Relationship between kidney function decline and initial risk factors for the progression of diabetic kidney disease: a retrospective analysis of 91 Japanese patients with type 2 diabetes

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Abstract

Background Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) in Japan. The clinical course and factors related to the progression of DKD to ESRD are important issues when treating patients with DKD.

Methods Ninety-one type 2 diabetic patients with DKD that had progressed from chronic kidney disease (CKD) stages G1–3 on their initial clinical visit to ESRD were enrolled. The decline in the estimated glomerular filtration rate (eGFR) was analyzed and the initial clinical factors that influenced the decline rate were explored.

Results There was a linear decline in eGFR before progression to ESRD, with a median annual decline rate (Δ eGFR) of 9.2 mL/min/1.73 m². In all patients, a history of coronary artery disease and increased levels of initial eGFR and high-density lipoprotein cholesterol (HDL-C) were positive predictors of log Δ eGFR, whereas age, history of cerebral infarction (CI), and an increased level of serum albumin were negative predictors of log Δ eGFR. In patients with CKD stages G1–2 on their first visit, male sex and increased diastolic blood pressure were positive predictors. In patients with CKD stage G3 on their first visit, an increased level of LDL-C was a positive predictor,

whereas a history of CI and an increased level of serum total bilirubin (TBil) were negative predictors.

Conclusion In addition to the common risk factors, initial eGFR, HDL-C, and TBil were identified as novel risk factors for ESRD. These risk factors may differ between patients with early and advanced stages of CKD.

Keywords Diabetic kidney disease · eGFR decline rate · Multivariate linear regression analysis · High-density lipoprotein cholesterol · Bilirubin

Introduction

In Japan, diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD) [1]. Once overt nephropathy occurs without specific intervention in typical diabetic nephropathy, the glomerular filtration rate (GFR) gradually decreases at a highly variable rate within several years [2].

A number of studies on estimated GFR (eGFR) decline rates in patients with type 1 diabetes have been reported [3–5]. eGFR trajectories until ESRD and the distribution of eGFR slopes were demonstrated in a study of 240 patients with proteinuria [4]. However, little is known about eGFR trajectories in patients with type 2 diabetes who are unresponsive to treatment and have reached ESRD. Analyzing these eGFR trajectories and eGFR decline rates in patients with type 2 diabetes is useful for evaluating the interval from overt nephropathy to ESRD. It is still unclear whether common risk factors for progression to DKD [6, 7], such as albuminuria and blood pressure (BP), could be predictors of eGFR decline rate.

We retrospectively analyzed the eGFR trajectories of 91 Japanese patients with DKD due to type 2 diabetes from

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the first clinical visit until ESRD was reached. We also searched for factors influencing eGFR decline rates on the first visit.

Methods

Study population

A total of 167 outpatients with type 2 diabetes who first visited the Chiba Central Medical Center (CCMC) from 1999 to 2013 and developed ESRD between 2003 and 2015 were enrolled. ESRD was defined as eGFR of <15 mL/min/1.73 m². The KDIGO 2012 clinical practice guidelines for the evaluation and management of chronic kidney disease (CKD) were used to classify CKD based on etiology, GFR, and category of albuminuria [6]. Patients with CKD stages G4–5 on their initial visit and those with any clinical or laboratory evidence of other kidney or urinary tract diseases were excluded.

After applying the exclusion criteria, 91 type 2 diabetic patients with DKD were included. DKD was diagnosed according to one of the following criteria: (1) presence of diabetic retinopathy (DR) and albuminuria on the first visit and (2) onset of DR followed by albuminuria (normo- or microalbuminuria) during follow-up [8]. At the time of data analysis, hemodialysis was initiated in 77 patients, and 2 patients died because of uremia.

This study was approved by the ethics review board of CCMC and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study design

Every 1–2 months, physical examination and laboratory data, including glycated hemoglobin (HbA1c) level, eGFR, and albumin-to-creatinine ratio (ACR), were retrospectively collected from the clinical records. HbA1c level was measured using high-performance liquid chromatography. Other variables, including body mass index (BMI), BP, low-density lipoprotein cholesterol (LDL-C) level, high-density lipoprotein cholesterol (HDL-C) level, serum creatinine level, ACR, and other biochemical marker levels, were determined by standard methods.

eGFR was calculated using the following equation proposed by the Japanese Society of Nephrology: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times [\text{age (years)}]^{-0.287} \times [\text{serum creatinine (mg/dL)}]^{-1.094} (\times 0.739, \text{ if female})$ [9]. For each patient, a multivariate linear regression analysis model of time versus eGFR (least squares method) was created; the slope of the regression line during CKD stages G3–4 was used to estimate the eGFR slope (ΔeGFR) in all patients.

To minimize the effects of eGFR fluctuation, all eGFR values in CKD stages G3–4 were used in the multivariate linear regression analysis. The ΔeGFR was expressed as mL/1.73 m² per year.

DR was assessed by ophthalmologists who examined the retina on the first visit and during the follow-up. The status of retinopathy was classified according to Fukuda's classification [10]. DR was defined as $>\text{A1}$ in this study. Coronary artery disease (CAD) and peripheral artery disease (PAD) were assessed and treated by cardiologists. CAD was defined as the need for percutaneous coronary intervention and/or coronary artery bypass graft surgery. PAD was defined as the need for percutaneous intervention for lower limb ischemia.

Statistical analysis

Matrix Laboratory (MATLAB) version 2015b for Windows (MathWorks, Natick, MA, USA) was used for all statistical analyses, including multivariate linear regression analyses. Variables that had a significant relationship with the logarithm of ΔeGFR ($\log \Delta\text{eGFR}$) were analyzed by multivariate linear regression analysis with forward stepwise selection of variables. All characteristics were presented as binary categorical variables; the characteristics listed in Tables 2 and 3 were used as explanatory variables. All reported *P* values were two-tailed, and a *P* value of <0.05 was considered significant.

Results

The clinical characteristics on the first visit are shown in Table 1. The male-to-female ratio of the study population was 3:1. Systolic and diastolic BPs did not reach the recommended levels [11]. The prevalence of smoking in this study was higher than that in the general Japanese adult population, which was 34 % among men and 9 % among women (2012, Ministry of Health, Labor and Welfare of Japan). The median diabetes duration was 12 years. Diabetes prevalence among patients who had a first-degree relative with diabetes was 60 %. Half the patients had previous intermittent treatments for more than 1 year. Sixty-six percent (60/91) of the patients had received treatment for diabetes before their first visit; 22 % (20/91) had not received treatment before their first visit, despite being diagnosed with diabetes; and 11 % (11/91) of the patients were diagnosed with diabetes on their first visit and subsequently received treatment. Other comorbid conditions included hypertension (HTN, 66 %), CAD (21 %), PAD (11 %), and cerebral infarction (CI, 11 %). Before the first visit and during the follow-up, 84 % of the patients were treated with calcium channel blockers

Table 1 Clinical characteristics of patients with DKD on their first clinical visit

Characteristics	Total (<i>N</i> = 91)	G1–2 (<i>N</i> = 40)	G3 (<i>N</i> = 51)	<i>P</i> value
Male/female	68/23	29/11	39/12	0.67 [†]
Age (years)	57 (48–65)	56 (44–62)	59 (52–68)	0.03*
BMI	24 (22–27)	24 (21–26)	26 (23–28)	0.02*
Systolic BP (mmHg)	150 (130–170)	140 (130–160)	150 (130–170)	0.18*
Diastolic BP (mmHg)	82 (73–92)	81 (73–91)	82 (73–95)	0.81*
Smoking (%)	60 (52/86)	64 (25/39)	57 (27/47)	0.53 [†]
Known duration of DM (years)	12 (6–18)	9 (5–13)	14 (10–20)	<0.01*
DM family history (%)	60 (52/86)	65 (26/40)	57 (26/46)	0.42 [†]
Intermittent treatment (%)	46 (42/91)	58 (23/40)	37 (19/51)	0.05 [†]
Cardiovascular diseases				
Hypertension (%)	66 (60/91)	53 (21/40)	76 (39/51)	0.02 [†]
CAD (%)	21 (19/91)	8 (3/40)	31 (16/51)	<0.01 [†]
PAD (%)	11 (10/91)	10 (4/40)	12 (6/51)	0.79 [†]
CI (%)	11 (10/91)	13 (5/40)	9.8 (5/51)	0.68 [†]
Medication				
CCB (%)	84 (70/83)	78 (29/37)	89 (41/46)	0.18 [†]
RASi (%)	95 (82/86)	97 (37/38)	94 (45/48)	0.42 [†]
Lipid-lowering drugs (%)	61 (50/82)	67 (24/36)	57 (26/46)	0.35 [†]
Antiplatelet drugs (%)	41 (37/91)	23 (9/40)	55 (28/51)	<0.01 [†]
Diet/ODA/insulin (%)	1 (1/91)/29 (26/91)/70 (64/91)	0 (0/40)/25 (10/40)/75 (30/40)	2 (1/51)/31 (16/51)/67 (34/51)	0.52 [†]

Data are presented as median (interquartile range) or as a proportion

BMI body mass index, *BP* blood pressure, *DM* diabetes mellitus, *CAD* coronary artery disease, *PAD* peripheral artery disease, *CI* cerebral infarction, *CCB* calcium channel blockers, *RASi* renin–angiotensin system inhibitors, *ODA* oral antidiabetic agents

* Wilcoxon's rank-sum test

[†] Pearson's chi-square test

Table 2 CKD stages of patients with DKD on their first clinic visit (*N* = 91)

eGFR	A1 (ACR ≤30 mg/g Cr)	A2 (ACR 30–299 mg/g Cr)	A3 (ACR ≥300 mg/g Cr)
G1 (eGFR ≥90 mL/min/1.73 m ²)	1	5	10
G2 (eGFR 60–89 mL/min/1.73 m ²)	1	5	18
G3 (eGFR 30–59 mL/min/1.73 m ²)	1	5	45

Data indicate the number of patients

eGFR estimated glomerular filtration ratio, *ACR* albumin to creatinine ratio

(CCBs), and 95 % were treated with renin–angiotensin system inhibitors (RASIs). Diabetes was treated with oral hypoglycemic agents in 29 % of the patients and with insulin in 70 %; lipid-lowering and antiplatelet drugs were prescribed in 61 and 41 % of the patients, respectively.

Table 2 shows the CKD stage of patients on their first clinical visit. CKD was categorized as stages G1–2 (*N* = 40) and stage G3 (*N* = 51) [6]. Albuminuria was categorized into stage A1 (*N* = 3), stage A2 (*N* = 15), and stage A3 (*N* = 73). Most patients had DR and albuminuria on their first visit; only three patients developed DR before CKD.

Comparison of the two groups of patients based on the CKD stage is shown in Table 1. Age, BMI, duration of diabetes, prevalence of HTN and CAD, and prescription of antiplatelet drugs were significantly higher in CKD stage G3 than in CKD stages G1–2.

Serum albumin (Alb), TBil, uric acid (UA), LDL-C, HDL-C, triglyceride (TG), and HbA1c levels as well as eGFR and ACR on the first visit are shown in Table 3. The median eGFR of all patients was 57 mL/min/1.73 m². Most patients were under poor glycemic control and had macroalbuminuria. Compared with patients with CKD stage G3, patients with CKD stages G1–2 had significantly

Table 3 Laboratory data of patients with DKD on their first clinic visit ($N = 91$)

Variables	Total ($N = 91$)	G1–2 ($N = 40$)	G3 ($N = 51$)	P value
eGFR (mL/min/1.73 m ²)	57 (45–77)	83 (69–93)	47 (40–52)	
Alb (g/dL)	4.0 (3.5–4.2)	4.0 (3.6–4.3)	4.0 (3.5–4.2)	0.49*
TBil (mg/dL)	0.5 (0.3–0.7)	0.5 (0.4–0.7)	0.5 (0.3–0.7)	0.18*
UA (mg/dL)	5.5 (4.6–6.4)	5.0 (4.2–5.8)	5.8 (5.0–6.7)	<0.01*
LDL-C (mg/dL)	120 (110–170)	120 (110–160)	130 (110–170)	0.37*
HDL-C (mg/dL)	50 (42–61)	54 (45–59)	48 (40–59)	0.04*
TG (mg/dL)	150 (100–230)	120 (94–210)	170 (120–270)	0.03*
HbA1c (%)	9.6 (8.1–11)	11 (9.8–12)	8.5 (7.7–10)	<0.01*
ACR (mg/g Cr)	921 (330–3000)	560 (190–1400)	1500 (580–3600)	<0.01*

Data indicate median (interquartile range)

eGFR estimated glomerular filtration ratio, Alb albumin, TBil total bilirubin, UA uric acid, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglyceride, HbA1c hemoglobin A1c, ACR albumin creatinine ratio

* Wilcoxon's rank-sum test

Fig. 1 eGFR trajectories from the first visit are separately plotted based on the CKD stage. The values for CKD stages G3–4 are between the dashed lines. eGFR estimated glomerular filtration rate, CKD chronic kidney disease

lower UA and TG levels and ACR but had higher HDL-C and HbA1c levels.

Figure 1 shows the comparison of the eGFR trajectories from the first visit until ESRD between CKD stages G1–2 and G3. In most patients in both groups, eGFR had already started to decline on the first visit. However, in some patients, eGFR remained stable at CKD stages G1–G2 for several years before linearly declining to the ESRD level.

To show the annual decline rate, Δ eGFR in each patient was calculated using the entire eGFR data in CKD stages G3–4. The overall distribution of patients categorized by Δ eGFR value is shown in Fig. 2a, whereas a comparison between the groups is shown in Fig. 2b. The median Δ eGFR (mL/min/1.73 m² per year) was 9.2 [interquartile range (IQR) 5.1–15] among all patients and was significantly higher in patients with CKD stages G1–2 than in

Fig. 2 Distribution of slopes of eGFR decline at CKD stages G3–4. **a** Overall; **b** according to CKD stages G1–2 (blue) and G3 (brown). *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *ΔeGFR* annual eGFR decline rate

those with CKD stage G3 [12 (IQR 7.6–19) vs. 6.0 (IQR 4.9–13); $P < 0.01$].

The factors influencing $\Delta eGFR$ were investigated in all patients and also according to the CKD stage by forward stepwise selection of variables; Akaike's information criterion was used as the indicator. Log $\Delta eGFR$ was used as the dependent variable because $\Delta eGFR$ was not normally distributed (Fig. 2a). A model using positive variables (history of CAD, initial eGFR, and HDL-C) and negative variables (age, history of CI, and Alb) was selected to predict log $\Delta eGFR$ in all patients (adjusted $R^2 = 0.42$, Table 4). In patients with CKD stages G1–2, male sex and diastolic BP were selected as the positive variables (adjusted $R^2 = 0.37$). In patients with CKD stage G3, LDL-C

was selected as the positive predictor, whereas history of CI and serum TBil were the negative variables (adjusted $R^2 = 0.37$). Patients were further divided into two groups based on the median $\Delta eGFR$ as cutoff; age, history of CI, initial eGFR, and Alb levels were significantly different between these two groups (Table 5).

Discussion

We analyzed the trajectories and rates of eGFR decline from the first clinical visit until ESRD in Japanese type 2 diabetes patients with DKD. In type 1 diabetes, it has been reported that once eGFR starts to decline, deterioration of renal function becomes abrupt and continues at an almost constant rate until ESRD is attained [5]. In our study population that comprised patients with type 2 diabetes, the eGFR trajectories from CKD stages G1–2 were similar to those reported for type 1 diabetic patients with DKD. Krolewski et al. proposed new models of diabetic nephropathy progression in type 1 diabetes: early and late renal declines [5]. In this study, the decline rates in patients with initial CKD stages G1–2 and stages G3–4 seemed to correspond with the previously reported early and late renal decline models, respectively. Therefore, it is possible that both early and late renal declines may also occur in patients with type 2 diabetes.

The distribution of $\Delta eGFR$ in our study population was similar to that reported for type 1 diabetes. More than 60 % of the patients in this study fulfilled the definition of rapid progressive decline of renal function in type 1 diabetes (eGFR slope >7 mL/min/year) [5]. Renal function has been reported to decline very rapidly (eGFR decline rate >50 mL/min/year) in some patients with type 1 diabetes [5]. We observed four patients with $\Delta eGFR$ of >30 mL/min/1.73 m^2 per year who rapidly progressed to ESRD. These patients may have suffered from acute kidney injury or other concomitant serious renal problems. However, there may be rare cases of type 2 diabetes, as well as some cases of type 1 diabetes, in which renal function declines very rapidly despite the absence of any documented evidence of acute kidney events such as acute kidney injury. Interestingly, the distribution of $\Delta eGFR$ differed according to the CKD stage on the first visit (stages G1–2 vs. stage G3); this suggested that initial eGFR influences $\Delta eGFR$. Multivariate linear regression analysis clearly showed initial eGFR as a positive predictor for log $\Delta eGFR$. It was suggested that treatment with BP-lowering medications, including RASI, was associated with an initial fall in GFR that was most likely due to a reduction in intraglomerular pressure [12–14]. It was also previously demonstrated that a decrease in eGFR during losartan treatment is negatively correlated with long-term eGFR decline [15]. Because

Table 4 Multivariate linear regression analysis of the factors affecting decline in renal function in patients with DKD according to CKD stage

Variables	Total (<i>N</i> = 91)			G1–2 (<i>N</i> = 40)			G3 (<i>N</i> = 51)		
	β	SE	<i>P</i> value	β	SE	<i>P</i> value	β	SE	<i>P</i> value
Intercept	3.3	0.60	<0.01	−0.29	0.62	0.64	1.8	0.30	<0.01
Male (<i>N</i> = 1)	–	–	–	0.49	0.20	0.018	–	–	–
Age (years)	−0.017	0.0052	<0.01	–	–	–	–	–	–
Diastolic BP (mmHg)	–	–	–	0.028	0.0075	<0.01	–	–	–
History of CAD (<i>N</i> = 1)	0.32	0.16	0.044	–	–	–	–	–	–
History of CI (<i>N</i> = 1)	−0.69	0.20	<0.01	–	–	–	−0.55	0.26	0.043
eGFR (mL/min/1.73 m ²)	0.011	0.0028	<0.01	–	–	–	–	–	–
Alb (g/dL)	−0.45	0.10	<0.01	–	–	–	–	–	–
TBil (mg/dL)	–	–	–	–	–	–	−0.87	0.36	0.021
LDL-C (mg/dL)	–	–	–	–	–	–	0.0049	0.0013	<0.01
HDL-C (mg/dL)	0.009	0.0034	0.013	–	–	–	–	–	–

Based on multivariate linear regression analysis with stepwise forward selection of variables using log Δ eGFR as the dependent variable

SE standard error, BP blood pressure, CAD coronary artery disease, CI cerebral infarction, eGFR estimated glomerular filtration ratio, Alb albumin, TBil total bilirubin, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol

Table 5 Comparison of variables based on level of Δ eGFR (*N* = 91)

Variables	Under the median (<i>N</i> = 45)	Over the median (<i>N</i> = 46)	<i>P</i> value
Age (years)	60 (55–67)	52 (41–62)	<0.01*
History of CAD	11/45	8/46	0.41 [†]
History of CI	8/45	2/46	0.041 [†]
eGFR (mL/min/1.73 m ²)	51 (43–66)	69 (48–92)	<0.01*
Alb (g/dL)	4.1 (3.8–4.3)	3.8 (3.3–4.2)	0.021*
HDL-C (mg/dL)	48 (41–58)	51 (43–68)	0.16*

CAD coronary artery disease, CI cerebral infarction, eGFR estimated glomerular filtration ratio, Alb albumin, HDL-C high-density lipoprotein cholesterol

* Wilcoxon's rank-sum test

[†] Pearson's chi-square test

most patients with low eGFR were treated with RASIs on the first visit, the lower Δ eGFR in these patients may be accounted for by RAS inhibition.

Among all patients, the common risk factors on the first visit for eGFR decline and progression to ESRD were age, history of CAD and CI, and Alb. Age is an established risk factor for ESRD [16–18]. Our findings suggest that an earlier onset of diabetes mellitus was associated not only with ESRD incidence but also with eGFR decline rate. The histories of CAD and CI were positive and negative predictors, respectively. Cardiovascular dysfunction reportedly leads to renal dysfunction [7]. Silent CI has been reported to be a predictor of progression of nephropathy in patients with type 2 diabetes [19]. However, a history of CI was a negative predictor for eGFR decline in the present study. We presume that this difference is due to the intake of medications for HTN, hyperlipidemia, and antiplatelets

in our patients who had overt CI even before their initial visit. However, this hypothesis needs to be verified.

ACR was associated with a faster eGFR decline in patients with DKD [20]. The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that proteinuria is the single most powerful predictor of adverse renal outcomes with respect to nephropathy progression in patients with type 2 diabetes [21]. In Japan, where ACR is generally not measured in patients with macroalbuminuria, it might be useful to evaluate Alb levels instead of ACR levels when attempting to predict Δ eGFR.

Unexpectedly, HDL-C was a positive predictor of log Δ eGFR. It was reported that a higher mean HDL-C level was associated with a lower risk of developing diabetic nephropathy in patients with type 2 diabetes [22]. It was also reported that a higher HDL-C level was not associated

with a reduced mortality risk and CAD severity in patients with reduced kidney function [23]. Furthermore, patients with CKD were reported to show changes in the composition of and decreased protective function of HDL-C [24]. The vascular effects of HDL-C in patients with DKD might differ from those in normal patients. A recent experiment using HDL-C obtained from blood of children and adults with CKD (G2–3) (HDL-CKD) demonstrated that HDL (CKD) promoted endothelial superoxide production, substantially reduced nitric oxide bioavailability, and subsequently increased arterial BP in mice compared with HDL-C from healthy people [25].

We performed separate multivariate linear regression analyses for patients with CKD stages G1–2 and G3. In patients with CKD stages G1–2, male sex and diastolic BP, which are established risk factors for DKD, were selected. In patients with CKD stage G3, history of CI, LDL-C, and TBil were selected. LDL-C, a factor that commonly contributes to renal function decline [7], was a positive predictor of log Δ eGFR; TBil levels were negatively correlated with log Δ eGFR. Bilirubin is known to be a potent endogenous antioxidant [26]; in fact, a recent study in rodents found that bilirubin has a protective effect against diabetic nephropathy by inhibiting oxidative stress through the downregulation of renal NADPH oxidase [27]. Several cross-sectional studies in humans have shown a protective effect of bilirubin on diabetic nephropathy. Inoguchi et al. showed a lower prevalence of vascular complications, as well as reduced markers of oxidative stress and inflammation, in patients with Gilbert syndrome (congenital hyperbilirubinemia) and diabetes [28]. Low serum bilirubin levels were also associated with diabetic nephropathy progression in patients with type 2 diabetes [29, 30]. A post hoc analysis in the RENAAL trial with independent replication of the Irbesartan diabetic nephropathy trial (IDNT) indicated an independent inverse association of bilirubin with progression of nephropathy [31]. Therefore, serum TBil level could be a predictor of the rate of kidney function decline in patients with advanced DKD.

Our study had some limitations. First, this retrospective study was based on a small sample size in a single center. Larger and longer-term studies at multiple centers will be needed to draw more concrete conclusions. Second, we diagnosed DKD based on the presence of DR and laboratory data. The presence of diabetic glomerulopathy on renal biopsy was confirmed in five patients only. It is important to carry out renal biopsy on more patients for a definitive diagnosis. Third, this study had insufficient standardization of treatment regimens and glycemic and BP goals, although the therapies for glycemic control and BP control were based on guidelines [6, 8]. Also, differences in clinician competency may have affected the choice of drug regimen and targets (i.e., glycemic and BP

control); unmeasured clinical and social interactions may have also influenced treatment efficacy [32].

In conclusion, based on our analyses of the trajectories and rates of eGFR decline until ESRD in Japanese type 2 diabetic patients with DKD, early and late renal declines may occur in type 2 diabetes, as seen in type 1 diabetes. In addition to the common risk factors for ESRD, initial eGFR, HDL-C, and TBil on the first visit were identified as novel risk factors that influence renal function decline. These risk factors might differ between patients with early-stage and advanced-stage CKD.

Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or its substitute was obtained from all patients before they were included in the study.

Conflict of interest There was no financial sponsor for this study.

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