ORIGINAL RESEARCH

Exploring Symptom Clusters in Chinese Patients with Diabetic Kidney Disease: A Network Analysis

Di-Fei Duan [iD][1,2,*], Min Liu[1,2,*], Deng-Yan Ma[1,2], Lin-Jia Yan[3], Yue-Yang Huang[1,2], Yi Chen[1,2], Wei Jiang[1,2], Xi Tang[2], An-Qi Xiong[4,5], Yun-Ying Shi[2]

[1]West China School of Nursing, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; [2]Department of Nephrology, Kidney Research Institute, West China Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; [3]The Nethersole School of Nursing Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, People's Republic of China; [4]Department of Nursing, West China Second University Hospital, Sichuan University, Chengdu, Sichuan Province, People's Republic of China; [5]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu, Sichuan Province, People's Republic of China

*These authors contributed equally to this work

Correspondence: Deng-Yan Ma, Email mdy5104@163.com

Purpose: The research on symptom management in patients with diabetic kidney disease (DKD) has shifted from separate symptoms to symptom clusters and networks recently. This study aimed to evaluate the unpleasant symptoms of DKD patients, and to investigate how these symptom clusters could affect patients.

Methods: 408 DKD patients were recruited in this cross-sectional study. The symptoms of DKD patients were measured using the modified Dialysis Symptom Index. Network analysis was employed to evaluate the symptom network and the characteristics of individual nodes, while factor analysis was utilized to identify symptom clusters.

Results: Blurred vision was the most prevalent symptom among DKD patients. The symptoms identified as the most distressing, severe, and frequent were light headache or dizziness, arteriovenous fistula/catheterization pain, and diarrhea, respectively. Five symptom clusters were obtained from factor analysis, and the most central symptom cluster in the entire symptom network was sexual dysfunction.

Conclusion: This study identified five symptom clusters in Chinese DKD patients, with sexual dysfunction emerging as the most central cluster. These findings carry significant clinical implications, underscoring the necessity of assessing symptom clusters and their associations to enhance symptom management in DKD patients. Further research is essential to elucidate the underlying mechanisms of symptoms and to clarify the associations among symptoms in DKD patients across different disease trajectories or treatment modalities.

Keywords: diabetic kidney disease, network analysis, symptom cluster, symptom management

Introduction

Diabetic kidney disease (DKD) stands as one of the most frequent and severe complications arising diabetes, becoming the leading cause of end-stage renal disease(ESRD).[1,2] Diabetes contributes to approximately 30–50% of ESRD cases in the United States.[3] A study in 2020 showed that the total prevalence of DKD in patients with Type 2 diabetes reached 21.8%,[4] with an estimated 24.3 million DKD patients in China.[5] Consequently, the global prevalence of DKD is witnessing a rapid increase, signifying the growth of a significant public health challenge worldwide.[6]

Patients with chronic kidney disease (CKD) frequently experience unpleasant symptoms, including psychological, gastrointestinal, cardiopulmonary, neurological, dermatological, painful or sleep-related disorders, as well as sexual dysfunction, and fatigue.[7,8] These symptoms often occur in clusters, with one being the primary symptom and the others

being secondary.[9] A "symptom cluster" is defined as two or more symptoms that occur together in interrelated patterns. These clusters represent cohesive sets of symptoms, maintaining relative independence from other clusters, thereby potentially unveiling distinct underlying symptom dimensions. Within a given cluster, the associations between symptoms are expected to be stronger than those between symptoms belonging to different clusters. It is noteworthy that symptoms within a cluster may not necessarily have a common cause.[10] Previous studies have suggested that a symptom cluster has a greater impact on health than that of an individual symptom,[11] as a certain cluster has synergistic effects on morbidity, mortality, prognosis, and quality of life. Thus, identifying and addressing symptom clusters is a critical strategy for effective symptom management, offering a more targeted approach to improving patient outcomes.[12]

The "unpleasant symptoms" theory offers a multidimensional view of symptoms, emphasizing the significance of understanding symptom clusters. This approach provides a comprehensive framework for researchers to explore symptom experiences holistically.[13,14] Recognizing the benefits of symptom clustering in enhancing patient survival and prognosis, network analysis emerges as a powerful tool.[15] It constructs partial correlation models to delineate the relationships between unpleasant symptoms and their clusters, facilitating the graphical representation of each symptom's importance and the intricate connections within the network from a holistic standpoint.[16] The identification of unpleasant symptoms thus plays a pivotal role in empowering DKD patients in their symptom management journey.[17]

The 2022 World Kidney Day emphasized quality of life supersedes quantity of life, and recommends the use of symptom clusters for symptom management in CKD patents.[18] Many studies focusing on CKD domain have revealed that interventions targeting symptom clusters can greatly improve the quality of life and reduce symptomatic burdens.[11,12] As a complication of CKD, DKD presents with numerous CKD-related symptoms,[19] thereby increasing the risk of adverse health outcomes and contributing significantly to the global disease burden.[20] Hence, prevention and management of DKD symptoms is a key goal in the comprehensive care of kidney and diabetic patients.[21]

Despite the recognized importance, existing research on symptom clusters has predominantly focused on dialysis treatment, leaving a gap in our understanding of these clusters in DKD patients. This lack of evidence impedes efforts to lessen patient burden and improve prognoses.[9,22] Therefore, this study aimed to 1) collect and evaluate the unpleasant symptoms of DKD patients, and 2) explore the symptom clusters affecting these patients by network analysis and factor analysis.

Methods

We used STROBE Checklist for more rigorous study design and improved article quality.

Study Design and Participants

This is a prospective cross-sectional study with data collected from a general tertiary hospital in Chengdu, Sichuan Province, China. Convenience sampling was adopted. Individuals discharged from this hospital and met the following inclusion criteria were eligible to participate: 1) diagnosed according to the Chinese guidelines for the clinical diagnosis and treatment of DKD,[23] and 2) willing to participate in this study. Participants with incomplete data were excluded to prevent measurement contamination. Initially, 486 participants were approached, with 408 providing complete data, resulting in a response rate of 83.95%. Details are shown in Supplementary Figure 1. No significant difference was found in sociodemographic data between participants who completed the study and those who did not (Supplementary Table 1).

Sample Size Calculation

As the rule of thumb for exploratory factor analysis,[24] the required sample size for this study was 5–10 times the number of variables. Considering the investigation of 40 to 50 symptoms in DKD patients, the minimum sample size was determined to be between 200 to 250 cases. The minimum sample size in network analysis is determined by assuming N symptoms and using the formula $N + [N*(N-1)/2]$. Increasing the sample size results in more reliable analysis outcomes.[16] Considering symptoms with a prevalence of less than 10%, and assuming N ranges from 20 to 30, the estimated minimum sample size for our study was between 210 and 465 cases. As recommended by literature,[25] the evaluations of network analysis outcomes should consider supplementary measures such as stability in conjunction with sample size. If these measures indicate favorable results, the findings may be deemed acceptable.

Data Collection and Ethic Consideration

Data were collected from April to July 2023. In addition to sociodemographic data, the primary outcomes of this study focused on the symptoms of DKD, which were evaluated using the CKD-Symptom Burden Index. Data collection was implemented by trained registered nurses via telephone inquiries. Besides, the clinical data of participants could be collected from the hospital information systems by researchers. Prior to the interviews, the purpose of the study, estimated time of completion, participants' authority, and privacy policy were provided for participants. All respondents were further asked to give their informed consent through a link sent by telephone or WeChat. The questionnaire items were answered independently by the participants and returned to the researcher immediately. During the process, researchers read out the items in a quiet setting and clarified any queries to ensure understanding. Participants had the right to withdraw at any stage without any negative consequences.

Measurements

Sociodemographic Data

A self-designed basic information form was used to record the following information of participants, including marital status, education level, ethnicity, gender, age, height, weight, employment status, medical insurance coverage, CKD stage, and disease duration. The Body Mass Index (BMI) is determined by dividing one's weight in kilograms by the square of their height in meters.

Symptoms of DKD

The symptoms of DKD were assessed using the CKD-Symptom Burden Index (CKD-SBI),[26] aiming to evaluate symptoms at different stages of CKD within the past month. It consists of four symptom dimensions-prevalence, distress, severity, and frequency-across 32 symptoms. Notably, symptoms reported by patients outside the CKD-SBI were also documented and included in the statistical analysis.[27] The prevalence scale assesses the presence or absence (Yes/No) of each symptom, and if a symptom is present, then evaluates its distress, severity, and frequency. Each of these four dimensions is rated on a scale from 0 to 10, with the "distress" subscale ranging from "none" to "very much", "severity" from "none" to "very severe", and "frequency" from "never" to "constant". The overall CKD-SBI score is derived by summing the scores from each subscale (prevalence, distress, severity, and frequency) and applying a constant multiplier of 0.1008, where a higher total score reflects a greater symptom burden.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows, version 26.0. Means, standard deviations, medians, interquartile ranges, proportions, and percentages were utilized to summarize the sociodemographic characteristics of participants and symptom information. To ensure a valid analysis, symptoms with a prevalence of less than 10% were removed from the dataset,[28,29] leaving 22 symptoms for further analysis. This adjustment confirmed that a sample size of 408 was sufficient for conducting factor analysis, a widely used technique in symptom cluster research.[30] The total score of symptom experience was utilized to create these clusters. The spindle factorization method, in conjunction with the maximum variance rotation method, was applied to extract eigenvalues greater than 1. After 25 iterations, symptoms with a factor loading of 0.45 or higher were categorized into distinct clusters.[31]

Network Analysis

Network analysis was performed using 22 symptoms to examine and visualize the relationships between the variables. In network analysis, variables are represented as nodes, and the associations between variables are depicted as edges. The strength of these connections, or edges, provides insights into the level of interconnection among the nodes. These connections can occur either directly between variables or indirectly through other variables. The primary focus of the symptom network analysis revolved around determining which symptom activation would more likely trigger the activation of other symptoms within the network. To assess this, three commonly employed centrality measures were utilized, namely strength, closeness, and betweenness.[32] The centrality of strength quantified the overall direct connections of a symptom with other symptoms, thereby representing its capacity to influence other symptoms. The centrality of

closeness gauged the reciprocal of the distance between a symptom and other symptoms, thereby indicating the symptom's central position within the network. Centrality between vertices reflected a measure of the number of shortest paths passing through a symptom, thereby highlighting its bridging function in the network. Symptoms exhibiting the highest centrality coefficients were identified as core symptoms. Given previous findings on the reliability of strength centrality, our analysis primarily focused on this measure (rs) to identify key symptoms. The Fruchterman-Reingold algorithm was utilized for visualizing the network, arranging nodes in a manner that minimizes the crossing of edges. The thickness of edges in the network visualization corresponds to the strength of the associations between variables. Stability and accuracy, crucial for assessing the network's reliability, were evaluated using the correlation stability coefficient (with a recommended threshold of 0.25 and a satisfactory level above 0.50) and the 95% confidence intervals (CIs) of edge weights, respectively.[33] To evaluate the accuracy of the estimated network connections, the 95% confidence intervals (CIs) of the edge weight values were calculated.[34] Nonparametric bootstrapping (1000 samples) was employed to determine CIs, ensuring the network's estimations were robust and reliable.

Results

Characteristics of Participants

This study included 408 participants in the final analysis. The sociodemographic and clinical information of the participants is shown in Table 1. The participants had a mean age of 51.56 years and a mean BMI of 24.38. The median scores for symptoms and the duration of kidney disease were 6.25 and 3 years, respectively. A majority of participants were covered by medical insurance (n=398, 97.55%), identified as Han ethnicity (n=382, 93.63%), had attained a high school education or higher (n=208, 50.98%), were married (n=331, 81.13%), unemployed (n=296, 72.55%), and male (n=252, 61.76%). Among them, 65(15.93%) underwent renal replacement therapy, and 183 (44.85%) reported having three or more comorbidities. The majority were in stages 3–5 CKD (n=303, 74.26%).

Table 1 Demographical and Clinical Characteristics of Participants (n=408)

Item		n (%) / Mean ± SD
Age		51.56±12.87
Sex	Male	252(61.76%)
	Female	156(38.24%)
Marital status	Unmarried or single	77(18.87%)
	Married	331(81.13%)
Educational level	Elementary school or below	71(17.40%)
	Secondary school	129(31.62%)
	High school	151(37.01%)
	Batchelor degree or above	57(13.97%)
Ethnic	Han	382(93.63%)
	Minority	26(6.37%)
Employment status	Employed	112(27.45%)
	Unemployed	296(72.55%)
Healthcare payment mode	No	10(2.45%)
	Yes	398(97.55%)
CKD stage	1	45(11.03%)
	2	60(14.71%)
	3	141(34.56%)
	4	97(23.78%)
	5	65(15.93%)

(*Continued*)

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Table 1 (Continued).

Item		n (%) / Mean ± SD
Numbers of the comorbidity	No	113(27.70%)
	One	93(22.79%)
	Two	19(4.66%)
	Three or above	183(44.85%)
The ways of renal replacement therapy	Non-dialysis	343(84.07%)
	Hemodialysis	58(14.22%)
	Peritoneal dialysis	7(1.72%)
Duration of disease (year), median (IQR)		3(2,5)
BMI		24.38±4.06
Total score of symptoms burden, median (IQR)		6.25(3.83, 9.17)

Abbreviations: BMI, Body mass index; SD, Standard Deviation; IQR, interquartile range; CKD, chronic kidney disease.

Symptom Prevalence, Distress, Severity, and Frequency

Regarding symptom prevalence, blurred vision (n=200, 49.00%) was the most prevalent symptom, followed by foam urine (n=199, 48.80%), and feelings of tired or lack of energy (n=192, 47.10%).

As for symptom distress, light headache or dizziness was the most distressing symptom (average score = 1.69), with arteriovenous fistula/catheterization pain (average score = 1.62) and hiccupping (average score = 1.48) following closely. In terms of symptom severity, the most severe symptom was arteriovenous fistula/catheterization pain (average score = 1.67), followed by coughing (average score = 1.66), and swelling in legs (average score = 1.49). Regarding the frequency of symptoms, the most frequent symptom was diarrhea (average score= 4.71), with changes in stool color (average score = 4.51) and light headache or dizziness (average score = 1.78) also frequently experienced. Detailed symptom characteristics of our sample are given in Table 2.

Summary of Cluster Symptoms

The factor loadings of each symptom and final symptom clusters are presented in Table 3. Through principal component analysis, we identified five distinct symptom clusters. Symptom Cluster A encompasses six symptoms: palpitation, numbness or tingling of hands and feet, bone or joint pain, trouble falling asleep, frequent waking, and feeling anxious. Symptom Cluster B is characterized by constipation, diarrhea, facial oedema, swelling in legs, dry mouth, and dry skin. Sexual dysfunction, defined by decreased interest in sex and difficulty with sexual arousal, constitutes Symptom Cluster C. Symptom Cluster D includes Nausea, muscle cramps, blurred vision, and feelings of being tired or lack of energy. Lastly, Symptom Cluster E comprises urinary symptoms, including 2 symptoms nocturia and foam urine. Itching and decreased appetite were found to have low factor loadings across all clusters, suggesting their classification as individual symptoms rather than part of a cluster.[31]

Overall Network

The network models, as depicted in Figures 1, illustrate the relationships among symptoms in the total sample of 408 participants. Notably, decreased interest in sex had a strong connection with difficulty becoming sexually aroused (r = 0.87); foam urine had a strong connection with nocturia (r = 0.50) and a moderate connection with itching coupled with dry skin (r = 0.35); Additionally, facial oedema had a moderate connection with swelling in the legs (r = 0.33), and frequent waking was moderately connected to trouble falling asleep (r = 0.30). There were also weak associations between bone or joint pain and numbness or tingling in the feet (r = 0.29), as well as between facial edema and both diarrhea and constipation (r = 0.23, r = 0.27, r = 0.20), as detailed in Supplementary Table 2.

Centrality analyses, shown in Figure 2 and Supplementary Table 3, revealed that decreased interest in sex (rs = 2.49, rc = 1.77, rb = 0.68) and difficulty becoming sexually aroused (rs = 2.33, rc = 1.77, rb = 1.44) were the most central

Table 2 Symptoms of DKD Patients (n=408)

Symptom	Prevalence		Distress	Severity	Frequency
Constipation	**118**	**28.92%**	**0.04±0.52**	**1.15±2.17**	**0.03±0.37**
Diarrhea	54	13.24%	1.29±2.25	0.86±2.02	4.71±4.60
Change in stool color	19	4.66%	1.15±2.06	0.22±1.03	4.51±4.57
Dysosmia	4	0.98%	1.35±1.62	1.10±2.13	1.41±1.74
Hiccup	39	9.56%	1.48±1.73	0.33±1.20	1.68±1.94
Nausea	49	12.01%	0.52±2.08	0.05±0.53	0.50±2.03
Vomiting	34	8.33%	0.12±0.71	0.21±1.00	0.13±0.79
Decreased appetite	62	15.20%	1.20±2.28	0.34±1.24	1.18±2.20
Muscle cramps	50	12.25%	0.47±1.36	1.40±1.69	0.47±1.36
Blurred vision	200	49.02%	0.23±1.18	0.27±1.37	0.25±1.29
Palpitation	58	14.22%	0.05±0.58	0.39±1.41	0.04±0.44
Syncope	32	7.84%	0.38±1.35	0.23±1.16	0.33±1.11
Facial oedema	42	10.29%	0.44±1.30	0.51±1.43	0.44±1.34
Swelling in legs	100	24.51%	0.35±1.29	1.49±2.54	0.31±1.09
Cough	35	8.58%	0.54±1.39	1.66±2.68	0.50±1.31
Shortness of breath	22	5.39%	0.41±1.20	0.43±1.32	0.40±1.20
Light headache or dizziness	38	9.31%	1.69±2.06	0.32±1.31	1.78±2.16
Restless legs	28	6.86%	0.53±1.48	0.88±1.72	0.50±1.42
Numbness or tingling in feet	103	25.25%	0.26±0.99	0.38±1.34	0.25±0.89
Feeling tired or lack of energy	192	47.06%	0.43±1.42	0.17±1.09	0.5±1.70
Dry mouth	110	26.96%	0.81±1.57	0.22±1.11	0.88±1.74
Bone or joint pain	67	16.42%	0.35±1.28	0.39±1.53	0.36±1.36
Chest pain	16	3.92%	0.20±0.97	0.52±2.06	0.22±1.02
Headache	20	4.90%	0.33±1.15	0.29±1.30	0.37±1.33
Muscle soreness	32	7.84%	0.37±1.54	0.68±1.85	0.32±1.38
Abdominal pain	9	2.21%	0.85±1.62	0.26±0.97	0.89±1.70
Arteriovenous fistula/catheterization pain	25	6.13%	1.62±1.95	1.67±1.92	1.62±1.96
Difficulty concentrating	27	6.62%	1.12±2.18	0.94±1.82	1.12±2.17
Dry skin	107	26.23%	0.69±1.78	0.48±1.64	0.66±1.76
Itching	172	42.16%	0.17±1.02	1.65±2.00	0.15±0.89
Perspiration	26	6.37%	0.23±1.17	1.53±2.10	0.24±1.22
Alopecia	38	9.31%	0.34±1.31	0.23±1.03	0.35±1.34
Trouble falling asleep	77	18.87%	0.13±0.96	1.06±2.05	0.08±0.60
Frequent waking	61	14.95%	0.24±1.06	0.12±0.79	0.24±1.15
Daytime sleepiness	26	6.37%	0.34±1.42	0.42±1.24	0.35±1.46
Snoring or sleep apnea	13	3.19%	1.12±2.20	0.37±1.39	1.13±2.21
Worrying	31	7.60%	1.55±2.15	0.16±0.93	1.51±2.13
Feeling anxious	106	25.98%	0.30±1.32	0.49±1.76	0.28±1.25
Feeling sad	31	7.60%	0.54±1.91	0.47±1.38	0.54±1.86
Feeling irritable	39	9.56%	0.83±1.98	0.12±0.94	0.89±2.08
Depression	20	4.90%	0.72±2.01	0.86±1.66	0.70±1.95
Decreased interest in sex	124	30.39%	0.17±1.09	0.05±0.61	0.18±1.11
Difficulty with sexual arousal	114	27.94%	0.43±1.65	0.34±1.43	0.40±1.61
Nocturia	181	44.36%	0.92±1.78	0.46±1.57	0.95±1.84
Foam urine	199	48.77%	0.31±1.28	0.53±1.41	0.35±1.39
Changes in urination ability (including dysuria)	28	6.86%	0.47±1.65	0.68±1.73	0.50±1.72

symptoms based on strength, indicating their significant influence within the symptom network. The result shows that their weights were high in the network, their influence was strong, and they were the most important symptoms in the symptom network.[35] Facial oedema (rs = 1.71, rc = 2.09, rb=2.81) had the highest closeness, were located in the center of the symptom network, and had the closest relationship with other symptoms.[36] Despite their high prevalence, blurred

Table 3 Factor Loading of Total Symptom Score in DKD Patients (n=408)

Symptoms	No	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E
Constipation	B3		0.58			
Diarrhea	B1		0.76			
Facial oedema	B2		0.75			
Swelling in legs	B4		0.57			
Dry mouth	B5		0.56			
Dry skin	B6		0.52			
Nausea	D3				0.56	
Muscle cramps	D1				0.77	
Blurred vision	D2				0.56	
Feeling tired or lack of energy	D4				0.45	
Palpitation	A4	0.62				
Numbness or tingling in feet	A6	0.50				
Bone or joint pain	A5	0.59				
Trouble falling asleep	A2	0.72				
Frequent waking	A1	0.79				
Feeling anxious	A3	0.65				
Decreased interest in sex	C2			0.90		
Difficulty becoming sexually aroused	C1			0.94		
Nocturia	E2					0.81
Foam urine	E1					0.82
Eigenvalue		3.49	3.17	2.04	2.01	1.64
Variance contribution rate (%)		15.88	14.41	9.25	9.14	7.47
Cumulative variance contribution rate (%)		15.88	30.30	39.54	48.68	56.15

vision, nocturia, and foam urine had low centrality, suggesting they may act as sentinel symptoms for other conditions.[34] The correlation coefficients related to strength consistently exceeded 0.5, affirming the network's stability (Figure 3). Furthermore, the analysis indicated that the ranking based on strength centrality was more stable compared to the rankings based on closeness and betweenness centrality measures. Bootstrap analysis of edge weights revealed narrow bootstrapped CIs, indicating that the edge weights in the current sample were consistent with those in the bootstrapped sample. This consistency suggests that the network structure is accurate. (Figure 4).

Discussion

This is a first study to demonstrate the symptomatic burden and its associations in Chinese DKD patients. Blurred vision emerged as the most prevalent symptom, while light headache or dizziness was identified as the most distressing, and arteriovenous fistula/catheterization pain as the most severe. The most frequent symptom was diarrhoea. Five symptom clusters were identified. Decreased interest in sex and difficulty becoming sexually aroused were symptoms with high coefficients of the centrality indices. Therefore, sexual dysfunction emerged as the most central symptom cluster within the entire symptom network.

The findings of this study indicate that blurred vision was the most prevalent symptom among DKD patients, aligning with prior research that identifies diabetic retinopathy as a common diabetes complication leading to blurred vision, often associated with diabetes duration, poor glycemic control, and hypertension.[37] Additionally, patients undergoing hemodialysis often present with ocular abnormalities, and only a minority have normal vision.[38] Light headache or dizziness also emerged as particularly distressing symptoms for DKD patients, potentially linked to depression, anxiety and neuropathy from prolonged DKD.[39] Studies have shown that cognitive impairment due to neuropathy could predict diabetic retinopathy progression.[40] Furthermore, arteriovenous fistula/catheterization pain was one of the most severe symptoms,[41] underscoring its significance in patients with chronic renal failure and diabetes, especially those on hemodialysis.[41] Diarrhea was the most frequent symptom, corroborating findings from another study indicating a high
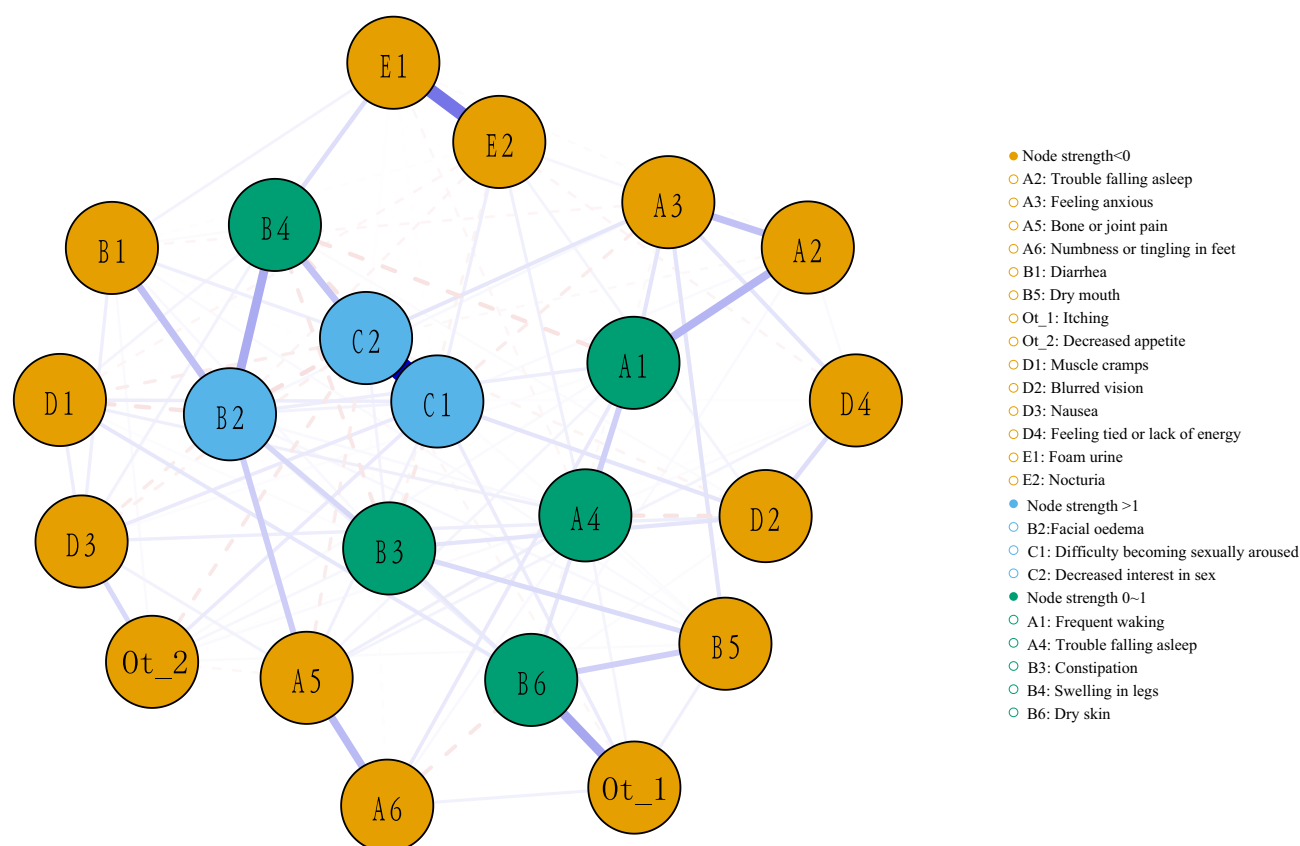
Figure I Network relationship map of symptoms in DKD patients. This figure illustrates the network of 22 symptom connections in 408 DKD patients, highlighting significant relationships: a strong link between decreased sexual interest and arousal difficulties, foam urine's strong tie to nocturia and moderate association with itching and dry skin, facial oedema's moderate link to leg swelling, and the moderate connection between frequent waking and sleep initiation troubles. This map offers a concise overview of symptom interactions in DKD.

prevalence of gastrointestinal symptoms among Chinese diabetes outpatients, with diabetes duration being a key contributing factor.[42] Overall, the above-mentioned evidence suggested that healthcare providers need to pay attention to the conscious state and routine vision testing in DKD patients in the future, as well as to the possible important role of pain management in alleviating discomfort and pain.

Our study, employing factor and network analysis, expanded upon previous research by identifying five symptom clusters in DKD patients, significantly enhancing our understanding of their symptomatic experiences. Symptom Cluster A included palpitation, numbness or tingling in feet, bone or joint pain, trouble falling asleep, frequent waking, and feeling anxious, which mainly reflected sleep and emotional problems in DKD patients. Clinical and experimental evidence suggests that sleep apnea, linked to renal injury, may be a covert risk factor for kidney disease progression,[43] highlighting the role of sleep disturbances in the worsening of renal function.[44] Consistent with previous studies, anxiety and depression are common yet frequently overlooked psychiatric symptom in patients undergoing ESRD,[45] and have been shown to be associated with higher morbidity and mortality.[46] Our study further stressed the necessity of early guidance to identify sleep and emotional problems in patients with DKD.[47] Furthermore, our network analysis revealed moderate correlations among symptoms such as bone or joint pain, numbness or tingling in feet, and sleep disturbances, indicating that the presence of one symptom could help caregivers in identifying related symptoms, thereby improving patient care.

Constipation, diarrhea, facial oedema, swelling in legs, dry mouth, and dry skin were included in Symptom Cluster B, mainly reflecting gastrointestinal and fluid retention symptoms. This is in accordance with previous study displayed that DKD patients may had gastrointestinal symptoms.[42] Consistent with research on CKD-related symptom clusters,[48] we found that diarrhea and constipation often occur in one symptom cluster, possibly due to a range of factors. For instance, constipation symptoms in patients could potentially be linked to factors such as the presence of uremic toxins and dietary
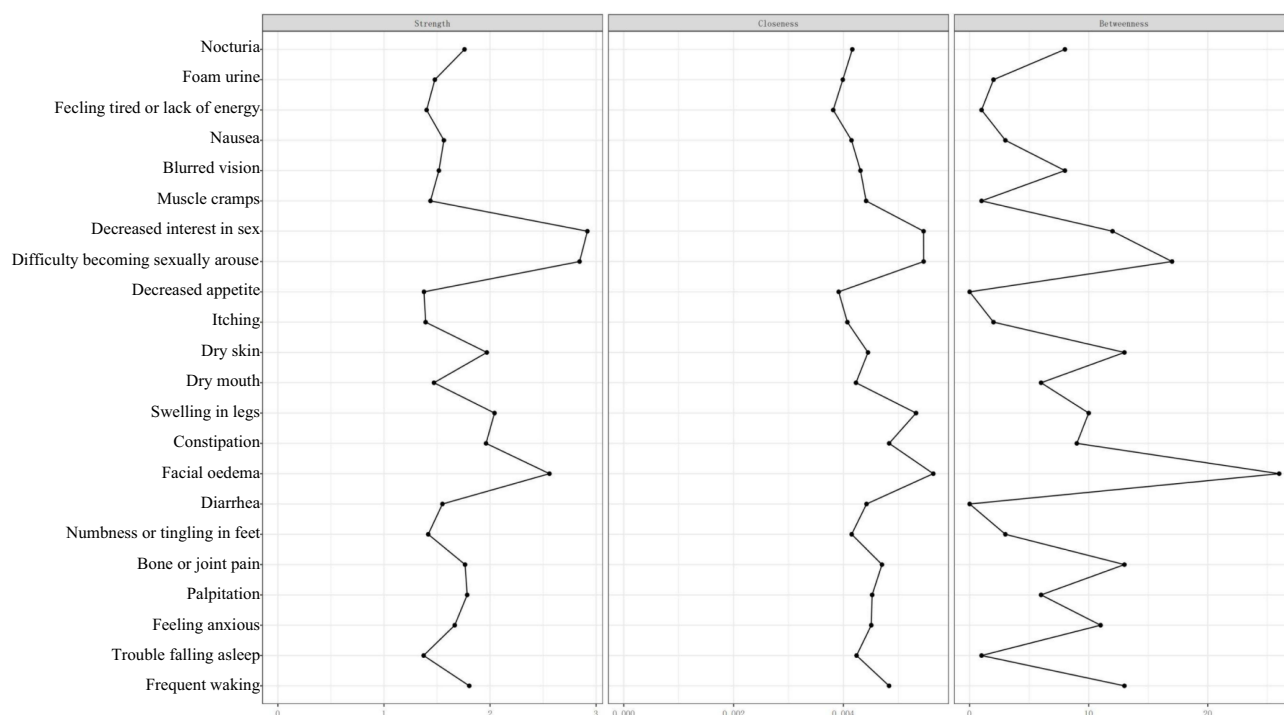
Figure 2 Centrality analysis of symptoms in DKD patients. The figure illustrates centrality analysis results for symptoms in DKD patients, pinpointing decreased interest in sex and difficulty becoming sexually aroused as the most central and influential symptoms based on strength. These key symptoms are highlighted for their significant roles within the network, marked by high weights and strong influence.

restrictions imposing limitations on fiber-rich foods.[49] Moreover, medications like sotagliflozin and Tenapanor, commonly prescribed to Chinese CKD patients, have been noted to contribute to diarrhea.[50,51] Additionally, the literature indicates a correlation between edema and DKD,[52,53] with fluid retention being associated with adverse renal outcomes,[54] potentially due to compensatory ultrafiltration by the remaining nephrons to offset the reduced sodium filtration load.[55] Our network analysis showed that facial edema was moderately associated with swelling in legs, and was also related to diarrhea and constipation, suggesting that facial edema may be a predictor of other symptoms, or has more correlation with other symptoms. Thus, it is crucial for healthcare professionals to promptly identify DKD patients with facial edema and implement targeted interventions.

Symptom Cluster C, encompassing decreased interest in sex and difficulty with sexual arousal. This underscores the importance for healthcare professionals to promptly recognize and address sexual dysfunction in DKD patients. As kidney disease management and patient survival rates continue to improve, sexual function should be pursued as the focus of patient-centered care to improve quality of life.[56] The impact of sexual dysfunction on quality of life is well recognized, and it has been proved to relate to low self-esteem and confidence, and higher rates of anxiety and depression.[57] CKD significantly impacts the body's hormonal balance, leading to various hormonal disturbances that can affect sexual function.[58] In CKD, the kidneys' diminished ability to filter blood and regulate hormones, such as testosterone in men and estrogen in women, contributes to hormonal imbalances. These imbalances are associated with symptoms like reduced libido, erectile dysfunction in men, and menstrual irregularities in women, directly impacting sexual health and function.[59,60] Furthermore, psychological stress and certain antidepressants may exacerbate sexual dysfunction in CKD patients.[61,62] Therefore, it is crucial to prioritize the identification and management of diverse factors contributing to sexual dysfunction in these patients.[61] Our network analysis identified sexual dysfunction as the most central symptom cluster, indicating its potential association with various symptoms. While the precise mechanisms remain to be fully understood, the significance of addressing sexual health issues, often neglected in clinical practice, cannot be overstated.

Nausea, muscle cramps, blurred vision, and feeling tired or lack of energy were included in Symptom Cluster D. These symptoms may be attributed to retinal neuropathy and neurological changes associated with DKD, as indicated
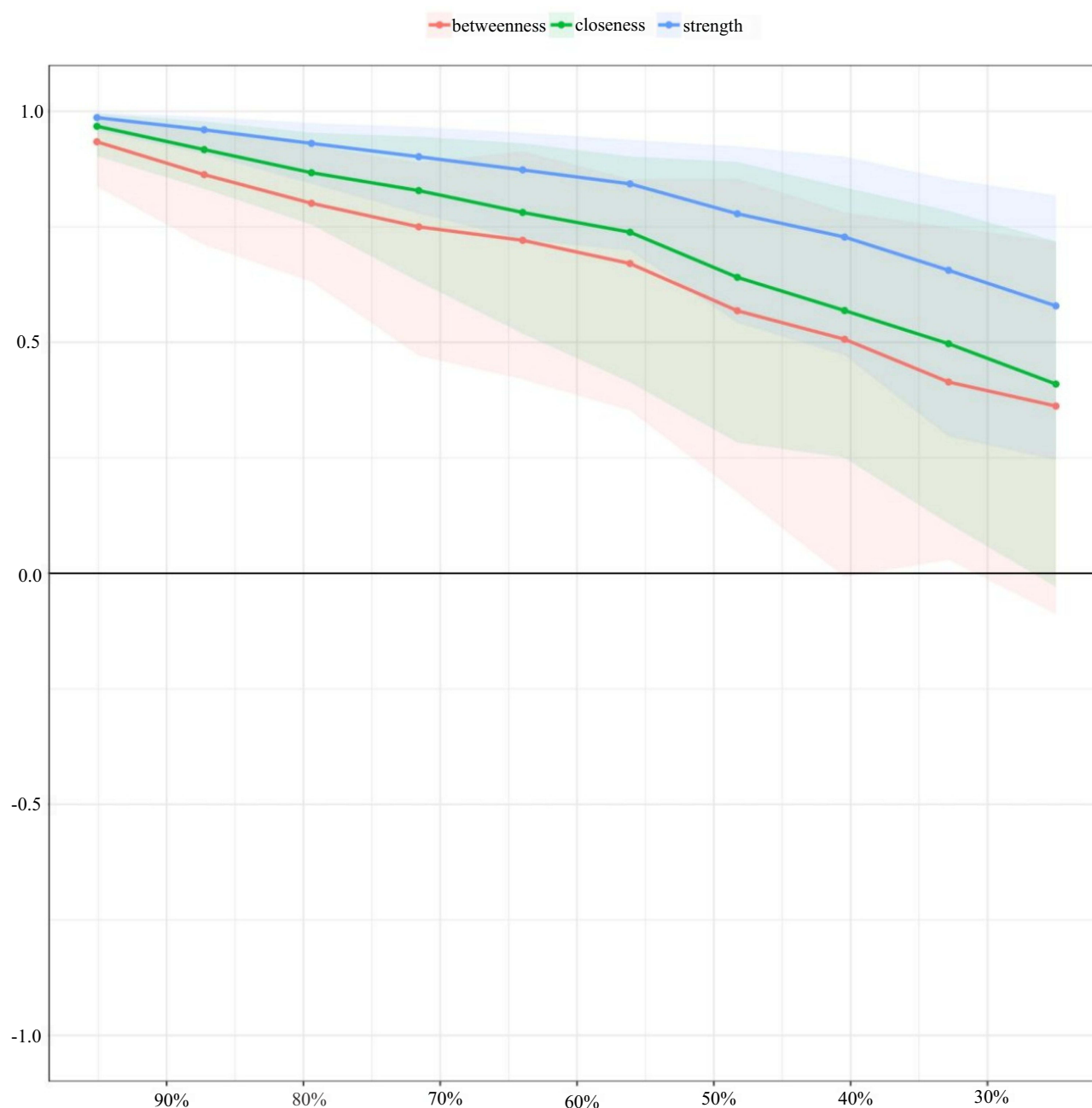
Figure 3 Correlation stability coefficient of symptoms network in DKD patients. The figure demonstrates the stability of the symptom network in DKD patients, with strength correlation coefficients consistently above 0.5, affirming network reliability. It also shows strength centrality's superior stability over closeness and betweenness measures.

by prior research.[40] Muscle cramps, particularly prevalent and painful, not only disrupt sleep and daily activities but also negatively impact the quality of life and dialysis outcomes.[63] Literature reports muscle cramp incidence rates of 33–78% in hemodialysis patients and 24–78% in diabetic patients.[64,65] In this study, the incidence of muscle cramp in patients with DKD was 12.5%. The connection between DKD and muscle cramps remains incompletely understood. It is hypothesized that one contributing factor is the accumulation of uremic toxins, a result of diminished renal excretion.[66] Additionally, complications arising from diabetes mellitus, such as electrolyte imbalances, diabetic neuropathy, and vascular complications, are believed to play a significant role in the development of muscle cramps.[67,68] Research suggests that patient-centered symptom management strategies, including incremental dialysis, conservative
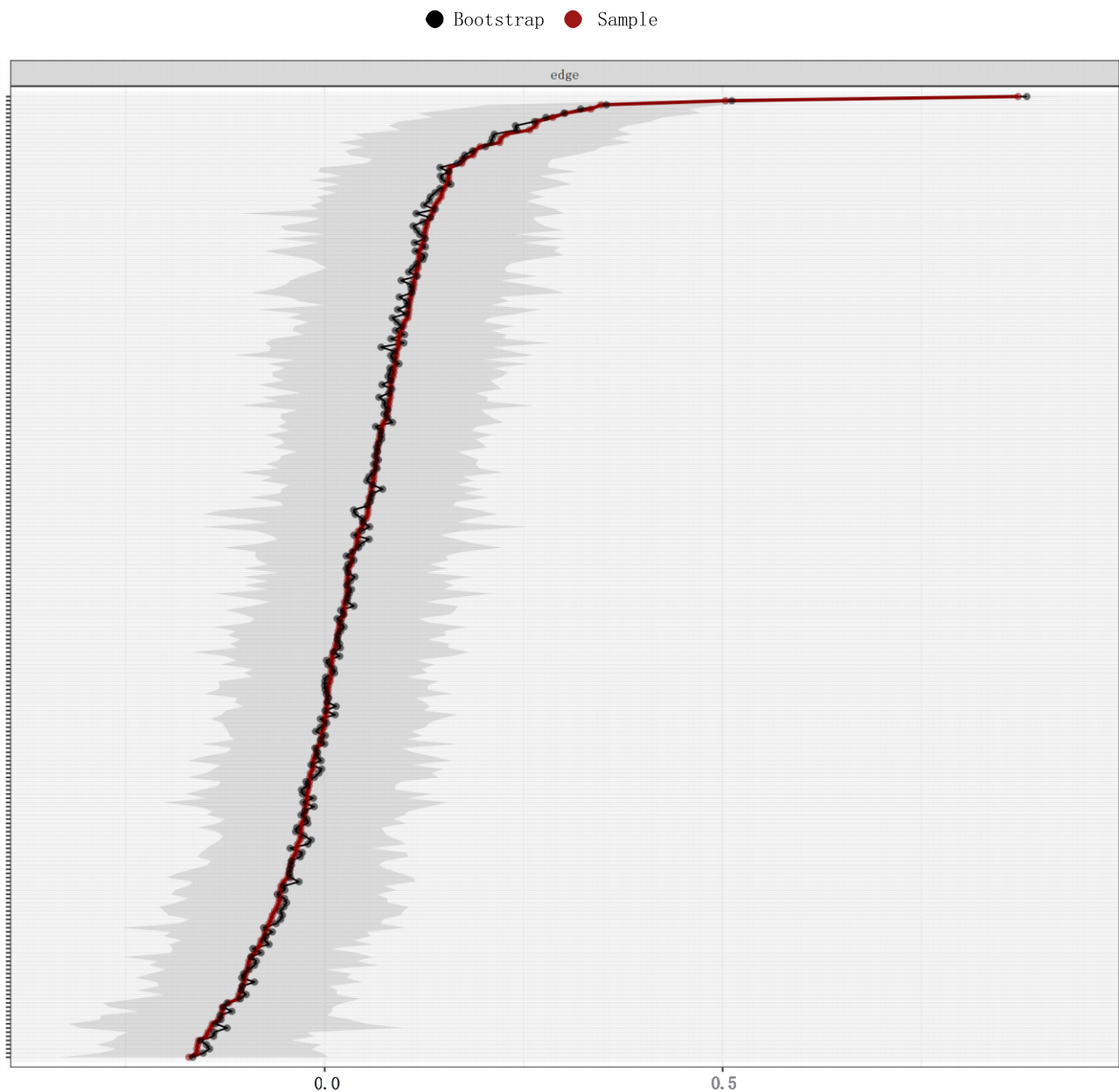
Figure 4 Bootstrap analysis results of the edge weights. This figure displays bootstrap analysis results, with the red line showing sample values and the gray area indicating bootstrapped confidence intervals. The consistent narrow confidence intervals across all edges, ordered by weight, confirm the accuracy of the network's structure.

care, exercise, or dietary modifications (eg, consuming spicy foods to stimulate oropharyngeal reflexes, leading to muscle relaxation), may help alleviate muscle spasms.[69] These findings point towards potential management strategies for DKD patients, emphasizing the importance of tailored approaches to symptom management.

Symptom Cluster E encompasses two symptoms: nocturia and foam urine. This finding aligns with a large population-based study indicating that nocturia serves as an independent predictor of albuminuria and is linked to kidney disease.[64] Prior research has established a connection between abnormal urination patterns and DKD, potentially due to the increased blood pressure associated with DKD.[69] In our study, nocturia and foamy urine were the most prevalent symptoms, yet they exhibited low centrality. This suggests that these symptoms may coexist with or act as predictors for other associated symptoms, highlighting their potential role in the broader symptom network of DKD patients.[34]

Limitations

This study has several limitations. First, our study only included participants with complete data from a tertiary hospital, potentially limiting the representativeness due to access to specialized care not universally available. Second, the symptoms included in this study were from CKD-SBI, which is not specific for patients with DKD. However, we compensated for this deficiency with the use of a system leveraging the self-reporting of symptoms. Thirdly, our cross-sectional data-based network analysis does not establish causality, requiring theory-supported interpretations for causal inferences. Fourth, since most participants were in stage 3 CKD or higher, we did not differentiate between early and late-stage DKD, highlighting an area for future research to examine symptom associations in patients with distinct disease trajectories or treatment modalities.

Conclusion

This study identified five symptom clusters in Chinese DKD patients, with sexual dysfunction emerging as the most central cluster. These findings carry significant clinical implications, underscoring the necessity of assessing symptom clusters and their interrelations to enhance symptom management in DKD patients. Further research is essential to elucidate the underlying mechanisms of symptoms and to clarify the associations among symptoms in DKD patients across different disease trajectories or treatment modalities.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Biomedical Ethics Review Committee of West China Hospital, Sichuan University (no.2023(1848)). Written informed consent was obtained from all participants.

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Disclosure

The authors declare they have no competing interests.

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