ORIGINAL ARTICLE

Visit-to-visit variability in albuminuria predicts renal function deterioration in patients with type 2 diabetes

Chih-Hung Lin[1,2] iD, Ying-Chuen Lai[1,2], Tien-Jyun Chang[1] iD, Yi-Der Jiang[1], Yi-Cheng Chang[1,3,4], Lee-Ming Chuang[1,2,5]* iD

[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan, [2]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan, [3]Graduate Institute of Genomics and Proteomics, College of Medicine, National Taiwan University, Taipei, Taiwan, [4]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, and [5]Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

ABSTRACT

Aims/Introduction: We aimed to study the predictive ability of visit-to-visit variability in albuminuria for changes in renal function in patients with type 2 diabetes mellitus.

Materials and Methods: The cohort study was carried out in a single medical center. In the model development cohort of 1008 subjects, we developed the albuminuria variability score (AVS) to evaluate the visit-to-visit variability in albuminuria, which was the percentage of the number of changes in the urine albumin : creatinine ratio ≥3.39 mg/mmol among all visit-to-visit urine albumin : creatinine ratio differences within an individual. Multivariate logistic regression was applied to predict the influence of AVS levels on the occurrence of study end-points. In another independent validation cohort of 310 participants, survival analysis was carried out to evaluate the ability of AVS in predicting the study end-point.

Results: In the model development cohort, a higher AVS was associated with higher adjusted odds of having a declined or rapidly declined estimated glomerular filtration rate (eGFR) trajectory (1.84, 95% confidence interval 1.23–2.76 and 5.70, 95% confidence interval 2.28–14.25, respectively), a resultant eGFR <60 mL/min/1.73 m^2 (2.61, 95% confidence interval 1.63–4.16) and a >40% decline in eGFR from baseline (6.44, 95% confidence interval 2.15–19.26). In the validation cohort, a higher AVS independently predicted a 5-year decrease of >40% in eGFR to <60 mL/min/1.73 m^2 (adjusted hazard ratio 3.33, 95% confidence interval 1.10–10.05). Integrated discrimination index and concordance statistics showed that AVS significantly improved the predictive ability of the models.

Conclusions: Visit-to-visit variability in albuminuria can independently predict long-term renal function deterioration in patients with type 2 diabetes mellitus. Further investigations are warranted to elucidate the potential clinical applications.

INTRODUCTION

The global prevalence of diabetes-associated chronic kidney disease (CKD) has grown tremendously in recent years, and remains the leading cause of end-stage renal disease worldwide[1–3]. The clinical diagnosis of CKD in patients with diabetes is made on the basis of the laboratory findings that suggest deteriorated renal function or the presence of markers of renal damage, such as increased urine albumin excretion (UAE). Increased UAE, also known as albuminuria, is regarded as a predictor of renal complications in both type 1 and 2 diabetes patients[4]. In patients with type 2 diabetes mellitus, small increases in UAE (30–300 mg/24 h, termed microalbuminuria) predict the development of overt proteinuria[5], whereas pronounced elevations in UAE (≥300 mg/24 h, termed macroalbuminuria) show an even more distinct association with rapid renal function decline and the development of end-stage renal disease[6,7].

One major obstacle in using albuminuria as a clinical predictor is its high intra-individual variation. Studies showed that the intra-individual coefficient of variation (CV) of UAE ranges from 20% to 50% in patients with diabetes[4]. An elevation in UAE might be induced by various causes, such as damage of glomerular basement membrane and podocytes caused by the diabetic milieu[8], or other conditions, including physical activity, infection, fever, congestive heart failure and menstruation[9]. In recent years, the standard care for patients with type 2 diabetes mellitus incorporates the use of renin–angiotensin–aldosterone system (RAAS) blockers, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors, which show the potential of improving albuminuria in patients with type 2 diabetes mellitus[10–16]. However, spontaneous improvement of albuminuria in these patients without specific treatment is not a rare phenomenon[17]. It is apparent that from visit-to-visit, certain differences in the measured values of albuminuria within an individual can be observed. Considering all the aforementioned factors related to change in UAE, it is plausible that such difference in albuminuria between visits could correlate with fluctuation in the homeostasis of renal microenvironment. Nevertheless, knowledge about the clinical significance of visit-to-visit variability in albuminuria (VVVa) is only limited to patients with type 1 diabetes[18]. The aim of the present study was to evaluate the association and predictive ability of VVVa for renal function changes in patients with type 2 diabetes mellitus, to assess the value of VVVa in clinical practice.

MATERIALS AND METHODS

Study participants in the model development and validation cohorts

The present cohort study was carried out at a single medical center in northern Taiwan. For the model development cohort, the medical records of patients with clinically diagnosed type 2 diabetes mellitus who participated in the Diabetes Shared Care Network and received regular follow up in the outpatient clinic between October 2008 and September 2018 were reviewed (median [interquartile range; IQR] number of visits 8 [6–9]). For the validation cohort, the data from the participants of another independent prospective study that aimed for the development of novel CKD biomarkers in diabetes between November 2011 and February 2020 were acquired (number of visits 17). Renal functions were assessed using the estimated glomerular filtration rate (eGFR) calculated with the Chronic Kidney Disease Epidemiology Collaboration equation[19]. The severity of albuminuria was determined on the basis of the urine albumin : creatinine ratio (UACR) in a random spot urine sample, which is generally considered to be a proper surrogate for 24-h UAE[20]. Patients with baseline eGFR $\geq$60 mL/min/1.73 m^2 and UACR <33.9 mg/mmol were eligible for the present study, whereas those without a consecutive follow up of at least 3 years were excluded. The study protocols were reviewed and approved by the Research Ethics Committee of the National Taiwan University Hospital (approval nos. 202002013RINC and 201107004RC, respectively), and carried out in accordance with the Declaration of Helsinki.

Measurements and data collection

Calibrated instruments were used to measure height, body-weight and blood pressure. Blood samples were collected after an overnight fast. Glycated hemoglobin (HbA$_{1c}$) concentrations were measured using high-performance liquid chromatography (HLC-723 G7 HPLC systems; Tosoh, Tokyo, Japan), which was certified according to the National Glycohemoglobin Standardization Program, and standardized to the Diabetes Control and Complications Trial reference assay. Biochemical profiles were measured by an automated analyzer (Toshiba TBA-200FR; Toshiba Medical Systems Co., Tokyo, Japan). Blood and urine creatinine levels were measured using the kinetic Jaffe method. Urinary albumin concentrations were measured using turbidimetric immunoassay. The complete physiological and biochemical profiles of the participants were documented once every year in the model development cohort and once every 6 months in the validation cohort. The changes in eGFR were calculated on the basis of the Chronic Kidney Disease Epidemiology Collaboration equation.

Albuminuria variability score

For an intuitive assessment of the VVVa, we developed a new scale named the albuminuria variability score (AVS), which adopted the concept of the HbA$_{1c}$ variability score in previous studies[21,22]. AVS is the count of measures within an individual where the UACR has changed, either increased or decreased by a certain degree, from the prior measured value as a percentage of the total number of visit-to-visit UACR differences during the follow-up period. In the model development cohort, UACR values in all visits were used for AVS calculation, with the thresholds of UACR change (ΔUACR) set at $\geq$3.39, $\geq$5.65, $\geq$8.48 and $\geq$11.30 mg/mmol for clinical practicability. Initially, participants were divided into the low and high AVS groups by the median value of AVS. To determine the optimal ΔUACR, the area under the receiver operating characteristic curve was used to compare end-point discriminations between high and low AVS values calculated using different ΔUACRs. In the validation cohort, the study period was truncated at visit 6. The UACR values in the first six visits were used to calculate AVS, whereas the visits after visit 6 were considered as the follow-up period. A flowchart of this study is presented in Figure S1. For comparison with a commonly used marker of variability, the participants were also divided into low and high CV groups by the median of UACR CV.

Study definitions and end-points

Hypertension was defined as a systolic blood pressure $\geq$130 mmHg, a diastolic blood pressure $\geq$80 mmHg or use of any kind of antihypertensive agent[23]. Use of an insulin secretagogue was defined as a prescription consisting of sulfonylurea

or glinide. Use of a RAAS blocker was defined as a prescription consisting of an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or aldosterone antagonist. The mean UACR was defined as the mean of the UACR measured during AVS calculation period. An increasing trend in the UACR was defined as a higher last UACR compared with the first UACR during the AVS calculation period.

Group-based trajectory modeling is a specialized application of finite mixture modeling that determines trends in longitudinal data by identifying clusters of individuals with similar data evolution over time[24]. We applied group-based trajectory modeling to analyze the trajectories of eGFR in the model development cohort (see the "Statistical analysis" section). According to the patterns of changes in eGFR, the trajectories were divided into stationary, declined and rapidly declined groups (Figure S2). The median (IQR) of the mean annual changes in eGFR (mL/min/1.73 m^2) of the stationary, declined, and rapidly declined eGFR trajectory groups were −0.1 (−0.7 to 1.1), −2.2 (−3.2 to −0.6) and −5.4 (−7.0 to −4.1), respectively. The declined and rapidly declined trajectories were included as study end-points. A resultant eGFR <60 mL/min/1.73 m^2 and a >40% decline in eGFR from baseline were also included as study end-points.

Statistical analysis

The group-based trajectory modeling of eGFR was carried out using a censored normal distribution, with the censors set at values well beyond the range of any data values (minimum eGFR = 0 mL/min/1.73 m^2 and maximum eGFR = 150 mL/min/1.73 m^2). A repeated trajectory analysis was carried out by gradually increasing the number of groups. The Bayesian information criterion was used to estimate the number of trajectory patterns. The number of groups with the highest Bayesian information criterion was considered the most appropriate. After the number of groups was decided, each group of trajectories was further tested as linear, quadratic or cubic to confirm the accurate graphical shape of change in eGFR by selecting the highest polynomial order to best characterize each trajectory group. The fitness of the trajectory models was diagnosed using the following criteria: (i) an average posterior probability >0.7; (ii) an odds of correct classification >5; and (iii) a close correspondence between the estimated probability and the proportion assigned according to the maximum posterior probability assignment rule[24].

Skewed continuous variables were presented as medians and IQRs. Categorical variables were reported as numbers and percentages. The Mann–Whitney U-test and χ^2-test were used to analyze the differences in clinical characteristics between the groups. In the model development cohort, multiple logistic regression was applied to predict the influence of AVS levels on the occurrence of study end-points. Simple and multiple linear regression models were applied to predict the effects of baseline clinical profiles on the average annual eGFR change, and the predictive margins of low or high AVS at different baseline eGFR were calculated[25]. In the validation cohort,

survival analysis of the AVS groups was carried out with Kaplan–Meier methods and tested by a log-rank test. Multivariate Cox proportional hazard models were carried out to evaluate the hazard ratios (HRs). The logistic regression and Cox proportional hazard models were adjusted for age, sex, body mass index, smoking, hypertension, use of RAAS blockers, eGFR (mL/min/1.73 m^2), HbA$_{1c}$, baseline and mean UACR (mg/mmol), and an increasing trend in UACR (yes vs no). Integrated discrimination index[26] and concordance statistics were used to evaluate the effect of incorporating different predictors into the predictive models. A two-tailed P-value <0.05 was considered statistically significant. Stata 14.0 for Windows (StataCorp LP, College Station, TX, USA) was used for statistical analyses.

RESULTS

Baseline clinical characteristics

The model development cohort consisted of 1,008 participants, of whom 500 belonged to the low AVS group, and 508 belonged to the high AVS group. The median (IQR, range) age was 60 years (53–67 years, 21–90 years). The median (IQR) follow-up period was 7.3 years (5.6–7.6 years). In the validation cohort consisting of 310 participants, the numbers (%) of participants having an AVS value of 0, 20, 40 and 60 were 256 (83), 31 (10), 20 (6) and 3 (1), respectively. By the AVS cut-off of 16.7, the validation cohort was divided into the low and high AVS groups comprising of 256 and 54 participants, respectively. The median (IQR, range) age was 63 years (56–69 years, 25–85 years). The median (IQR) follow-up period was 5.4 years (4.9–5.4 years). The baseline characteristics of the participants are shown in Table 1. There were only a few participants treated with sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, so these two variables were removed in the subsequent analyses. Participants in the high AVS groups of both cohorts had higher body mass index and prevalence of hypertension. They also had higher baseline UACR levels. The proportion of male participants and HbA$_{1c}$ level were higher in the high AVS group of the model development cohort. The proportion of RAAS blocker use was higher in the high AVS group of the validation cohort. There was no significant difference in age and baseline eGFR between the low and high AVS groups of both cohorts.

Discriminant power of AVSs calculated using different ΔUACRs

The event numbers (%) of the different study end-points in the low and high AVS groups calculated using ΔUACR ≥3.39, ≥5.65, ≥8.48 and ≥11.30 mg/mmol in the model development cohort are shown in Table S1. The area under the receiver operating characteristic curves of the high versus low AVS for reaching a specific study end-point after adjusting for baseline age, sex, UACR and eGFR are shown in Table 2. The median (IQR) of ΔUACRs documented in the model development cohort was 0.7 mg/mmol (0.2–2.6 mg/mmol), which led to a

Table 1 | Baseline characteristics of the study subjects in the model development and validation cohort

	Development cohort		Validation cohort	
	Low AVS $n = 500$	High AVS $n = 508$	Low AVS $n = 256$	High AVS $n = 54$
Age (years)	60 (53–67)	60 (53–68)	63 (56–69)	64 (57–70)
Male, n (%)	281 (57)	246 (48)*	151 (59)	25 (46)
Duration (years)	10 (7–15)	9 (6–14)	13 (10–18)	13 (9–19)
Follow-up period (years)	7.4 (6.5–7.8)	6.6 (4.7–7.5)*	5.4 (4.9–5.4)	5.4 (4.9–5.4)
BMI (kg/m^2)	24.5 (22.4–26.7)	25.6 (23.1–28.4)*	24.2 (21.9–26.2)	25.9 (23.3–27.7)*
SBP (mmHg)	130 (120–140)	130 (120–140)*	129 (120–135)	133 (128–140)*
DBP (mmHg)	75 (70–80)	80 (70–85)*	75 (69–80)	77 (70–85)*
Hypertension, n (%)	311 (62)	369 (73)*	182 (71)	49 (91)*
Smoking status, n (%)				
Smoker	60 (12)	59 (12)	30 (12)	6 (11)
Ever-smoker	79 (16)	78 (15)	47 (19)	8 (15)
HbA$_{1c}$ (%)	7.0 (6.5–7.5)	7.2 (6.6–7.9)*	7.0 (6.6–7.5)	7.1 (6.5–8.0)
eGFR (mL/min/1.73 m^2)	81 (72–93)	84 (71–96)	90 (76–97)	84 (65–99)
UACR (mg/mmol)	1.0 (0.7–1.7)	2.1 (0.9–6.0)*	0.9 (0.6–1.7)	6.2 (2.5–11.7)*
TC (mmol/L)	4.6 (4.0–5.1)	4.4 (3.9–5.1)*	4.2 (3.6–4.6)	4.1 (3.5–4.8)
LDL-C (mmol/L)	2.4 (2.0–2.8)	2.4 (1.9–2.8)	2.5 (2.0–2.8)	2.4 (2.0–2.7)
HDL-C (mmol/L)	1.2 (1.0–1.4)	1.1 (1.0–1.3)*	1.2 (1.0–1.3)	1.2 (1.0–1.3)
TG (mmol/L)	2.7 (1.9–3.7)	3.1 (2.1–4.6)*	2.9 (2.1–3.9)	3.5 (2.2–5.7)*
Use of medications, n (%)				
Insulin secretagogue	345 (69)	337 (66)	168 (66)	35 (65)
Metformin	427 (86)	449 (88)	218 (85)	44 (81)
Thiazolidinedione	118 (24)	94 (19)*	4 (2)	1 (2)
α-Glucosidase inhibitor	13 (3)	18 (4)	5 (2)	0 (0)
DPP-4 inhibitor	17 (3)	45 (9)*	34 (13)	8 (15)
Insulin	65 (13)	122 (24)*	47 (18)	14 (26)
β-Blocker	38 (8)	59 (12)*	41 (16)	12 (22)
Calcium channel blocker	80 (16)	130 (26)*	53 (21)	20 (37)*
RAAS blocker	199 (40)	223 (44)	115 (45)	37 (69)*
Diuretic	18 (4)	28 (6)	17 (7)	2 (4)
Statin	193 (39)	235 (46)*	122 (48)	22 (41)
Antiplatelet agent	78 (16)	91 (18)	54 (21)	14 (26)

Data are shown in the median (25th–75th percentile) or number (%). BMI, body mass index; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; HbA$_{1c}$, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UACR, urine albumin : creatinine ratio. *Significantly different ($P < 0.05$) from the low albuminuria variability score (AVS) group.

very similar distribution pattern of AVS calculated by the pre-defined ΔUACRs. As low and high AVS were defined according to the median of AVS, increasing ΔUACR from ≥3.39 to ≥11.30 mg/mmol did not show a significant change in the discriminant power of study end-points. As a result, the ΔUACR threshold of ≥3.39 mg/mmol was selected for AVS calculation, and the cut-off value of low and high AVS was set at 16.7, which was the median of AVS calculated by ΔUACR ≥3.39 mg/mmol.

Higher AVS was associated with poorer renal outcomes

We carried out multiple logistic regression to analyze the influence of AVS and UACR CV on the occurrence of different study end-points in the model development cohort. Compared

with the participants with a low AVS, the crude and adjusted odds ratios (95% confidence intervals [CIs]) in the participants with a high AVS were 1.73 (1.23–2.43) and 1.84 (1.23–2.76) for having a declined eGFR trajectory, 5.56 (2.70–11.48) and 5.70 (2.28–14.25) for having a rapidly declined eGFR trajectory, 2.83 (1.95–4.12) and 2.61 (1.63–4.16) for reaching a resultant eGFR <60 mL/min/1.73 m^2, and 5.53 (2.44–12.53) and 6.44 (2.15–19.26) for having a >40% decline in eGFR from baseline, respectively. In contrast, participants with a high CV had consistently higher crude and adjusted odds than participants with a low CV only for reaching a resultant eGFR <60 mL/min/1.73 m^2. The results are presented in Figure 1. The improvement of model prediction with the incorporation of AVS is shown in Table S2. To minimize the effect of baseline UACR

Table 2 | Area under the receiver operating characteristic curve for specific study end-points of above versus below median albuminuria variability scores defined by different urine albumin : creatinine ratio changes in the model development cohort

	AUROC	SE	95% CI
Declined eGFR			
ΔUACR ≥3.39 mg/mmol	0.7734	0.0188	0.7366–0.8102
ΔUACR ≥5.65 mg/mmol	0.7734	0.0189	0.7363–0.8106
ΔUACR ≥8.48 mg/mmol	0.7734	0.0189	0.7363–0.8106
ΔUACR ≥11.30 mg/mmol	0.7744	0.0189	0.7373–0.8115
Rapidly declined eGFR			
ΔUACR ≥3.39 mg/mmol	0.8344	0.0254	0.7845–0.8842
ΔUACR ≥5.65 mg/mmol	0.8343	0.0249	0.7855–0.8831
ΔUACR ≥8.48 mg/mmol	0.8343	0.0249	0.7855–0.8831
ΔUACR ≥11.30 mg/mmol	0.8262	0.0279	0.7715–0.8808
Resultant eGFR <60 ml/min/1.73 m^2			
ΔUACR ≥3.39 mg/mmol	0.8537	0.0160	0.8222–0.8851
ΔUACR ≥5.65 mg/mmol	0.8513	0.0163	0.8195–0.8832
ΔUACR ≥8.48 mg/mmol	0.8513	0.0163	0.8195–0.8832
ΔUACR ≥11.30 mg/mmol	0.8472	0.0172	0.8135–0.8808
Resultant eGFR decline >40% from baseline			
ΔUACR ≥3.39 mg/mmol	0.8283	0.0327	0.7643–0.8924
ΔUACR ≥5.65 mg/mmol	0.8259	0.0311	0.7649–0.8870
ΔUACR ≥8.48 mg/mmol	0.8259	0.0311	0.7649–0.8870
ΔUACR ≥11.30 mg/mmol	0.8064	0.0376	0.7328–0.8800

AUROC, area under the receiver operating characteristic; CI, confidence interval; eGFR, estimated glomerular filtration rate; SE, standard error; UACR, urine albumin : creatinine ratio.

difference, the influence of AVS on the occurrence of different study end-points was analyzed in 774 participants with a baseline UACR <3.39 mg/mmol. Compared with the 460 participants with a low AVS, the adjusted odds ratios (95% CIs) in the 314 participants with a high AVS were 6.29 (2.21–17.89) for having a rapidly declined eGFR trajectory, 2.12 (1.25–3.59) for reaching a resultant eGFR <60 mL/min/1.73 m^2 and 4.31 (1.20–15.45) for having a >40% decline in eGFR from baseline, respectively.

Relationship between AVS and average annual change in eGFR

A simple regression analysis was carried out for each independent variable that potentially had an impact on renal function separately to assess its correlation with the average annual change in eGFR. As shown in Table S3, the average annual change of eGFR was negatively correlated with age, body mass index, eGFR, UACR, high AVS, hypertension and use of RAAS blockers. In the multiple regression analyses, age, eGFR, UACR, high AVS and hypertension remained as independent factors correlated with average annual change of eGFR. The predictive average annual changes in eGFR of low or high AVS at different eGFR levels are presented in Figure S3. The result showed a more prominent predictive average annual eGFR decline in

the high AVS group as compared with the low AVS group across all levels of baseline eGFR.

Predictive ability of AVS for 5-year renal function deterioration

During the follow up of the validation cohort, 12 and 10 end-point events were observed in the low and high AVS groups, respectively. The Kaplan–Meier survival curves are presented in Figure 2a. Compared with participants with low AVS, participants with high AVS had a higher risk of reaching a composite end-point of a >40% decline in eGFR to <60 mL/min/1.73 m^2. The crude and adjusted HRs (95% CIs) were 4.36 (1.88–10.10) and 3.33 (1.10–10.05), respectively. In contrast, neither the crude nor adjusted HR of reaching the composite end-point between the high and low CV groups was statistically significant. The results are shown in Figure 1. With the incorporation of AVS, the predictive ability of the fully-adjusted model to distinguish paired participants (one had a >40% decline in eGFR to <60 mL/min/1.73 m^2 and one did not) increased from 70% to 76%. With different variables added into the model in a stepwise fashion, AVS (high vs low) consistently increased the concordance statistics. For a double validation of its predictive ability, the validation cohort was further truncated at visit 3 (1 year from the observation baseline), and a new set of AVS was calculated according to the first two ΔUACRs documented. As shown in Figure 2b, in the remaining median (IQR) follow-up period of 4.5 years (4.0–4.5 years), participants with a high AVS had a higher risk of reaching the composite end-point of a >40% decline in eGFR to <60 mL/min/1.73 m^2 compared with the participants with a low AVS. The crude and adjusted HRs (95% CI) were 3.51 (1.42–8.71) and 4.67 (1.46–14.93), respectively.

DISCUSSION

The effects of long-term fluctuations in various clinical parameters on the outcomes of diabetes have gradually gained attention in recent years. Several studies have reported the association between VVV in blood pressure and the development or progression of CKD[27–31], the risk of cardiovascular diseases[32], and all-cause mortality[32,33]. An increase in either fasting glucose or HbA$_{1c}$ VVV could predict the future development of vascular events and all-cause mortality[22,31,33,34]. In patients with type 2 diabetes mellitus, VVV in low-density lipoprotein cholesterol was an independent determinant of carotid intima-media thickness[35]. To the best of our knowledge, this is the first study to focus on the effects of VVVa on the prediction of long-term renal function deterioration in patients with type 2 diabetes mellitus.

The findings in the aforementioned studies show the importance of maintaining physiological and biochemical homeostasis in managing patients with diabetes. Fluctuations in blood pressure or blood glucose might lead to the emergence of oxidative stress and inflammatory response, which have a negative impact on disease outcomes. In patients with diabetes, one of
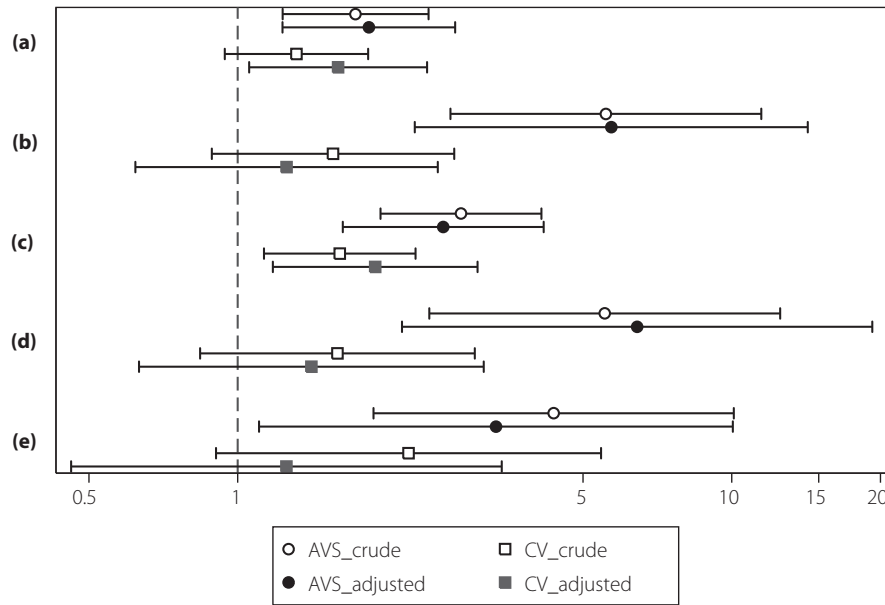
Figure 1 | Graphical summary of the present study showing the odds ratios (95% confidence intervals) for (a) having a declined estimated glomerular filtration rate (eGFR) trajectory, (b) having a rapidly declined eGFR trajectory, (c) resultant eGFR <60 mL/min/1.73 m^2 and (d) resultant eGFR decline >40% from baseline in the model development cohort, and (e) the hazard ratio (95% confidence interval) of reaching the composite end-point of a > 40% decline in eGFR to <60 mL/min/1.73 m^2 in the validation cohort. Circle, high versus low albuminuria variability score (AVS); square, high versus low coefficient of variation (CV); white, crude value; black, adjusted value.
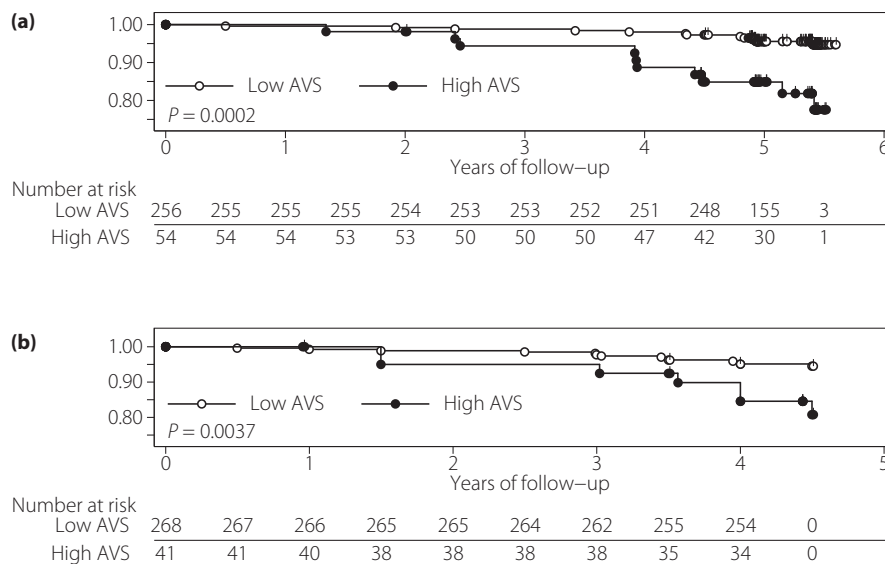

Figure 2 | The Kaplan–Meier survival curves by albuminuria variability score (AVS) for a > 40% decline in estimated glomerular filtration rate to <60 mL/min/1.73 m^2 in the (a) original and (b) truncated validation cohort

the important factors related to the progression of CKD is intraglomerular pressure[36]. As UAE is correlated with the level of intraglomerular pressure[37], a fluctuation in the level of albuminuria might indicate an unsteady intraglomerular pressure, which could bring unfavorable effects on the pathogenesis of CKD in patients with diabetes.

The presence of albuminuria is generally considered as a marker of CKD. However, acute damage to the glomerulus or

proximal tubule could also interfere with the filtration or reabsorption of urine albumin[38]. In the cohort of the Atherosclerosis Risk in Communities (ARIC) study, higher UAE was positively and independently associated with the risk of development of acute kidney injury (AKI)[39]. In the animal model of toxin-induced renal tubular injury, early elevation of urine albumin level was observed[40]. Ware *et al*.[41] showed an elevated expression of albumin gene in the renal cortex of experimental AKI animal models, and an increased urinary albumin excretion in patients with AKI. Such evidence shows the probability of albuminuria as a marker of AKI. In the present study, a higher AVS represented more frequent fluctuations in the level of albuminuria, which could also reflect the frequency of repeated acute injuries to the kidneys. As previous studies have shown that AKI episodes can accelerate the progression of CKD[42,43], it could be another explanation why individuals with a higher AVS had poorer renal outcomes. Further studies are required to validate such hypothesis.

The major strength of the present study was to develop a simple scoring system to evaluate VVVa, and provide evidence of the effect of VVVa on renal function deterioration in patients with type 2 diabetes mellitus. Many studies applied the standard deviation or CV of a clinical parameter to describe its variability, which would involve sophisticated calculations and thus limit its use in daily practice. The application of AVS, on the contrary, could provide a clearer and more intuitive picture of the VVVa. It also provides additional information to the prediction of renal function deterioration in patients with type 2 diabetes mellitus by routine clinical parameters, such as UACR and eGFR. The present study, however, was subject to a few limitations. First, despite a high AVS independently predicting a significant decline in eGFR in 5 years, due to the limited study population and duration, we were unable to evaluate the predictive ability of AVS on hard renal outcomes, such as end-stage renal disease, although we used the strict surrogate end-point of a >40% decline in eGFR to <60 mL/min/1.73 m^2. Second, owing to the limited use of glucagon-like peptide-1 receptor agonists and SGLT2i in the present study, the effect of these novel antihypoglycemic agents with renoprotective potential cannot be evaluated by AVS analysis and deserves future study. Third, the AVS developed and validated in the present study was based on a longer observation interval. Whether the fluctuation of albuminuria within a shorter duration could reproduce similar results for the prediction of renal function deterioration remains to be further clarified.

In conclusion, the present study shows that VVVa can independently predict long-term renal function deterioration in patients with type 2 diabetes mellitus. Further investigations are warranted to elucidate the underlying mechanisms and potential clinical use in precision management and prevention of renal function deterioration in patients with type 2 diabetes mellitus.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study protocols were reviewed and approved by the Research Ethics Committee of the National Taiwan University Hospital (202002013RINC on 2020/4/8 and 201107004RC on 2011/7/19).

Informed consent: All informed consent was obtained from the participants.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Flowchart of the present study.

Figure S2 | The mean (95% confidence interval) changes in the estimated glomerular filtration rate of the stationary (white circles), declined (black circles) and rapidly declined (white squares) estimated glomerular filtration rate trajectory groups in the model development cohort.

Figure S3 | The predictive average annual changes in estimated glomerular filtration rate at low (white circles) and high (black circles) albuminuria variability score levels in the model development cohort.

Table S1 | The event number (%) of different study endpoints in albuminuria variability score groups calculated by different urine albumin : creatinine ratio changes in the model development cohort.

Table S2 | Improvement of model prediction with the incorporation of different predictors in the model development cohort.

Table S3 | The regression coefficients and 95% confidence intervals in the single and multiple linear regression of average annual estimated glomerular filtration rate change on baseline data in the model development cohort.