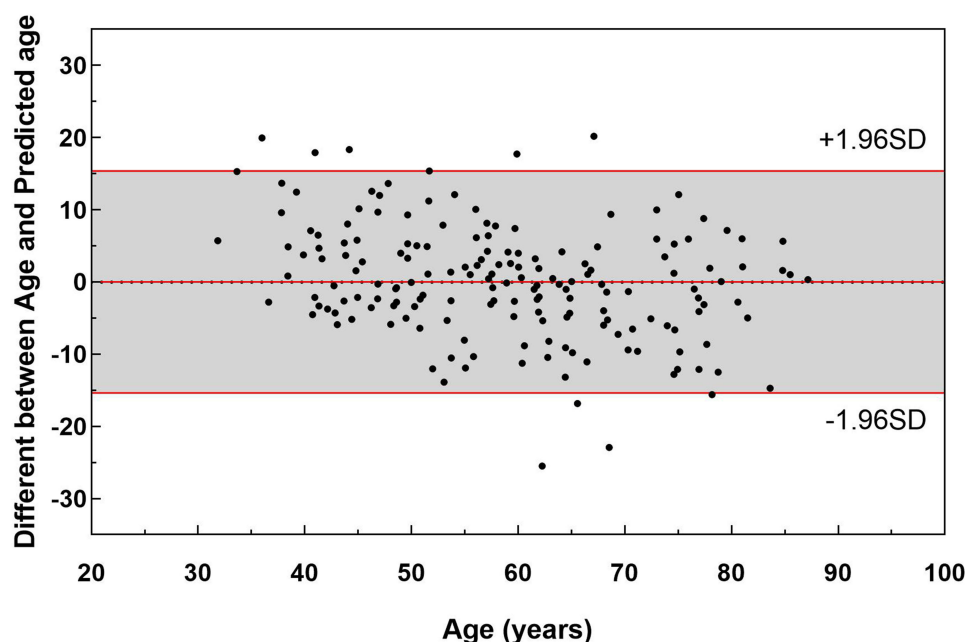
Table 2 Predicted Age of Kidney Model Construction Through Step-Wise Forward Method

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Constant	97.610	141.633	127.774	86.412	129.270	116.971	103.423	103.821
eGFR	-0.342	-0.345	-0.305	-0.186	-0.175	-0.148	-0.147	-0.160
log ₁₀ Cr/uCREA		23.516	23.040	21.130	18.710	18.268	18.412	18.019
ALD			0.056	0.059	0.055	0.059	0.060	0.053
CYSC				26.338	23.936	22.545	21.454	18.995
log ₁₀ KIM-1/uCREA					11.639	12.088	12.792	12.283
BUN						2.028	1.930	1.846
GLU							3.153	3.044
AngII								0.028
R	0.610	0.717	0.769	0.798	0.816	0.831	0.838	0.842
Adjusted R ²	0.368	0.508	0.585	0.628	0.656	0.679	0.689	0.695
Durbin-Watson								1.716

Notes: Model 1. Predictors: (constant), eGFR. Model 2. Predictors: (constant), eGFR, log₁₀Cr/uCREA. Model 3. Predictors: (constant), eGFR, log₁₀Cr/uCREA, ALD. Model 4. Predictors: (constant), eGFR, log₁₀Cr/uCREA, ALD, CYSC. Model 5. Predictors: (constant), eGFR, log₁₀Cr/uCREA, ALD, CYSC, log₁₀KIM-1/uCREA. Model 6. Predictors: (constant), eGFR, log₁₀Cr/uCREA, ALD, CYSC, log₁₀KIM-1/uCREA, BUN. Model 7. Predictors: (constant), eGFR, log₁₀Cr/uCREA, ALD, CYSC, log₁₀KIM-1/uCREA, BUN, GLU. Model 8. Predictors: (constant), eGFR, log₁₀Cr/uCREA, ALD, CYSC, log₁₀KIM-1/uCREA, BUN, GLU, AngII. Dependent variable: age.

KIM-1 Can Construct a Model to Predict Kidney Age with Other Biomarkers

Clinical biomarkers reflecting the function of organs accounted for a substantial proportion of age on disease and hospital admissions in the UK Biobank. They have the potential to be used and evaluated as a broader-based approach to risk identification and prevention.²⁰ Moreover, the biological age presented results more significant than age in patients with stroke recurrence, which means biological age was independently associated with a high risk of developing stroke recurrence.²¹ Therefore, we tried to construct a reasonable model with these typical biomarkers for evaluating kidney age. Finally, we achieved an explained variance of 69.5% and a standard error of the estimate of 7.84 years with 8 excellent biomarkers. An Immunity Clock model reached an adjusted R² of 80.3% and a standard error of 4.74 years with 5 variables.²² A DNA methylation clock reached a median absolute error of 3.6-year with the 353 CpG sites²³ and a deep learning method reached a mean absolute error of 5.5 years with 41 blood cytology and biochemistry parameters.²⁴ The

**Figure 4** The difference between age and predicted age following Bland-Altman analysis.

kidney age prediction models in Korean females and males reached the R^2 of 0.501 and 0.651, respectively.²⁵ Our results are similar but the limitations should not be ignored. Firstly, our sample size is small, although we selected nearly equal people in different age groups to eliminate the disturbance. Secondly, only kidney-related biomarkers were selected for the model. However, aging is a comprehensive and multifactorial process that can not merely be explained by any single organ or system. The age of participants considered to be kidney healthy may mix the other factors of organs and systems. More accurate and progressive mathematical methods need to be developed in the future.

Conclusions

We made several reliable and useful findings in our attempt to assess healthy kidney age. Firstly, the level of urinary KIM-1 increases and correlates to age in healthy people; Secondly, our model constructed by KIM-1 and the other 7 biomarkers can predict kidney age in healthy people; Thirdly, some injury-related biomarkers are not only meaningful in diseases but also useful in healthy people; Fourthly, age-related kidney biomarkers can be used to assess kidney age. But biomarkers must stand for the function comprehensively but collinearity each other as little as possible. Last but not the least, excellent biomarkers and strict inclusion criteria of health are the foundation of age-predicted models.

Abbreviations

$\log_{10}$ KIM-1/uCREA, urinary KIM-1 normalized by uCREA concentration; BUN, urea nitrogen; CREA, creatinine; eGFR, estimated glomerular filtration rate; MALB, urinary microalbumin; ACR, urinary albumin/creatinine ratio; GLU, blood glucose; HBA1C, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; B2MG, beta2 microglobulin; CYSC, cystatin C; AngII, aldosterone; ALD, angiotensin-2; KIM-1, kidney injury molecule-1; uCREA, urinary creatinine; $\log_{10}$ K/uCREA, urinary potassium normalized by uCREA concentration; $\log_{10}$ Na/uCREA, urinary sodium normalized by uCREA concentration; $\log_{10}$ Cl/uCREA, urinary chlorine normalized by uCREA concentration; $\log_{10}$ Ca/uCREA, urinary calcium normalized by uCREA concentration; $\log_{10}$ Mg/uCREA, urinary magnesium normalized by uCREA concentration; $\log_{10}$ P/uCREA, urinary phosphorus normalized by uCREA concentration.

Ethical Approval

Research involving human subjects complied with all relevant national regulations, and institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and has been approved by Huashan Hospital Institutional Review Board (N0.KY2020-004).

Informed Consent

Informed consent was obtained from all individuals included in this study.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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