A retrospective cohort study of clinical characteristics and outcomes of type 2 diabetic patients with renal disease

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Background: Type 2 diabetes mellitus(T2DM) with chronic kidney disease (CKD) poses a serious health threat and becomes a new challenge. T2DM patients with CKD fall into three categories, diabetic kidney disease (DKD), non-diabetic kidney disease (NDKD), and diabetic kidney disease plus non-diabetic kidney disease (DKD+NDKD), according to renal biopsy. The purpose of our study was to compare the clinical characteristics and renal outcomes of DKD, NDKD, and DKD+NDKD patients.

Methods: Data on clinical characteristics, pathological findings, and prognosis were collected from June 2016 to July 2022 in patients with previously diagnosed T2DM and confirmed DKD and or NDKD by renal biopsy at Tongji Hospital in Wuhan, China. The endpoint was defined as renal transplantation, dialysis, or a twofold increase in serum creatinine.

Results: In our 6-year retrospective cohort research, a total of 268 diabetic patients were admitted and categorized into 3 groups by renal biopsy. The 268 patients were assigned to DKD (n=74), NDKD (n=109), and DKD+NDKD (n=85) groups. The most frequent NDKD was membranous nephropathy (MN) (n=45,41.28%). Hypertensive nephropathy was the most common subtype in the DKD+NDKD group (n=34,40%). A total of 34 patients (12.7%) reached the endpoint. The difference between the Kaplan-Meier survival curves of the DKD, NDKD, and DKD+NDKD groups was significant ($p < 0.05$). Multifactorial analysis showed that DKD [HR(95% CI): 0.201(0.067-0.598), p=0.004], increased SBP[HR(95% CI): 1.018(1.000-1.035), p=0.046], Scr[HR(95% CI): 1.006(1.000-1.012), p=0.037] and reduced serum ALB[HR(95% CI): 0.888(0.832-0.947), p=<0.001] were risk factors for outcomes in the T2DM patients.

Conclusions: This research based on a Chinese cohort demonstrated that the risk of endpoint events differed among DKD, NDKD, and DKD+NDKD patients. In T2DM patients with CKD, DKD patients were more often responsible for the renal endpoints. Increased SBP, higher Scr, and decreased serum ALB may be correlated with adverse renal outcomes in T2DM patients.

A retrospective cohort study of clinical characteristics and outcomes of type 2 diabetic patients with renal disease

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Abstract

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events differed among DKD, NDKD, and DKD+NDKD patients. In T2DM patients with CKD, DKD patients were more often responsible for the renal endpoints. Increased SBP, higher Scr, and decreased serum ALB may be correlated with adverse renal outcomes in T2DM patients.
Keywords: Diabetic kidney disease; Non-diabetic kidney disease; Type 2 diabetes mellitus; Renal biopsy.

Introduction

More than 500 million people around the world, accounting for over 10.5% of the global adult population are affected by diabetes mellitus (Sun et al. 2022). Type 2 diabetes mellitus(T2DM) comprises the majority of cases. There has been an increase in the population with T2DM from 1990 to 2019 universally in a systematic analysis of T2DM (Ye et al. 2023). The incidence of T2DM among Chinese adults was 12.4%, higher than the world estimate reported by Wang, L. et al(Wang et al. 2021).

Chronic exposure to hyperglycaemia affects the microvasculature in multiple organs, including the renal, the ocular, the peripheral nervous systems and so on(Barrett et al. 2017). Based on the pathological diagnosis, T2DM patients with chronic kidney disease (CKD) can be classified into diabetic kidney disease (DKD), non-diabetic kidney disease (NDKD), and diabetic kidney disease plus non-diabetic kidney disease (DKD+NDKD)(Anders et al. 2018). DKD affects approximately one-quarter of the diabetic population, which is the primary etiology of end stage renal disease (ESRD) (Faselis et al. 2020). In China, the prevalence of DKD was nearly one-fifth of patients with T2DM (21.8%) (Zhang et al. 2020). The prevalence of DKD has remained stable while the prevalence of NDKD in T2DM fluctuated greatly. The prevalence of NDKD ranged from 6.5% to 94%, with an average of 41.3% (Zhang et al. 2022). Part of the reason for the difference in prevalence is the discrepancy in clinical practice. This is a reflection of the wide range of considerations by clinicians before a patient undergoes a renal biopsy. NDKD can be either a solitary disease or a coexistence with DKD. The diagnosis of NDKD is important since NDKD can be made completely reversible with accurate diagnosis and prompt treatment.

The pathological feature and clinical characteristics of T2DM with CKD are likely to change under the conditions of aging population, increasing incidence of infections and malignancies, and the environmental pollution (Prasad et al. 2023).

Therefore, it is imperative to reassess CKD in T2DM and know the spectrum of T2DM with CKD considering the huge burden of T2DM and diabetes-related kidney diseases in China. Our study focus on the clinical characteristics and prognostic factors of T2DM with CKD which is appropriate for the Chinses population.

Materials & Methods

Study design and patients

Patients with previously diagnosed T2DM with CKD by renal biopsy were enrolled from 1 June 2016 to 31 July 2022, at Tongji Hospital, Wuhan, China in this retrospective study.

The inclusion criteria for this study were as followed: (i) age >18 years (ii) clinical diagnosis of T2DM (iii) underwent renal biopsy. The exclusion criteria included the items below: (i)ESRD

diagnosed before renal biospy or estimated glomerular filtration rate (eGFR) <15 ml/min per 1.73 m^2 (ii)patients with other types of diabetes mellitus or combined malignancy (iii)severe clinical data deficit (iii)renal transplantation, acute kidney injury and urinary tract infection. The endpoint was defined as renal transplantation, dialysis or a twofold increase in serum creatinine. This study adhered to the tenets of the Declaration of Helsinki declaration. Informed consent was waived by the Ethics Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology(No.TJ-IRB20210929).

Data acquisition

Demographic factors (age and sex), blood pressure factors [systolic blood pressure (SBP) and diastolic blood pressure (DBP)], and medication history were extracted from the electronic medical record. All original examination dates were derived from patients initial admission. Clinical data included hemoglobin (Hb), serum albumin(ALB), 24h proteinuria, eGFR, serum creatinine (Scr), hemoglobin A1C(HbA1C), immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), complement 3 (C3), and complement 4 (C4).

Statistical analysis

SPSS (version 25.0, IBM, US) software and R software (version 4.2.2, https://www.r-project.org) were used to analyze the full analysis set. Data were presented as median (interquartile range, IQR) or mean (standard deviation, SD) after normality tests on continuous variables, and as numbers and percentages on categorical variables. Missing values were imputed by predictive mean of closest points. The one-way ANOVA test, the Kruskal-Wallis test, and the χ^2 test were used to assessed differences. Endpoints were defined as dialysis, death, or twofold increase in serum creatinine. Kaplan-Meier analysis and Cox regression analysis were utilized to perform time-to-event analysis. Kaplan-Meier survival curves were plotted for patients in the DKD, NDKD, and DKD+NDKD groups. The results were compared using log-rank tests. Relevant risk factors and covariates with p values <0.1 were included in Cox regression proportional risk models. Covariates included indicators that met the requirements or were clinically significant after univariate analysis.

Results

Baseline characteristics of three groups

From a cohort of 315 T2DM patients underwent renal biopsy between 2016 and 2022, we excluded 47 non-compliant patients after applying exclusion criteria. The remaining 268 patients included 74 in the DKD group, 109 in the NDKD group, and 85 in the DKD+NDKD group, or 27.61%, 40.67%, and 31.72% of the cohort, respectively (Fig.1).

Table 1 presents the baseline characteristics of our study. 180(67.2%) of the 268 patients with inclusion criteria were male and 88(32.84%) were female. The median (±IQR) age of all those included in the criteria was 52.50±15 years, varying from 26 to 73 years. The median age of the DKD group was 50 years and it was 54 years (IQR 15) in the NDKD group, and 53 years (IQR

12) in the DKD+NDKD group. We followed patients for an average of 16.44 months. The mean duration of DM was 60 months, in order of NDKD, DKD+NDKD, DKD, from shortest to longest. Immunosuppressants and glucocorticoids were most commonly used in the NDKD group. Insulin was the predominant treatment in the DKD group. Statistically meaningful differences were observed in the three groups with regard to gender ($p=0.001$), duration of T2DM ($p<0.05$), diabetic retinopathy ($p<0.001$), red blood cell count ($p<0.05$), urinary sediment red blood cell count ($p<0.01$), glycosylated hemoglobin ($p<0.01$), HDL ($p<0.05$), and C3 ($p<0.05$) (table 1).

Pathological characteristics of renal alterations in T2DM patients

The most prevalent pathological type in the NDKD group was membranous nephropathy (n=45). Other subtypes within the NDKD category were IgA nephropathy(n=26), hypertensive nephrosclerosis(n=10), Henoch-Schoenlein purpura nephritis(n=5), obesity-related glomerulopathy(n=4), focal segmental glomurular sclerosis(n=3), renal diseases associated with plasma cell dyscrasias(n=1), renal amyloidosis(n=1), tubulointerstitial nephritis(n=2), thrombotic Microangiopathy(n=2), hepatitis B virus-related nephropathy(n=1), sclerosing glomerulonephritis(n=3), minimal change disease(n=2), proliferative glomerular lesions(n=4). Hypertensive nephropathy (n=34) was the dominant subtype, followed by IgA nephropathy (n=15) in the DKD+NDKD group (table 2).

The compassion of the cumulative incidence of endpoints in T2DM with CKD patients

Our average follow-up in this cohort was 16.44 months. The study's endpoints were all-cause death, renal transplantation, dialysis, and a twofold increase in serum creatinine. For an overall endpoint frequency of 12.7%, a total of 34 patients met the endpoint. After analyzing the incidence of the endpoints, our study found that the number of patients with endpoints in the three groups was 13, 9, 12, with proportions of 17.57%, 8.26%, 14.12%. Endpoint incidence was notably greater in the DKD group compared to the other groups ($p<0.05$) (Fig 2). The median survival time remained at 52.0 months for NDKD and 34.5 months for DKD. The median survival time of DKD+NDKD group can't be estimated as there were few endpoints in this group and most survival times correspond to survival probabilities greater than 0.5. One-year survival rate of kidney in each group were 93.24%, 92.66%, 98.82% and five-year survival rate were 82.43%, 89.91%, 90.59%.

Prognostic factors for endpoints

The proportional hazards (PH) assumption tests were conducted for the variables in the endpoints. The test results indicated that all variables satisfied the PH assumption. A multivariate Cox proportional hazards regression model included baseline variables that were deemed clinically relevant or univariately associated with the outcomes. The final model was simplified by careful selection of variables based on the number of events available (table 3). Lower serum albumin[HR(95%CI): 0.694(0.568-0.848), $p<0.001$], 24h proteinuria[HR(95%CI): 0.999(0.999-1), $p=0.013$], and SBP[HR(95%CI): 1.053(1.004-1.104), $p=0.035$] were determined to be important contributors to adverse renal outcomes in the DKD group by multivariate Cox

regression analysis (Table 4). NDKD patients with higher Scr[HR(95%CI): 1.016(1.006-1.026), p=0.002], lower serum albumin[HR(95%CI): 0.802(0.664-0.968), p=0.021], higher IgM [HR(95%CI): 14.313(3.29-62.272), p<0.001], older age[HR(95%CI): 0.868(0.773-0.974), p=0.016] were at increased risk for adverse renal effects (Table 4). Multivariate Cox regression results showed that hematuria[HR(95%CI): 0.969(0.941-0.997), p=0.03], 24h proteinuria[HR(95%CI): 1.000(1.000-1.001), p=0.037], C3[HR(95%CI): 0(0.000-0.12), p=0.007] were significant risk indicators for the endpoint event in the cohort of the DKD+NDKD group (Table 4). T2DM patients showed that DKD[HR(95%CI): 0.201(0.067-0.598), p=0.004], SBP[HR(95%CI): 1.018(1.000-1.035), p=0.046], ALB[HR(95%CI): 0.888(0.832-0.947), p<0.001], Scr[HR(95%CI): 1.006(1.000-1.012), p=0.037] were independent indicators of risk for the adverse renal outcomes.

Discussion

T2DM with CKD patients were divided into three groups in this study according to renal biopsy. Our results found that 40.67% of biopsied T2DM patients were diagnosed with NDKD and the incidence of DKD+NDKD was more than one-third (31.72%) of T2DM patients. Previous study showed that the prevalence of NDKD averaged 41.3%(Zhang et al. 2022) and Prevalence in the DKD+NDKD group varied from 4.7% to 19.72% (Fontana et al. 2021; Liu et al. 2016; Shadab et al. 2022). The above study demonstrates that a high proportion of T2DM patients with CKD still have NDKD, and that there is a great heterogeneity in the prevalence.

MN was the most prevalent with 41.28 %, followed by IgA nephropathy with 23.85 % in our study, consistent with the findings reported by Wang (Wang et al. 2019). But some researchers conclude that the major pathologic subtype of NDKD is IgA nephropathy (Byun et al. 2013; Zhou et al. 2008). Regional and ethnic differences, as well as the mechanism of renal pathologic diagnosis, may contribute to the pathologic distribution of the NDKD group.

Progression of T2DM, poor glycemic control, DR, deterioration of renal function, hematuria, hypertension can guide to differentiation between DKD and NDKD in many studies(Li et al. 2020; Popa et al. 2021; Saini et al. 2021), which were in consistent with our findings. Pallayova, M. et al. found that an strong predictor of NDKD was low serum HbA1c level (Pallayova et al. 2015). The ratio of glycated albumin to HbA1c, according to Wang, was better biopsy-proven DKD indicators than HbA1c (Wang et al. 2017). DKD and DR, as the two most important microvascular diseases of T2DM, share many pathophysiologic and pathologic similarities. DR was closely correlated with DKD (±NDKD), and the absence of DR was a highly predictive of NDKD(Lin et al. 2018), while Kritmetapak et al. found that in a multivariate analysis, DR was not an independent predictor (Kritmetapak et al. 2018) and the association between DKD and DR is not exactly parallel conducted by Li, M. et al (Li et al. 2021). Usually, lack of DR is predictive of NDKD, but does not exclude DKD.

The hemoglobin levels in the DKD patients were markedly lower as opposed to the NDKD patients. In the primal stages of kidney disease, studies have revealed that CKD patients with T2DM may become anemic (Xie et al. 2023). A recent cohort study in Japan showed that serum

Hb concentration, reflecting the onset of renal fibrosis, may be useful in predicting the development of DKD (Yamanouchi et al. 2022). Ito, K. considered that because of severe interstitial fibrosis and tubular atrophy, DKD is associated with anemia and anemia may aid in clinical differentiation between isolated DKD and NDKD (Ito et al. 2021). Furthermore, erythrocytes deformability and lifespan are also reduced by chronic inflammation and advanced glycation end products (Tsai & Tarng 2019).

In our study, HDL levels differed at baseline levels, but did not affect the prognosis. Nevertheless low HDL-C and high TG levels, in an Italian study, were considered independent risk factors for DKD prognosis over 4-year period (Russo et al. 2016). The cause of high TG and low HDL-C may be caused by metabolic syndrome, and may result from underlying insulin resistance. Multiple aspects of renal function, including renal hemodynamics and tubular function, are adversely affected by insulin resistance (Artunc et al. 2016).

The pathological classification of CKD with T2DM, in our results, was significantly associated with renal prognosis. Sun et al have also shown that DKD patients had relatively poorer outcomes than NDKD (Sun et al. 2023). DKD patients have a faster progression to ESRD than other CKD etiologies, requiring earlier renal replacement therapy, which results in a significant health and economic burden.

To further investigate potential predictors of the endpoint of DKD, we conducted the multivariate Cox regression analyses and found that lower serum ALB, elevated SBP and 24h proteinuria were independent risk factors for the endpoint of DKD patients. In Japanese patients with CKD, there was a negative and non-linear relationship between ALB and the decline in renal prognosis (Cheng et al. 2023). Moreover, patients with more than 5 years of T2DM and a 2-year history of hypertension, despite untypical features, were more likely to have DKD (Eswarappa et al. 2022).

Hypertension, identified as an independent predictor of microvascular complications (Asghar et al. 2023), induces oxidative stress and inflammation in the kidney (Lopes de Faria et al. 2011). Dynamic monitoring of proteinuria and blood pressure levels is critical for assessing the prognosis of patients with DKD and detecting high-risk populations.

In our findings, we observed that decreased ALB and increased Scr and IgM were identified as putative risk features for the endpoint in the NDKD group. Additionally, hematuria, 24h proteinuria, and C3 were possible risk elements for the outcome in patients with DKD+NDKD. Further, it has been found that hematuria is linked to a higher risk of ESRD in individuals with early diabetic CKD (Chong et al. 2012). Recent evidence suggests that dysmorphic erythrocytes are more effective than hematuria in indicating NDKD (Dong et al. 2016). The existence of differences in hematuria among different groups in our study aligns with findings from previous studies. Furthermore, Zhang J et al. identified in their study that decreased IgG levels and increased C3 levels were independent indicators of NDKD (Zhang et al. 2019). The role of IgM in NDKD is not yet known. Whether the complement deposition is a result of the severely damaged tissue or whether the secondary complement deposition is directly accelerating the kidney damage caused by the diabetic injury is still unknown and requires further investigation (Heybeli et al. 2019). Taken together, these indicators were associated with declining renal

function. Predictive models for diabetes-related kidney disease have been developed by many researchers (Anderson et al. 2021; Riphagen et al. 2015). Nevertheless, the majority of predictive models were developed using small cross-sectional studies or post-hoc analyses of randomized controlled trials. The development of follow-up prediction models with broader applicability requires further investigation.

There are some limitations of this study and the analysis of the results may be biased. We analyzed risk factors affecting prognosis using only a single-center cohort of individuals from China. In our cohort, there was insufficient follow-up time for some patients, but it is emphasized that the majority of patients enrolled in our study were not newly diagnosed with diabetes at the start of the follow-up period. This aspect partially mitigated the limitations of our relatively short follow-up duration.

Conclusions

In conclusion, this respective single-center cohort research based on a Chinese population demonstrated that the risk of endpoint events differed among DKD, NDKD, and DKD+NDKD groups. Patients with DKD were susceptible to getting the renal endpoints. In the diabetic population, it has been found that DKD, increased SBP, Scr, and low serum ALB were independent risk parameters for the occurrence of endpoint events. Therefore, it is crucial to focus on the DKD group and implement early preventive or therapeutic measures in order to delay the occurrence of these endpoints.

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Figure 1

Flow chart of participant selection in this study.

From the 315 patients in our single center, we screened patients who met the inclusion criteria. A total of 268 participants were included and divided into three groups based on renal puncture results.

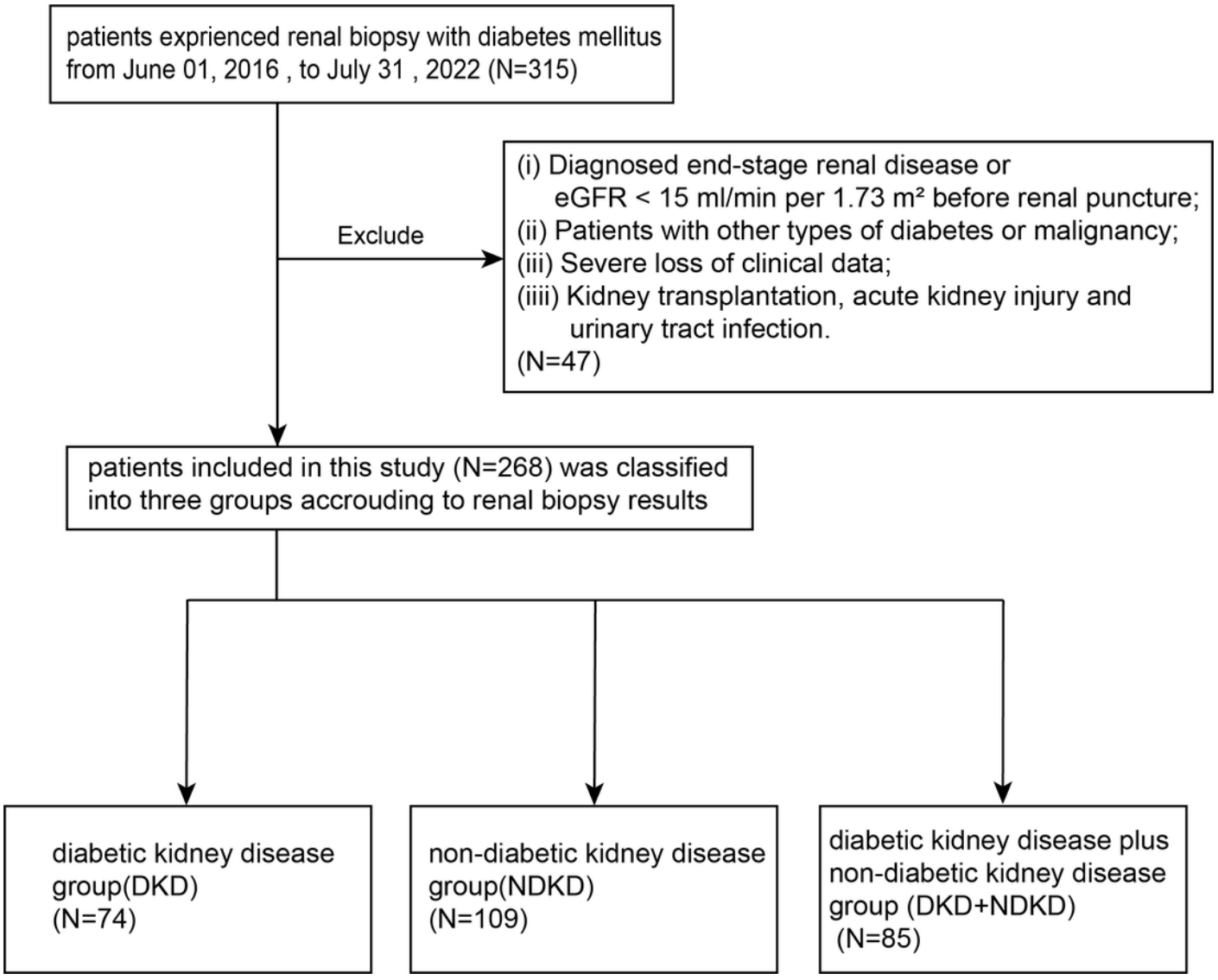

Figure 2

Comparison of renal survival rate in the DKD group, NDKD group and DKD+NDKD group.

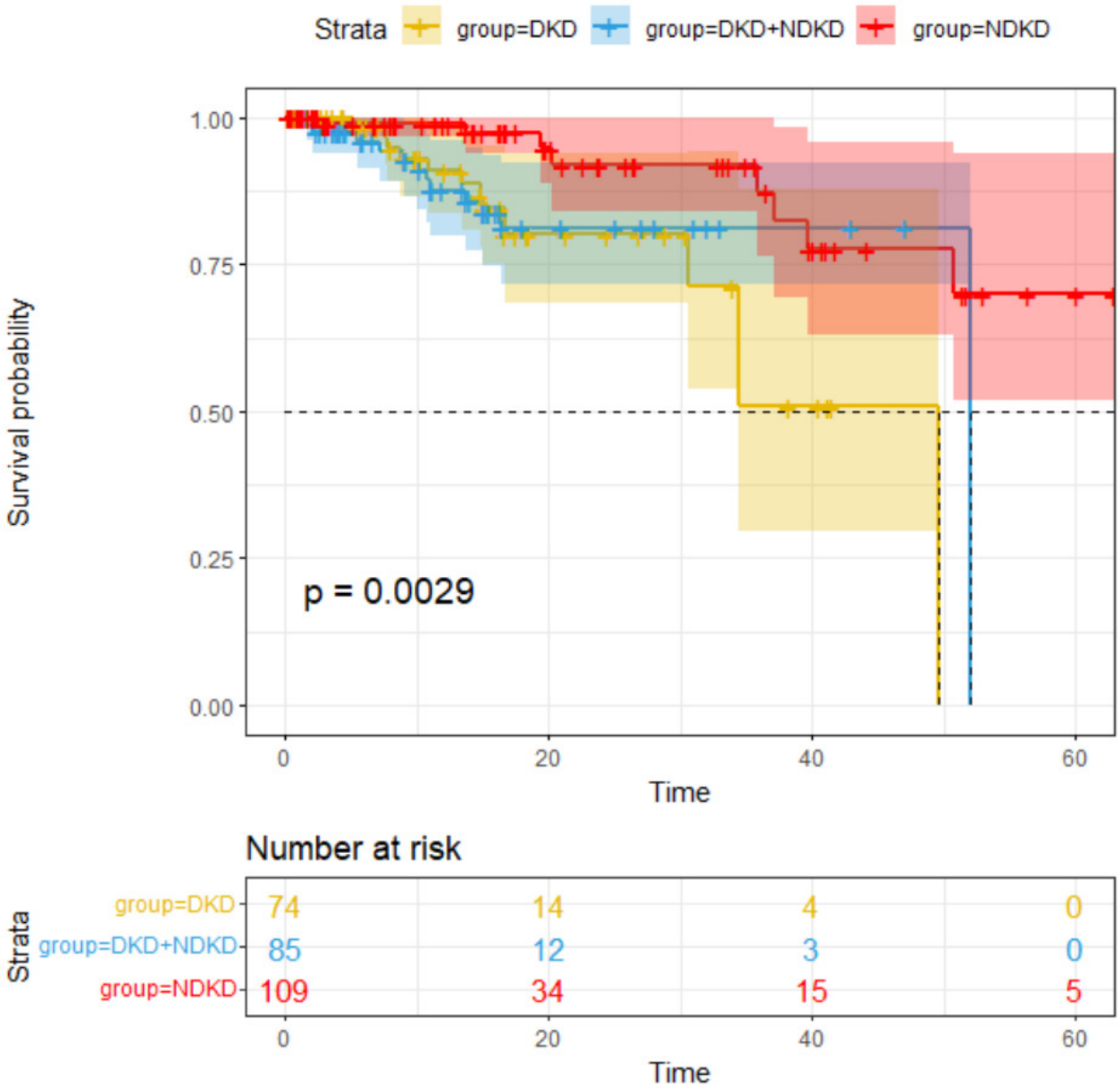

Table 1(on next page)

Baseline characteristics and drug treatment of patients in the DKD group, NDKD group and DKD+NDKD group.

1

Characteristic	Overall(n=268)	DKD(n=74)	NDKD(n=109)	DKD+NDKD(n=85)	p-value
Age(median [IQR])	52.50(15.00)	50.00(18.00)	54.00(15.00)	53.00(12.00)	0.133
Gender = male (%)	180.00 (67.20)	55.00(74.30)	59.00(54.10)	66.00(77.60)	0.001**
Cigarette (%)	60.00 (22.40)	21.00(28.40)	18.00(16.50)	21.00(24.70)	0.138
RASi (%)	184 (68.70)	53.00(71.60)	80.00(73.40)	51.00(60.00)	0.101
Immunosuppressant(%)	23.00 (8.60)	3.00 (4.10)	16.00 (14.70)	4.00 (4.70)	0.013*
Glucocorticoid (%)	51 (19.00)	1.00 (1.40)	40.00(36.70)	10.00 (11.80)	0.000**
Insulin (%)	122(45.50)	46.00 (62.20)	37.00(33.90)	39.00(45.90)	0.000**
Follow-up time(mean (SD))	16.44(13.74)	15.32(10.00)[a]	16.44 (19.00)[b]	15.00(11.00)[a]	0.009**
The duration of DM (median [IQR])	36.00(82.25)	60.00(111.00)[a]	24.00(57.00)[b]	42.00(79.50)[a]	0.007**
DR(%)	43.00(16.00)	27.00(36.50)	4.00(3.70)	12.00(14.10)	0.000**
Sbp(mean (SD))	138.43 (22.81)	141.70(22.74)	136.97(21.30)	137.46(24.66)	0.348
Dbp(mean (SD))	86.93(13.68)	87.99(12.73)	86.97(13.76)	85.94(14.46)	0.643
Hb (mean (SD))	125.82(23.73)	122.01(5.75)[a]	129.69(20.61)[b]	125.04(25.05)	0.048*
RBC (median [IQR])	4.29(1.00)	4.16(1.13)[a]	4.34(1.01)[b]	4.30(1.13)	0.043*
24h proteinuria(median [IQR])	2484.76(4431.73)	3438.53(5331.20)	2148.00(4583.10)	1925.80(3860.20)	0.055
24h urine protein >3.5g(%)	87.00(32.46)	30.00(40.54)	34.00(31.19)	23.00(27.06)	0.126
Urinary sediment RBC(median[IQ	30.15(49.84)	25.15(28.15)[a]	41.30(87.95)[b]	14.20(63.62)[a]	0.004**

R])					
BUN (median[IQR])	7.29(3.97)	8.21(4.53) [a]	6.60(3.00) [b]	7.97(4.08) [a]	0.000**
Scr (median [IQR])	103.50(77.75)	115.00(84.38)[a]	89.00(48.50) [b]	122.00(100.50) [a]	0.000**
EGFR(median[IQR])	64.95 (48.35)	59.10(50.48) [a]	78.00(41.95) [b]	55.50(44.25) [a]	0.000**
ALB(median[IQR])	37.80(13.48)	34.95(11.55)	38.80(15.65)	39.70(10.90)	0.139
Blood glucose(median [IQR])	8.32(4.47)	8.98(5.49)	8.26(3.80)	8.23(4.41)	0.162
Glycosylated hemoglobin(median [IQR])	6.85(1.50)	7.60(1.80) [a]	6.60(1.10) [b]	6.80(1.00) [b]	0.002**
TC(median [IQR])	4.77(1.99)	4.90(1.74)	4.80(2.20)	4.58(1.80)	0.233
TG(median [IQR])	2.51(2.48)	2.72(3.01)	2.61(2.47)	2.39(2.23)	0.265
HDL-C(median[IQR])	0.98(0.38)	0.96(0.34)	1.04(0.38)[a]	0.93(0.39)[b]	0.043*
LDL-C(median[IQR])	2.65(1.27)	2.60(1.10)	2.74(1.32)	2.45(1.42)	0.448
IgG (mean (SD))	9.87(3.74)	9.70(4.40)	9.60(5.55)	10.49(3.94）	0.059
IgA (median [IQR])	2.54(1.43)	2.45(1.49)	2.64(1.61)	2.53(1.19)	0.730
IgM (median[IQR])	0.97(0.60)	0.98(0.61)	1.05(0.68)	0.89(0.37)	0.101
C3 (median [IQR])	0.96(0.25)	0.92(0.23) [a]	1.03(0.26) [b]	0.94(0.18) [a]	0.003**
C4 (median [IQR])	0.26(0.09)	0.27(0.09)	0.26(0.10)	0.25(0.09)	0.609

Notes: Data are presented as medians with ranges, or counts and percentages. [a] and [b] represent instances where there are significant differences between [a] and [b]. P*<0.05, P**<0.01, P***<0.001
Abbreviations: DR, diabetic retinopathy; DM, diabetes mellitus; UACR, urinary albumin/creatinine ratio; Sbp, systolic blood pressure; Dbp, diastolic blood pressure;Hb; BUN, Blood Urea Nitrogen ; Scr, serum creatinine; EGFR, estimated glomerular filtration rate; ALB, albumin; TC, total cholesterol;TG, triglyceride; HDL-C, high density lipid-cholesterol; LDL-C, low density lipid-cholesterol.

Table 2(on next page)

Comparison of pathological characteristics between NDKD and DKD+NDKD groups .

1

Pathological characteristic	NDKD（109）	DKD+NDKD（85）
IgA nephropathy	26	15
Membranous nephropathy	45	12
Hypertensive nephrosclerosis	10	34
Henoch-Schoenlein purpura nephritis	5	0
Obesity-related nephropathy	4	0
Focal segmental glomerulosclerosis	3	3
Renal diseases associated with plasma cell dyscrasias	1	0
Renal amyloidosis	1	0
Tubulointerstitial nephritis	2	8
Thrombotic Microangiopathy	2	1
Hepatitis B virus-related nephropathy	1	1
Sclerosing glomerulonephritis	3	2
Minimal change disease	2	1
Proliferative glomerular lesions	4	1
Anti-neutrophil cytoplasmic antibody-associated vasculitis	0	2
Acute tubular necrosis	0	2
HCV associated glomerulonephritis	0	1
Post-infectious glomerulonephritis	0	1
Crescentic glomerulonephritis	0	1

2

Table 3(on next page)

Univariate Cox regression analyses for endpoints

1

	DKD		NDKD		DKD+NDKD	
Characteristic	HR(95%CI)	p-value	HR(95%CI)	p-value	HR(95%CI)	p-value
Age	1.008(0.957-1.062)	0.756	1.003 (0.925-1.087)	0.95	1.027 (0.959-1.101)	0.441
Gender	0.961(0.498-1.857)	0.907	0.398 (0.101-1.566)	0.188	0.636 (0.155-2.602)	0.528
SBP	1.047(1.019-1.076)	0.001*	1.032(1.003-1.062)	0.028*	0.99 (0.957-1.025)	0.58
Hb	0.935(0.899-0.973)	0.001**	0.976(0.953-0.999)	0.042*	0.976(0.939-1.015)	0.221
Urinary sediment RBC	1.027(1.008-1.048)	0.007*	1.00(1.00-1.00)	0.769	0.993(0.975-1.011)	0.452
Serum Alb	0.792(0.704-0.893)	0.000**	0.931(0.872-0.993)	0.029*	0.93(0.859-1.006)	0.071
Scr	1.013(1.005-1.022)	0.002**	1.004(1.002-1.007)	0.003**	0.997 (0.98-1.015)	0.777
24h urine protein	1.00(1.00-1.00)	0.047*	1.00(1.00-1.00)	0.463	1.00(1.00-1.00)	0.05*
TC	1.093(0.721-1.657)	0.676	1.056(0.729-1.528)	0.774	1.004(0.652-1.545)	0.986
TG	0.813(0.65-1.017)	0.07	0.947(0.728-1.232)	0.684	1.01(0.818-1.246)	0.928
HDL	1.606(0.44-5.866)	0.473	1.734(0.277-10.838)	0.556	2.389(0.325-17.535)	0.392
LDL	1.163(0.642-2.107)	0.618	1.214(0.771-1.912)	0.402	0.761(0.382-1.513)	0.436
IgG	0.757(0.588-0.974)	0.03*	0.949(0.789-1.141)	0.579	0.759(0.581-0.991)	0.043*
IgA	1.428(0.818-2.492)	0.21	1.07(0.583-1.964)	0.828	0.586(0.263-1.306)	0.191
IgM	0.523 (0.16-1.709)	0.283	4.049(1.537-10.668)	0.005**	1.568(0.33-7.462)	0.572
C3	0.173 (0.005-6.185)	0.336	0.142(0.002-11.771)	0.386	0.02(0-0.937)	0.046*

2

Table 4(on next page)

Multivariate Cox regression analyses for endpoints.

(A) DKD

Characteristic	HR(95%CI)	p-value
ALB	0.694(0.568-0.848)	<0.001***
24h proteinuria	0.999(0.999-1)	0.013*
SBP	1.053(1.004-1.104)	0.035*
DR	2.729(0.506-14.723)	0.243
age	0.905(0.811-1.01)	0.075

(B) NDKD

Characteristic	HR(95%CI)	p-value
ALB	0.802(0.664-0.968)	0.021*
Scr	1.016(1.006-1.026)	0.002**
hematuria	1.000(0.999-1.000)	0.377
IgM	14.313(3.29-62.272)	<0.001***
SBP	1.043(0.990-1.099)	0.117
age	0.868(0.773-0.974)	0.016*

(C) DKD+NDKD

Characteristic	HR(95%CI)	p-value
Scr	0.978(0.956-1.001)	0.056
Hb	0.949(0.894-1.008)	0.088
hematuria	0.969(0.941-0.997)	0.03*
24h proteinuria	1.000(1.000-1.001)	0.037*
IgG	0.653(0.414-1.03)	0.067
C3	0.000(0.000-0.12)	0.007**

(D) Total patients

Characteristic	HR(95%CI)	p-value
DKD	0.201(0.067-0.598)	0.004**
SBP	1.018(1.000-1.035)	0.046*
Hb	0.981(0.959-1.003)	0.085
24h proteinuria	1.000(1.000-1.000)	0.307
ALB	0.888(0.832-0.947)	<0.001***
Scr	1.006(1.000-1.012)	0.037*
age	0.97(0.929-1.013)	0.171

p* < 0.05; P** < 0.01; P***<0.001