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Characterization of diabetic kidney disease in 235 patients: clinical and pathological insights with or without concurrent non-diabetic kidney disease

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Abstract

Background This study aimed to explore the clinical and pathological features of patients with diabetic kidney disease (DKD), with and without non-diabetic kidney disease (NDKD), through a retrospective analysis. The objective was to provide clinical insights for accurate identification.

Methods A retrospective analysis of 235 patients admitted to the Department of Nephrology at Hangzhou Hospital of Traditional Chinese Medicine was conducted between July 2014 and December 2022. These patients underwent renal biopsy and received a pathology-based diagnosis of DKD. They were categorized into the DKD alone group (93 cases) and the DKD + NDKD group (142 cases).

Results In the DKD alone group, gender distribution was even, with ages mainly between 50 and 59 years, and a disease duration of less than 5 years, primarily presenting nodular diabetic glomerulosclerosis. In contrast, the DKD + NDKD group had a higher male incidence, a wider age range, longer disease duration, and prevalent diffuse diabetic glomerulosclerosis. Acute and chronic tubulointerstitial lesions and IgA nephropathy were the predominant types of combined NDKD, accounting for 40.14% and 35.21%, respectively. Clinical correlation analysis revealed associations between glomerular grading, tubulointerstitial lesions, renal arteriolar vitelliform lesions, renal vascular atherosclerosis, and clinical parameters such as 24-hour urine protein, hemoglobin, and urinary specific gravity. Multifactorial logistic regression analysis identified independent factors affecting DKD + NDKD, including body mass index, blood creatinine level, microscopic erythrocyte grade, urinary immunoglobulin G/creatinine ratio, and serum immunoglobulin A.

Conclusion The research underscores distinctions in age, gender distribution, disease duration, and renal pathology between DKD alone and DKD + NDKD groups. Additionally, significant discriminative factors including BMI, blood creatinine level, microscopic erythrocyte grade, UIgG/urine creatinine ratio, and serum IgA levels help differentiate DKD from NDKD, thereby enabling personalized treatment approaches. Furthermore, the study highlights the role of

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RASi as the most commonly used drug in the treatment of both DKD and NDKD, with emerging drugs such as SGLT2 inhibitors showing promising renal protective effects.

Keywords Diabetes mellitus, Diabetic kidney disease, Non-diabetic kidney disease, Pathologic features, Clinical features

Introduction

Diabetic kidney involvement primarily manifests as diabetic kidney disease (DKD), which is a leading cause of end-stage kidney disease (ESKD) [1, 2]. However, some diabetic patients may solely present with diabetes mellitus or non-diabetic kidney disease (NDKD), or DKD combined with NDRD [3, 4]. This study statistically analyzed patients with DKD and DKD + NDKD, investigating their pathological and clinical characteristics, and identifying the independent factors associated with DKD + NDKD to aid clinical differentiation.

Materials and methods

Study design and population

This single-center retrospective investigation included 235 patients diagnosed with diabetic kidney disease who underwent renal biopsy at the Nephrology Department of Hangzhou Hospital of Traditional Chinese Medicine between July 2014 and December 2022. Inclusion criteria were: (1) clinical diagnosis of diabetes mellitus; (2) nephropathologic diagnosis of DKD or DKD + NDKD; (3) availability of complete clinical and pathological data. Exclusion criteria were: (1) pathology indicating NDKD; (2) incomplete clinical and pathological data; (3) patients with acute illnesses, immunological disorders, malignancies, or infections. Details of the inclusion and exclusion criteria are summarized in Fig. 1.

Data collection

General clinical data, laboratory examination results, and renal biopsy pathology data were collected from patients diagnosed with DKD who underwent renal pathology biopsy at Hangzhou Hospital of Traditional Chinese Medicine. The data were categorized into the DKD alone group and the DKD + NDKD group. DKD pathology grading criteria published in the American Journal of Kidney Diseases were used as a reference for grading [5]. Grade I represents simple glomerular basement membrane thickening, characterized by the absence or presence of mild specific changes under light microscopy. Electron microscopy reveals glomerular basement membrane thickening, exceeding 395 nm in women and 430 nm in men (age ≥ 9 years), with pathological changes not reaching grades II, III, or IV. Grade IIa represents mild tethered basement membrane widening, with mild widening observed in over 25% of the glomeruli and no pathological changes reaching grades III or IV. Grade IIb denotes severe thylakoid stromal widening, with over 25% of glomeruli exhibiting severe widening and pathological changes not extending to grades III or IV. Grade III manifests as nodular sclerosis, characterized by more than one Kimmelstiel–Wilson nodule (K-W nodules), with pathological changes not reaching grade IV. Grade IV indicates advanced diabetic glomerulosclerosis, with over 50% total glomerulosclerosis accompanied by concurrent grade I-III pathological changes. For tubulointerstitial lesions, the interstitial fibrosis and tubular atrophy (IFTA) score was based on the percentage of the involved area of interstitium and tubules, with a score of 0 indicating no IFTA, 1 indicating less than 25% involvement, 2 indicating 25–50% involvement, and 3 indicating more than 50% involvement. The interstitial inflammation score was based on inflammatory infiltrates (T lymphocytes and macrophages), with a score of 0 indicating no infiltrates, 1 indicating infiltrates around atrophic tubules, and 2 indicating infiltrates in areas beyond atrophic tubules. For vascular lesions, arteriolar hyalinosis was scored as 0 for none, 1 for one arteriole affected, and 2 for more than one arteriole affected. Arteriosclerosis was scored based on the most severely affected artery: 0 for no intimal thickening, 1 for intimal thickening less than the thickness of the media, and 2 for intimal thickening greater than the thickness of the media. Renal biopsy pathology was evaluated by the same experienced renal pathologist, and based on the criteria, the pathological findings were classified as follows: early diabetic kidney injury in Grade I, diffuse diabetic glomerulosclerosis in Grades IIa and IIb, nodular diabetic glomerulosclerosis in Grade III, and advanced diabetic glomerulosclerosis in Grade IV.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 software. Measurement data following normal distribution were presented as $\bar{x} \pm s$ and compared between groups using the independent samples t-test. Non-normally distributed measurement data were presented as M (P_{25}, P_{75}) and compared between groups using the Kruskal–Wallis rank-sum test. Counting data were expressed as the number of cases and percentage, and were compared between groups using the χ^2 test or Fisher's exact probability method. Statistical significance was set at $P < 0.05$.

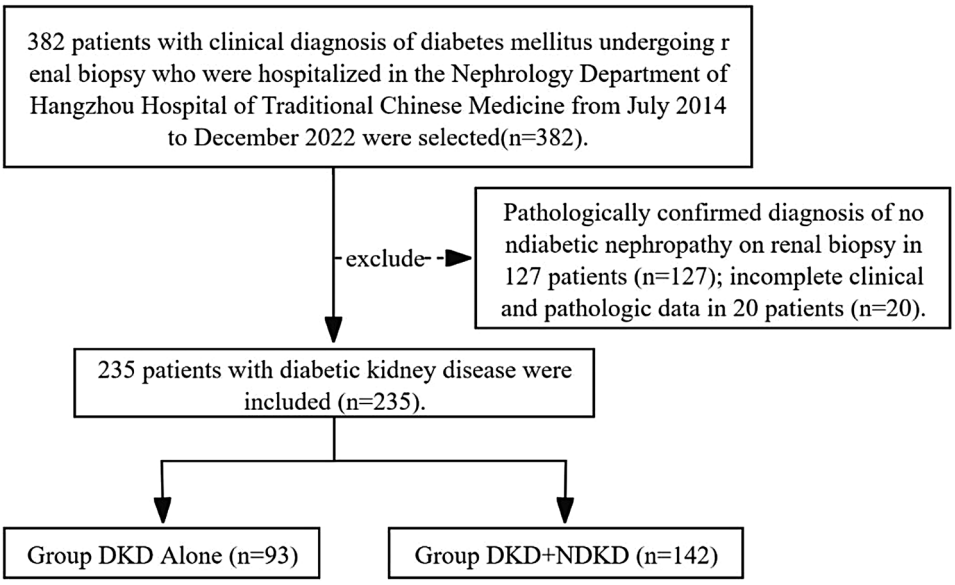

Fig. 1 Screening process for selecting patients with diabetic kidney disease

Results

Clinical data

Among the 235 patients diagnosed with DKD, 93 were classified in the DKD alone group, while 142 were categorized in the DKD + NDKD group. There were 65 (69.89%) males and 28 (30.11%) females in the DKD Alone group and 117 (82.39%) males and 25 (17.61%) females in the DKD + NDKD group. Both DKD Alone and DKD + NDKD groups had the highest percentage of patients in the age range of 50–59 years, accounting for 40.86% and 38.03%. There was no significant difference in the duration of diabetes mellitus between the two groups, with the highest percentage of patients with a history of disease < 5 years. 26.88% and 37.32% were in the DKD alone group and the DKD + NDKD group, respectively. This was followed by patients with 10 years ≤ history < 15 years, accounting for 25.81% and 24.65%, respectively. The least were patients with diabetes history > = 20 years with only 7.53% and 7.75%.

In comparing clinical data between the two groups, significant differences were observed in sex, body mass index (BMI), hemoglobin, urine osmolality, blood creatinine, microscopic erythrocyte grade, urinary immunoglobulin G (UIgG)/creatinine ratio, and serum IgA. The proportion of men and the proportion of microscopic erythrocyte grade in the DKD + NDKD group were higher than those in the DKD alone group. Moreover, BMI, hemoglobin, urine osmolality, blood creatinine, and serum IgA were higher in the DKD + NDKD group. Urinary IgG/creatinine ratio was higher in the DKD alone group compared to the DKD + NDKD group. These results are presented in Table 1.

Renal pathology

Distribution of pathological types

In the DKD alone group, the predominant pathological findings were nodular diabetic glomerulosclerosis, followed by diffuse diabetic glomerulosclerosis, early diabetic nephropathy, and advanced diabetic glomerulosclerosis. Within the DKD + NDKD group, the most frequent DKD pathologic findings were Diffuse Diabetic Glomerulosclerosis, followed by Nodular Diabetic Glomerulosclerosis, then Early Diabetic Nephropathy and Advanced Diabetic Glomerulosclerosis. combined NDKD, the most prevalent pathological types were acute and chronic tubulointerstitial disease (ATID, CTID) and IgA nephropathy. Furthermore, concurrent cases of IgA nephropathy, CTID, and membranous nephropathy (MN), MN with ATID and CTID, and other renal injuries (such as monoclonal Ig secondary kidney damage, crescentic glomerulonephritis, hepatitis B virus-associated secondary nephritis, lupus nephritis, proliferative sclerosing glomerulonephritis, crystalline nephropathy, dry syndrome kidney injury, or obesity-associated kidney injury) were observed. The distribution of pathological types is shown in Figs. 2 and 3. The example of pathologic staining results for DKD is shown in Fig. 4.

3.2.2 Renal pathology grading and scoring

As patients with early diabetic nephropathy in the sample did not yet exhibit significant glomerular, tubulointerstitial, and renal vascular lesions, pathological grading of diabetic nephropathy was not applicable. Excluding 65 patients with pathology suggestive of early diabetic nephropathy, the distribution of glomerular grading, tubulointerstitial lesions (IFTA score, interstitial

Table 1 Comparative analysis of clinical characteristics among patient cohorts

		DKD Alone[b] (*n* = 93)	DKD + NDKD[b] (*n* = 142)	Ratio	χ^2/Z	*P*
Sex	Male	65	117	64.30%	5.029	0.025*
	Female	28	25	47.20%		
Age(years)	< 30	1	0	0.00%	3.386	0.641
	30–39	8	17	68.00%		
	40–49	19	23	54.76%		
	50–59	38	54	58.70%		
	60–69	23	39	62.90%		
	≥ 70	4	9	69.23%		
History of diabetes(years)	< 5	25	53	67.90%	4.846	0.303
	< 10	22	31	58.50%		
	< 15	24	35	59.30%		
	< 20	15	12	44.40%		
	≥ 20	7	11	61.10%		
Hypertension	No	3	11	78.60%	2.050	0.152
	Yes	90	131	59.30%		
Non-diabetic Retinopathy	No	84	118	58.40%	2.430	0.119
	Yes	9	24	72.70%		
High blood fat disease	No	36	58	61.70%	0.107	0.744
	Yes	57	84	59.60%		
Metabolic acidosis	No	85	117	57.90%	3.774	0.052
	Yes	8	25	75.80%		
Microscopic erythrocyte grade[a]	-	53	77	59.20%	13.040	0.023*
	+-	23	22	48.90%		
	+	11	11	50.00%		
	++	4	19	82.60%		
	+++	2	9	81.80%		
	++++	0	4	100%		
Antinuclear Antibodies	Abnormal	22	25	53.20%	1.286	0.257
	Normal	71	117	62.20%		
Blood light chain KAP/LAM[b]	Abnormal	59	89	60.10%	0.014	0.905
	Normal	34	53	60.90%		
Age		54(47 ~ 61)	56(48 ~ 63)		-1.132	0.258
BMI[b]		23.71 ± 2.86	25.27 ± 3.23		2.344	< 0.001*
Average arterial blood pressure		106.31 ± 15.70	108.35 ± 1.34		0.1	0.337
Hemoglobin		116.12 ± 22.59	123.36 ± 22.06		0.013	0.016*
Urine osmolality		457(376 ~ 574)	513(421.75 ~ 632)		-2.112	0.035*
Blood creatinine		114.7(75 ~ 165)	131.5(91 ~ 176)		-2.108	0.035*
Blood uric acid		390(327.5 ~ 458)	408(354 ~ 491)		-1.827	0.068
Glycosylated hemoglobin		7.4(6.4 ~ 8.35)	7.1(6.3 ~ 7.6)		-1.875	0.061
24-hour urine protein		3.02(1.48 ~ 5.02)	2.265(0.883 ~ 5.388)		-1.095	0.274
UIgG/urine creatinine ratio[b]		0.213(0.073 ~ 0.650)	0.113(0.034 ~ 0.303)		-2.869	0.004*
Serum immunoglobulin G		1050(873.5 ~ 1290)	1020(793.25 ~ 1292.5)		-0.999	0.318
Serum immunoglobulin A		233(182.5 ~ 302.5)	263.5(201 ~ 353.5)		-2.361	0.018*
Serum immunoglobulin M		83(61 ~ 114.5)	84(61.5 ~ 118)		-0.005	0.996
Complement C3		103(92 ~ 114)	102(91 ~ 116)		-0.006	0.995
Complement C4		26(22 ~ 31)	26(22 ~ 31)		-0.437	0.662

Note: a.Microscopic erythrocytes: "-" denotes < 3, "+-" signifies 4–9, "+" represents 10–30, "++" indicates > 30, "+++" denotes microscopic erythrocytes greater than three-quarters of the field of view, and "++++" signifies an entire field of view littered with erythrocytes

b.diabetic kidney disease(DKD), non-diabetic kidney disease(NDKD), Kappa(KAP), Lambda(LAM), body mass index(BMI), urinary immunoglobulin G(UIgG)

c.The asterisk symbol (*) indicates statistical significance at $P < 0.05$

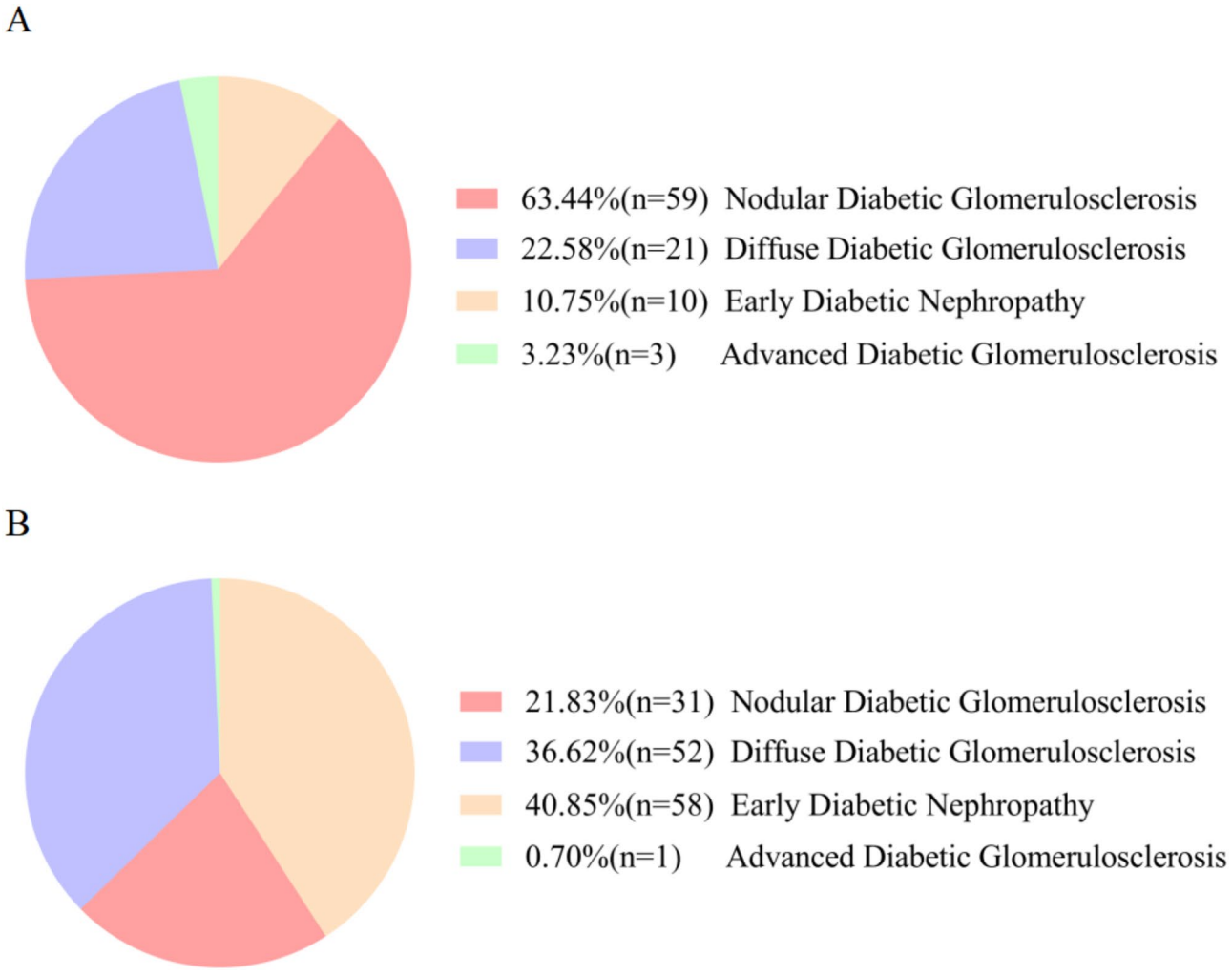

Fig. 2 Pathology of DKD alone group (**A**) and DKD + NDKD group (**B**). Note: Figure A represents the distribution of diabetic nephropathy pathology in the DKD alone group; Figure B represents the distribution of diabetic nephropathy pathology in the DKD + NDKD group

inflammation score), and renal vasculature (arteriolar hyalinosis, arteriosclerosis) among patients in the DKD alone group and the DKD + NDKD group is detailed in Table 2.

Clinicopathological correlation

The grading of glomerular lesions showed a significant positive correlation with 24-hour urine protein quantification, diabetic retinopathy (DR), and peripheral neuropathy (PN), while demonstrating a highly significant negative correlation with hemoglobin levels, urinary specific gravity, and osmolality. Additionally, a significant positive correlation was observed between DR and PN. Tubulointerstitial lesions (IFTA score, interstitial inflammation score) demonstrated a significant positive correlation with blood creatinine and uric acid levels and a significant negative correlation with estimated glomerular filtration rate (GFR). Renal arteriolar hyalinosis displayed a significantly positive correlation with age and blood creatinine levels, and a substantially negative correlation with urine osmolality and GFR. Renal vascular atherosclerosis showed a significant positive correlation with age and a negative correlation with GFR. These findings are summarized in Fig. 5.

Independent factors of DKD + NDKD

The results of univariate logistic regression analysis indicated that sex, BMI, hemoglobin levels, urine osmolality, blood creatinine levels, microscopic erythrocyte grade, UIgG/urine creatinine ratio, and serum IgA levels were significant factors influencing DKD + NDKD ($P < 0.05$). Multifactorial logistic regression analysis revealed that BMI (odds ratio [OR] = 1.193, 95% confidence interval [CI]: 1.072 ~ 1.327, $P = 0.001$), blood creatinine level (OR = 1.007, 95% CI 1.003 ~ 1.011, $P = 0.001$), microscopic erythrocyte grade (+++) (OR = 5.879, 95% CI 1.529 ~ 22.604, $P = 0.01$), UIgG/urine creatinine ratio (OR = 0.242, 95% CI 0.089 ~ 0.661, $P = 0.006$), and serum

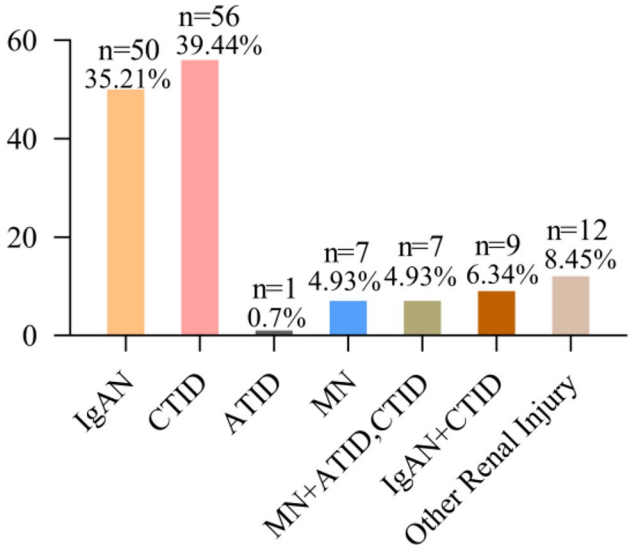

Fig. 3 Pathology of DKD + NDKD group. Note: Legend depicts renal pathology. IgA nephropathy (IgAN); Acute tubulointerstitial disease (ATID); Chronic tubulointerstitial disease (CTID); Membranous nephropathy (MN)

IgA (OR = 1.005, 95% CI 1.002 ~ 1.008, $P = 0.003$) were independently correlated with DKD + NDKD, as shown in Table 3. The prediction was performed with a classification table utilizing a binary logistic regression model, achieving a prediction accuracy of 73.6%, as presented in Table 4.

Treatment medications

A total of 360 instances of medication use were recorded. The most commonly used medication class was Renin-Angiotensin System Inhibitors (RASi), which include Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB), accounting for 42.50% of the patients. The second most commonly used medication class was Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors, accounting for 16.39%, as shown in Fig. 6. This treatment pattern was consistent across both the DKD and DKD + NDKD patient groups, with RASi being the predominant therapy, followed by SGLT2 inhibitors. Significant differences were observed in the utilization of SGLT2 inhibitors, Tripterygium Glycosides Tablets, glucocorticoids, immunosuppressive agents, and GLP-1 RA between the DKD alone and DKD + NDKD groups. Specifically, the DKD alone group used SGLT2 inhibitors and Tripterygium Glycosides Tablets at significantly higher rates and did not use glucocorticoids or immunosuppressive agents. The DKD + NDKD group, on the other hand, did not use GLP-1 RA, as presented in Table 5.

Discussion

This study examined individuals who underwent renal biopsy at Hangzhou Hospital of Traditional Chinese Medicine between July 2014 and December 2022 and received a pathological diagnosis of DKD. By exploring the relationship between various pathological and clinical factors, comparing variances between the DKD alone and DKD + NDKD cohorts, and investigating independent factors associated with DKD + NDKD, the aim is to identify patients with diabetic kidney disease combined with non-diabetic kidney disease DKD + NDKD early and intervene promptly.

Consistent with the findings of a previous retrospective study, there were no significant differences in age between patients in the DKD alone group and those in the DKD + NDKD group. However, what differs is that the results of this study suggest a difference in gender between the two groups, with no significant difference in the duration of diabetes. In the DKD alone group, the ratio of males to females is relatively balanced, with ages primarily concentrated between 50 and 59 years, and most patients having a disease duration of less than 5 years. In the DKD + NDKD group, there is a higher proportion of males, with a wide age distribution, although the most common age range remains 50–59 years. The disease duration tends to be longer, mainly falling within the < 5 years and 10–15 years categories [6].

Nodular glomerulosclerosis has been consistently identified as the primary pathological change in the group of DKD alone [7]And in the group of DKD + NDKD, the most pathological findings of diabetic nephropathy were diffuse diabetic glomerulosclerosis. Epidemiological investigations have indicated that MN is the most common pathology in DKD + NDKD, followed by IgA nephropathy [8]. However, in the present study, ATID/CTID and IgA nephropathy emerged as the predominant pathological types in the DKD + NDKD group, diverging from previous findings. IgA nephropathy remains a prevalent subtype among patients with diabetes [9–11]. The present study results indicate that DKD combined with IgA nephropathy is one of the most common forms of DKD + NDKD pathology. IgA nephropathy and DKD can lead to glomerular lesions. Glomerular endothelial dysfunction may also play a crucial role in this process. Research has indicated that endothelial-to-mesenchymal transition (EndMT) can occur in the glomeruli, promoting the fibrotic process and ultimately leading to glomerulosclerosis [12]. Furthermore, endothelial cell dysfunction may result in the loss of antioxidant and anti-inflammatory functions in the glomeruli, thereby further accelerating the progression of the disease [13]. While DKD was traditionally associated primarily with pathological glomerular changes [14], recent studies have highlighted a considerable correlation of tubulointerstitial

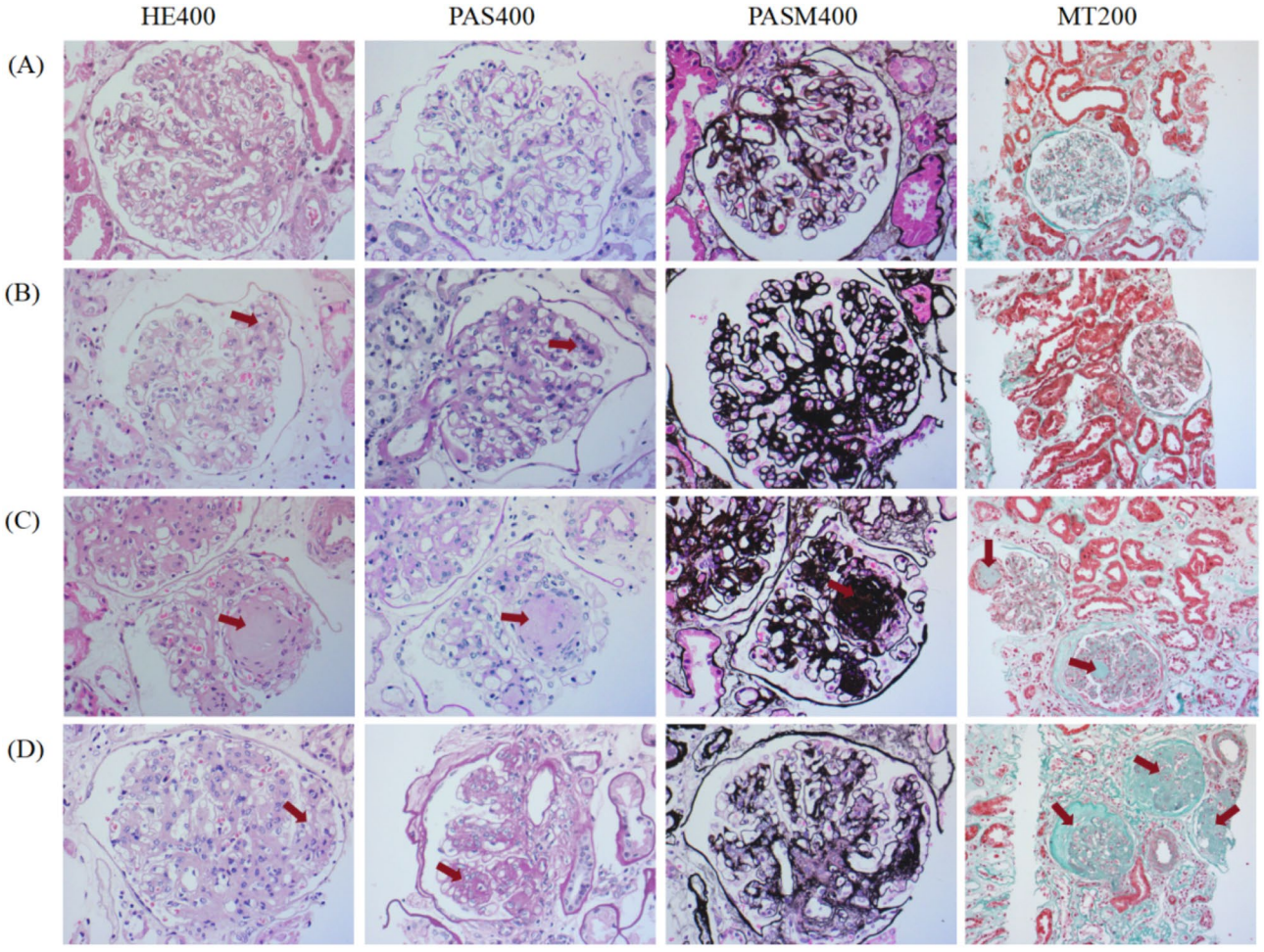

Fig. 4 Examples of pathological staining results in DKD. Note: (**A**) Early diabetic nephropathy, (**B**) diffuse diabetic glomerulosclerosis, (**C**) Nodular diabetic glomerulosclerosis, (**D**) advanced diabetic glomerulosclerosis. Hematoxylin and eosin (HE) staining; periodic acid-schiff (PAS) stainingPeriodic; acid-silver methenamine (PASM) staining; masson's trichrome (MT) staining

Table 2 Renal pathology grading and scoring in both groups

		DKD Alone ($n=93$)	DKD + NDKD ($n=142$)	F	*P*
Glomerular classification	IIa	3(3.61%)	19(21.84%)	27.267	< 0.01
	IIb	16(19.28%)	30(34.48%)		
	IIb-III	11(13.25%)	14(16.09%)		
	III	50(60.24%)	22(25.29%)		
	IV	3(3.61%)	2(2.30%)		
IFTA	1	12(14.46%)	13(14.94%)	0.567	0.753
	2	52(62.65%)	50(57.47%)		
	3	19(22.89%)	24(27.59%)		
interstitial inflammation	1	66(79.52%)	55(63.22%)	5.501	0.019
	2	17(20.48%)	32(36.78%)		
arteriolar hyalinosis	1	15(18.07%)	19(21.84%)	0.377	0.539
	2	68(81.93%)	68(78.16%)		
Arteriosclerosis	0	13(15.66%)	14(16.09%)	2.832	0.243
	1	59(71.08%)	68(78.16%)		
	2	11(13.25%)	5(5.75%)		

damage extent with renal function progression and prognosis [15, 16]. Tubulointerstitial lesions may manifest independently of glomerular lesions [17–19], with immunoinflammation [20–22] hypothesized to play a pivotal role in the onset and progression of renal tubular injury in DKD. Early disease stages frequently exhibit hypertrophic phenomena, characterized by increased renal tubular epithelial cell numbers and thickening of the tubular basement membrane, which are critical in triggering and accelerating renal tubular interstitial fibrosis [23]. Prolonged hyperglycemia, ischemia, and hypoxia lead to apoptosis, atrophy, and degeneration of renal tubular cells [24], along with inflammatory cell infiltration, increased inflammatory factors, interstitial fibrosis, interstitial arteriolar atherosclerosis, and small artery hyalinization, all influencing lesion development and progression [25, 26]. Correlation analyses have revealed a positive association between glomerular grading and 24-hour urine protein quantification, suggesting that glomerular structural damage may increase urinary protein excretion [27]. This

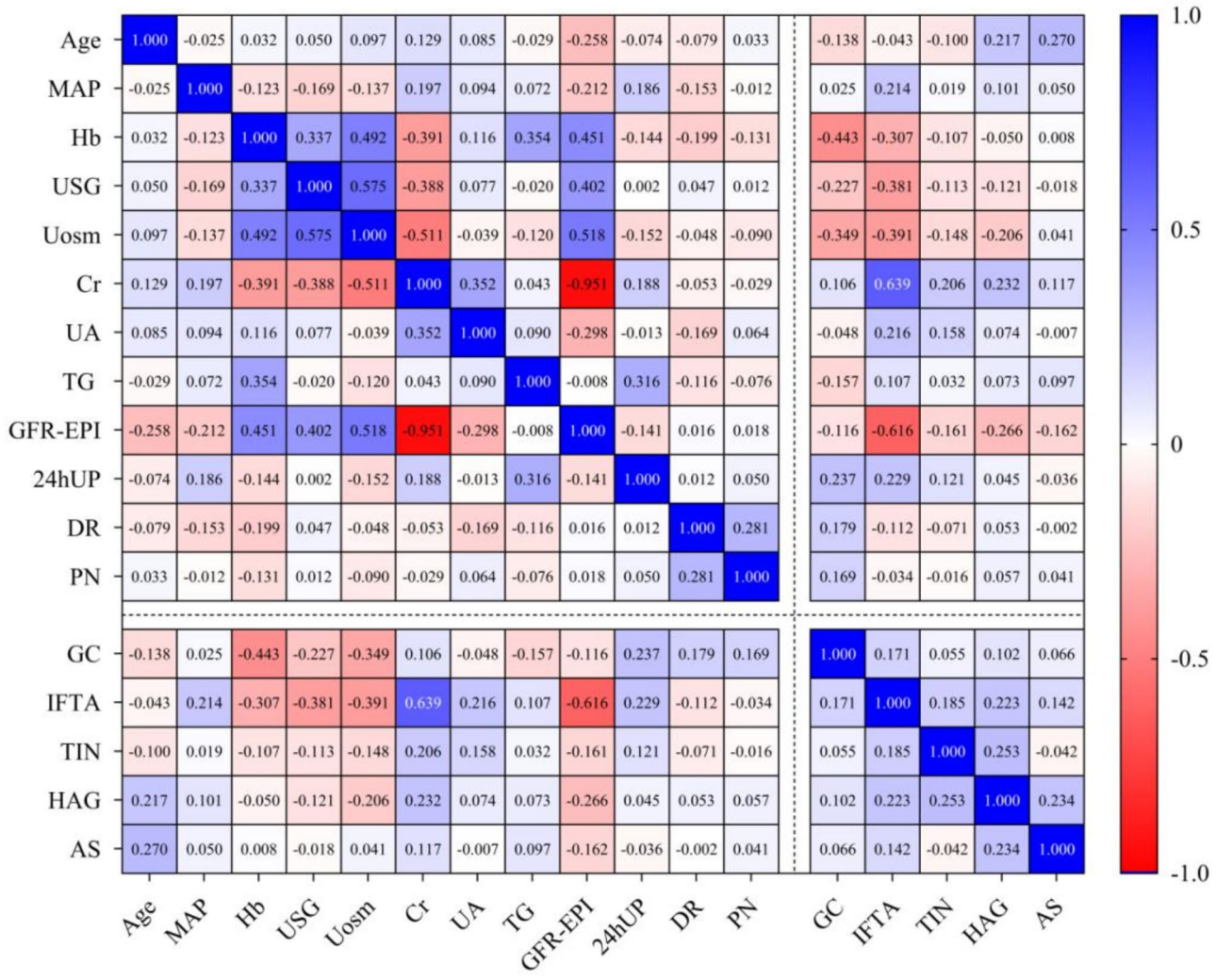

Fig. 5 Heatmap of clinicopathological correlation. Note: Mean arterial pressure (MAP); hemoglobin (Hb); urinary specific gravity (USG); urine osmolality (Uosm); blood creatinine (Cr); blood uric acid (UA); triglycerides (TG); glomerular filtration Rate (GFR-EPI); 24-hour Urinary Protein (24hUP); peripheral neuropathy (PN); diabetic retinopathy (DR); glomerular classification (GC); interstitial fibrosis and tubular atrophy (IFTA); tubular interstitial inflammation (TIN); arteriolar hyalinosis (HAG); atherosclerosis (AS)

phenomenon could stem from increased filtration membrane permeability and decreased tubular reabsorption. Moreover, shared pathogenic mechanisms such as hyperglycemia, oxidative stress, and microvascular dysfunction may explain the significant positive correlation between glomerular grading and both diabetic retinopathy and peripheral neuropathy [28, 29]. The significant negative correlation between glomerular grading and hemoglobin levels likely results from worsening renal function associated with increasing glomerular grading, leading to reduced renal erythropoietin (EPO) secretion and consequent exacerbation of anemia [30].

Therefore, a significant negative correlation exists between the progression of glomerular grading and the exacerbation of renal anemia. Glomerular grading demonstrated a significant negative correlation with urinary specific gravity and urine osmolality, indicating that more severe glomerular injury is associated with lower specific gravity and osmolality. This result is likely due to glomerular injury frequently leading to tubulointerstitial damage, which decreases tubular concentrating capacity and lowers urinary specific gravity and osmolality.

Tubulointerstitial lesions exhibited a significant positive correlation with blood creatinine and a significant negative correlation with GFR, reflecting the close association between tubulointerstitial lesions and renal function. Damage to the tubulointerstitial stroma affects the filtration and excretory functions of the kidneys, resulting in a weakened ability to filter waste products, such as creatinine, leading to their accumulation in the body, elevated blood creatinine levels, and decreased renal function. The positive correlation between tubulointerstitial

Table 3 Logistic regression analysis of DKD + NDKD factors

		Univariate logistic regression		Multivariate logistic analysis	
		χ^2/Z	*P*	OR (95% CI)	*P*
Sex	Male Female	5.029	0.025*	0.911(0.409 ~ 2.026)	0.818
BMI(kg/m^2)		2.344	< 0.001*	1.193(1.072 ~ 1.327)	0.001*
Hemoglobin(g/L)		0.013	0.016*	1.015(0.997 ~ 1.034)	0.102
Urine osmolality(mOsm/kg)		-2.112	0.035*	1.002(0.999 ~ 1.004)	0.202
Blood creatinine(umol/L)		-2.108	0.035*	1.007(1.003 ~ 1.011)	0.001*
Microscopic erythrocyte grade	-	13.040	0.023*		0.071
	+-			1469427539.261	0.999
	+			1.111(0.505 ~ 2.448)	0.793
	++			1.393(0.439 ~ 4.422)	0.574
	+++			5.879(1.529 ~ 22.604)	0.01*
	++++			5.863(0.937 ~ 36.687)	0.059
UIgG/Urine creatinine(mg/mgCr)		-2.869	0.004*	0.242(0.089 ~ 0.661)	0.006*
Serum immunoglobulin A(mg/dl)		-2.361	0.018*	1.005(1.002 ~ 1.008)	0.003*

Table 4 Predictions from the binary logistic regression model

Prediction	DKD + NDKD			
		No	Yes	Percentage correct (%)
DKD + NDKD	No	55	38	59.1
	Yes	24	118	83.1
Overall percentage				73.6

Table 5 Medications for DKD alone group and DKD + NDKD group treatment

	DKD(%)	DKD + NDKD(%)	χ^2	*P*
RASi	60(41.96%)	93(42.86%)	0.024	0.878
SGLT2 Inhibitors	31(21.68%)	28(12.90%)	5.540	0.019*
Tripterygium Glycosides Tablets	27(18.88%)	25(11.52%)	4.258	0.039*
Diuretics	14(9.79%)	25(11.52%)	0.264	0.607
Glucocorticoids	0(0.00%)	26(11.98%)	19.147	< 0.001*
Microvascular Protective Agent	5(3.50%)	5(2.30%)	0.475	0.491
Hydroxychloroquine	0(0.00%)	1(0.46%)	0.658	0.417
Combined Preparations	2(1.40%)	4(1.84%)	0.100	0.751
Immunosuppressive Drugs	0(0.00%)	8(3.69%)	5.424	0.02*
Biologics	0(0.00%)	2(0.92%)	1.321	0.25
GLP-1 RA	4(2.80%)	0(0.00%)	6.213	0.013*

Note: The following medications were used in the treatment of kidney diseases in this study:

Renin-Angiotensin System Inhibitors (RASi): Valsartan, Losartan Potassium, Telmisartan, Irbesartan, Benazepril, Perindopril

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors: Canagliflozin, Dapagliflozin, Empagliflozin

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA): Liraglutide

Diuretics: Hydrochlorothiazide, Torsemide, Furosemide, Spironolactone

Microvascular Protective Agent: Calcium Dobesilate

Combined Preparations: Valsartan-Amlodipine, Sacubitril-Valsartan

Immunosuppressive Drugs: Cyclophosphamide, Tacrolimus

Biologics: Rituximab

lesions and blood uric acid may be attributed to hyperuricemia causing vascular and tubulointerstitial damage by activating the renin-angiotensin system and immune system response [31].

Furthermore, tubulointerstitial lesions can hinder uric acid excretion, contributing to secondary hyperuricemia.

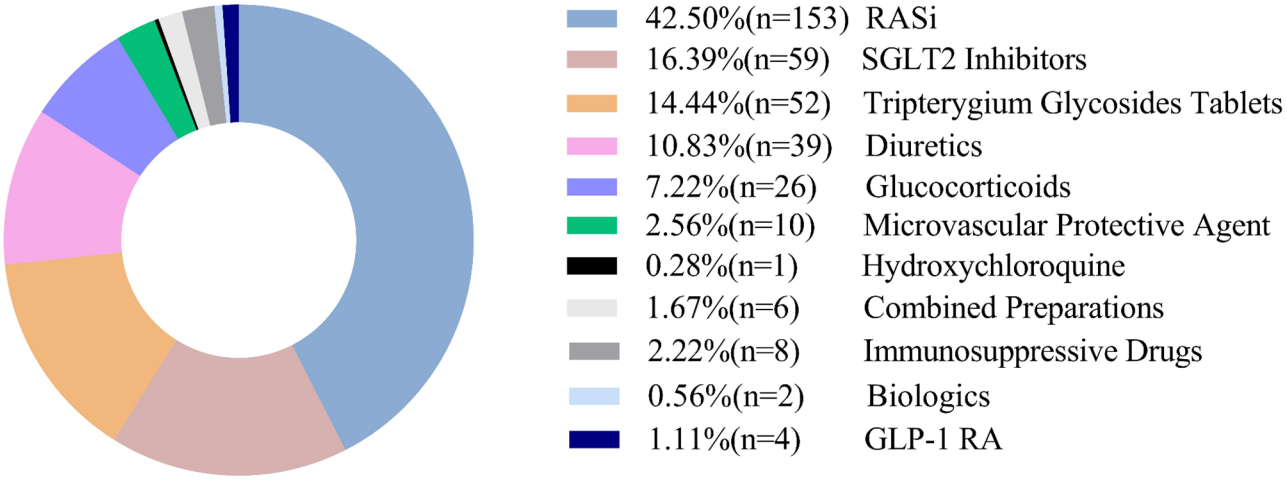

Fig. 6 Treatment medications. Note: The following medications were used in the treatment of kidney diseases in this study: Renin-angiotensin system inhibitors (RASi): valsartan, losartan potassium, telmisartan, irbesartan, benazepril, perindopril. sodium-glucose cotransporter 2 (SGLT2) inhibitors: canagliflozin, dapagliflozin, empagliflozin. glucagon-like peptide-1 receptor agonist (GLP-1 RA): liraglutide. diuretics: hydrochlorothiazide, torsemide, furosemide, spironolactone. microvascular protective agent: calcium dobesilate. combined preparations: valsartan-amlodipine, sacubitril-valsartan. immunosuppressive drugs: cyclophosphamide, tacrolimus. biologics: rituximab

Vitrification of renal arterioles was positively correlated with age and blood creatinine levels, and negatively correlated with urine osmolality and GFR. Physiological aging of blood vessels accelerates the vitrification of renal arterioles with increasing age. Diabetes-induced vitrification of renal arterioles reduces vascular elasticity, affecting renal blood supply and disrupting kidney filtration function, resulting in decreased GFR and impaired creatinine removal from the blood. The severity of renal arteriolar vitrification is negatively correlated with urine osmolality due to ischemic damage to glomeruli and tubules associated with the diseased arterioles. Consequently, the concentrating and reabsorbing functions of both distal and proximal tubules are impaired, resulting in decreased urine osmolality and increased nocturia.

Renal vascular atherosclerosis is positively correlated with age and negatively correlated with GFR. Renal vascular sclerosis may be part of systemic arteriosclerosis, affecting multiple organ blood supply and function, including the glomeruli. Increased renal vascular atherosclerosis severity is more likely to cause renal artery narrowing, leading to renal ischemia, glomerular atrophy, fibrosis, and necrosis, thereby reducing GFR.

Comparison of clinical and pathological data between the two groups revealed significant differences in glomerulopathy grading, tubulointerstitial lesions, Sex, BMI, microscopic erythrocyte grade, urine osmolality, blood creatinine, UIgG/urine creatinine, and serum IgA ($P < 0.05$). Multifactorial logistic regression analysis identified BMI, blood creatinine level, microscopic erythrocyte grade, UIgG/urine creatinine, and serum IgA as independent correlates of DKD + NDKD. Specifically, BMI, blood creatinine level, microscopic erythrocyte grade (+++), and serum IgA were identified as risk factors for DKD + NDKD, while UIgG/urine creatinine was identified as a protective factor. Previous studies have confirmed the role of hematuria and blood creatinine in identifying DKD + NDKD, suggesting that NDKD accelerates the deterioration of renal function in patients with type 2 diabetes [32].

Previous studies have hinted at a higher BMI in patients with NDKD [7]. This study similarly suggests that patients with comorbid NDKD exhibit a higher BMI compared to those with DKD, potentially indicating a link to obesity-associated nephropathy. Elevated levels of IgA in humoral immunity frequently signify an abundance of IgA or its immune complexes, which, coupled with factors such as local inflammatory responses, increase the risk of IgA nephropathy. UIgG/urine creatinine, relatively unaffected by other factors, might offer insights into diagnosing DKD. Considering IgG's sizeable molecular size, when the glomerular basement membrane's function is impaired, increased basement membrane leads to more frequent excretion of urinary large-molecule proteins, suggesting a likelihood of DKD. These findings provide critical factors for identifying patients with DKD + NDKD, aiding in accurate prediction of the pathological type and individualized treatment planning.

In our study, assessing the binary logistic regression model's predictive performance through a classification table yielded a prediction accuracy of 73.6%. While this result demonstrates substantial efficacy in sample classification for DKD + NDKD prediction, additional metrics are necessary for comprehensive performance evaluation. Further validation efforts are imperative to ensure the model's reliability and applicability.

In this study, the most commonly used therapeutic agents were RASi, accounting for 42.50% of all cases. This reflects the continued central role of RASi in the current clinical management of DKD and NDKD, owing to their significant effects in reducing proteinuria, controlling blood pressure, and improving renal function [33, 34]. However, research on the therapeutic effects of GLP-1 receptor agonists and SGLT2 inhibitors has become standard in the treatment of DKD and is increasingly being applied to patients with both DKD and NDKD. GLP-1 receptors are primarily expressed in the glomerulus, with reduced expression levels in the renal cortex of long-term diabetic patients. GLP-1 receptor agonists exert potential renal protection by activating the cAMP/PKA signaling pathway and inhibiting inflammation associated with diabetic kidney disease, with effects that include diuresis, antihypertensive action, and anti-inflammatory effects [35]. Furthermore, GLP-1 receptor agonists have been shown to significantly reduce the risk of kidney-specific composite outcomes and worsening proteinuria [36]. SGLT2 inhibitors have demonstrated significant clinical relevance in reducing proteinuria, slowing disease progression, halving serum creatinine levels, and initiating renal replacement therapy [37]. In this study, SGLT2 inhibitors accounted for 16.39% of therapeutic use. Although their application remains relatively limited, this suggests a growing adoption of SGLT2 inhibitors in kidney disease treatment, particularly due to their beneficial effects on cardiovascular health and renal protection [38]. Overall, the widespread use of RASi reflects clinicians' continued reliance on traditional treatment methods. However, the efficacy of GLP-1 receptor agonists and SGLT2 inhibitors further enhances their importance in the treatment of DKD and NDKD, marking a shift in therapeutic strategies. These strategies aim to achieve more comprehensive metabolic management while focusing on both cardiovascular and renal protection. The renal biopsies in this study were primarily performed between July 2014 and December 2022, during which period fenelidone was not used. This study not only underscores the continued use of traditional RASi but also highlights the emergence of new drugs that offer

additional treatment options, especially for patients inadequately controlled under traditional therapies.

An analysis of the medication use in the two groups showed significant differences in their use of SGLT2 inhibitors, Tripterygium Glycosides Tablets, glucocorticoids, immunosuppressants, and GLP-1 receptor agonists. Specifically, the DKD alone group used SGLT2 inhibitors and Tripterygium Glycosides Tablets at significantly higher rates and did not use glucocorticoids or immunosuppressive agents. The DKD + NDKD group, on the other hand, did not use GLP-1 RA. This difference reflects the different therapeutic strategies employed in the two groups. The DKD alone group made greater use of SGLT2 inhibitors and GLP-1 receptor agonists, which are highly nephroprotective and contribute to better control of proteinuria and improved renal function. In contrast, the DKD + NDKD group may have other comorbidities or underlying diseases (e.g., immune disorders), and therefore requires the use of therapies such as glucocorticoids and immunosuppressants to suppress inflammatory and immune responses. The significance of distinguishing between these two groups lies in the difference in treatment strategies, reflecting the fact that patients with different pathological conditions require different treatments. For patients with DKD alone, the focus is on slowing disease progression through glucose-lowering, antihypertensive, and renoprotective therapies. For patients in the DKD + NDKD group, treatment regimens need to emphasize both immunomodulation and control of other complications. Therefore, it is important to consider the presence or absence of comorbid non-diabetic nephropathy when formulating a treatment plan to avoid a one-size-fits-all approach and ensure that treatment is more precise and individualized.

This study was constrained by single-site, single-sample sources, failing to encompass geographic, population, and healthcare system diversities. Its retrospective nature restricted analysis to baseline data, precluding insights into long-term prognosis across diverse pathology types. Moreover, the study overlooked factors such as genetic predispositions and lifestyle influences beyond the clinical and pathologic data examined. Future investigations should address these limitations by broadening geographic and sample source scopes, conducting multicenter studies for enhanced patient representation, and incorporating long-term prospective follow-up. These initiatives would facilitate the development of more accurate prediction models by monitoring disease progression and treatment responses over extended periods. Moreover, integrating genetic and lifestyle information would enable a comprehensive understanding of diabetic nephropathy mechanisms, informing improved clinical management and treatment strategies.

Conclusion

In summary, this study identifies independent risk factors for DKD + NDKD, including BMI, blood creatinine, microscopic erythrocyte grade, urine IgG/urine creatinine ratio, and serum IgA levels. These clinical factors suggest a high likelihood of comorbid NDKD in these patients, highlighting the need for further renal biopsy. Clinicians should closely monitor these factors to inform a more individualized treatment plan. Based on pathological results, timely adjustments to the treatment regimen are essential, ensuring that therapeutic strategies are optimized to address both DKD and any coexisting NDKD, thereby improving patient outcomes.

Abbreviations

DKD	Diabetic kidney disease
NDKD	Non-diabetic kidney disease
ESKD	End-stage kidney disease
K-W nodules	Kimmelstiel–Wilson nodule
BMI	Body mass index
UIgG	Urinary immunoglobulin G
KAP	Kappa
LAM	Lambda
ATID	Acute tubulointerstitial disease
CTID	Chronic tubulointerstitial disease
MN	Membranous nephropathy
IFTA	Interstitial fibrosis and tubular atrophy
HE	Hematoxylin and Eosin
PAS	Periodic Acid-Schiff
PASM	Periodic Acid-Silver Methenamine
MT	Masson's Trichrome
GFR	Glomerular filtration rate
MAP	Mean Arterial Pressure
Hb	Hemoglobin
USG	Urinary Specific Gravity
Uosm	Urine Osmolality
Cr	Blood Creatinine
UA	Blood Uric Acid
TG	Triglycerides
GFR-EPI	Glomerular Filtration Rate
24hUP	24-hour Urinary Protein
PN	Peripheral Neuropathy
DR	Diabetic Retinopathy
GC	Glomerular classification
TIN	Tubular Interstitial Inflammation
HAG	Arteriolar hyalinosis
AS	Atherosclerosis
RASi	Renin-Angiotensin System Inhibitors
ACEI	Angiotensin-Converting Enzyme Inhibitors
ARB	Angiotensin II Receptor Blockers
SGLT2	Sodium-Glucose Cotransporter 2
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
CCB	Calcium Channel Blockers
EndMT	endothelial-to-mesenchymal transition
OR	Odds ratio
EPO	Erythropoietin

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Data availability
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval
This study received approval from the Ethics Committee of Hangzhou Hospital of Traditional Chinese Medicine (Ethics No. 2023KLL002). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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