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Studying the role of cadherin-11 as a novel biomarker of kidney fibrosis

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ABSTRACT

Introduction: Kidney fibrosis is the ultimate common pathway observed in all chronic nephropathies, which arises due to the pathological accumulation of extracellular matrix (ECM) components in response to persistent injury. While biopsy is widely regarded as the preferred diagnostic method, it is an invasive procedure with inherent limitations. Alternatively, cadherin-11 (CDH-11) serves as an exceptional noninvasive biomarker for kidney fibrosis.

Objectives: To measure serum CDH-11 among patients indicated for native kidney biopsy. In addition, this study aimed to examine the correlation between CDH-11 levels and kidney biopsy's interstitial fibrosis tubular atrophy (IFTA) score to investigate its sensitivity and specificity as a biomarker of kidney fibrosis.

Patients and Methods: The current study adopted a cross-sectional design involving 100 clinically indicated patients for native kidney biopsy. All participants were subjected to serum CDH-11 measurement on the biopsy day. This study was carried out in Ain Shams University Hospitals.

Results: The results indicated that the median value of CDH-11 was 3.9 ng/mL (2.2–7.6). This value was found to be significantly higher in cases with arteriosclerosis at a P value <0.001. It was highest in grade 3, followed by 2, then 1, then zero of all chronicity grading scale points (global and segmental, tubular atrophy, and interstitial fibrosis) at a *P* value <0.001. Consequently, it was highest in severe, followed by moderate, then mild, and lowest in minimal IFTA with (median of 12.0 (7.6–16.0), 6.1 (4.4–7.7), 3.5 (2.2–4.6), 1.2 (0.5–2.6), respectively. The area under the curve was 0.645, and the optimal cut-off level was ≥5.6 ng/dL (90.9% sensitivity and 71.8% specificity).

Conclusion: Based on the current study findings, it can be determined that CDH-11 serves as a highly accurate and precise indicator in patients with kidney fibrosis. Furthermore, the level of CDH-11 can predict the degree of fibrosis across various etiologies of kidney disease.

Implication for health policy/practice/research/medical education:
Kidney fibrosis plays a crucial role in the pathogenesis of chronic kidney disease, significantly impacting the affected individual's overall health and quality of life. The potential benefits of identifying biomarkers linked to fibrosis include the facilitation of early intervention and the ability to predict the progression of the disease.

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Original Article

Introduction

Chronic kidney disease (CKD) has been identified as the primary cause of mortality worldwide. According to epidemiological research, this disease affects more than 10% of the global population (1). It should be noted that kidney fibrosis serves as the definitive shared route in the advancement of renal disease (2).

Fibrosis results from the pathological accumulation of extracellular matrix (ECM) elements in response to chronic injury and inflammation. The aforementioned reaction can be elicited by various stimuli, such as autoimmune responses, infections, or ischemic and toxic injuries (3).

Biopsy is the gold standard for assessing fibrosis with

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histological techniques. Interstitial fibrosis and tubular atrophy (IFTA) are considered highly dependable histologic markers for the progression of CKD, regardless of the underlying etiology (4). Nevertheless, the utilization of kidney biopsy is limited by several constraints.

Despite recent safety improvements, renal biopsy still presents complications, including minor and significant hemorrhaging, discomfort, arteriovenous fistulas, and soft tissue infections in the peri-renal area. The aforementioned complications have the potential to lead to prolonged hospitalization, deterioration of renal function, and ultimately mortality (5). Furthermore, it is important to note that the financial implications associated with the procedure are significant. Moreover, there are instances where the quantity of tissue procured from a needle core biopsy is inadequate to evaluate the severity of a disease. Histological changes are typically assessed using a semi-quantitative scoring system, which involves an element of subjectivity. Additionally, serial renal biopsies are challenging (6). Finally, the main inherent limitation in evaluating fibrosis via biopsy is the presence of sampling bias associated with the technique (7). Therefore, novel biomarkers can efficiently measure the extent and advancement of fibrosis. These biomarkers are crucial for aiding in the diagnosis, monitoring the progression of the disease, and evaluating the effectiveness of targeted treatments (8).

Kidney fibrosis is a pathological condition characterized by interstitial expansion due to the accumulation of proliferating myofibroblasts under chronic injury conditions. Myofibroblasts' secretion of matrix proteins disrupts the kidney architecture and ultimately leads to parenchymal loss (9). Therefore, myofibroblasts constitute a crucial therapeutic target in fibrosis and CKD. Currently, there is ongoing development of anti-fibrotic agents that specifically target myofibroblasts. Nevertheless, the absence of noninvasive techniques to assess kidney fibrosis presents a substantial obstacle in effectively implementing these treatments. Hence, an optimal biomarker for kidney fibrosis would exhibit specific expression in myofibroblasts or ECM proteins, given their accumulation in fibrotic diseases (10).

Cadherin-11 (CDH-11), a member of the cadherin family, is a crucial adhesion molecule responsible for mediating calcium-dependent cell-to-cell adhesion in a classical manner (11). Its significance is evident in its substantial impact on tissue development and cellular migration, although its implications are beyond these fundamental functions (12).

Research has shown that the pathophysiologic mechanisms underlying the development of kidney fibrosis involve various factors, including CDH-11. The modulation of ECM production and the induction of fibroblasts to produce interleukin-6 have been observed (13). The upregulation of its expression has been observed in individuals diagnosed with kidney fibrosis, suggesting its potential as a noninvasive biomarker for this condition (14).

In the current study, we hypothesized that CDH-11 would significantly correlate with the severity of kidney fibrosis, thereby suggesting its potential as a promising noninvasive biomarker.

Objectives

The objective of this study was to measure serum CDH-11 among patients indicated for native kidney biopsy and to examine the correlation between these levels and the interstitial fibrosis tubular atrophy (IFTA) score obtained from the kidney biopsy. In addition, it aimed to determine the sensitivity and specificity of serum CDH-11 as a potential biomarker of kidney fibrosis.

Patients and Methods

Study population

The present cross-sectional investigation was conducted at Ain Shams University Hospitals from 2021 to 2023. The targeted study population comprised 100 patients aged ≥18 years. Subjects who were clinically indicated for renal biopsy due to acute kidney injury, non-nephrotic proteinuria, proteinuria with coexisting hematuria or isolated hematuria, nephrotic syndrome, progressive CKD, and unexplained rapid decline in renal function. However, patients presenting with contraindications for renal biopsy, such as small hyperechoic kidney, solitary kidney, multiple and bilateral cysts or renal tumors, anatomical kidney anomalies, active renal, perirenal, or biopsy site infection, malignancy, severe resistant hypertension, or uncontrollable bleeding disorder, were excluded from this study. Pregnant women were also excluded from this investigation.

Written informed consent was collected from all participants. In addition, we conducted relevant history taking, including sociodemographic history (age, gender, and residence) and clinical examination.

Laboratory tests

The following laboratory tests were analyzed at baseline, using commercially available kits: complete blood count, urea, serum creatinine, sodium, potassium, serum albumin, calcium, phosphorus, parathyroid hormone (PTH) level , ANA, Ani-DNA, C3, C4, virology for hepatitis B, C and HIV, urine analysis, protein/creatinine ratio, in addition calculation of the estimated glomerular filtration rate (eGFR) by using the equation of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and serum CDH-11 was measured on the day of biopsy.

Renal biopsy

A renal biopsy was conducted, and the specimens were prepared for light microscopy. Then, the renal pathologist evaluated the histologic characteristics and severity of IFTA. This condition is a semi-quantitative and standardized method for evaluating chronic alterations in native kidney biopsies. These alterations include glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. The findings of these alterations are presented as an overall chronicity grade. Glomerulosclerosis is characterized by the global or segmental collapse of glomerular capillary walls, leading to the consolidation of the glomerular tuft by the ECM. This subsequently results in capillary luminal obliteration. Tubular atrophy is characterized by the shrinkage of tubules that may demonstrate variable thickening of the tubular basement membrane and flattening of the tubular epithelium. The accumulation of fibrous tissue between the tubules marks interstitial fibrosis. Tubular atrophy and interstitial fibrosis frequently occur together and are designated IFTA, yet they can rarely develop independently. Arteriosclerosis is defined as the intima's fibrous thickening and/or hyalinosis. Scoring and subsequent grading of the chronic changes are suggested as follows:

- Global and segmental are scored from (0-3)
- Tubular atrophy from (0-3)
- Interstitial fibrosis from (0-3)
- Arteriosclerosis from (0-1)

In the context of tissue compartments, a score of 0 indicates no observable impact, while a score of 1 corresponds to a range of 10% to 25% affected. Similarly, a score of 2 signifies an impact ranging from 26% to 50%, while a score of 3 denotes an impact exceeding 50% of the tissue compartment. In the context of arteriosclerosis, a score of 0 is assigned when the intimal thickness is less than the thickness of the media. In contrast, a score of 1 is assigned when the intimal thickness is higher.

The score was then added (total renal chronicity score) to grade the overall severity of the chronic lesion into:

- Minimal (0-1 total score)
- Mild (2-4 total score)
- Moderate (5-7 total score)
- Severe (8-10 total score)

This study emphasizes that the evaluation and grading of chronic changes do not constitute a classification. Nonetheless, it is a methodical and partially quantitative approach for appraising and documenting chronic lesions (15).

Serum CDH-11 enzyme-linked immunosorbent assay

Serum CDH-11 levels were measured on the day of renal biopsy. Blood samples were collected at baseline and then allowed to rest for 10–20 minutes at room temperature to clot. Subsequently, samples were centrifuged at (2000-3000 RPM) for approximately 20 minutes to remove impurities, then stored frozen at -80 °C until assayed. CDH-11 levels were measured using the human CDH-11 double antibody sandwich enzyme-linked immunosorbent assay (ELISA) assay kit (catalog No: E3272Hu). Serum specimens were introduced into pre-coated wells containing CDH-11 (CDH-11/CAD11) monoclonal antibody followed by incubation. Afterward, biotin-labeled anti-CDH-11/CAD11 antibodies were used to form an immune complex with streptavidin-HRP. Following incubation, unbound enzymes were removed by washing. Chromogen solutions A and B were introduced, causing the solution to transition from blue to yellow due to the effects of acid. The hues of the solution and concentration of human CDH-11 (CDH-11/CAD11) were positively correlated. Each sample's optical density was measured under 450 nm wavelength, with the blank well serving as zero. The standard concentration and corresponding optical density value were utilized to generate a standard curve linear regression equation, which was subsequently applied to the optical density values of the samples to calculate their corresponding concentrations. Serum CDH-11 was reported as the amount of serum CDH-11 in nanograms per milliliter (ng/mL).

Statistical analysis

The collected data were revised, coded, tabulated, and statistically analyzed utilizing IBM SPSS Statistics software version 28.0, developed by IBM Corp. (Chicago, USA) in 2021. The quantitative data were subjected to a normality test using the Shapiro-Wilk test. Data with normal distribution were described as mean SD (standard deviation) in addition to the minimum and maximum of the range. The median (1st and 3rd interquartile) was conducted to describe non-normally distributed data, which was then compared using the Mann-Whitney U test (two independent groups) or the Kruskal Wallis test (three independent groups). The qualitative data were described as a number and percentage and compared using the chi-square and Fisher's exact tests for variables with small, expected numbers. Correlations were determined using the Spearman test, while post hoc comparisons were conducted utilizing the Bonferroni test. The significance level was set at P value <0.05.

Results

The present investigation was carried out on a sample of 100 patients who were clinically recommended to undergo native kidney biopsy at Ain Shams University Hospitals. The patients' demographic characteristics revealed a mean age of 35.7±15.1 years, with 57% male and 43% female.

Among the participants, 52% had hypertension, 17% had diabetes, 28% had autoimmune disease, and 18% were identified as analgesic abusers. Additionally, 21% of the patients were prescribed diuretics, while 15% were on angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as shown in Table 1.

Regarding the laboratory data among the studied cases, the mean hemoglobin, albumin, and protein/creatinine ratio were 10.4±2.2 g/dL, 2.7±0.6 g/dL, and 3.8 mg/mg (2.3–6.5), respectively. The median values for creatinine, eGFR, PTH, and CDH-11 were 3.2 mg/dL (1.1–6.0), 20.0 mL/min/1.73 m^2 (9.0–70.8), 88.5 pg/mL (41.5–203.0), and 3.9 (2.2–7.6) ng/mL respectively. Additionally, 76% of the population under study exhibited active urinary sediments (Tables 2 and 3).

The total studied cases included 21% with minimal IFTA, 35% with mild IFTA, 22% with moderate IFTA, and 22% with severe IFTA grades (Figures 1-4).

In our study, CDH-11 had significant positive correlations with age, serum potassium, phosphate, urea, creatinine, PTH, and total renal chronicity score of IFTA and significant negative correlations with eGFR with (*P* value <0.001), as highlighted in (Table 4). Moreover, CDH-11 was highest in grade II/III nephropathy, followed by grade I, and was lowest in grade 0 with median values of 7.2 (4.1–16.3), 6.7 (2.8–11.7 , 3.2 (1.7–5.7), respectively, as depicted in (Table 5).

The expression of CDH-11 was found to be significantly elevated in individuals diagnosed with arteriosclerosis, as indicated by a *P* value of less than 0.001. The highest values on the chronicity grading scale points (global and segmental, Tubular atrophy, and interstitial fibrosis) were observed in grade 3, followed by two, one, and zero, with *P* value <0.001. Consequently, the severity of the condition was found to be highest in the severe category, followed by moderate, mild, and lowest in minimal IFTA.

Table 1. Demographic characteristics and risk factors for kidney diseases among the studied cases

Characteristics	Value
Age (y), Mean ± SD (range)	35.7±15.1 (18.0–72.0)
Gender, No. (%)	
Male	43 (43.0)
Female	57 (57.0)
Hypertension, No. (%)	52 (52.0)
Diabetes mellitus, No. (%)	17 (17.0)
Ischemic heart disease, No. (%)	6 (6.0)
Autoimmune diseases, No. (%)	28 (28.0)
ACEIs or ARBs, No. (%)	15 (15.0)
Diuretics, No. (%)	21 (21.0)
Analgesic abuse, No. (%)	18 (18.0)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

The corresponding median values were (median 12.0 (7.6–16.0), 6.1 (4.4–7.7), 3.5 (2.2–4.6), 1.2 (0.5–2.6), respectively as explained in (Table 6).

The cut-off point for detecting fibrosis using CDH-11 was determined to be ≥5.6 ng/dL with 90.9% sensitivity, 71.8% specificity, the area under the curve (AUC)

Table 2. Laboratory data among the studied population, including CDH-11

Laboratory	Mean SD	Range
Hemoglobin (g/dL)	10.4±2.2	5.1–17.0
TLC (×10^3/mL)	8.0±3.4	2.3–20.0
Platelets (×10^3/mL)	249.7±105.5	14.0–595.0
Albumin (g/dL)	2.7±0.6	1.3–4.4
Sodium (mEq/L)	136.7±4.2	127.0–148.0
Potassium (mEq/L)	4.4±0.9	3.1–6.9
Calcium (mg/dL)	8.2±0.9	5.5–10.0
Phosphorus (mmol/L)	4.9±1.7	2.0–10.2
	Median (1st–3rd IQ)	**Range**
Urea (mg/dL)	75.0 (28.0–129.5)	8.0–320.0
Creatinine (mg/dL)	3.2 (1.1–6.0)	0.3–24.0
eGFR (ml/min/1.73m^2)	20.0 (9.0–70.8)	1.0–195.0
PTH (pg/mL)	88.5 (41.5–203.0)	6.0–695.0
C3 (mg/dL)	91.5 (53.4–121.5)	2.8–206.0
C4 (mg/dL)	24.0 (15.3–37.5)	0.9–127.0
CDH-11 (ng/mL)	3.9 (2.2–7.6)	0.1–22.9
	Number	**%**
ANA positive	30	30.0%
Anti-DNA positive	20	20.0%
HCV Ab positive	8	8.0%
HBs Ag positive	0	0.0%
HIV Ab positive	0	0.0%

TLC, Total leukocytes count; eGFR, estimated glomerular filtration rate; PTH, Parathyroid hormone; C3, Complement 3; C4, Complement 4; ANA, Antinuclear antibody; anti-DNA, Anti-double stranded DNA antibody; HCVAb, Hepatitis C virus antibody; HbsAg, Hepatitis B virus surface antigen; HIVAb, Human immunodeficiency virus antibody.

Table 3. Urine analysis and proteinuria findings among the studied population

Laboratory parameters	Median (1st–3rd IQ)	Range
24-h urinary proteins (g)	4.4 (2.5–6.9)	0.2–15.6
Protein/creatinine ratio (mg/mg)	3.8 (2.3–6.5)	0.2–17.1
	Number	**%**
Albuminuria (qualitative)	80	80.0%
Pyuria (>5 cells/HPF)	57	57.0%
Hematuria (>5 cells/HPF)	61	61.0%
Active sediments	76	76.0%

0.645, and a *P* value of 0.038. These results indicate that CDH-11 had a high sensitivity of 90.9% and a negative predictive value of 96.6%. However, it had significantly low diagnostic performance in differentiating severe IFTA (it can be used to exclude severe fibrosis but not to confirm it). The diagnostic performance of ultrasound in detecting fibrosis is limited, with a sensitivity of 68.2% and a specificity of 67.9%. This indicates that ultrasound grades do not significantly differentiate severe IFTA, exhibiting poor diagnostic characteristics in this regard (Figure 5).

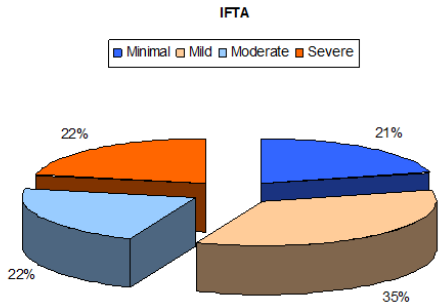

Figure 1. IFTA grades among the studied cases.

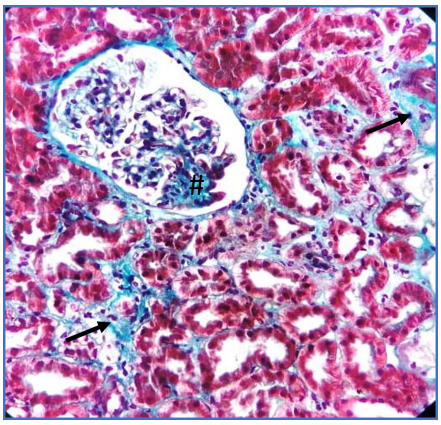

Figure 2. A case with mild IFTA showing a glomerulus with segmental sclerosis (#), mild tubular atrophy, and mild interstitial fibrosis (arrows) (Masson's trichrome×200).

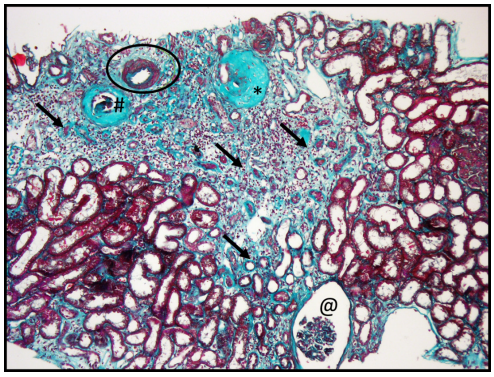

Figure 3. A case with moderate IFTA showing a globally sclerosed glomerulus (*), a glomerulus with near-global sclerosis (#), and one normocellular glomerulus with an ischemic collapsed tuft (@) mild tubular atrophy, mild interstitial fibrosis, and inflammation (arrows)along with mild hyaline arteriolosclerosis(circle) (Masson's trichrome×40).

Discussion

With the increase in CKD cases, biomarkers are urgently needed to detect and predict CKD progression. Currently, the only clinical tool available to diagnose fibrosis is a kidney biopsy (4), which is invasive, carries certain risks, and is therefore not performed routinely (6). It is crucial to identify biomarkers of fibrosis to comprehend CKD

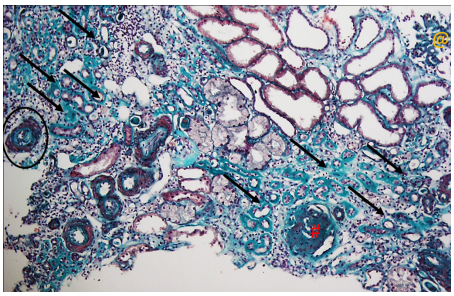

Figure 4. A case with a high chronicity index showing a globally sclerosed glomerulus (#), a normocellular glomerulus (@), marked tubular atrophy and interstitial fibrosis along with moderate mononuclear inflammatory cell infiltrate (arrows), and moderate arteriolosclerosis (circle) (Masson's trichrome ×100).

Table 4. Correlations between CDH-11 among the studied population to all variables

Characteristics (N=100)	R	*P* value
Age (y)	0.227	**0.023***
Albumin (g/dL)	0.235	0.118
Sodium (mEq/L)	0.146	0.147
Potassium (mEq/L)	0.268	**0.007***
Calcium (mg/dL)	-0.064	0.528
Phosphorus (mmol/L)	0.320	**0.001***
Urea (mg/dL)	0.392	**<0.001***
Creatinine (mg/dL)	0.362	**<0.001***
eGFR (ml/min/1.73m^2)	-0.345	**<0.001***
PTH (pg/mL)	0.562	**<0.001***
C3 (mg/dL)	-0.086	0.395
C4 (mg/dL)	-0.021	0.836
24-h urinary proteins (g)	-0.167	0.096
Protein/creatinine ratio(mg/mg)	-0.098	0.333
Global and segmental	0.613	**<0.001***
Tubular atrophy	0.740	**<0.001***
Interstitial fibrosis	0.744	**<0.001***
Total renal chronicity score	0.769	**<0.001***

eGFR, estimated glomerular filtration rate; PTH, Parathyroid hormone; C3, Complement 3; C4, Complement 4.
*Significant (<0.050) (Spearman's correlation coefficient test).

Table 5. Comparison of CDH-11 based on ultrasound findings in the studied population

Ultrasound grade	n	Median (1st–3rd IQ)	*P* value#
Grade-0 nephropathy	60	3.2 (1.7–5.7)[a]	<0.001*
Grade-I nephropathy	31	6.7 (2.8–11.7)[b]	
Grade-II/III nephropathy	9	7.2 (4.1–16.3)[b]	

Note: # Kruskal-Wallis test. *Significant (<0.050). Homogenous groups had the same symbol, "a,b" based on the post-hoc Bonferroni test

Table 6. Comparison according to biopsy findings among the studied population regarding CDH-11

Characteristics		n	Median (1st–3rd IQ)	*P* value
Arteriosclerosis	Positive	78	5.3 (2.8–8.8)	**<0.001***
	Negative	22	2.5 (1.2–3.8)	
Global and segmental	Grade-0	38	2.3 (1.2–3.5) a	**<0.001*#**
	Grade-1	14	4.4 (3.2–6.6) b	
	Grade-2	21	6.0 (2.8–8.1) b	
	Grade-3	27	11.0 (5.7–15.1) c	
Tubular atrophy	Grade-0	28	1.8 (0.5–2.8) a	**<0.001*#**
	Grade-1	38	3.8 (2.7–5.9) ab	
	Grade-2	25	7.7 (5.9–11.7) b	
	Grade-3	9	17.3 (15.1–20.6) b	
Interstitial fibrosis	Grade-0	27	1.2 (0.5–2.6) a	**<0.001*#**
	Grade-1	39	3.9 (2.8–6.1) b	
	Grade-2	26	7.9 (5.9–11.7) c	
	Grade-3	8	17.8 (10.4–21.1) c	
IFTA	Minimal	21	1.2 (0.5–2.6) a	**<0.001*#**
	Mild	35	3.5 (2.2–4.6) ab	
	Moderate	22	6.1 (4.4–7.7)bc	
	Severe	22	12.0 (7.6–16.0) c	

IFTA: Interstitial fibrosis with tubular atrophy.
#Kruskal-Wallis test. *Significant (<0.050). Homogenous groups had the same symbol, "a,b,c" based on the post-hoc Bonferroni test.

progression, which can provide vital information in a non-invasive manner. Furthermore, there is a necessity for a reliable panel of fibrosis biomarkers to identify a subgroup of patients who are at risk and can be targeted for future clinical trials to enhance CKD outcomes (16). The present study investigated the performance of CDH-11 in predicting kidney fibrosis compared to histological findings on renal biopsy. According to the findings of our study, CDH-11 may be a novel biomarker of kidney fibrosis.

In our study, 52% of the studied cases were hypertensive, 17% were diabetics, 28% had autoimmune disease, and 18% were analgesic abusers. In addition, 21 % of patients were on diuretics, and 15% were on ACEIs or ARBs. This finding is consistent with the study by Schmidt et al in 2021 (10), who studied CDH-11 serum and urinary levels and other biomarkers in patients clinically indicated for a native kidney biopsy on the day of biopsy in Boston Kidney Biopsy Cohort study (BKBC). The majority of patients were hypertensive 49.8 %, followed by people with diabetes 21.2%, 12.6% had systemic lupus erythematosus, 32.2 % were on ACEIs, and 14.7% were on ARBs. In contrast, Craciun et al (8) studied the urinary level of CDH-11 in equal groups of CKD patients and healthy individuals. They found that 86.7 % of patients were hypertensive, 36.7% were diabetics, 50% were on ACEIs, and 53.3% were on diuretics.

Our study revealed that most of the patients were anemic and had hypoalbuminemia, with a median eGFR of 20.0 mL/min/1.73 m^2 (9.0–70.8), median protein/creatinine ratio of 3.8 mg/mg (2.3–6.5), and serum CDH-11 level ranged between 0.1–22.9 ng/dL with median 3.9 ng/dL (2.2–7.6). This finding agrees with the study by Schmidt et al (10) where the mean eGFR was 56.6 ± 35.9 mL/min/1.73 m^2, while the median urine albumin-to-creatinine ratio was 1.7 mg/mg (0.4 – 4.4) and median CDH-11 was 1.8 ng/dL (0.8 –3.3).

In our study, CDH-11 had significant positive

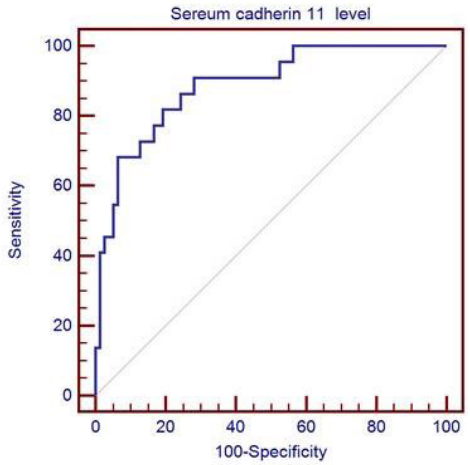

Figure 5. ROC curve for CDH-11 and ultrasound grade in predicting severe fibrosis.

correlations with age, serum urea, creatinine, potassium, phosphate, and PTH. Moreover, it was significantly higher in cases with oliguria and risk factors of CKD, such as hypertension, diabetes mellitus, and ischemic heart disease. However, Craciun et al (8) posited no correlation between elevated levels of urinary CDH-11 and specific etiologies suggested to be responsible for CKD, which contradicts the prior findings.

In our study, CDH-11 had significant positive correlations with global and segmental tubular atrophy and interstitial fibrosis. Therefore, total renal chronicity highlights its positive correlation with all chronicity factors. Consequently, CDH-11 has been identified as a potential biomarker for the noninvasive evaluation of kidney fibrosis, as corroborated by Schmidt et al (10). The study highlights that doubling plasma CDH-11 is linked to an increased likelihood of being in a higher IFTA category (OR=1.20, 95% CI 1.02 to 1.41). Similarly, doubling urinary CDH-11/creatinine increases the likelihood of being in a higher IFTA category (OR=1.24; 95% CI 1.12 to 1.38).

Our study did not find any statistically significant correlation between serum CDH-11 and proteinuria (*P* value > 0.05), which aligns with the study by Schmidt et al (10). They showed no statistically significant correlation between serum CDH-11 and proteinuria (*P* value > 0.077). However, there was a positive correlation between urine CDH-11 and proteinuria (*r*: 0.17, *P*<0.001).

In line with the study by Schmidt et al (10), who demonstrated plasma CDH-11 correlated inversely with eGFR (*r*: –0.25 to *P*<0.001) and the same for urine biomarker/creatinine (*r*: –0.39, *P*<0.001), CDH-11 in our study had significant negative correlations with eGFR (*r*: -0.345, *P* <0.001), suggesting that lower eGFR was consistently associated with higher levels of serum cadherin.

Based on the biopsy findings obtained in our study, a positive correlation was observed between the serum CDH-11 level and the chronicity score, indicating that as the chronicity score increased, the serum CDH-11 level also increased. Moreover, there was a notable increase in conditions associated with arteriosclerosis. The prevalence of global and segmental tubular atrophy and interstitial fibrosis exhibited an ascending pattern across the total chronicity scores, with the highest occurrence observed in score 3, followed by score 2, score 1, and the lowest incidence observed in score 0. According to the findings of Schmidt et al (10), the highest levels of CDH-11 were observed in cases of severe IFTA, with a mean value of 2.69 ng/dL (1.29–4.04). This finding was followed by moderate cases of IFTA, where CDH-11 had a mean value of 2.59 (1.44–4.13). In mild cases of IFTA, CDH-11 had a mean value of 2.02 ng/dL (0.94–2.87), while the lowest levels of CDH-11 were observed in cases of minimal IFTA, with a mean value of 1.48 ng/dL (0.85–2.63). These findings align with our findings.

In our study, the grade of nephropathy by ultrasound was significantly increased along with the increase in IFTA grades. The current study result is consistent with several studies on the correlation between ultrasonographic parameters and CKD stage assessment. For instance, Ahmed et al (17) demonstrated a statistically significant association between serum creatinine and the grade of echogenicity (*P*=0.0005). Furthermore, Yaprak et al (18) suggested that ultrasonographic CKD scores could be beneficial in distinguishing between stage 1 and 2 CKD and stage 3-5 CKD. Moreover, Kodikara et al (19) revealed a diagnostic role of index ultrasonic parameters in different stages of CKD. Furthermore, the index ultrasound and biochemical parameters showed a complementary role in predicting renal dysfunction.

Meanwhile, a receiver operating characteristic (ROC) analysis was conducted to assess the diagnostic reliability of serum CDH-11 (ng/dL) in relation to the severity of kidney fibrosis, as measured by IFTA grades. The analysis revealed that CDH-11 demonstrated a performance level with an AUC value of 0.645, indicating moderate accuracy. Furthermore, the sensitivity of CDH-11 was found to be 90.9%, while the specificity was 71.8%. The present discovery suggests that CDH-11 exhibited a notable sensitivity of 90.9% and a negative predictive value of 96.6%. However, it demonstrated limited diagnostic efficacy in distinguishing severe IFTA, as it can be utilized to rule out the presence of severe fibrosis but cannot definitively confirm its occurrence. This discovery aligns with the research conducted by Craciun et al (8), which showed a statistically significant increase (*P*<0.05) in urinary CDH-11 levels (approximately two-fold) among individuals with CKD. Therefore, CDH-11

has been identified as a potentially valuable biomarker for kidney fibrosis, exhibiting prognostic significance in assessing the likelihood of kidney disease progression in individuals with CKD. However, there is a disagreement with Craciun et al (8) regarding detecting CDH-11 in urine samples obtained from control subjects (individuals without kidney abnormalities). This finding is consistent with the findings reported by Schmidt et al (10), which suggest that CDH-11 may serve as a promising biomarker for identifying kidney fibrosis. The biomarker exhibits prognostic significance and can be employed for estimating the probability of disease progression in patients with CKD.

Conclusion

One way to predict the degree of fibrosis in different causes of kidney disease is by measuring the levels of CDH-11, which has been found to be a sensitive and specific marker for kidney fibrosis in patients. Therefore, it can serve as a biomarker for the noninvasive assessment of kidney fibrosis.

Limitations of the study

The study has limitations such as a small sample size of patients and the necessity to analyze markers in urine samples.

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Authors' contribution

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine of Ain Shams University (reference number; FWA 000017585). Prior to any intervention, all participants provided written informed consent. The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

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