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Kidney Age Index (KAI): A novel age-related biomarker to estimate kidney function in patients with diabetic kidney disease using machine learning

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ABSTRACT

Background and objective: With aging, patients with diabetic kidney disease (DKD) show progressive decrease in kidney function. We investigated whether the deviation of biological age (BA) from the chronological age (CA) due to DKD can be used (denoted as Kidney Age Index; KAI) to quantify kidney function using machine learning algorithms.

Methods: Three large datasets were used in this study to develop KAI. The machine learning algorithms were trained on PREVEND dataset with healthy subjects (N = 7963) using 13 clinical markers to predict the CA. The trained model was then used to predict the BA of patients with DKD using RENAAL (N = 1451) and IDNT (N = 1706). The performance of four traditional machine learning algorithms were evaluated and the KAI = BA-CA was estimated for each patient.

Results: The neural network model achieved the best performance and predicted the CA of healthy subjects in PREVEND dataset with a mean absolute deviation (MAD) = 6.5 ± 3.5 years and pearson correlation = 0.62. Patients with DKD showed a significant higher KAI of 15.4 ± 11.8 years and 13.6 ± 12.3 years in RENAAL and IDNT datasets, respectively.

Conclusions: Our findings suggest that for a given CA, patients with DKD shows excess BA when compared to their healthy counterparts due to disease severity. With further improvement, the proposed KAI can be used as a complementary easy-to-interpret tool to give a more inclusive idea into disease state.

1. Introduction

Normal aging contributes to an estimated physiological decline of glomerular filtration rate by 1 mL/min/year [1]. Lifestyle-related complications such as hyperglycemia, hypertension, dyslipidemia, albuminuria, among others, accelerate this decline at an exponential rate which directly impacts blood biochemistry, cell counts, and other molecular and cellular aspects [2]. These changes can significantly impact the biological aging of a patient with chronic kidney disease (CKD) [3] which can be different from the chronological age (CA). These changes in the biological age (BA) between individuals within the same age group may provide important information about kidney age in patients with CKD.

Currently, estimated glomerular filtration rate (eGFR) used to assess kidney functionality, and several equations to calculate eGFR have already been developed. However, a recent study demonstrates large variability in all eGFR formulae to calculate overall renal function resulting in unreliable estimations [4]. One reason is that serum creatinine used for eGFR formulae varies from day to day, and a second reason is that the coefficients used in current eGFR formulae are population-based estimated using limited data and are less efficient at an individual level. Hence, there is a need for new biomarkers and methods to more accurately identify kidney functionality at an individual level.

In recent years, several methods have already been developed to predict the CA in healthy groups using various physiological [5], imaging [6], genetic [7], molecular and cellular biomarkers [8,9]. These techniques are now being applied to unhealthy groups to provide insights about how their BA is affected by the disease severity, which can be much larger than their CA [5]. Motivated by this concept, we developed a novel age-related biomarker for estimating kidney age using machine learning techniques. We first developed a machine learning framework to accurately predict CA

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of individuals from clinical measurements without any history of cardiovascular, neurological or chronic kidney diseases in a healthy cohort. After developing the model to accurately predict the CA in healthy cohorts, we then predicted the BA of patients with diabetic kidney diseases (DKD). The deviation of the BA from the CA, denoted as Kidney Age Index (KAI) can serve as a potential biomarker to estimate kidney functionality at an individual level. We hypothesized that the BA of patients with DKD will be older when compared to their CA. KAI could reflect the functional changes in the kidney and identify factors that make a patient's BA older than their CA. To test the generalizability of this approach, we validated this framework on two independent clinical trial datasets of patients with DKD.

2. Methods

2.1. Dataset

We used datasets from three different sources in this study: PREVEND (N = 8592) [10], RENAAL (N = 1513) [5] and IDNT (N = 1715) [6]. The Prevention of Renal and Vascular End-stage Disease (PREVEND is a prospective cohort study, designed to investigate the impact of urinary albumin excretion (UAE) on renal and cardiovascular outcomes in the general population. In 1997–1998, the participants of the PREVEND cohort were selected from 40,856 inhabitants of the city of Groningen, the Netherlands. Selection was based on the albumin concentration in a spot morning urine sample to obtain a cohort enriched for the presence of elevated albuminuria levels. In total, 8592 participants completed the first screening round in 1997–1998. At approximately 3 year intervals, participants in this study are invited to visit an outpatient department for measurements concerning their health status. Details of the study protocol have been published elsewhere [10].

The Reduction of endpoints in NIDDM (Non-insulin dependent diabetes mellitus type II) and the Angiotensin II antagonist losartan (RENAAL) and irbesartan type II diabetic nephropathy trial (IDNT) investigated the efficacy of an ARB (irbesartan in IDNT, losartan in RENAAL) on renal outcomes in subjects with type 2 diabetes and nephropathy. The detailed design, rationale, and study outcome for these trials have been previously published [11–13]. The IDNT trial additionally included a calcium channel blocker (amlodipine) treatment arm. Inclusion criteria in IDNT and RENAAL were similar with only minor differences. Patients with type 2 diabetes, hypertension and nephropathy aged 30–70 years were eligible for both trials. Serum creatinine levels ranged between 1.0 mg/dL and 3.0 mg/dL. All subjects had proteinuria, defined as 24 h urinary protein excretion of > 900 mg in the IDNT trial whereas for RENAAL a urinary albumin to creatinine ratio (UACR) of > 300 mg/g based on single first morning void or a 24 h urinary protein excretion > 500 mg/day was required. Exclusion criteria for both trials were type 1 diabetes or non-diabetic renal disease. Patients in the RENAAL trial were randomly allocated to treatment with losartan 100 mg/day or matched placebo whereas patients in the IDNT trial were randomly allocated to treatment with irbesartan 300 mg/day, amlodipine 10 mg/day or matched placebo. The trials were designed to keep the dose of the ARBs stable during follow-up. Additional antihypertensive agents (but not Angiotensin Converting Enzyme inhibitors (ACEis) or Angiotensin Receptor Blockers (ARBs) in RENAAL and ACEis, ARBs, or calcium channel blocker in IDNT) were allowed during the trial to achieve the target blood pressure.

2.2. Predictive risk markers

Multiple varying number of risk markers were present in different datasets and we only used 13 baseline predictive risk markers that were available in all three datasets to train the machine learning models sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, albumin-creatinine ratio, hemoglobin, uric acid, potassium, albumin, glucose, serum creatinine and diabetes status. Supplementary Table 1 summarizes the baseline characteristics of these markers from all three datasets used in this study. Missing samples were imputed using a k-nearest neighbor algorithm. We only included subjects in the age group between 30 and 70 years due to insufficient number of samples outside this range. In addition, we excluded subjects with existing cardiovascular and renal disorders in PREVEND data to include only healthy subjects. This resulted in a total of 7963, 1451 and 1706 subjects in PREVEND, RENAAL and IDNT datasets, respectively. The percentage of risk markers imputed in all three datasets is shown in supplementary Table 2.

2.3. Machine learning model development

The outline of the machine learning model development process is shown in Fig. 1. First, we randomly divided healthy patients in the PREVEND dataset into a training set (80%, N = 6370) and testing set (20%, N = 1593). The training set was further divided into training sub-set (80%, N = 5096) and validation (20%, N = 1274) sets for tuning the machine learning model hyper-parameters. The distribution of the CA of patients in these subsets from PREVEND dataset is shown in supplementary Fig. 1. Grid search of hyper-parameters was performed to evaluate the performance of 4 machine learning algorithms logistic regression with elastic-net regularization, support vector machine, random forests and neural networks summarized in supplementary Table 3. The hyper-parameter that provided minimum mean absolute deviation (MAD) between the predicted BA and the CA was used as the optimal hyperparameter to train the machine learning model on the initial training set. In this way, the model tuning and selection was performed only on the training set and strictly excluded patients in the testing set during this process. The CA of patients in the testing set was then estimated using the tuned prediction model, and the KAI was estimated for each patient. We standardized markers in the training set to have uniform mean and standard deviation by subtracting the mean and dividing by the standard deviation. Markers in the testing set were standardized with respect to the mean and standard deviation of the training set before using them for model development.

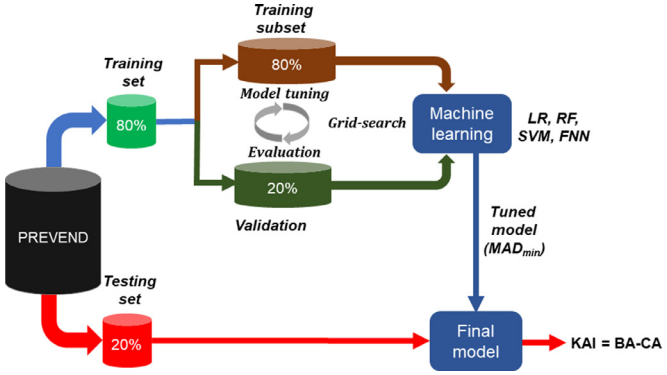

Fig. 1. Illustration of the machine learning model development process using PREVEND dataset. The performance of four traditional machine learning models: logistic regression with elastic net regularization (LR), random forest (RF), support vector machine (SVM) and feed-forward neural netrowk (FNN) were evaluated. The model that provided the least mean absolute deviation (MAD) between the predicted biological age (BA) and chronological age (CA) was used as the final optimal model to estimate Kidney Age Index (KAI).

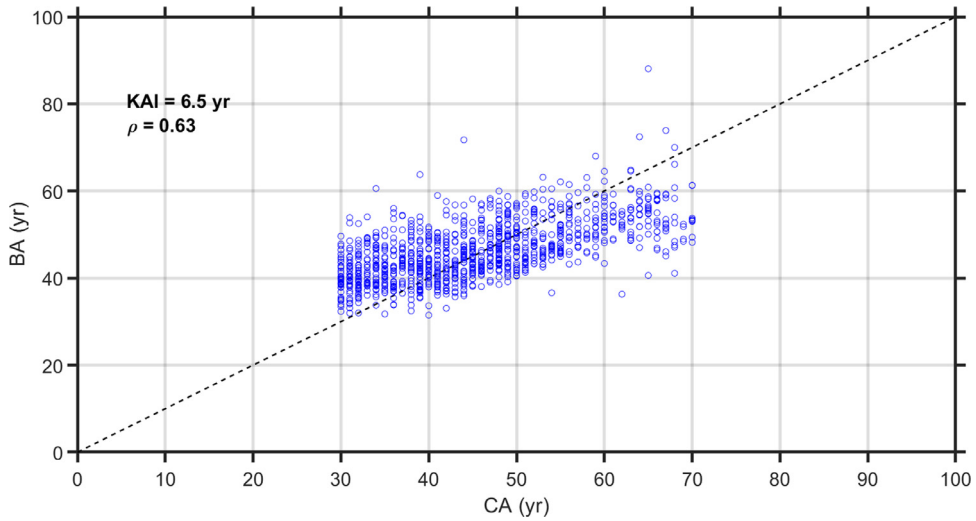

Fig. 2. Scatter plot of predicted biological age (BA) versus the chronological age (CA) for each healthy subject in PREVEND dataset using feed-forward neural network. The mean Kidney Age Index (KAI) was 6.5 years and the Pearson's correlation (ρ) was 0.62.

Table 1
Comparison of different machine learning models to predict KAI during validation and testing of healthy cohorts in PREVEND data. The best performance was obtained using the neural network model. Results are presented as mean (± standard deviation).

Testing cohort Model	Validation	Testing
Logistic regression with elastic-net regularization	8.5 (± 5.8)	8.4 (± 5.5)
Support vector machine	8.4 (± 6.5)	8.5 (± 6.6)
Random forest	7.2 (± 6.1)	7.3 (± 6.1)
Neural network	6.4 (± 3.8)	6.5 (± 3.5)

Since we used four machine learning algorithms, we identified a model that provided the least MAD on the testing set as the final optimal model. This model was then used to estimate the BA of patients with DKD and the KAI (KAI = BA-CA) was then obtained for each patient.

3. Results

All results are reported as mean ± standard deviation unless stated otherwise.

3.1. Internal validation

Table 1 summarizes the performance of machine learning models to predict CA of healthy cohorts in the PREVEND data using 13 risk markers. The neural network (NN) model outperformed other models and predicted the CA with MAD = 6.5 ± 3.5 years. Fig. 2 shows the scatter plot of predicted BA using neural networks against the CA of patients in the testing set. Pearson's correlation (ρ) between the predicted and actual CA was 0.62.

Since it was not possible to estimate predictor importance from the NN model, we estimated feature importance using elastic-net regularization and random forest methods as shown in supplementary Fig. 1. In both these methods, the level of cholesterol was the most important predictor of age followed by SBP, glucose level, and BMI. To assess the prediction importance of these markers, we removed these four predictors from the analysis and the performance of the NN model dropped by 3% (from MAD = 6.5 ± 2.5 years to 9.6 ± 3.1 years).

3.2. External validation

Next, we predicted the KAI of patients with DKD in RENAAL and IDNT datasets using the NN model, and the results are shown in Fig. 3. The MAD of BA from CA was nearly similar in both datasets: KAI = 15.4 ± 11.8 years, ρ = 0.17; KAI = 13.6 ± 12.3 years, ρ = 0.21 in RENAAL and IDNT, respectively.

The population-level comparison of KAI between patients with DKD and healthy cohorts is shown in Fig. 4. Relative to the healthy cohorts where the mean KAI was close to 0 (0.5 years), the mean KAI of patients with DKD was 11.2 and 8.5 years in RENAAL and IDNT, respectively.

3.3. Effect of cardiovascular disease

To investigate the effect of cardio vascular disease (CVD) on the KAI, we excluded all patients with a history of CVD in RENAAL and IDNT and estimated the KAI for each patient. At a population level, the KAI for patients only with DKD (RENAAL: 13.6 ± 10.2 years, IDNT: 11.5 ± 9.4 years) was 2 years lower when compared to patients with both DKD and history of CVD.

4. Discussion

In this work we developed a novel age-related biomarker, termed as Kidney Age Index (KAI), using a machine learning framework to estimate an individual's kidney age. The machine learning algorithms were initially trained on a dataset of healthy participants to predict their CA, which achieved an acceptable performance (ρ = 0.62, MAD = 6.5 ± 3.5 years). The trained model was then used to predict the BA of patients with DKD using two clinical trial datasets. For a given CA, patients with DKD have a significant older BA (i.e. higher KAI) when compared to their healthy counterparts at least by 10 years at the population level - suggesting that the presence of diabetes-related complications (i.e. renal and cardiovascular diseases) significantly affects the normal aging of an individual. Among several risk markers used for estimating KAI, the level of cholesterol, SBP, glucose level, and BMI had greater influence in elevating the BA of the patients from their CA.

The proposed machine-learning framework to estimate KAI has several clinical applications. First, it combines multiple risk markers associated with diabetic nephropathy in to a single easy-to-interpret index (termed as KAI) to estimate a patient' s deterio-

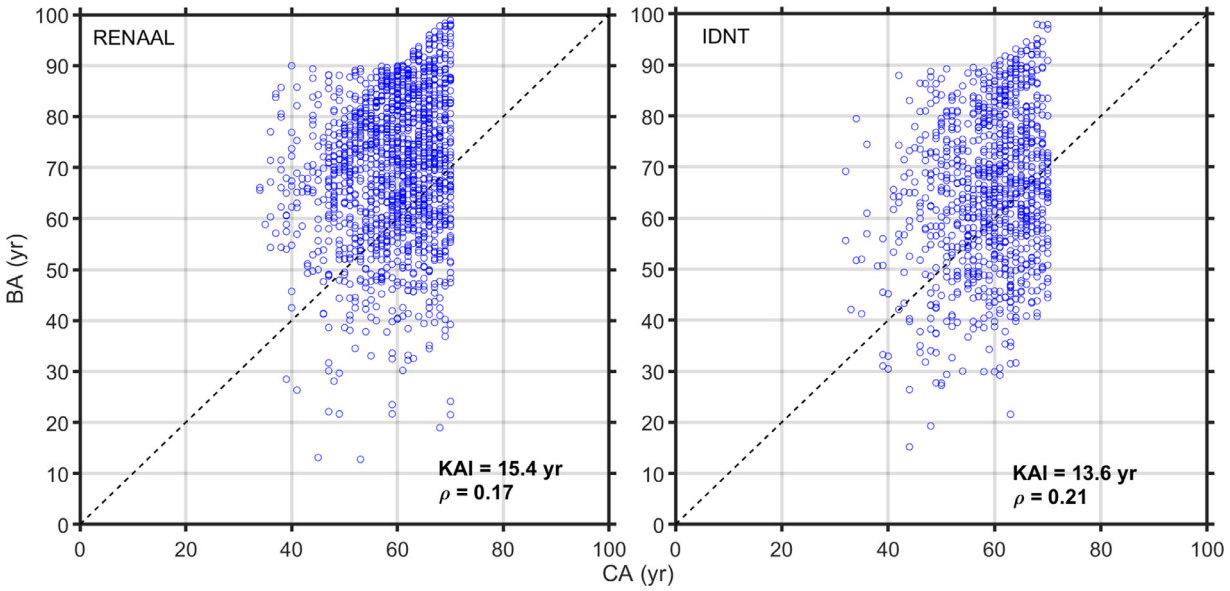

Fig. 3. Scatter plot of predicted biological age (BA) versus the chronological age (CA) for each patient with DKD in RENAAL and IDNT datasets using feed-forward neural network. The mean Kidney Age Index (KAI) = 15.4 years, Pearson's correlation (ρ) was 0.17; KAI = 13.6, ρ = 0.21 were obtained in RENAAL and IDNT, respectively.

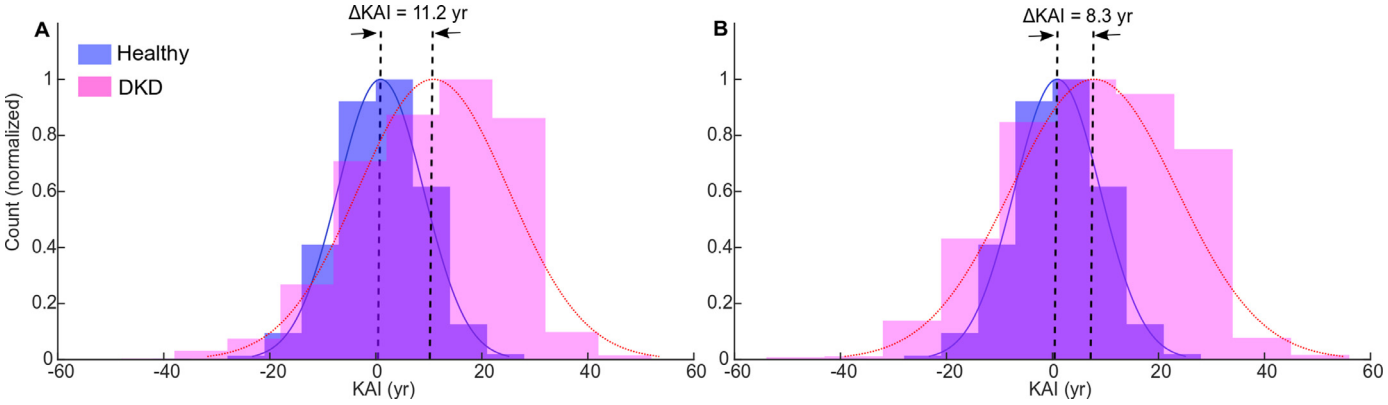

Fig. 4. Histograms of Kidney Age Index (KAI) for subjects without any diabetic kidney disease (DKD; blue) and with DKD (red). The KAI of group means is 11.2 and 8.3 years in (A) RENAAL and (B) IDNT datasets, respectively.

ration due to underlying conditions. This is not possible by expert clinicians who should interpret individual markers separately to come up with an intervention strategy. In addition, it is very difficult to identify the dependencies between the markers by clinicians. Second, it can used as a personalized patient monitoring tool where the machine learning model is retrained as and when the new measurements are available at different time intervals. Increase of decrease in KAI directly reflects the iterventiion efficacy. Third, the proposed KAI can be used as an early identification tool for patients who are a high risk of developing CKD.

DKD is a hetergeonious disease that does not always follow a predictable clinical course. Currently staging of DKD relies on two established biomarkers, eGFR and albuminuria, which their limitations have been well defined in literature [4,14–17]. In addition, it is difficult to develop a tailored therapy based only on these two biomarkers [18]. Despite their limitations, clinical diagnosis and treatment guidelines are based on eGFR and albuminuria staging [19]. However, missing from CKD staging is expected kidney function appropriate to age [20,21]. It is generally accecpted that the effect of normal aging processes results in a kidney function decrease of 1 mL/min/year, and oftentimes clinicians must subjectively make the age and disease approriate calculation of kidney function. This ambuguity around age-appropriate kidney function can lead to non-optimal treatment plans and/or miscommunication with patients, among other issues.

Kidney disease includes a wide range of kidney health states from commonly prevalent subclinical, asymptomatic disease to rare end-stage renal disease requiring dialysis or kidney transplantation. Early stage CKD in older patients is normal and can be managed in primary care settings [22]. However, studies have shown that many patients find being informed of their CKD distressing, even in its early stages [20]. KAI has the potential to help clinicians explain actual kidney health in context of the actual clinical situation in a more easy to understand manner than CKD stage or renal function. Instead of focusing on only one or two biomarkers (i.e. eGFR or albuminuria), the focus can be on the contribution of multipanel biomarkers to the overall health status [18]. For example, a health care provider could tell their patient that their kidney age is 5–10 years older than their actual age, and this identified deviation (KAI) can lead to a discussion for further monitoring or preventative measures for risk of cardiovascular disease or end-stage renal disease. The message of kidney age is clear and easily understood by patients, and it is not a confusing, abstract, or mathematical concept like absolute risk [20]. Accordingly, KAI can be used to improve medication adherence and better communicate risk.

Expectedly, KAI was higher in patients with DKD compared to healthy patients. DKD is based in part by a (more than average) progressive decline in kidney function, the presence of albumin in urine, high blood pressure, and metabolic disturbances. Notably, DKD remains one of the most frequent complications of diabetes, and diabetes is the leading cause of end-stage renal disease (ESRD), accounting for approximately 50% of cases in the developed world [17]. Development of DKD is associated with many alterations in the structure of multiple kidney compartments, all of which have an impact on (patho) physiology and aging processes [23].

The machine learning model identified total cholesterol, blood pressure, BMI, and glucose were the strongest predictors in the machine learning algorithm. This comes of no surprise as these four markers are viewed as "traditional" risk factors in the progression of DKD [17]. However, these four markers could be viewed as a proxy for lifestyle and can be viewed as modifiable. Treatment plans aimed at lowering cholesterol and blood pressure to more healthy leaves, incorporating nutritional and fitness plans to achieve a healthy body weight, and regulating glucose levels are all accepted actions be improve renal and cardiovascular risk.

It should be noted that though many of the identified markers are modifiable (such as BMI, BP, TC, glucose), a number of other markers are not easily modifiable, or are a risk markers instead of a risk factors (or both). The cumulative consequences of these risk factors have more wide spread endothelial (cardiovascular) effects, which can cause renal dysfunction, but are not specific to only kidney function as the diabetes and its complications are multi-factorial. A person with diabetes often is overweight, has high blood pressure, high cholesterol, high glucose levels, etc. This further reiterates our conclusions that many markers are needed to accurately predict renal risk in diabetes and that the total set of markers together is a better predictor than any single marker. In several cases, it is possible that individuals who have a more unfavorable profile of risk factors have not developed renal or cardiovascular disease, or vice versa. The difficulty of renal and cardiovascular disease is that presence of these risk factors does not necessarily imply an unconditional cause and effect for disease. Alternatively, individuals with high risk factors may not have had enough time to develop renal or cardiovascular disease (long enough follow-up time). Our study aims at prediction of kidney age (as we include data from patients with diabetic nephropathy), and is not designed to identify the causal pathways of renal and cardiovascular disease.

The main strength of our study is that we used three independent datasets for model development and validation. Training the model on a healthy cohort is important to estimate KAI in patients with DKD, and we achieved this using PREVEND dataset. However, we could not achieve perfect age prediction (MAD = 6.5 ± 3.5 years). Validating the performance of the model using a large testing set is important to evaluate the robustness and stability of the model, and we achieved this using datasets from two large clinical trials–RENAAL and IDNT. Another strength is that used of machine learning algorithms instead of traditional parametric or knowledge driven approach. Machine learning algorithms can directly learn from the data and can captures interactions between multiple markers which cannot be achieved using traditional approaches.

Despite promising results, there are several limitations of this study, and the proposed model is not yet ready for clinical deployment. (1) We only included patients between 30 and 70 years due to limited number of patients beyond this range. (2) We did not achieve perfect age prediction in healthy subjects due to limited sample size (see supplementary Fig. 2). This led to higher BA estimation in younger patients (in Fig. 2) which we believe is due to the poor model performance. Including additional samples and /or markers can help in significantly improving the prediction performance of the model. (3) Further improvement and external validation of the KAI, and determining feasibility of using such a tool in clinical practice (in addition to eGFR and/or albuminuria) with health care providers and patients are of course necessary next steps for the development of KAI. In addition, since this is a proof-of-concept study to develop a framework, we only evaluated the performance of commonly used four traditional machine learning algorithms. Future work involves evaluating the performance of additional machine learning algorithms such as boosting algorithms, extreme learning machines etc.

5. Conclusions

We developed a novel age-related biomarker, denoted as KAI, using a machine learning framework to estimate an individual's kidney age. Our findings suggest that for a given CA, patients with DKD shows excess BA patients by approximately 10 years than the population level when compared to their healthy counterparts. This excess is most likely due to disease severity, as the KAI's composition of multiple clinical markers allows for a better representation of disease state that just age or renal function alone. With further improvement, the proposed machine learning based novel age related biomarker can be used as a tool to discuss with patients with DKD about their risk of renal and CV disease in a more easy to grasp, conceptual manner than absolute risk or laboratory values.

Declaration of Competing Interest

All authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cmpb.2021.106434.

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