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Associations between depressive and anxiety symptoms and incident kidney failure in patients with diabetic nephropathy

Chunmei Qin[1,2,3], Yucheng Wu[1,2], Yutong Zou[1,2], Yuancheng Zhao[1,2], Deying Kang[4] and Fang Liu[1,2*]

Abstract

Objective This study aimed to analyze the associations between depressive and anxiety symptoms and risk of incident kidney failure in patients with biopsy-proven diabetic nephropathy (DN).

Methods This retrospective study enrolled 241 type 2 diabetic patients with biopsy-proven DN. Huaxi Emotional-Distress Index (HEI) was used to evaluate the depression and anxiety status of patients on admission. According to the HEI score, DN patients were divided into HEI score ≤ 8 group (without depression and anxiety) and HEI score > 8 group (with depression and anxiety). The study endpoint was defined as progression to kidney failure. The cox proportional hazard analysis was performed to investigate the risk factors for progression to kidney failure in DN patients.

Results Twenty-three patients had HEI score > 8, accounting for about 9.5% of all patients. Compared with HEI score ≤ 8 group, those with HEI score > 8 had more severe proteinuria, higher systolic blood pressure, and lower baseline eGFR and serum albumin levels. During a median follow-up of 28 months, the outcome event occurred in 89 (36.9%) of all the patients. After multivariable adjustment, HEI score > 8 (HR 1.825, 95% CI 1.050–3.172) was associated with an increased risk of progression to kidney failure.

Conclusion Depressive and anxiety symptoms might be associated with an increased risk of progression to kidney failure in patients with DN, which implied psychosocial issues should be early screened, assessed and intervened to delay the progression of DN.

Keywords Diabetic nephropathy, Huaxi emotional-distress index, Depression and anxiety, Kidney failure

Introduction

Diabetic nephropathy (DN), a well-recognized microvascular complication of diabetes, represents the leading cause of chronic kidney disease (CKD) and kidney failure [1, 2]. The primary therapeutic interventions for DN include renin-angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors, incretin-based therapies, and non-steroidal mineralocorticoid receptor antagonists, collectively referred to as the "fantastic four" of DN management [3]. However, despite these treatments, many patients with DN inevitably progress to kidney failure. DN has emerged as a significant global health

*Correspondence:
Fang Liu
liufangfh@163.com
[1]Division of Nephrology, West China Hospital of Sichuan University, No. 37, Guoxue Alley, Chengdu 610041, Sichuan Province, China
[2]Laboratory of Diabetic Kidney Disease, Centre of Diabetes and Metabolism Research, West China Hospital of Sichuan University, Chengdu, China
[3]Division of Nephrology, Luzhou People's Hospital, Luzhou, China
[4]Division of Project Design and Statistics, West China Hospital of Sichuan University, Chengdu, China

concern due to its association with diminished quality of life and elevated mortality rates [4, 5]. Emotional disorders, such as depression and anxiety, are among the factors influencing quality of life and mortality in patients with DN [6–9].

Individuals with DN frequently experience psychological challenges, including depression and anxiety. Numerous studies have demonstrated a correlation between symptoms of depression and anxiety and adverse clinical outcomes, such as mortality, initiation of dialysis, hospitalization, and reduced quality of life [10–13]. Consequently, the effective screening and management of depression and anxiety in patients with DN are crucial, particularly in the context of busy non-psychiatric clinical settings in China. HuaXi emotional-distress index (HEI) is a local scale made by the Mental Health Center of West China Hospital that can screen anxiety and depression in non-psychiatric clinical settings [14]. HEI has been widely used in West China Hospital, and its reliability and validity have been verified [14].

It is widely recognized that anxiety and depression often co-occur and depression correlated significantly with anxiety [15]. A recent study involving 3886 diabetic kidney disease patients in Washington reported that depression (based on the Patient Health Questionnaire-9) may lead to an increased risk of kidney failure [16]. However, the relationship between depressive and anxiety symptoms and risk of incident kidney failure was not reported in DN. Moreover, no comparable studies have been conducted in China. Therefore, to better understand the course of DN in Chinese patients and find more effective treatment, we conducted a biopsy-based cohort study to investigate the association between depressive and anxiety symptoms and risk of incident kidney failure in patients with biopsy-proven DN.

Materials and methods

Patient selection

A total of 305 patients with type 2 diabetes mellitus (T2DM) who underwent renal biopsies at West China Hospital of Sichuan University between January 2016 and February 2021 were analyzed. The diagnosis and classification of T2DM were based on the criteria of the American Diabetes Association [17] and biopsy-proven DN was according to the standards of the Renal Pathology Society (RPS) in 2010 [18]. The general principles for renal biopsy in this study were T2DM patients with renal injury (defined as eGFR decline or proteinuria) who lacked absolute contraindications, especially T2DM patients without diabetic retinopathy, or T2DM patients with short diabetic duration (< 5 years). Subsequent follow-ups of these patients were performed 2–4 times per year. The study outcome was incident kidney failure, defined as eGFR < 15 ml/min/1.73 m^2, or the initiation of long-term renal replacement therapy. The exclusion criteria were as follows (Fig. 1): (1) patients with follow-up time < 1 year; (2) patients with type 1 diabetes; (3) coexisting nondiabetic renal disease; (4) patients with kidney failure at baseline; (5) patients with incomplete questionnaire information.

This study was approved by the Ethics Committee of West China Hospital. The study protocol conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before kidney biopsy for study participation.

Assessment instruments: HEI

HEI is a preliminary screening tool for emotional disorders (depression and anxiety), which has been widely used and validated for reliability and validity in West China Hospital. The Cronbach's α of HEI was 0.90, and sensitivity and specificity were 0.880 and 0.766, respectively [14]. The assessment method of HEI is that the nursing staff sent the paper version of HEI questionnaire to the patient, and the patient filled in the results according to their actual situation. Then, the nursing staff uploaded the results filled out by the patient to the HIS system, and the doctors of mental health centre checked the patient's filling results through the HIS system and timely feedbacked the report.

The self-report questionnaire consists of nine items in total, including core symptoms of depression and anxiety. The score of each item is ranked from 0 to 4 according to the occurrence frequency of the emotional experience in the recent month ("0" equals "Never"; "1" equals "Occasionally"; "2" equals "Some of the time"; "3" equals to "Most of the time"; "4" equals to "Nearly all the time"; respectively). The outcome is ranked using the total score: normal (0–8 points), mild negative emotions (9–12 points), moderate negative emotions (13–16 points) and severe negative emotions (17–36 points) [19–21]. Details of the HEI are shown in Supplemental Table 1.

Clinical and renal pathologic data

Clinical data was collected at baseline from electronic medical records at or close to the time of renal biopsy, including age, gender, duration of diabetes, presence of diabetic retinopathy, systolic and diastolic blood pressures, fasting blood glucose, 24 h urinary protein, serum creatinine, serum albumin, total cholesterol, triglyceride levels and hemoglobin, etc. Medication history, such as lipid-lowering agents, antidiabetic therapy and renin-angiotensin-aldosterone system inhibitor was collected at the time of renal biopsy as well. Polypharmacy was five or more medications daily [22] and the eGFR was calculated by the creatinine-based CKD Epidemiology Collaboration equation [23]. The paper version of the HEI questionnaire was sent to patients at the time of admission

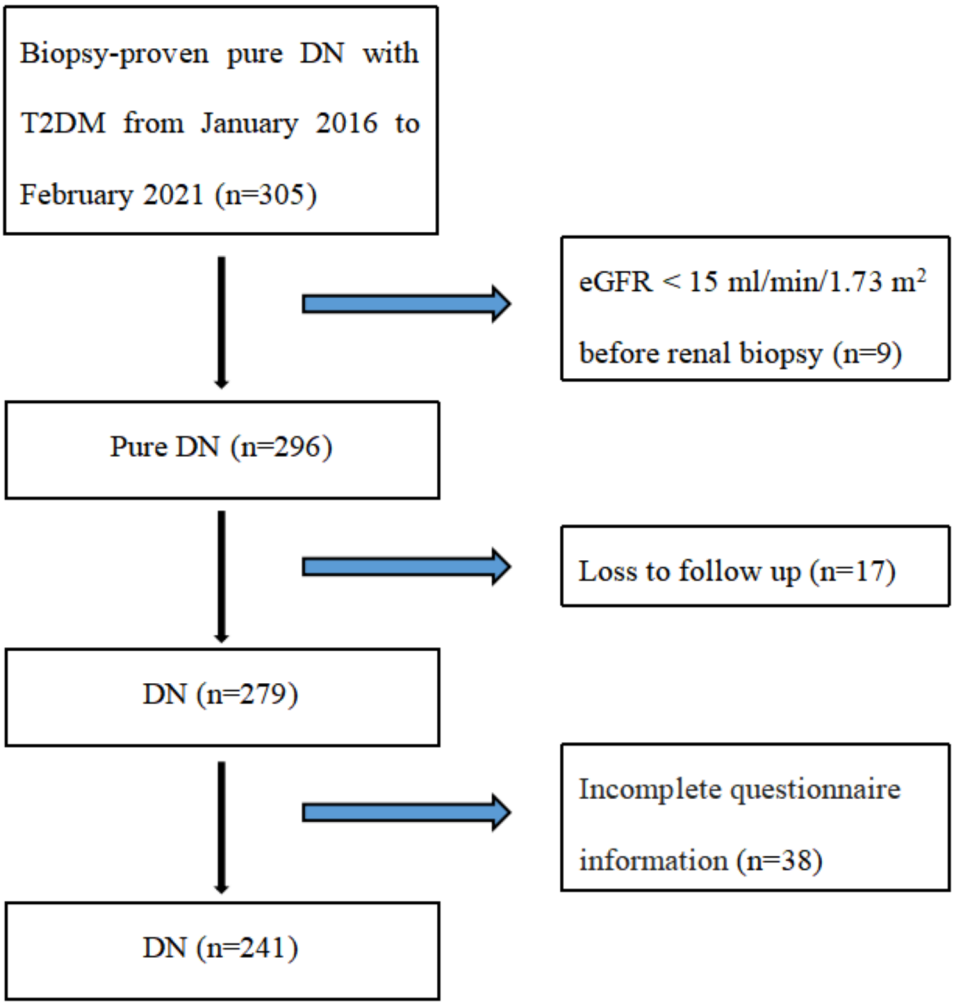

Fig. 1 Flowchart of study participants

for renal biopsy. Kidney tissue was obtained by needle biopsy and processed routinely for light microscopy, immunofluorescence, and electron microscopy to evaluate renal pathological alterations. Renal specimen was evaluated by two renal pathologists, diagnosed with DN and classified based on the 2010 RPS classification [18] (including glomerular class, interstitial fibrosis and tubular atrophy (IFTA), arteriolar hyalinosis and interstitial inflammation).

Statistical analysis

Statistical analysis was performed using SPSS 26.0 statistical software (SPSS, Chicago, IL, USA) and R version 4.1.2 (The R Foundation, Vienna, Austria). Variables were presented as the mean ± standard deviation, the medians with interquartile ranges (25th and 75th percentiles) or counts and percentages. Appropriate approach, which concluded t test, Mann-Whitney U test and chi-square test, was selected to compare the difference between two groups. The renal survival curves were assessed by the Kaplan-Meier method and compared by using the log-rank test. Univariable and multivariable logistic regressions were performed to assess the association between risk factors and HEI score > 8. Cox proportional hazard models were performed to analyze the influence of emotional disorders on renal outcomes. Area under the receiver operating curve (AUC) was also used to establish the discrimination ability of different models. A two-way $p < 0.05$ was considered significant.

Results

Baseline features of the patients with DN

A total of 241 individuals were included in this study (Fig. 1). The baseline clinical characteristics of all the patients were showed in Table 1. The mean age was 51.4 ± 9.6 years old and 73.9% were male. The median of diabetic duration was 96 (48, 144) months. Hypertension was present in 82.2% of the patients, 53.5% had diabetic retinopathy. The median of eGFR and proteinuria were 60 (43, 93) mL/min/1.73 m^2 and 4.3 (1.9, 8.0) g/d,

Table 1 Baseline clinical characteristics of enrolled patients

Variables	All	HEI score groups		*p*-value
	(*n* = 241)	HEI score ≤ 8 (*n* = 218)	HEI score > 8 (*n* = 23)	
Men (*n*, %)	178 (73.9)	160 (73.4)	18 (78.3)	0.613
Age (years)	51.4 ± 9.6	51.7 ± 9.7	48.7 ± 7.7	0.164
Body mass index (kg/m2)	25.80 ± 3.73	25.74 ± 3.75	26.36 ± 3.59	0.455
Current Smoker (n, %)	171 (71.8)	156 (72.2)	15 (68.2)	0.688
Hypertension(n, %)	198 (82.2)	176 (80.7)	22 (95.7)	0.076
Systolic blood pressure (mmHg)	144 ± 23	143 ± 23	155 ± 24	0.018
Diastolic blood pressure (mmHg)	86 ± 13	86 ± 13	85 ± 14	0.972
Diabetic duration (months)	96 (48, 144)	102 (48, 156)	108 (60, 144)	0.88
Diabetic retinopathy (n, %)	122 (53.5)	106 (51.5)	16 (72.7)	0.057
Fasting blood glucose (mmol/L)	7.36 (5.69, 9.84)	7.39 (5.79, 10.17)	6.55 (4.91,9.61)	0.105
Serum albumin (g/L)	35.3 (29.2,40.4)	36.5 (30.3, 41.5)	28.8 (24.8,32.5)	< 0.001
Glycosylated hemoglobin(%)	7.5 (6.5, 8.7)	7.4 (6.5, 8.6)	8 (6.6, 9)	0.577
Serum creatinine (μmol/L)	114 (80, 150)	111 (78, 149)	134 (113, 223)	0.009
eGFR (mL/min/1.73 m2)	60 (43, 93)	61 (43, 93)	52 (28, 59)	0.005
Uric acid (μmol/L)	379 ± 93	379 ± 95	379 ± 72	0.987
Triglyceride (mmol/L)	1.82 (1.31, 2.45)	1.84 (1.32, 2.54)	1.69 (1.19, 1.98)	0.213
Total cholesterol (mmol/L)	5.03 (4.15, 6.18)	4.99 (4.02, 6.14)	5.26 (4.38,6.75)	0.215
LDL-C (mmol/L)	2.74 (2.00, 3.66)	2.73 (1.99, 3.65)	2.97 (2.27,3.75)	0.382
HDL-C (mmol/L)	1.19 (1, 1.61)	1.18 (0.99, 1.60)	1.34 (1.12, 1.71)	0.213
Proteinuria (g/24 h)	4.3 (1.9, 8.0)	3.8 (1.8, 7.8)	6.7 (5.2, 17.7)	< 0.001
Stage 1, 2, 3, 4 CKD (KDIGO), *n*	63/58/97/23	62/54/85/17	1/4/12/6	0.004
Progressed to kidney failure (%)	89 (36.9)	68 (31.2)	21 (91.3)	< 0.001
RAAS inhibitors (*n*, %)	195 (80.9)	178 (81.7)	17 (73.9)	0.369
Oral antihyperglycemic drugs (n, %)	153 (63.7)	137 (63.1)	16 (69.6)	0.542
SGLT2 inhibitors (n, %)	19 (7.9)	18 (8.3)	1 (4.3)	0.505
DPP4 inhibitors (n, %)	38 (15.8)	34 (15.7)	4 (17.4)	0.830
Thiazolidinediones (n, %)	29 (12.1)	28 (12.9)	1 (4.3)	0.231
Sulfonylureas (n, %)	52 (21.8)	46 (21.2)	6 (27.3)	0.511
Metformin (n, %)	148 (61.7)	132 (60.8)	16 (69.6)	0.413
α-glucosidase inhibitors (n, %)	101(42.1)	93 (42.8)	8 (34.8)	0.456
Meglitinides (n, %)	7 (2.9)	7 (3.2)	0	0.382
Polypharmacy (n, %)	131 (54.6)	120 (55.3)	11 (47.8)	0.494
Insulin use (*n*, %)	194 (80.5)	174 (79.8)	20 (87)	0.411
Statins (n, %)	132 (55.2)	121 (56)	11 (47.8)	0.453

Data are presented as a mean ± SD, or median [IQR], or count (percentage). A two-tailed $p < 0.05$ was considered statistically significant. *eGFR* estimated glomerular filtration rate, *HDL-C* high-density lipoprotein-cholesterol, *LDL-C* low-density lipoprotein-cholesterol, *RAAS* renin-angiotensin-aldosterone system, *SGLT2* sodium glucose cotransporter-2, *DPP4* dipeptidyl peptidase-4 inhibitors

respectively. Among them, 80.9% of the subjects used RAS inhibitors.

In terms of the histopathological glomerular classification, 4.1% were in class I, 17.8% in class IIa, 10.8% in class IIb, 37.8% in class III, 29.5% in class IV. The majority of the patients had IFTA (94.2%), arteriolar hyalinosis (86.7%) and interstitial inflammation (86.7%) histopathological presentations (Table 2).

According to the HEI score, DN patients in this study were divided into two groups: HEI score ≤ 8 group (without anxiety and depression; $n = 218$) and HEI score > 8 group (with anxiety and depression; $n = 23$). 9.5% had a HEI score of > 8. Among group CKD stage 1, 2, 3 and 4 based on eGFR levels, 1.6%, 6.9%, 12.4% and 26.1% patients had depression and anxiety, respectively.

Relationships between HEI score and clinicopathological features

Compared with HEI score ≤ 8 group, those with HEI score > 8 were more likely to have lower baseline eGFR (52 [28, 59] vs. 61 [43, 93] mL/min/1.73 m2, $P = 0.005$), and serum albumin (28.8 [24.8, 32.5] vs. 36.5 [30.3, 41.5] g/L, $P < 0.001$), but higher proteinuria (6.7 [5.2, 17.7] vs. 3.8 [1.8, 7.8] g/24 h, $P < 0.001$), systolic blood pressure (155 ± 24 vs. 143 ± 23 mmol/L, $P = 0.018$), and serum creatinine levels (134 [113, 223] vs. 111 [78, 149] mmol/L, $P = 0.009$). No differences were observed in terms of age,

Table 2 Baseline pathologic characteristics of enrolled patients

Variables	All	HEI score groups		*p*-value
	(*n* = 241)	HEI score ≤ 8 (*n* = 218)	HEI score > 8 (*n* = 23)	
Glomerular class (n, %)				0.106
I	10(4.1)	10(4.6)	0(0)	
IIa	43(17.8)	43(19.7)	0(0)	
IIb	26(10.8)	23(10.6)	3(13)	
III	91(37.8)	81(37.2)	10(43.5)	
IV	71(29.5)	61(28)	10(43.5)	
IFTA (n, %)				0.686
0	14(5.8)	13(6)	1(4.3)	
1	106(44)	97(44.5)	9(39.1)	
2	100(41.5)	88(40.4)	12(52.2)	
3	21(8.7)	20(9.2)	1(4.3)	
Interstitial inflammation (n, %)				0.058
0	32(13.3)	29(13.3)	3(13)	
1	170(70.5)	157(72)	13(56.5)	
2	39(16.2)	32(14.7)	7(30.4)	
Arteriolar hyalinosis (n, %)				0.230
0	32(13.3)	31(14.2)	1(4.3)	
1	141(58.5)	124(56.9)	17(73.9)	
2	68(28.2)	63(28.9)	5(21.7)	

Data are presented as percentages for categorical variables. A two-tailed $p < 0.05$ was considered statistically significant. *IFTA* interstitial fibrosis and tubular atrophy

gender, DM duration, body mass index, smoking, polypharmacy, or glycosylated hemoglobin levels between the two groups. As for histopathological characteristics, there were no significant differences in the histopathologic changes between two groups.

We next investigated the association between potential risk factors and HEI score > 8. Univariable logistic regression showed that eGFR [odds ratio (OR) 0.973, 95% CI 0.954–0.991, $P = 0.004$], proteinuria (OR 1.123, 95% CI 1.035–1.218, $P = 0.005$), and glomerular class (OR 1.937, 95% CI 1.076–3.485, $P = 0.027$) were associated with HEI score > 8. Furthermore, multivariable logistic regression indicated that lower levels of eGFR (OR 0.969, 95% CI 0.946–0.993, $P = 0.010$) and higher degree of proteinuria (OR 1.097, 95%CI 1.003–1.199, $P = 0.042$) were independently associated with HEI score > 8 (Table 3).

HEI score and incident kidney failure in patient with DN

During the median follow-up of 28 months, 89 of 241(36.9%) patients progressed to kidney failure. Compared with HEI score ≤ 8 group, those with HEI score > 8 were likely to have higher incidence of kidney failure, as shown in Table 1. Kaplan-Meier analysis indicated that DN patients with HEI score > 8 had a significant higher risk for progression to kidney failure ($P < 0.001$, Fig. 2). Univariable Cox proportional hazard analysis revealed that HEI score > 8 were also predicted higher risk of incident kidney failure (HR 3.599, 95% CI 2.196–5.896, $P < 0.001$), as shown in Table 4. However, eGFR, proteinuria, glycosylated hemoglobin, glomerular lesion, IFTA and interstitial inflammation were risk factors for progression to kidney failure. After adjustment for age, gender, hypertension, baseline eGFR, proteinuria, glycosylated hemoglobin, emotional disorders, and histopathological parameters, HEI score > 8 were still associated with a higher incidence of kidney failure (HR 1.825, 95% CI 1.050–3.172, $P = 0.033$).

HEI score and the prediction of incident kidney failure

For the prediction of kidney failure, the AUC for prediction model 1 (including baseline age, gender, hypertension, eGFR, proteinuria, glycosylated hemoglobin, emotional disorders, and histopathological parameters) and prediction model 1 + HEI score > 8 for progression to kidney failure were 0.821 (95% CI, 0.768–0.875) and 0.851 (95% CI, 0.802–0.899),

Table 3 Results of logistic regression analysis showing risk factors associated with HEI score > 8 in patients with diabetic nephropathy

Variables	Univariate			Multivariable		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Age	0.970	0.929–1.013	0.165	0.950	0.901–1.002	0.059
Female	0.766	0.272–2.158	0.614	0.803	0.257–2.502	0.705
eGFR	0.973	0.954–0.991	0.004	0.969	0.946–0.993	0.010
Proteinuria	1.123	1.035–1.218	0.005	1.097	1.003–1.199	0.042
Glycosylated hemoglobin	1.005	0.785–1.287	0.970			
Diabetic retinopathy	2.516	0.947–6.685	0.064			
Polypharmacy	0.741	0.313–1.752	0.495			
Glomerular class	1.937	1.076–3.485	0.027	1.356	0.671–2.740	0.396
IFTA	1.072	0.598–1.923	0.815	0.455	0.185–1.119	0.086
Interstitial inflammation	1.727	0.779–3.830	0.179	1.837	0.674–5.004	0.234
Arteriosclerosis	1.072	0.539–2.131	0.843	0.994	0.448–2.204	0.988

CI, confifidence interval. A two-tailed $p < 0.05$ was considered statistically significant. *eGFR* estimated glomerular filtration rate, *IFTA* interstitial fibrosis and tubular atrophy

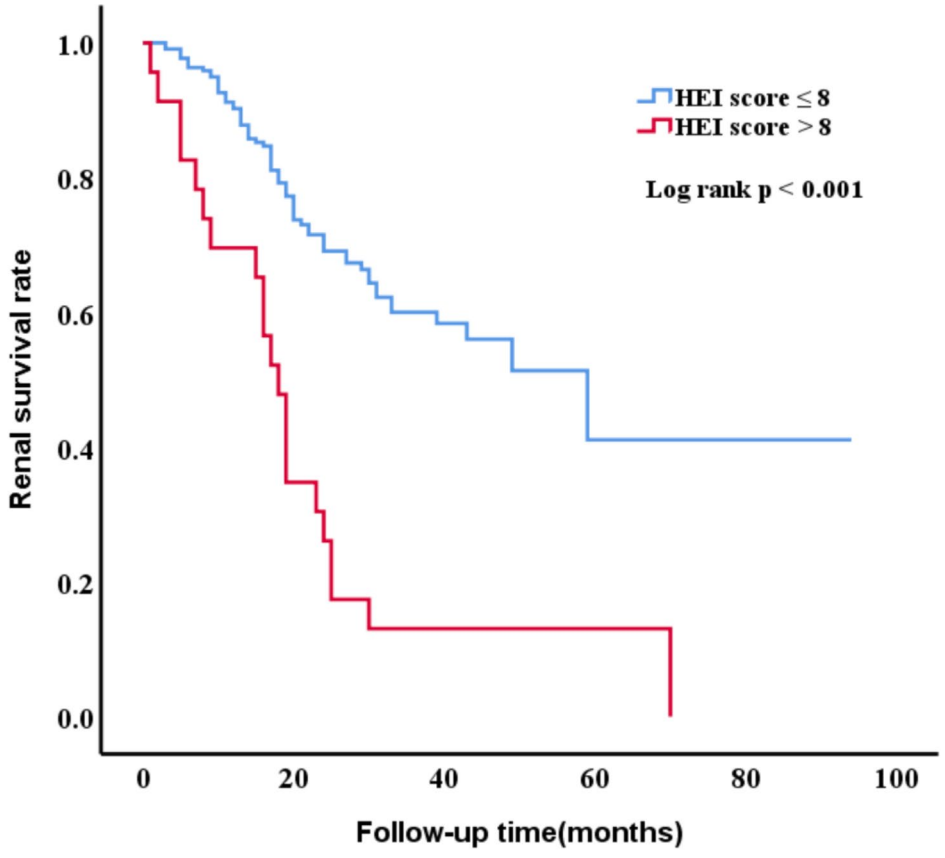

Fig. 2 Kaplan–Meier curves of renal survival rate in patients with different HEI scores

Table 4 Univariable and multivariable Cox proportional hazard analyses for the prediction of ESRD in diabetic nephropathy

Variables	Univariate HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Age	0.990 (0.971, 1.010)	0.330	0.979 (0.957, 1.001)	0.062
Female	0.954 (0.595, 1.527)	0.843	0.937 (0.570, 1.543)	0.799
Hypertension	1.536 (0.851, 2.773)	0.154	0.973 (0.524, 1.807)	0.931
eGFR	0.973 (0.964, 0.982)	< 0.001	0.979 (0.968, 0.991)	< 0.001
Proteinuria	1.087 (1.052, 1.124)	< 0.001	1.074 (1.031, 1.118)	< 0.001
Glycosylated hemoglobin	0.865 (0.755, 0.991)	0.036	0.956 (0.827, 1.105)	0.539
HEI score > 8	3.599 (2.196, 5.896)	< 0.001	1.825 (1.050, 3.172)	0.033
Pathology characteristics				
Glomerular class	1.941 (1.481, 2.545)	< 0.001	1.224 (0.868, 1.727)	0.249
IFTA	1.630 (1.222, 2.174)	0.001	1.053 (0.694, 1.597)	0.810
Interstitial inflammation	2.054 (1.373, 3.071)	< 0.001	1.411 (0.925, 2.153)	0.110
Arteriosclerosis	1.327 (0.925, 1.904)	0.124	0.960 (0.626, 1.474)	0.853

Multivariable model was adjusted for age, sex, eGFR, proteinuria, serum albumin, hemoglobin, and all pathological parameters. *HR* hazard ratio, *eGFR* estimated glomerular filtration rate, *HEI* Huaxi Emotional-distress Index, *IFTA* interstitial fibrosis and tubular atrophy

respectively (Fig. 3). The AUC curve was increased for the model 1 + HEI score > 8 in contrast to the model 1 (P = 0.025). It indicated that the model adding depression and anxiety was superior.

Discussion

To our knowledge, this investigation might be the first biopsy-based study to clarify the relationship between depressive and anxiety symptoms and risk of incident kidney failure in patients with DN. In this retrospective study, we observed that compared with patients without depression and anxiety, patients with depression and anxiety had more severe proteinuria, higher systolic blood pressure and serum albumin, and lower eGFR. Multivariate analysis showed that symptoms of depression and anxiety were significantly associated with higher risk of kidney failure in patients with DN.

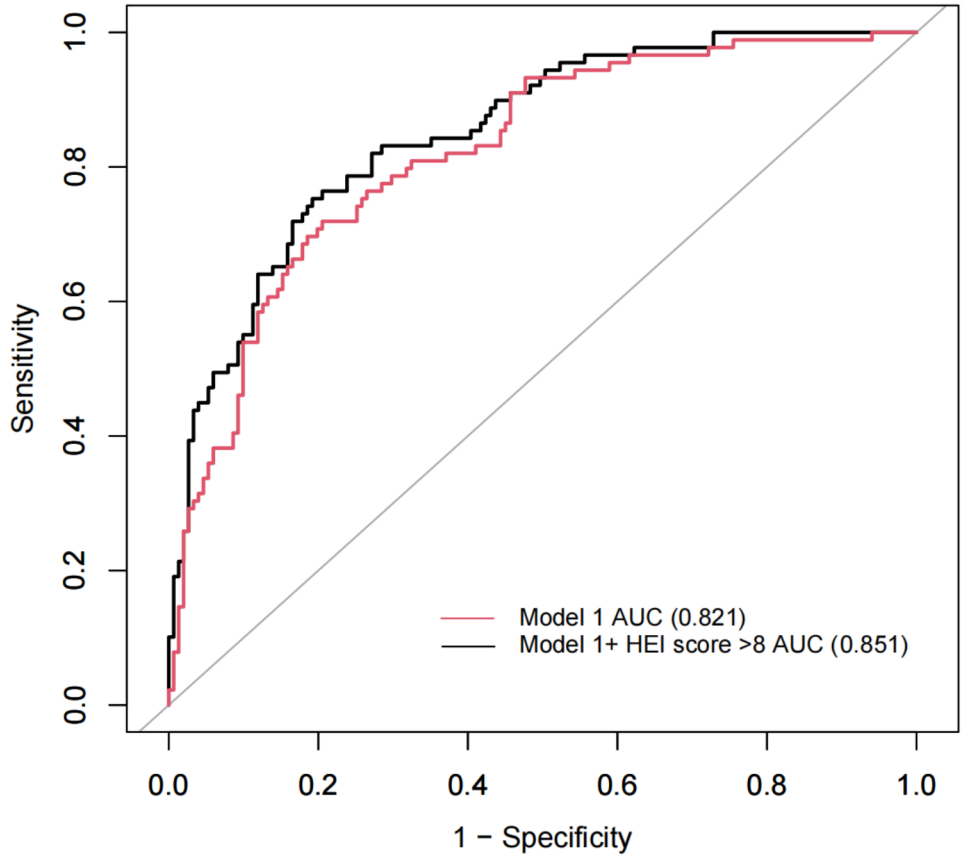

Fig. 3 The prediction of models for kidney failure evaluated with receiver operating characteristic curve

An analysis of community-based surveys from 27 countries showed a very high rate of comorbidity between depression and anxiety disorders; the risk of developing generalized anxiety disorder was about seven times in those with major depression even after 15 years (hazard ratio = 6.6; 95% CI = 5.7–7.7) [24]. In addition, various studies have shown a strong association of diabetes mellitus or CKD with symptoms of depression and anxiety [9, 12]. Compared with diabetic patients without renal complications, the prevalence of depression in diabetic kidney disease patients increased by 3.2 times [25]. However, depression studies in patients with DN rarely consider the presence of comorbid anxiety (and vice versa). The prevalence of depression and anxiety in our study was 9.5%, which was lower than the prevalence of depression and anxiety in Dutch CKD patients(23%) assessed by the Beck Depression Scale and the Beck Anxiety Scale [12]. This was most likely due to differences in social environment, sample size, the heterogeneity of the populations studied and instruments used to measure these psychological parameters. Moreover, the data of the included cases in this study were all from the first questionnaire of the patients at the time of admission for renal biopsy. Patients had high expectations for the treatment and the curative effect of diseases when they were just admitted due to their great trust in our hospital. These reasons might contribute to the low prevalence of emotional disorders in our cohort.

Notably, patients with CKD frequently experience distress due to a perceived lack of understanding from others and the behavioral constraints imposed by their condition, such as dietary restrictions [26]. Symptoms of depression and anxiety in these patients are associated with a poorer prognosis, characterized by increased severity, greater chronicity, and prolonged treatment duration [27]. The American Diabetes Association has recommended the screening and assessment of psychosocial issues in all patients with T2DM, as emotional well-being is linked to favorable diabetes outcomes [28]. Our findings indicate that among patients with biopsy-confirmed DN, those experiencing depression and anxiety are at an elevated risk of kidney failure compared to those without these psychological conditions, corroborating previous research. For instance, Yu et al. [16] demonstrated in a cohort of 3,886 individuals with diabetic kidney disease in Washington that major depressive symptoms were significantly associated with an increased risk of kidney failure, even after adjusting for diabetes self-care quality. Similarly, another study [29] involving 2,212 Japanese patients with diabetes and clinically

diagnosed diabetic kidney disease suggested that the progression of nephropathy is likely to be associated with increased risk and severity of depression. However, patients with diabetic kidney disease enrolled in these studies were all clinical diagnosed, which might cause misdiagnosis for non-diabetic renal diseases, and they did not investigate the impact of anxiety symptoms on renal outcomes. Our study added evidence to support the role of depression and anxiety in DN among biopsy-confirmed cohort, which might clarify the direct renal complication caused by T2DM. Moreover, we found that the inclusion of depression and anxiety into the model based on traditional predictors significantly enhanced the prediction power of DN developing to kidney failure. These findings demonstrated that the associations between depressive and anxiety symptoms and incident kidney failure were robust in patients with DN.

Interestingly, the present study showed that the proportions of patients with depression and anxiety increased in a stepwise manner from patients in CKD stage 1 to CKD stage 4. Also, Takasaki K et al. [29] found that both the proportions of patients with mild depression and those with moderate or severe depression increased in a stepwise manner from patients in stage 1 to the patients on dialysis in stage 5. Lee et al. [30] found that anxiety worsened as CKD stage increased for all CKD patients. More severe kidney dysfunction in CKD patients was associated with more emotional disorders [30]. Studies have shown that the prevalence of inflammation and oxidant stress increases in CKD patients, leading to emotional disorders [31, 32]. Depression and anxiety, which worsen as the CKD stage increases, are possibly due to differences in comorbidities, chronic inflammation, oxidant stress, and individual perception of health caused by CKD. Indeed, the biomarkers (creatinine levels) appeared predictive for negative emotional adaptations: high level of creatinine were found to be positively associated with psychological distress [33]. Consistent with this, patients with higher HEI scores in this study were more likely to have higher baseline creatinine levels and lower eGFR values. Therefore, not only may depression and anxiety lead to a faster decline in renal function, but the reverse might also be true - those patients with more severe kidney disease or faster decline in renal function might also suffer more from depression and anxiety. As CKD stage increases, more attention should be paid to not only physical care, but also mental care for these patients.

Depression and anxiety may be associated with kidney failure risk through several potential mechanisms. In patients with diabetes, depression is associated with a higher number of cardiovascular risk factors compared with those patients without depression [34]. Although we attempted to control for common cardiovascular risk factors, we were unable to account for actual blood pressure measurements or changes in cardiovascular risk factors over time. Depression is associated with medication nonadherence and poorer diabetes self-care [35]. Optimists understood their disease more correctly, and had more motivation for a healthy life as compared with emotional disorders [36], which might, to a small extent, mediate the association between symptoms of depression and anxiety and kidney failure. Unfortunately, we did not collect information about dietary habit, physical activity and medication adherence, and thus, could not assess whether these factors might have confounded the association between psychosocial factors and DN found in the present study. In addition, an association has been shown between depression and a proinflammatory state [37]. It is well known that inflammation plays important roles in the pathogenesis of DN [38], might link symptoms of depression and anxiety and progression of DN. Lutgendorf et al. [39] showed that older women with anxiety and depression had higher levels of interleukin-6 as compared with those without. Lastly, It is reported that poor psychosocial conditions is associated with hyperactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis and sympathetic nervous system (SNS) [40, 41]. Optimists showed a lower level of HPA response than depression and anxiety in the face of adversity and illness [42]. This difference might influence the development of DN, as HPA response affects glycemic control and obesity [43]. Whether these neuroendocrine abnormalities in depression and anxiety are associated with the progression of DN is unknown. Further elucidation of these mechanisms is warranted to establish whether therapeutic measures tailored toward HPA, SNS, or inflammation may provide alternative means for prevention and treatment of DN in the setting of depression and anxiety.

Of course, there are some limitations in our study. First, this research was conducted in a single center in Chinese patient with biopsy-proven DN, selection bias also cannot be ruled out and the findings cannot be generalized to all patients with DN. Second, this is a retrospective study, which means that we can't exclude some other factors that may influence analysis results, such as socioeconomical status, life style, genetic factors, comorbidities, etc. Third, the study lacked dynamic evaluation of HEI scores or assessed additional scores to validate our findings. Finally, our sample size is limited, and the tendency of unintentional bias cannot be ruled out. Moreover, the patients included in this study have a relatively short follow-up time, so further studies with a larger sample size and longer follow-up time should be conducted to confirm our findings, and further multicenter validation in China is required.

In conclusion, our study provided new evidence that depressive and anxiety symptoms were associated with an increased risk of progression to kidney failure in

patients with DN, which implied psychosocial issues should be early screened, assessed and intervened to delay the progression of DN.

Supplementary Information

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Supplementary Material 1

Author contributions

Conception and design of the study: CM Qin, F Liu; Acquisition and analysis of data: CM Qin, YC Wu, YT Zou, YC Zhao, DY Kang, F Liu; Drafting the manuscript or figures: CM Qin, F Liu.

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Data availability

Datasets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board at the West China Hospital of Sichuan University. The approval number was 2013R01.

Consent for publication

Not applicable.

Patient consent form

The patient has given informed consent.

Competing interests

The authors declare no competing interests.

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