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ORIGINAL ARTICLE

Sudomotor dysfunction independently predicts incident cardiovascular–renal events and all-cause death in type 2 diabetes: the Joint Asia Diabetes Evaluation register

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ABSTRACT

Background. Early detection and risk factor control prevent chronic kidney disease (CKD) progression. Evaluation of peripheral autonomic dysfunction may detect incident cardiovascular–renal events in type 2 diabetes (T2D).

Methods. SUDOSCAN, a non-invasive tool, provides an age-adjusted electrochemical skin conductance (ESC) composite score incorporating hands/feet ESC measurements, with a score ≤53 indicating sudomotor dysfunction. A consecutive cohort of 2833 Chinese adults underwent structured diabetes assessment in 2012–13; 2028 participants without preexisting cardiovascular disease (CVD) and CKD were monitored for incident cardiovascular–renal events until 2015.

Results. In this prospective cohort {mean age 57.0 [standard deviation (SD) 10.0] years; median T2D duration 7.0 [interquartile range (IQR) 3.0–13.0] years; 56.1% men; 72.5% never-smokers; baseline ESC composite score 60.7 (SD 14.5)}, 163 (8.0%) and 25 (1.2%) participants developed incident CKD and CVD, respectively, after 2.3 years of follow-up. The adjusted hazard ratios (aHRs) per 1-unit decrease in the ESC composite score for incident CKD, CVD and all-cause death were 1.02 [95% confidence interval (CI) 1.01–1.04], 1.04 (1.00–1.07) and 1.04 (1.00–1.08), respectively. Compared with participants with an ESC composite score >53, those with a score ≤53 had an aHR of 1.56 (95% CI 1.09–2.23) for CKD and 3.11 (95% CI 1.27–7.62) for CVD, independent of common risk markers. When added to clinical variables (sex and duration of diabetes), the ESC composite score improved discrimination of all outcomes with appropriate reclassification of CKD risk.

Conclusions. A low ESC composite score independently predicts incident cardiovascular–renal events and death in T2D, which may improve the screening strategy for early intervention.

Keywords: autonomic dysfunction, chronic kidney disease, cohort study, mortality

INTRODUCTION

The prevalence of diabetes has increased from 108 million to 422 million over the past three decades. In this pandemic, the low- and middle-income countries (LMICs) experienced the largest surge due to rapidly changing lifestyles and environment [1]. Diabetes is the leading cause of end-stage renal disease (ESRD) worldwide. The incidence of diabetes-associated ESRD has been estimated to be 10 times higher than in those without diabetes [2]. In both community- and clinic-based settings, albuminuria and estimated glomerular filtration rate (eGFR) are independent predictors of cardiovascular–renal complications and premature death in people with diabetes [3].

Chronic kidney disease (CKD) is treatable with intensive risk factor control and the use of renoprotective agents [4, 5]. Professional organizations recommend CKD screening using urinary albumin and eGFR every 6–12 months for early identification and timely intervention [6]. However, there are huge regional disparities in the implementation of these recommendations, ranging from 12.6% to 67.9% [7, 8]. Low socio-economic status, limited resources (e.g. funding, facilities and workforce), large patient volume and poor disease awareness in both patients and health care providers are major barriers in improving care, leading to increased morbidity and premature death, especially in LMICs [9, 10].

Sudomotor dysfunction is the earliest manifestation of distal small-fibre neuropathy in type 2 diabetes (T2D) and may aid in CKD screening and detection [11–13]. By placing electrodes on the palms and soles, which are rich in sweat glands,

SUDOSCAN evaluates sudomotor (peripheral autonomic) function through measurement of electrochemical skin conductance (ESC) using reverse iontophoresis and chronoamperometry [11]. Herein we examine the utility of the method to detect individuals with T2D at risk of developing cardiovascular–renal events in a prospective cohort.

MATERIALS AND METHODS

Study design and population

Figure 1 depicts the study flow. The Joint Asia Diabetes Evaluation (JADE) Programme and cross-sectional evaluation of the study have been reported [14, 15]. Briefly, this was a prospective follow-up study involving Chinese adults ≥18 years of age with T2D and free from cardiovascular–renal diseases recruited between 2012 and 2013 from the Diabetes and Endocrine Centre, Prince of Wales Hospital (PWH) and Yao Chung Kit Diabetes Assessment Centre, Chinese University of Hong Kong (CUHK). All participants underwent comprehensive assessment for risk factors and complications, including eye/feet examination and blood/urine tests [14], with simultaneous ESC measurement at enrolment. All anonymized data were entered into the web-based JADE portal for analysis [14].

SUDOSCAN (Impeto Medical, Paris, France), a non-invasive and painless tool, comprises two sets of electrodes for the hands and feet that are connected to a computer for analysis [11, 16]. An incremental low voltage (1–4 V) was applied with left and right electrodes acting as cathode and anode alternately. While the keratinized epidermis is electrically insulated at voltages <10 V, the sweat glands can transmit electrically charged ions to the electrodes placed on the cutaneous surface (reverse iontophoresis method). The sweat chloride ion current, which is reported as the ESC (microSiemens, μS), reflects the C fibre innervation and function of the sweat glands [11]. Collectively, this technology provides rapid (2–3 min) and precise ESC measurements of the hands and feet, of which the mean global skin conductance is calculated as $0.5 \times [(\text{right} + \text{left hand})/2 + (\text{right} + \text{left foot})/2]$ [11, 16]. The hands/feet ESC measurements and participant's age are incorporated into a proprietary built-in algorithm to calculate the ESC composite score, which ranges from 0 to 150. Compared with the ESC composite score of ≤60 for sudomotor dysfunction defined by the manufacturer, ethnic-specific thresholds for CKD screening have been reported, such as a composite score ≤53 or ≤55 for Hong Kong Chinese and <59.5 for mainland Chinese [15, 17, 18] or a mean feet ESC measurement ≤37.6 for African Americans and ≤44.4 for European Americans [13].

All participants were referred from community-/hospital-based clinics operated by the Hospital Authority, which used a territory-wide clinical management system that captured all laboratory, hospitalization and drug data. The majority of participants were followed up in the medical clinics at intervals of 3–4 months with measurement of renal function every 6–12 months. Serum creatinine was measured by the isotope dilution mass spectroscopy–traceable Jaffe kinetic method (Dade Behring, Deerfield, IL, USA). We estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [19]. All assays were performed by the Department of Clinical Pathology at PWH with external accreditation.

All hospital discharges were coded according to the *International Classification of Diseases, Ninth Revision*. The code listed as principal diagnosis was used for outcome definition with data censored on 31 May 2015 (Supplementary data, Table S1). The primary outcomes were incident CKD (defined as eGFR <60 ml/min/1.73 m^2, need for renal replacement therapy or death from renal causes) and cardiovascular disease (CVD; defined as any new-onset fatal/non-fatal coronary heart disease, stroke or peripheral vascular disease) (Supplementary data, Tables S1–S2). We defined CKD using the last available eGFR in 6 months before and after the censor date, whereby the measurement closest to the censor date was selected [20]. The exploratory outcome was all-cause death. This study was approved by the local institutional review board. All participants provided written informed consent.

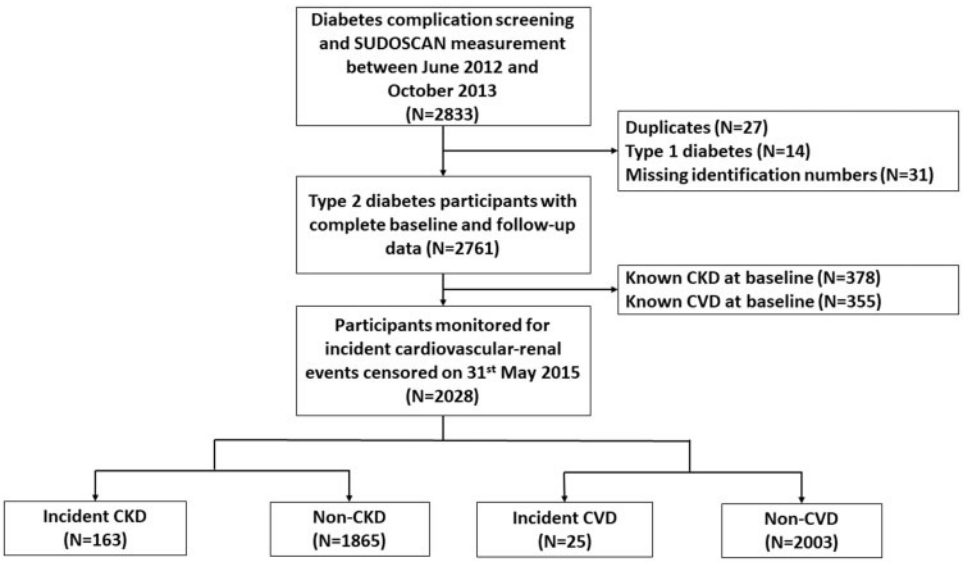


FIGURE 1: Overview of the study cohort.

Statistical analysis

All data are expressed as mean [standard deviation (SD)], median [interquartile range (IQR)] and number (percentage), as appropriate. Triglyceride and urinary albumin:creatinine ratio (ACR) were logarithmically transformed. Categorical variables were compared using either χ^2 or Fisher's exact test and continuous variables with either independent *t* or Mann–Whitney test. Cox regression analyses were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for clinical events with either the ESC composite score or individual ESC measurements as the independent variable. The covariables for adjustment included sex, duration of diabetes, haemoglobin A1c, systolic blood pressure (SBP), low-density lipoprotein (LDL) cholesterol, triglyceride, waist circumference, baseline eGFR, ACR, smoking and drug usage [oral glucose-lowering agents, insulin, renin–angiotensin system (RAS) inhibitors and statins]. There was collinearity between age and ESC composite score (Pearson correlation −0.837) but not with individual ESC measurements.

Subgroup analyses were stratified by pre-defined thresholds of ESC composite score, individual ESC measurements, eGFR >80 mL/min/1.73 m^2 and/or albuminuria status (<3 or <30 mg/mmol) and annual eGFR decline calculated using a linear mixed-effects model with ≥3 eGFR measurements [21]. In the current Kaplan–Meier analysis, which included 2028 participants recruited in the previous study, ESC composite scores ≤53 versus >53 were used to estimate the survival rate of participants with incident CKD. Taking into account the presence of competing risk of mortality, we performed cumulative incidence functions and subdistribution hazard models to estimate the incidence of cardiovascular–renal events [22, 23].

We assessed the predictive discrimination of the ESC composite score for 3-year risk of all outcomes using the receiver operating characteristics (ROC) area under the curve [AUC; ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination)] [24], integrated discrimination improvement (IDI; quantification of predicted probabilities of events and non-events based on inclusion of the ESC composite score in the model) and net reclassification improvement (NRI; the probability that patients are appropriately classified into high and low risk) [25, 26]. Two prediction models were used: basic clinical variables (sex and duration of diabetes) and both clinical variables and composite score. An NRI <0.2, ∼0.4 and >0.6 is considered weak, intermediate and strong, respectively [27]. All statistical analyses were conducted using R software version 3.4.2 (R Project for Statistical Computing, Vienna, Austria) [28]. A two-sided P-value <0.05 denotes statistical significance.

RESULTS

Baseline characteristics

During a mean follow-up of 2.3 years, 2028 (71.6%) participants were prospectively monitored for clinical events. The mean age of the cohort was 57.0 (SD 10.0) years, 56.1% were men and the median duration of T2D was 7.0 (IQR 3.0–13.0) years. The mean baseline ESC composite score was 60.7 (SD 14.5). One in four participants had albuminuria and more than 40% were treated with either RAS inhibitors or statins. Participants with an ESC composite score ≤53 were older, had longer disease duration, had higher rates of microvascular complications and were more likely to be on organ-protective agents than those with a score >53 (Table 1). Compared with participants without CKD, those with CKD were older, had longer disease duration and a more adverse clinical profile, including obesity with increased medication use, and had a lower ESC composite score (Supplementary data, Tables S3–S4).

Clinical outcomes

Table 2 shows the relationship between the ESC composite score and the incidence of cardiovascular–renal events and all-cause death. During this observation period, 163 (8.0%) and 25 (1.2%) of the participants developed incident CKD and CVD, respectively. The ESC composite score independently predicted incident CKD, with every unit decrease associated with a 6% increased risk [HR 1.06 (CI 1.05–1.07)]. This risk was attenuated to 2% after adjustment for baseline cardiometabolic risk factors, renal function and use of organ-protective agents [adjusted HR (aHR) 1.02 (95% CI 1.01–1.04)], albeit still significant. Individual ESC measurements were associated with excess risk of incident CKD, but their predictive power was less robust than the ESC composite score (1% versus 2%).

When we stratified the ESC composite score using the three previously reported thresholds, that is, 53, 55 and 60 (15, 18), only the first two thresholds independently predicted incident CKD in our Chinese cohort. Compared with those with a composite score >53, participants with a score ≤53 had an aHR of 1.56 (95% CI 1.09–2.23) for CKD. The corresponding aHR for a score ≤55 was 1.49 (95% CI 1.04–2.14).

Every unit decrease in the ESC composite score was associated with a 3% excess risk of incident CVD [HR 1.03 (95% CI 1.00–1.06)]. The effect size increased to 4% when adjusted for clinical covariates [aHR 1.04 (95% CI 1.00–1.07)]. Participants with an ESC composite score ≤53 or ≤55 had an increased aHR of 3.11 (95% CI 1.27–7.62) and 3.42 (95% CI 1.39–8.38), respectively, for incident CVD, but the association with individual ESC measurements was not significant. Consistent results for incident cardiovascular–renal events were confirmed in the presence of a competing risk of mortality (Table 3). Figure 2 and Supplementary data, Figure S1 show the Kaplan–Meier curve and cumulative incidence of cardiovascular–renal events in participants with an ESC composite score ≤53 and >53, respectively.

Table 2 shows the time-to-event analysis of all-cause death, with a total event rate of 15 (0.7%), with the ESC composite score being an independent predictor, adjusted for sex and disease duration [aHR 1.04 (95% CI 1.00–1.08)]. Participants with a composite score ≤55 had an aHR of 3.89 (95% CI 1.09–13.90) compared with those with a high score. When we analysed participants with an ACR <30 mg/mmol and/or baseline eGFR ≥80 mL/min/1.73 m^2, a low ESC composite score remained an independent predictor of incident cardiovascular–renal events, albeit its relationship with all-cause death was negated due to fewer events (Supplementary data, Tables S5–S8).

Table 1. Clinical characteristics of participants without prevalent cardiovascular–renal diseases at baseline, stratified by baseline ESC composite score ≤53 or >53

Characteristics	All ($n = 2028$)		ESC composite score ≤53 ($n = 574$)		ESC composite score >53 ($n = 1454$)		P-value
	n		*n*		*n*		
At baseline							
Demographic data							
Age (years)	2028	57.0 (10.0)	574	66.8 (6.5)	1454	53.1 (8.4)	<0.001
Men, *n* (%)	2028	1137 (56.1)	574	297 (51.7)	1454	840 (57.8)	0.014
Smoking history	2027		574		1453		<0.001
Current smoker, *n* (%)		231 (11.4)		42 (7.3)		189 (13.0)	
Ex-smoker, *n* (%)		327 (16.1)		130 (22.6)		197 (13.6)	
Never smoker, *n* (%)		1469 (72.5)		402 (70.0)		1067 (73.4)	
Duration of diabetes (years), median (IQR)	1955	7.0 (3.0–13.0)	573	9.0 (5.0–16.0)	1382	6.0 (3.0–12.0)	<0.001
Duration of follow-up (years)	2028	2.3 (0.4)	574	2.4 (0.4)	1454	2.3 (0.4)	0.245
Cardiometabolic risk factors							
HbA1c, NGSP (%)	2028	7.5 (1.4)	574	7.3 (1.3)	1454	7.5 (1.5)	0.008
SBP (mmHg)	2028	130.8 (16.5)	574	135.4 (17.0)	1454	128.9 (15.9)	<0.001
Diastolic blood pressure (mmHg)	2028	78.3 (9.8)	574	77.1 (9.8)	1454	78.8 (9.8)	<0.001
Total cholesterol (mmol/L)	1982	4.5 (0.9)	561	4.3 (0.8)	1421	4.5 (0.9)	<0.001
LDL cholesterol (mmol/L)	2007	2.4 (0.8)	569	2.3 (0.8)	1438	2.5 (0.8)	<0.001
HDL cholesterol (mmol/L)	2027	1.3 (0.4)	573	1.4 (0.4)	1454	1.3 (0.4)	0.015
Men	1136	1.3 (0.3)	296	1.3 (0.4)	840	1.2 (0.3)	0.025
Women	891	1.4 (0.4)	277	1.5 (0.4)	614	1.4 (0.4)	0.655
Triglyceride (mmol/L), median (IQR)	2028	1.2 (0.9–1.8)	574	1.2 (0.9–1.6)	1454	1.2 (0.9–1.8)	0.007
Body mass index (kg/m^2)	2028	25.9 (4.2)	574	24.9 (3.6)	1454	26.3 (4.4)	<0.001
Waist circumference (cm)	2028	90.0 (10.8)	574	88.7 (10.0)	1454	90.6 (11.1)	<0.001
Men	1137	92.1 (10.1)	297	90.7 (9.8)	840	92.7 (10.1)	0.003
Women	891	87.3 (11.2)	277	86.5 (9.7)	614	87.7 (11.7)	0.104
eGFR (mL/min/1.73 m^2)	2028	94.0 (13.7)	574	85.3 (12.1)	1454	97.4 (12.8)	<0.001
Urinary ACR (mg/mmol), median (IQR)	2024	1.1 (0.5–3.3)	573	1.3 (0.6–4.2)	1451	1.0 (0.5–3.1)	0.001
Complications at baseline							
Sensory neuropathy, *n* (%)	2028	39 (1.9)	574	19 (3.3)	1454	20 (1.4)	0.004
Diabetic retinopathy, *n* (%)	2027	366 (18.1)	573	128 (22.3)	1454	238 (16.4)	0.002
Albuminuria	2024		573		1451		0.075
<3 mg/mmol, *n* (%)		1486 (73.4)		403 (70.3)		1083 (74.6)	
3–30 mg/mmol, *n* (%)		438 (21.6)		143 (25.0)		295 (20.3)	
≥30 mg/mmol, *n* (%)		100 (4.9)		27 (4.7)		73 (5.0)	
Medication use							
Oral glucose-lowering agents, *n* (%)	2028	1741 (85.8)	574	498 (86.8)	1454	1243 (85.5)	0.459
Insulin, *n* (%)	2028	391 (19.3)	574	107 (18.6)	1454	284 (19.5)	0.647
RAS inhibitors, *n* (%)	2028	833 (41.1)	574	279 (48.6)	1454	554 (38.1)	<0.001
Statins, *n* (%)	2028	973 (48.0)	574	317 (55.2)	1454	656 (45.1)	<0.001
ESC measurements (μS)							
Mean global ESC	2028	59.4 (18.5)	574	46.4 (18.3)	1454	64.5 (15.9)	<0.001
Hands ESC	2027	55.6 (20.6)	574	43.5 (21.7)	1453	60.3 (18.1)	<0.001
Feet ESC	2028	63.0 (18.0)	574	49.4 (18.4)	1454	68.5 (14.7)	<0.001
ESC composite score	2028	60.7 (14.5)	574	44.2 (7.3)	1454	67.2 (11.1)	<0.001
Incidence of events at 2.3 years of follow-up							
CVD, *n* (%)	2028	25 (1.2)	574	13 (2.3)	1454	12 (0.8)	0.008
CKD, *n* (%)	2028	163 (8.0)	574	98 (17.1)	1454	65 (4.5)	<0.001
ESRD, *n* (%)	2028	4 (0.2)	574	1 (0.2)	1454	3 (0.2)	1.000
All-cause death, *n* (%)	2028	15 (0.7)	574	7 (1.2)	1454	8 (0.6)	0.147

Data are expressed as mean (SD) unless stated otherwise. eGFR was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation. CVD is defined as the presence of any coronary heart disease, stroke or peripheral vascular disease. The mean global ESC was calculated using $0.5 \times [(\text{right} + \text{left hand ESC}/2) + (\text{right} + \text{left foot ESC}/2)]$.
ESRD, end-stage renal disease; HDL, high-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

In the whole cohort, every unit decrease in the composite score was also independently associated with faster eGFR decline [β −0.005 (standard error 0.002), P = 0.048] (Supplementary data, Table S9).

Table 4 shows the discrimination and reclassification analyses that assessed the use of the ESC composite score in predicting the 3-year risk of cardiovascular–renal events and all-cause death. For the basic model (sex and duration of diabetes), the AUC was 0.63 (95% CI 0.59–0.67) for CKD, which increased to 0.74 (95% CI 0.70–0.78) with an estimated NRI of 0.29 (95% CI 0.14–0.41) and an absolute IDI change <1% after addition of the ESC composite score. There was a similar trend for CVD and death, but the ESC composite score did not improve their reclassifications.

Table 2. Cox proportional hazards models of baseline ESC composite score and risk of incident cardiovascular–renal events and all-cause death (including participants without prevalent cardiovascular–renal diseases at baseline)

	Incident CKD								
	Model 1 ($n = 2028$)			Model 2 ($n = 1955$)			Model 3 ($n = 1934$)		
	Event, *n* (%)	HR (95% CI)	P-value	Event, *n* (%)	HR (95% CI)	P-value	Event, *n* (%)	HR (95% CI)	P-value
ESC composite score[a]	163 (8.0)	1.06 (1.05–1.07)	<0.001	162 (8.3)	1.06 (1.05–1.07)	<0.001	158 (8.2)	1.02 (1.01–1.04)	0.001
ESC composite score[b]									
Score ≤53 versus >53	163 (8.0)	4.06 (2.97–5.55)	<0.001	162 (8.3)	3.60 (2.61–4.97)	<0.001	158 (8.2)	1.56 (1.09–2.23)	0.015
Score ≤55 versus >55	163 (8.0)	3.74 (2.72–5.16)	<0.001	162 (8.3)	3.35 (2.41–4.65)	<0.001	158 (8.2)	1.49 (1.04–2.14)	0.029
Score ≤60 versus >60	163 (8.0)	4.07 (2.80–5.92)	<0.001	162 (8.3)	3.60 (2.45–5.28)	<0.001	158 (8.2)	1.38 (0.92–2.07)	0.118
Mean global ESC	163 (8.0)	1.02 (1.01–1.03)	<0.001	162 (8.3)	1.01 (1.00–1.02)	0.004	158 (8.2)	1.01 (1.00–1.02)	0.024
Hands ESC	163 (8.0)	1.02 (1.01–1.03)	<0.001	162 (8.3)	1.01 (1.00–1.02)	0.004	158 (8.2)	1.01 (1.00–1.02)	0.037
Feet ESC	163 (8.0)	1.02 (1.01–1.03)	<0.001	162 (8.3)	1.01 (1.00–1.02)	0.017	158 (8.2)	1.01 (1.00–1.02)	0.040
	Incident CVD								
	Model 1 (n=2028)			Model 2 (n=1955)			Model 3 (n=1934)		
	Event, *n* (%)	HR (95% CI)	P-value	Event, *n* (%)	HR (95% CI)	P-value	Event, *n* (%)	HR (95% CI)	P-value
ESC composite score[a]	25 (1.2)	1.03 (1.00–1.06)	0.032	25 (1.3)	1.03 (1.00–1.06)	0.061	25 (1.3)	1.04 (1.00–1.07)	0.030
ESC composite score[b]									
Score ≤53 versus >53	25 (1.2)	2.73 (1.25–5.99)	0.012	25 (1.3)	2.65 (1.19–5.93)	0.018	25 (1.3)	3.11 (1.27–7.62)	0.013
Score ≤55 versus >55	25 (1.2)	2.94 (1.32–6.54)	0.008	25 (1.3)	2.91 (1.29–6.58)	0.010	25 (1.3)	3.42 (1.39–8.38)	0.007
Score ≤60 versus >60	25 (1.2)	2.25 (0.97–5.22)	0.058	25 (1.3)	2.14 (0.91–5.04)	0.082	25 (1.3)	2.33 (0.90–6.02)	0.080
Mean global ESC	25 (1.2)	1.01 (0.99–1.03)	0.473	25 (1.3)	1.01 (0.98–1.03)	0.637	25 (1.3)	1.00 (0.98–1.03)	0.700
Hands ESC	25 (1.2)	1.01 (0.99–1.02)	0.621	25 (1.3)	1.00 (0.98–1.02)	0.742	25 (1.3)	1.00 (0.98–1.02)	0.722
Feet ESC	25 (1.2)	1.01 (0.99–1.03)	0.406	25 (1.3)	1.01 (0.99–1.03)	0.606	25 (1.3)	1.00 (0.98–1.02)	0.735
	All-cause death								
	Model 1 (n=2028)			Model 2 (n=1955)			Model 3 (n=1934)		
	Event, *n* (%)	HR (95% CI)	P-value	Event, *n* (%)	HR (95% CI)	P-value	Event, *n* (%)	HR (95% CI)	P-value
ESC composite score[a]	15 (0.7)	1.03 (0.99–1.06)	0.167	14 (0.7)	1.04 (1.00–1.08)	0.045	13 (0.7)	1.04 (1.00–1.09)	0.067
ESC composite score[b]									
Score ≤53 versus >53	15 (0.7)	2.18 (0.79–6.00)	0.133	14 (0.7)	2.60 (0.89–7.56)	0.080	13 (0.7)	3.53 (0.99–12.49)	0.050
Score ≤55 versus >55	15 (0.7)	2.20 (0.80–6.08)	0.127	14 (0.7)	2.69 (0.92–7.89)	0.072	13 (0.7)	3.89 (1.09–13.90)	0.036
Score ≤60 versus >60	15 (0.7)	2.09 (0.72–6.12)	0.178	14 (0.7)	2.68 (0.83–8.69)	0.101	13 (0.7)	2.56 (0.70–9.39)	0.158
Mean global ESC	15 (0.7)	1.00 (0.97–1.03)	0.870	14 (0.7)	1.00 (0.97–1.02)	0.754	13 (0.7)	0.99 (0.96–1.02)	0.646
Hands ESC	15 (0.7)	1.01 (0.98–1.03)	0.530	14 (0.7)	1.00 (0.98–1.03)	0.925	13 (0.7)	1.00 (0.97–1.03)	0.956
Feet ESC	15 (0.7)	0.99 (0.96–1.02)	0.672	14 (0.7)	0.99 (0.96–1.02)	0.453	13 (0.7)	0.98 (0.95–1.02)	0.318

[a]Continuous variable.
[b]Categorical variable. The HR represents the relative change in the hazard function per 1-unit decrease in the independent variable. The mean global ESC was calculated using 0.5 × [(right + left hand ESC)/2 + (right + left foot)/2].
Model 1: unadjusted.
Model 2: adjusted for sex, duration of T2D (when either mean global, hands or feet ESC was used as the independent variable, age was added in the model).
Model 3: model 2 plus HbA1c, SBP, LDL cholesterol, logarithmically transformed triglyceride, waist circumference, baseline eGFR, logarithmically transformed urinary ACR, smoking status and use of RAS inhibitors, statins, oral glucose-lowering agents or insulin.

DISCUSSION

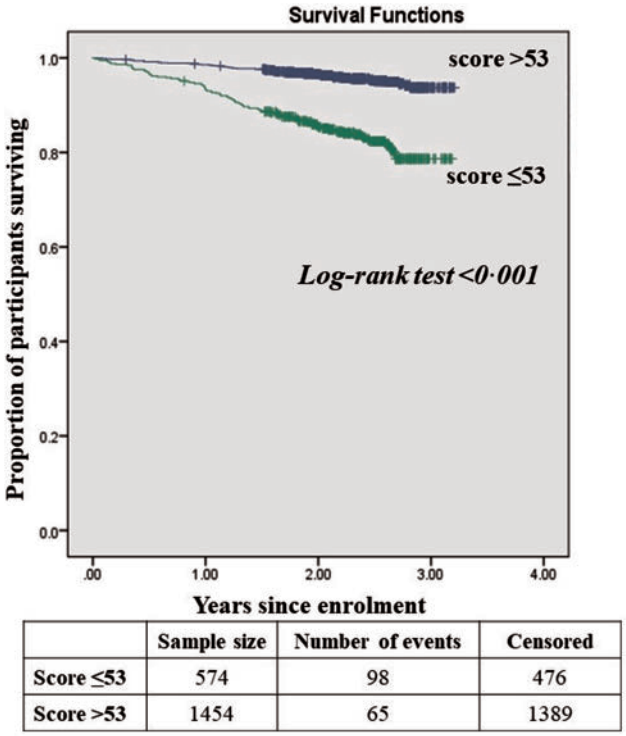
In Chinese patients with T2D, one-third of the participants had cardiovascular–renal diseases at enrolment to the JADE register. Among those without prevalent cardiovascular–renal diseases, a low ESC composite score independently increased the HR by 1.5–4 for incident cardiovascular–renal events and all-cause death compared with those with a score >53 or >55 after 2 years of follow-up. Only 28% of the cohort had a low ESC composite score ≤53, but 60% developed CKD. In contrast, 72% of participants had a high ESC composite score >53 and only 40% developed CKD. Low individual ESC measurements also predicted a higher incidence of CKD. After adjusting for sex and disease duration, the ESC composite score remained robust in discriminating all outcomes and reclassifying CKD risk. Taken together, SUDOSCAN can be a useful non-invasive tool to identify high-risk individuals for cardiovascular–renal diseases for definitive evaluation and intervention.

SUDOSCAN is an approved technology for measuring autonomic nerve function [16]. Autonomic and somatic nerve dysfunctions measured by different methods have been shown to predict poor cardiometabolic outcomes and death in the diabetic population [29–31]. However, use of these measurements in clinical practice (e.g. Michigan Neuropathy Screening Instrument, Utah Early Neuropathy Scale, nerve conduction studies and intraepidermal nerve fibre density) is limited by their subjective nature or technical challenges requiring special staff training [11, 32]. SUDOSCAN has been shown to correlate well with these clinical instruments for evaluation of nerve

Table 3. Comparison of Cox proportional and subdistribution hazards models for incident cardiovascular–renal events ($n = 1934$)

	Cox proportional hazards model, HR (95% CI)				Subdistribution hazard model, SHR (95% CI)			
	Incident CKD ($n = 158$)	P-value	Incident CVD ($n = 25$)	P-value	Incident CKD ($n = 158$)	P-value	Incident CVD ($n = 25$)	P-value
ESC composite score[a]	1.02 (1.01–1.04)	0.001	1.04 (1.00–1.07)	0.030	1.02 (1.01–1.04)	0.002	1.04 (1.00–1.07)	0.033
ESC composite score[b]								
Score ≤53 versus >53	1.56 (1.09–2.23)	0.015	3.11 (1.27–7.62)	0.013	1.57 (1.09–2.24)	0.014	3.09 (1.42–6.69)	0.004
Score ≤55 versus >55	1.49 (1.04–2.14)	0.029	3.42 (1.39–8.38)	0.007	1.50 (1.04–2.16)	0.028	3.40 (1.49–7.74)	0.004
Score ≤60 versus >60	1.38 (0.92–2.07)	0.118	2.33 (0.90–6.02)	0.080	1.37 (0.92–2.04)	0.117	2.32 (1.04–5.14)	0.039
Mean global ESC	1.01 (1.00–1.02)	0.024	1.00 (0.98–1.03)	0.700	1.01 (1.00–1.02)	0.024	1.00 (0.99–1.02)	0.635
Hands ESC	1.01 (1.00–1.02)	0.037	1.00 (0.98–1.02)	0.722	1.01 (1.00–1.02)	0.044	1.00 (0.98–1.02)	0.724
Feet ESC	1.01 (1.00–1.02)	0.040	1.00 (0.98–1.02)	0.735	1.01 (1.00–1.02)	0.039	1.00 (0.99–1.02)	0.642

[a]Continuous variable.
[b]Categorical variable. Each cell illustrates the hazard per 1-unit decrease of the given independent variable, with different interpretations in both models. For each outcome, the HR represents the relative change in the hazard function in the Cox proportional hazards model. The SHR represents the relative incidence in the subdistribution hazard model. The mean global ESC was calculated using 0.5 × [(right + left hand ESC)/2 + (right + left foot)/2].
Models were adjusted for sex, duration of T2D, HbA1c, SBP, LDL cholesterol, logarithmically transformed triglyceride, waist circumference, baseline eGFR, logarithmically transformed urinary ACR, smoking status and the use of RAS inhibitors, statins, oral glucose-lowering agents or insulin (when either mean global, hands or feet ESC was used as the independent variable, age was added in the model).
SHR, subdistribution HR.



	Sample size	Number of events	Censored
Score ≤53	574	98	476
Score >53	1454	65	1389

FIGURE 2: Kaplan–Meier curve of incident CKD (eGFR <60 ml/min/1.73 m^2, need for renal replacement therapy or death from renal causes), stratified by baseline ESC composite score ≤53 (lower line) and >53 (upper line).

dysfunction [33, 34]. In this analysis, we further confirmed the utility of SUDOSCAN to measure sudomotor dysfunction for detecting individuals at risk of developing cardiovascular–renal complications. Given its user friendliness and non-invasive nature, the use of this technology might help prioritize screening and intervention strategies, especially in cost-restrained settings.

Globally, 500 million adults ≥20 years of age are suffering from CKD, 80% of whom are living in LMICs [35], where only one-third of affected individuals were diagnosed [2]. The Global Burden of Disease 2016 Study reported a 30% increase in the death rates attributable to diabetic kidney disease, totalling 500 800 deaths worldwide in the past decade [36], although this estimate was likely to be conservative. Hong Kong has a highly subsidized health care system. Since 2000, a team-based structured diabetes assessment and management programme has been progressively introduced in public health care institutions, with a demonstrable decline in the incidence of cardiovascular–renal complications and death. Despite this, the burden of ESRD has remained high, with a crude incidence of 22.5 per 1000 person-years, especially in people with ≥15 years of diabetes, pointing to a need for earlier detection to enable more aggressive management during the early stages of disease [37].

Diabetic kidney disease is treatable if detected early and treated intensively [4, 5]. In the UK Prospective Diabetes Study, the annual progression to microalbuminuria was 2% and from microalbuminuria to overt proteinuria was 2.8%, meaning that one in four patients with T2D might develop either microalbuminuria or worsening nephropathy within 10 years of diagnosis [38]. Universal screening for CKD provides opportunities to implement preventive strategies to arrest or slow disease progression. However, one in three patients with T2D in LMICs failed to receive routine CKD screening [8]. Even in high-income nations such as the UK, a National Diabetes Audit showed a sustained reduction in regular microalbuminuria screening from 84.4% (2013–14) to 65.2% (2016–17) [39]. Factors pertaining to the health care system (infrastructure support, access to and high cost of *in vitro* diagnostic tests), health care providers (inefficient communication, lack of trained personnel and ongoing support) and patients (sociodemographic disparities and poor awareness) are common obstacles in optimizing care [8, 10]. In a multinational survey involving 75 058 individuals screened for non-communicable diseases in LMICs, >90% of affected individuals were unaware of CKD [9]. Among those who were aware of CKD, fewer than half had intervention for CKD, which would progress silently to ESRD with poor quality of life and increased socio-economic burden [9].

Table 4. The ROC curve, IDI and NRI of the use of ESC composite score in addition to clinical variables in predicting the 3-year risk of cardiovascular–renal diseases and all-cause death

	C-index (95% CI)		Absolute IDI (95% CI)	NRI (95% CI)
	Model 1	Model 2		
CKD				
ESC composite score (continuous)	0.63 (0.59–0.67)	0.74 (0.70–0.78)	0.08 (0.04–0.11)	0.29 (0.14–0.41)
ESC composite score (53 cut-point)		0.72 (0.68–0.76)	0.05 (0.02–0.08)	0.32 (0.16–0.44)
CVD				
ESC composite score (continuous)	0.65 (0.56–0.75)	0.70 (0.59–0.80)	0.003 (0.00–0.02)	0.22 (−0.12–0.42)
ESC composite score (53 cut-point)		0.72 (0.63–0.81)	0.004 (0.00–0.03)	0.24 (0.00–0.47)
All-cause death				
ESC composite score (continuous)	0.58 (0.41–0.74)	0.67 (0.50–0.85)	0.002 (0.00–0.05)	−0.15 (−0.35–0.25)
ESC composite score (53 cut-point)		0.66 (0.50–0.82)	0.001 (0.00–0.02)	0.03 (−0.19–0.35)

Model 1: sex, duration of T2D.
Model 2: model 1 plus ESC composite score.

Diagnosis of asymptomatic early-stage CKD, which accounts for 80–90% of all cases, requires measurement of urinary albumin and GFR [2]. Although GFR is generally estimated from serum creatinine and/or cystatin, these renal parameters are often not measured in audit reports [8, 40]. The large inter-individual and day-to-day variability of microalbuminuria also has limited predictive value in identifying patients with prevalent CKD or those who are at risk of developing CKD [41]. With increasing usage of RAS inhibitors and better risk factor control, remission of microalbuminuria has been reported in 20–60% of individuals with diabetes. Of note, individuals with normoalbuminuria and reduced GFR could also have poor clinical outcomes [41–43]. In this light, diabetic kidney disease is a heterogeneous condition, with normoalbuminuria *per se* being associated with structural kidney damage where 20–40% of these individuals might continue to progress despite being treated with RAS inhibitors [42]. Various measurements of albuminuria (e.g. ACR, protein:creatinine ratio and urine dipstick) are even harder to standardize, with qualitative measurement using dipstick having the lowest accuracy [44].

Autonomic dysfunction, such as prolonged QT interval, is a strong prognostic predictor in T2D. One in two to four affected individuals might die within 5–10 years of diagnosis compared with those without [45]. Glucotoxicity-mediated pathological processes, for example, accumulation of advanced glycosylation end-products, increased oxidative stress, activation of protein kinase C and polyol pathways, can cause direct neuronal injury, chronic endoneural ischaemia and nerve hypoxia [32, 45]. Patients with diabetic peripheral neuropathy had small sweat glands with reduced ductal diameter. This was attributable to abnormal thickening of the capillary endothelium causing damage to cutaneous microvasculatures [11]. Autonomic neuropathy involving cardiovascular and sudomotor functions affects 60% of people with CKD [46]. Neurovascular damage shares common risk factors and frequently coexist. Given its confirmed utility in predicting autonomic and sensory neuropathy, the predictive value of the ESC composite score in detecting incident cardiovascular–renal events and all-cause death, via indirect assessment of sudomotor function, is biologically plausible. This proposition is supported by consistent results from our case–control [18], cross-sectional [15] and prospective analysis, although these results will need to be replicated in other populations.

This is the first report indicating the feasibility of using a point-of-care tool to detect individuals with T2D and preserved renal function who were at high risk of developing cardiovascular–renal events and all-cause death after 2 years. In this prospective analysis, we confirmed the preferred use of the Chinese-specific threshold of the ESC composite score ($\leq$53) to detect incident CKD compared with other ethnic-specific thresholds derived from cross-sectional studies such as an ESC composite score $<$59.5 for mainland Chinese or a mean feet ESC measurement of 37.6–44.4 for African Americans and European Americans [13, 17, 18]. Given the detailed data management of the JADE register, we were able to examine the effects of various cardiometabolic risk factors, comorbidities and medication use on the ESC composite score to confirm its independent utility.

Regarding the limitations, the definition of CKD in our study was based on reduced eGFR derived from serum creatinine. Despite the potential confounding effects of drug treatment and the wide intra-individual variability of albuminuria, our results remained robust after adjustment in our multivariable analyses. The results of incident CVD and all-cause death should be interpreted with caution given the relatively low event rates, short duration of follow-up and wide 95% CIs when stratified by different thresholds of the ESC composite score, eGFR category and albuminuria status. Longitudinal studies are required to validate and evaluate the significance of other subscores. Although sudomotor assessment holds promise in promoting CKD screening and detection in our cohort, urinary albumin and GFR assessments remain the gold standard in the diagnosis and management of CKD.

Given its simple-to-use and non-invasive nature with reliable repeat measurements, SUDOSCAN can be part of opportunistic CKD surveillance programmes in routine primary care services, especially in low-resource settings. In line with the International Society of Nephrology Closing the Gaps CKD Initiative, increasing accessibility to accurate point-of-care testing, for example, SUDOSCAN, can facilitate care prioritization and informed decision making to facilitate early diagnosis and management [44]. However, the optimal thresholds of the ESC composite score will need to be determined in a more diverse

population taking ethnicity into consideration. In sum, a low ESC composite score is a useful risk prediction marker for cardiovascular–renal events and all-cause death in the Chinese population with T2D. By distinguishing the high-risk from the low-risk group, use of the ESC composite score may select patients for definitive evaluation and intensive management, although formal cost-effectiveness analysis is needed to quantify these benefits.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

J.C.N.C. conceptualized the study design. J.C.N.C., A.P.S.K., R.C.W.M., A.O.Y.L., R.O., K.K.T.C. and A.W.C.F. participated in the data acquisition. L.L.L., E.S.H.L. and A.W.C.F. performed the analysis with support from J.C.N.C. and A.P.S.K. L.L.L. wrote the first draft and J.C.N.C. finalized the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final version of the article.

CONFLICT OF INTEREST STATEMENT

J.C.N.C. is the Chief Executive Officer of ADF on a pro bono basis. R.C.W.M. received research funding from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme and Takeda for conducting clinical trials, speaker honorarium or consultancy in advisory boards. All proceeds have been donated to the CUHK to support diabetes research. All other authors declared no potential conflicts of interest. We confirm that the results presented in this article have not been published previously in whole or part.

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Effects of uric acid on kidney function decline differ depending on baseline kidney function in type 2 diabetic patients

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ABSTRACT

Background. Most existing data regarding effects of uric acid (UA) on diabetic kidney disease have considered patients with preserved kidney function. We examined a hypothesis that there are differences in the effects of serum UA levels on the decline in kidney function depending on baseline kidney function in diabetic patients.

Methods. In this historical cohort study, 7033 type 2 diabetic patients were analyzed and classified into two groups as follows: nonchronic kidney disease (non-CKD), with an estimated glomerular filtration rate (eGFR) $\geq$60 mL/min/1.73 m^2 ($n = 4994$), and CKD, with an eGFR <60 mL/min/1.73 m^2 ($n = 2039$). The composite endpoint was *a* $\geq$30% decrease in eGFR from baseline or the initiation of renal replacement therapy. The hazard ratio (HR) of serum UA levels at baseline was estimated using multivariate Cox proportional hazards models.

Results. There was a significant interaction between UA levels and baseline eGFR with respect to the endpoint ($P < 0.001$). The HRs of 1 mg/dL increase in UA levels were 1.13 [95% confidence interval (CI) 1.05–1.22, $P = 0.002$] and 0.93 (95% CI 0.88–0.99, $P = 0.02$) in the non-CKD and CKD groups, respectively. When patients were classified by quintile of UA levels,