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Panel miRNAs are potential diagnostic markers for chronic kidney diseases: a systematic review and meta-analysis

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Abstract

Background Accurate detection of kidney damage is key to preventing renal failure, and identifying biomarkers is essential for this purpose. We aimed to assess the accuracy of miRNAs as diagnostic tools for chronic kidney disease (CKD).

Methods We thoroughly searched five databases (MEDLINE, Web of Science, Embase, Scopus, and CENTRAL) and performed a meta-analysis using R software. We assessed the overall diagnostic potential using the pooled area under the curve (pAUC), sensitivity (SEN), and specificity (SPE) values and the risk of bias by using the QUADAS-2 tool. The study protocol was registered on PROSPERO (CRD42021282785).

Results We analyzed data from 8351 CKD patients, 2989 healthy individuals, and 4331 people with chronic diseases. Among the single miRNAs, the pooled SEN was 0.82, and the SPE was 0.81 for diabetic nephropathy (DN) vs. diabetes mellitus (DM). The SEN and SPE were 0.91 and 0.89 for DN and healthy controls, respectively. miR-192 was the most frequently reported miRNA in DN patients, with a pAUC of 0.91 and SEN and SPE of 0.89 and 0.89, respectively, compared to those in healthy controls. The panel of miRNAs outperformed the single miRNAs (pAUC of 0.86 vs. 0.79, $p < 0.05$). The SEN and SPE of the panel miRNAs were 0.89 and 0.73, respectively, for DN vs. DM. In the lupus nephritis (LN) vs. systemic lupus erythematosus (SLE) cohorts, the SEN and SPE were 0.84 and 0.81, respectively. Urinary miRNAs tended to be more effective than blood miRNAs ($p = 0.06$).

Conclusion MiRNAs show promise as effective diagnostic markers for CKD. The detection of miRNAs in urine and the use of a panel of miRNAs allows more accurate diagnosis.

Key Learning Points
1. The diagnostic performance of miRNAs in chronic kidney diseases needs to be investigated, as previous systematic reviews and meta-analyses are scarce, and individual cohort studies have confirmed their importance in kidney pathophysiology.
2. Using multiple miRNAs as biomarkers can lead to more precise CKD diagnosis, as they outperform single miRNAs compared to healthy and people with chronic disease groups. The overall diagnostic accuracy of urinary miRNAs

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tended to be greater than that of blood samples, suggesting that they are noninvasive and readily available diagnostic markers in CKD patients.

3. Incorporating miRNAs as diagnostic markers for CKD in combination with traditional markers might improve the accuracy and efficiency of diagnosis. To optimize miRNA diagnostic performance, it is essential to consider the various biological sample types, comparison groups (control), and different kidney diseases.

Keywords microRNA, Diagnostic accuracy, Chronic kidney disease, Biomarker

Introduction

By 2040, chronic kidney disease (CKD) is expected to be the fifth most common cause of death worldwide [1], raising awareness of the need for sensitive diagnostic biomarkers and novel therapeutic strategies. To assess the degree of renal damage, monitor disease progression, and evaluate the response to treatment, kidney function should be assessed by the estimated glomerular filtration rate (eGFR) from the serum creatinine level or by measuring the degree of proteinuria as a standard diagnostic procedure. However, controversy still exists regarding the staging, diagnosis, and prediction of complications in CKD [2].

MicroRNAs (miRNAs), the largest family of short noncoding RNAs, have recently emerged as potential diagnostic markers and therapeutic agents [3, 4]. Initial studies were conducted in 2004 and 2005 to identify miRNAs specific to or enriched in the kidney [5, 6]. The significance of miRNAs in kidney function was revealed in 2007 [7], leading to the implementation of the Human MicroRNA Disease Database [8] and a subsequent increase in research evidence. However, the diagnostic performance of miRNAs in CKD needs to be investigated, as preclinical studies have confirmed their importance in kidney pathophysiology [9]. In addition, miRNAs exhibit superior stability in degraded RNA samples, which makes them more suitable biomarkers [10].

Furthermore, miRNAs may outperform conventional markers; for instance, a pilot study demonstrated that sets of miRNAs show alterations days before an increase in the serum creatinine concentration [11]. Serum and urine miRNAs are used for diagnostic purposes in patients with CKD [11–13], and some miRNAs may be specific to the disease or to the sample during kidney damage. The sensitivity (SEN), specificity (SPE), positive predictive value (PPV), and negative predictive value (NPV) are the most common values used to estimate diagnostic accuracy. However, for more accurate analysis, it is essential to consider the receiver operating characteristic (ROC) curve and the area under the curve (AUC) for overall diagnostic accuracy.

We aimed to assess the accuracy of single and panel miRNAs for diagnosing kidney disease using various sample types by using receiver operating characteristic (ROC) analysis and area under the curve (AUC) analysis. We also investigated the diagnostic performance of miRNAs by comparing patients with overt kidney disease groups with healthy individuals and chronic disease groups (such as DM patients and SLE patients without nephropathy or patients with different kidney diseases).

Methods

The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42021282785). No ethical approval was needed, as all the data were previously published in peer-reviewed journals, and no patients were involved in the study's design, conduct, or interpretation. We report our study based on the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [14] (Supplementary Table S1), while we followed the Cochrane Handbook (version 6.2) [15].

Eligibility criteria

To define our clinical question and eligibility criteria, we applied the PIRD framework as follows: the population (P) consisted of individuals with (case group) and without CKD (healthy and chronic disease groups); the index test (I) was miRNA detection performed by qRT−PCR; the reference test (R) was clinical diagnosis confirmed by biopsy or laboratory parameters; and the diagnosis (D) was chronic kidney disease. Studies were considered eligible if they met the following criteria: (1). The diagnostic accuracy of miRNA for CKD was provided; (2) all patients with CKD were diagnosed by the gold standards in diagnostics (biopsy or laboratory); (3) AUC, ROC curve, SEN and SPE were provided; (4) observational and interventional studies were included.

Studies were excluded from the systematic meta-analysis review if (1) the inclusion criteria were not met, (2) data on outcomes of interest were impossible to extract from the published results and upon request from the corresponding author, (3) the exposed group included acute kidney injury, CKD with coronary artery calcification, congenital kidney diseases, polycystic kidney disease, or Alport syndrome, (4) the study design included reviews, meta-analyses, case series and reports or letters, or (5) overlapping studies.

Search strategy and selection process

The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Embase, Scopus, and MEDLINE (via NCBI PubMed) databases were screened using an electronic search strategy (see Supplementary Methods). The first search was conducted up to November 25, 2021, and updated by the second search on November 26, 2022. There were no language restrictions or filters imposed. The references used were managed in EndNote 20 (Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates automatically and manually, two independent investigators performed article selection based on predefined eligibility criteria in a two-step manner—first considering the title and abstract and, subsequently, the full-text content. Cohen's kappa index was calculated at each selection step. A third investigator resolved disagreements. The reference lists of the included studies were also assessed for additional eligible reports.

Data collection

Two independent investigators performed the data collection. Disagreements were resolved by consensus. The following data were extracted: study characteristics (first author, publication year, country, study population), eligibility criteria, definition of case and control groups, definition of kidney disease, stages of CKD (as defined in each study either by the histology score or laboratory parameters or eGFR), sample number and type. The following variables were extracted for the purposes of miRNA diagnostic accuracy: miRNA name, miRNA detection, normalization method, fold change, AUC value, cutoff point for the ROC curve, overall diagnostic accuracy, SEN, SPE, and correlation coefficient between miRNA expression and laboratory parameters, if available. Standardized Microsoft Excel sheets (Microsoft Office 365, Redmond, WA, USA) were used for data collection. In the case of missing data, the study authors were contacted for retrieval. WebPlotDigitizer [16] was used to extract the area under the curve (AUC), negative value (SE), and specificity (SPE) values if only the ROC curves were available instead of the abovementioned statistics.

Data synthesis and analysis

In terms of clinical applicability, the data were pooled, taking into account the following moderators: (1) comparison of CKD patients with healthy individuals and people with chronic diseases, (2) individual kidney diseases, (3) biological sample types, (4) single miRNAs or panel miRNAs, and (5) ethnicity. We analyzed the most frequent miRNAs in the included studies separately. The statistical analysis was performed using R software (version 4.1.2.) [17]. A p value less than 0.05 indicated

statistical significance. We collected AUC values and computed their standard deviation using the confidence interval or the method of Hanley and colleagues [18] when the confidence interval was not available. For rigorous pAUC values, we considered the correlations between sample errors and random effects corresponding to the miRNAs present in the same study by a multivariate mixed-effect model supplemented with the robust approach [19]. Univariate and multivariate analyses of AUC values were performed to determine the effect of moderator variables. In addition, we applied well-known methods [20–22] to obtain pooled SEN and SPE. To address these correlations, we randomly selected SEN and SPE; we chose only one miRNA from each study and then calculated the pooled SEN and SPE. According to the ROC plot visualization, the size of the prediction region provided insight into heterogeneity.

In the case of the meta-analysis of specific miRNAs, we performed classical inverse variance AUC meta-analysis due to the lack of the abovementioned correlations. In these cases, the heterogeneity was calculated by I^2. We created AUC funnel plots showing all available data to assess publication bias. Similarly, as above, we performed Egger's test after randomly selecting one result from each study. Studies reporting only CKD without a specific diagnosis were excluded from the meta-analysis to avoid selection bias. For a detailed description of the statistical analysis, see the Supplementary Methods section.

Risk of bias and quality assessment

Three independent investigators (D.G., U.N.D.T., and G.G.) assessed the risk of bias in each study. The details are provided in the Supplementary Material. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [23] guidelines were used to evaluate study quality and assess the following variables: patient selection, index test, reference standard, and flow and timing (see Supplementary Material). Each variable was evaluated for risk of bias, and the first three domains were evaluated for applicability. The answer to each question was "yes," "no," or "unclear." A "yes" response indicated a low likelihood of bias, whereas a "no" or "unclear" response indicated the opposite.

Results

Search and selection

Eighty-seven studies met the eligibility criteria, and all were included in the meta-analysis [24–106]. All included records were reported as peer-reviewed full-text publications. The study selection process is described in detail in Supplementary Fig. 1.

A.

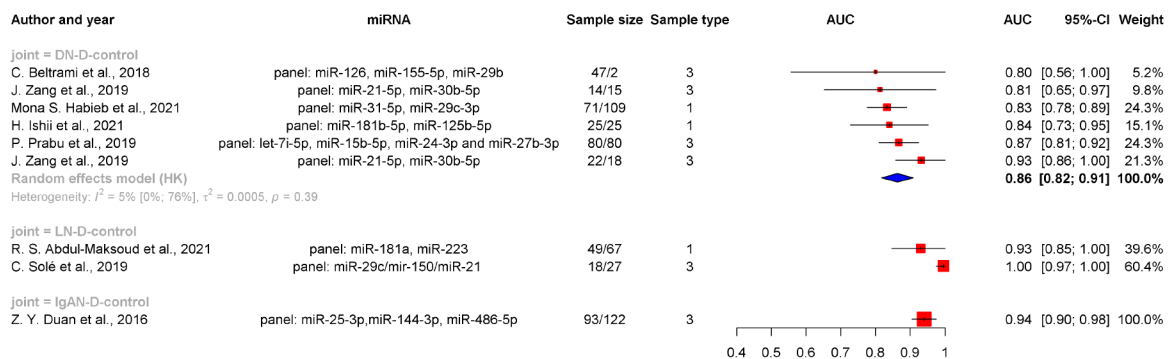| Author and year	miRNA	Sample size	Sample type	AUC	AUC	95%-CI	Weight
joint = LN-H-control							
E. Navarro-Quiroz et al., 2016	panel: miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p	140/40	1		0.82	[0.72; 0.92]	30.3%
S. Z. Vahed et al., 2018	panel: miR-125a, miR-142-3p, miR-146, miR-155-5p	26/26	1		0.89	[0.80; 0.98]	32.8%
M. Nakhjavani et al., 2019	panel: miR-21, miR-150,miR-423	26/26	1		0.93	[0.85; 1.00]	36.9%
Random effects model (HK)					**0.89**	**[0.75; 1.00]**	**100.0%**
Heterogeneity: $I^2 = 32\%$ [0%; 93%], $\tau^2 = 0.0009$, $p = 0.23$							
joint = DN-H-control							
S. Eissa et al., 2016	panel: miR-15b, 34a, 636	136/44	3		0.91	[0.86; 0.96]	100.0%
joint = FSGS-H-control							
B. Xiao et al., 2018	panel: miR-17, miR-451, miR-106a, miR-19b	24/35	1		0.82	[0.77; 0.87]	48.3%
C. Zhang et al., 2015	panel: miR-125b, miR-186, miR-193a-3p	100/100	1		0.96	[0.92; 1.00]	51.7%
joint = IgAN-H-control							
J. Wu et al., 2018	panel: miR-148a-3p, miR-150-5p, miR-20a-5p, miR-425-3p	83/82	1		0.75	[0.68; 0.82]	35.3%
G. Serino et al., 2016	panel: let-7b, miR-148b	245/183	1		0.80	[0.76; 0.84]	42.7%
Shuyun Li et al., 2022	panel: miR-451a, et-7d-3p	20/20	3		0.81	[0.68; 0.95]	22.0%
Random effects model (HK)					**0.79**	**[0.72; 0.86]**	**100.0%**
Heterogeneity: $I^2 = 0\%$ [0%; 90%], $\tau^2 = 0$, $p = 0.50$							
joint = MN-H-control							
L. Wu et al., 2021	panel: miR- 106a, miR- 19b, miR- 17	55/58	1		0.81	[0.73; 0.89]	100.0%

0.4 0.5 0.6 0.7 0.8 0.9 1

B.

Author and year	miRNA	Sample size	Sample type	AUC	AUC	95%-CI	Weight
joint = DN-D-control							
C. Beltrami et al., 2018	panel: miR-126, miR-155-5p, miR-29b	47/2	3		0.80	[0.56; 1.00]	5.2%
J. Zang et al., 2019	panel: miR-21-5p, miR-30b-5p	14/15	3		0.81	[0.65; 0.97]	9.8%
Mona S. Habieb et al., 2021	panel: miR-31-5p, miR-29c-3p	71/109	1		0.83	[0.78; 0.89]	24.3%
H. Ishii et al., 2021	panel: miR-181b-5p, miR-125b-5p	25/25	1		0.84	[0.73; 0.95]	15.1%
P. Prabu et al., 2019	panel: let-7i-5p, miR-15b-5p, miR-24-3p and miR-27b-3p	80/80	3		0.87	[0.81; 0.92]	24.3%
J. Zang et al., 2019	panel: miR-21-5p, miR-30b-5p	22/18	3		0.93	[0.86; 1.00]	21.3%
Random effects model (HK)					**0.86**	**[0.82; 0.91]**	**100.0%**
Heterogeneity: $I^2 = 5\%$ [0%; 76%], $\tau^2 = 0.0005$, $p = 0.39$							
joint = LN-D-control							
R. S. Abdul-Maksoud et al., 2021	panel: miR-181a, miR-223	49/67	1		0.93	[0.85; 1.00]	39.6%
C. Solé et al., 2019	panel: miR-29c/mir-150/miR-21	18/27	3		1.00	[0.97; 1.00]	60.4%
joint = IgAN-D-control							
Z. Y. Duan et al., 2016	panel: miR-25-3p,miR-144-3p, miR-486-5p	93/122	3		0.94	[0.90; 0.98]	100.0%

0.4 0.5 0.6 0.7 0.8 0.9 1

Fig. 1 The pooled AUC values of panel miRNAs in CKD patients compared with (**A**) healthy controls and (**B**) people with chronic diseases. Legend: Pooled AUC values (≥ 3 study) for panel miRNAs in patients with different kidney diseases; (**A**) healthy and (**B**) chronic disease groups stratified by sample type. Sample sizes are indicated as case/control groups. Sample types are illustrated by 1 (blood) and 3 (urine) abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; H, healthy individuals; D, people with chronic diseases; DN, diabetic nephropathy

Study characteristics

Eighty-seven articles (from 2013 to 2022) reported 238 single and 34 panel miRNA results, including 8351 patients with kidney diseases, 2989 healthy individuals and 4331 patients with SLE and diabetes mellitus (DM), e.g., as a control population (see Supplementary Table S2). Forty-seven studies were conducted with patients with CKD vs. healthy controls, and 40 were conducted with patients with CKD vs. people with chronic diseases (patients with SLE or T2DM without kidney disease or patients with different kidney diseases; see Supplementary Table S2). Several studies reported more than one kidney disease. All the studies used quantitative real-time reverse transcription PCR (qRT−PCR) to detect miRNAs. Regarding biological sample types, 28 studies detected miRNAs in urine, 56 in blood (15 in blood, 4 in PBMCs, 18 in plasma, 20 in serum, and two in serum exosomes), and 3 in kidney samples. Eighty-seven studies reported the pAUC values for single and panel miRNAs (Supplementary Table S3). The summary ROC curve was reported in 77 studies for single miRNAs and 20 studies for panel miRNAs. In total, 71 studies were included in the meta-analysis. The characteristics of the included studies are presented in Supplementary Table S4.

Area under the curve values

The healthy control studies had an overall pAUC of 0.84 (95% CI=0.81–0.87), while the chronic disease studies had a pAUC of 0.80 (95% CI=0.77–0.82). The difference between the two control groups was significant ($p=0.01$) (Supplementary Figure S2). We performed all the other analyses separately for the healthy and chronic disease groups.

The results from univariate and multivariate analyses agreed, except for the findings related to the sample type moderator. In the healthy and chronic disease groups, only the effect of the panel miRNA variable was significant, with pAUC values of 0.88 and 0.91, respectively (Supplementary Figure S3).

Table 1 Multivariate analysis of AUC values (panel miRNA – sample - disease interaction model with healthy control groups)

Coefficient	Estimate	SE	t-stat	d.f. (Satt)	*p*-val (Satt)	Sig.
Reference	0.84	0.02	34.95	16.67	< 0.001	***
Sample: Urine	0.05	0.03	2.05	18.05	0.06	.
Disease: Focal segmental glomerulosclerosis	-0.07	0.05	-1.41	6.27	0.21	
Disease: Lupus nephritis	-0.03	0.03	-0.83	19.92	0.42	
Disease: membranous nephropathy	-0.06	0.06	-1.12	4.39	0.32	
Disease: IgA nephropathy	-0.08	0.05	-1.85	9.3	0.10	.
Panel miRNA	0.08	0.02	4.61	8.88	0.001	**

Legend: contains the multivariate analysis of the panel – sample type - disease interaction in the model with healthy control groups. The reference variables were diabetic nephropathy (DN) – sample type: blood - single miRNAs. Significance: $p<0.001***, p<0.01**, p>0.05*$.

Table 2 Multivariate analysis of AUC values (panel miRNA – sample - disease interaction model with diseased control groups)

Coefficient	Estimate	SE	t-stat	d.f (Satt)	*p*-val (Satt)	Sig.
Reference	0.78	0.02	40.45	23.27	< 0.001	***
Sample: Urine	0.01	0.03	0.32	22.54	0.75	
Disease: Lupus nephritis	0.03	0.03	1.23	8.42	0.25	
Disease: IgA nephropathy	-0.004	0.08	-0.05	2.43	0.97	
Panel miRNA	0.08	0.01	6.13	6.46	< 0.001	***

Legend: Table 1 contains the multivariate analysis of when panel – sample type - disease interaction in the model with diseased control groups. The reference variables are Diabetic nephropathy (DN) – sample type: blood - single miRNAs. Significance; $p<0.001 ***, p<0.01**, p>0.05*$

Moreover, there was no significant difference between urine and blood sample types in studies that included people with chronic diseases. However, according to our multivariate analysis, urine tended to have a slightly greater AUC than blood ($p=0.06$) (Table 1). Unfortunately, kidney biopsy sample data were unavailable for multivariate analysis, but the overall pAUC was 0.82 for kidney diseases compared to people with chronic diseases (Supplementary Figure S4).

Among the DN patients and healthy controls, only the area under the curve (AUC) values for a panel of miR-15b, miR-34a, and miR-636 were reported (0.91, 95% CI=0.86–0.96) (Fig. 1), and the pAUC for a single miRNA was 0.86 (95% CI=0.82–0.89) (Supplementary Figure S5).

The pAUC of DN vs. DM was 0.86 (95% CI=0.82–0.91) for the panel miRNAs (Fig. 1) and 0.80 (95% CI=0.76–0.83) for the single miRNAs (Supplementary Figure S5). Among the individual studies, the miR-21 and miR-30-b-5p panels had higher AUCs in DN patients than in DM patients (0.93; 95% CI=0.86-1.0) (Fig. 1).

The LN patients in the SLE control group had a greater AUC than did those in the other kidney disease group, e.g., the panel containing miR-29c, miR-150, and miR-21 had an AUC of 1.00 (95% CI=0.97-1.00) (Fig. 1).

The pAUC of the panel of miRNAs in IgAN patients vs. healthy controls was 0.79 (95% CI=0.72–0.86) (Fig. 1).

Overall, the moderator variables were highly interdependent and affected the interpretation of the results. To eliminate some of the dependencies between the moderators, we omitted ethnicity from the multivariate analysis (Tables 1 and 2) but conducted univariate analyses (Supplementary Figure S6).

The pAUC values of the most frequently reported single miRNAs, miR-192, miR-21, and miR-146a, were analyzed. In contrast, compared with those of healthy individuals and T2DM patients without nephropathy, the pAUC of miR-192 was 0.91 (95% CI=0.67-1.0), and the pAUC was 0.78 (95% CI=0.76–0.81) for the diagnosis of DN (Fig. 2). miR-146a had a greater pAUC (0.92; 95% CI=0.70-1.0) in LN patients than in healthy controls (0.60; 95% CI=0.43–0.77) in LN patients vs. SLE patients (Supplementary Figure S7).

Sensitivity and specificity in studies with healthy controls

For single miRNAs, the pooled SEN and SPE for DNs compared to those for healthy controls were 0.91 (95% CI=0.86s-0.95) and 0.89 (95% CI=0.77–0.95), respectively (Fig. 3A). In patients with LN, the pooled SEN was 0.81 (95% CI=0.68–0.90), and the SPE was 0.80 (95% CI=0.72–0.87) (Fig. 3B). The pooled analysis of other kidney diseases is shown in Fig. 3C-E. Among the included studies, miR-192 was most frequently reported in DN patients compared to healthy controls, with a pooled SEN of 0.89 (95% CI=0.82–0.94) and SPE of 0.89 (95% CI=0.72–0.96) (Fig. 4).

Sensitivity and specificity in studies including people with chronic diseases

The pooled SEN and SPE values for single miRNAs in DN patients compared to those in T2DM patients were 0.82 (95% CI=0.76–0.87) and 0.81 (95% CI=0.74–0.86), respectively (Fig. 3A). When the LN patients were
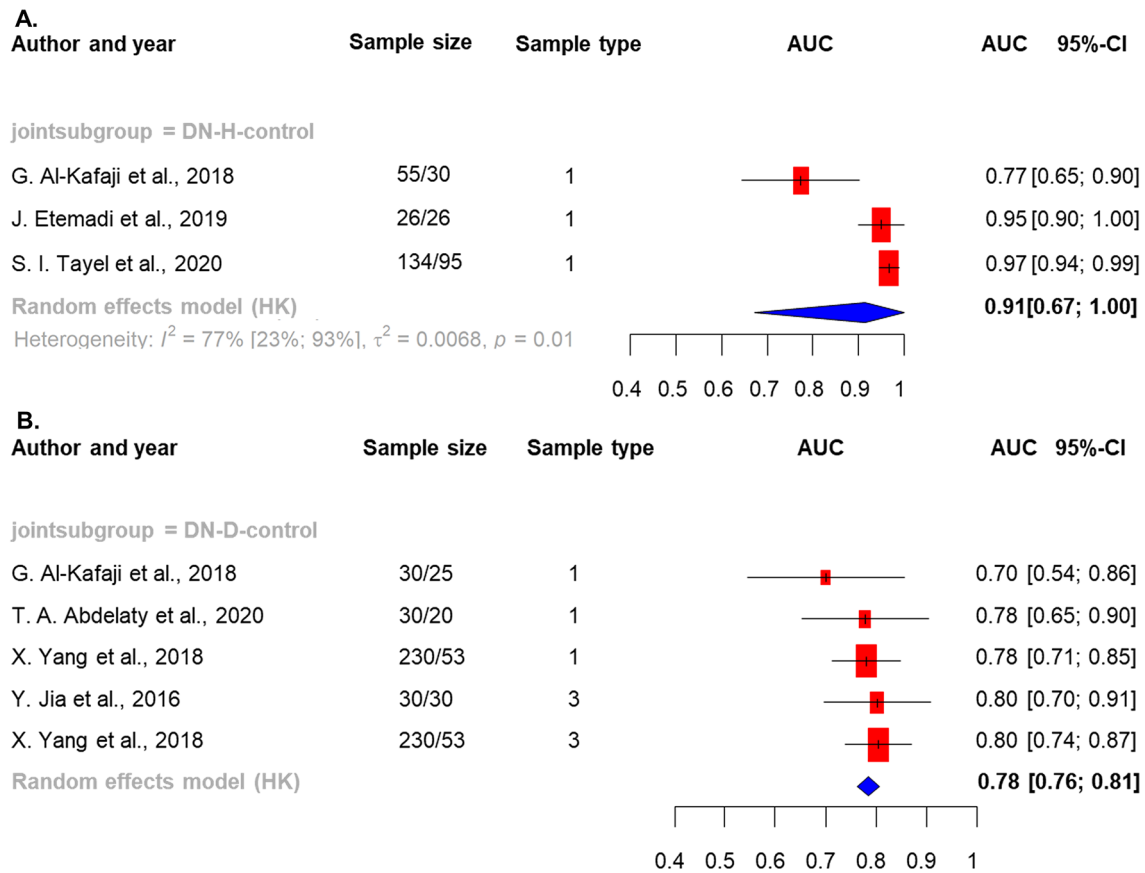
Fig. 2 The pooled AUC values of miR-192 in the diabetic nephropathy group compared with those in the (**A**) healthy controls and (**B**) chronic disease groups (diabetes mellitus). Legend: The pooled AUC values of miR-192 in diabetic nephropathy (DN) patients compared to those in (**A**) healthy individuals and (**B**) diabetes mellitus patients. Sample sizes are indicated as case/control groups. Sample types are illustrated by 1 (blood) and 3 (urine) abbreviations: AUC, area under the curve; 95% CI, 95% confidence interval; H, healthy indivdiual; D, chronic disease group; DN, diabetic nephropathy

compared to the SLE patients, the pooled SEN was 0.84 (95% CI=0.74–0.91), and the SPE was 0.81 (95% CI=0.72–0.88) (Fig. 3B). Figure 3C-E shows the pooled analysis of other kidney diseases. Among the panel miRNAs, the pooled SEN and SPE were 0.89 (95% CI=0.78–0.94) and 0.73 (95% CI=0.66–0.79), respectively, for DN compared with patients with T2DM (Fig. 5).

Sensitivity analysis for meta-analysis
The different analyses served as sensitivity analyses for each other. Moreover, we repeated the procedures with different correlation imputations to account for correlations. In the case of random selection, we repeated the process several times with roughly the same results.

Publication bias
If there were more than ten articles, a publication bias analysis was conducted and made available for DN, LN, IgAN, FSGS, and MN studies (Supplementary Figures S8-16). As a result, only LN studies with SLE control groups had no publication bias (Egger's test, *p*=0.09) (Supplementary Figure S10).

Risk of bias assessment
Supplementary Figure S17 and Table S5 of the QUADAS-2 assessment show that all CKD patients included in the studies were diagnosed according to clinically proven diagnostic criteria. All the studies had case−control or cohort designs, which may have introduced high or unclear risks to the selection field.

Discussion
To our knowledge, this is the first comprehensive systematic review and meta-analysis investigating the diagnostic accuracy of miRNAs in different biological samples and control groups for several types of kidney diseases. In our study, we found that the panel of miRNAs more effectively detected kidney diseases than did the single miRNAs. Furthermore, regarding the overall diagnostic performance of the miRNAs, the pAUC was better when comparing kidney disease patients to healthy controls than when comparing chronic disease groups. In addition, urinary miRNAs generally showed greater diagnostic accuracy than blood samples, with an overall pAUC of 0.86 and an overall pAUC of 0.82, respectively.
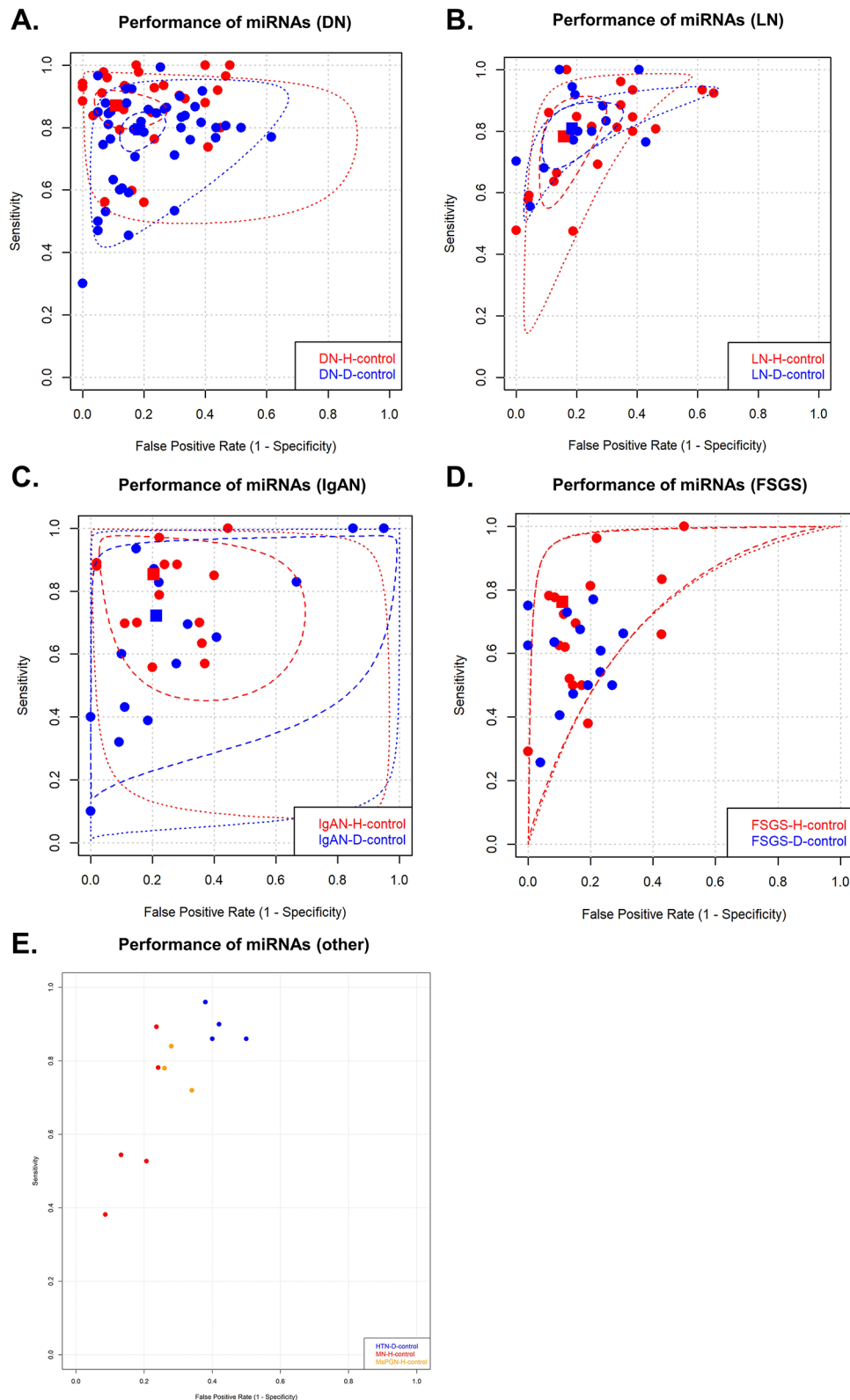
Fig. 3 The pooled sensitivity and specificity of single miRNAs in CKDs. Legend: Representative ROC curves of the sensitivity and specificity of single miR-NAs are shown for kidney diseases; (**A**) Diabetic nephropathy (DN), (**B**) Focal segmental glomerulosclerosis (FSGS), (**C**) IgA nephropathy (IgAN), (**D**) Lupus nephritis (LN) and (**E**) other kidney diseases. The pooled sensitivity and specificity are pooled if there are more than four studies and visualized by squares: red – healthy individuals and blue–chronic disease groups. Other kidney diseases include hypertensive nephropathy (HTN), membranous nephropathy (MN), and mesangial proliferative glomerulonephritis (MsPGN)
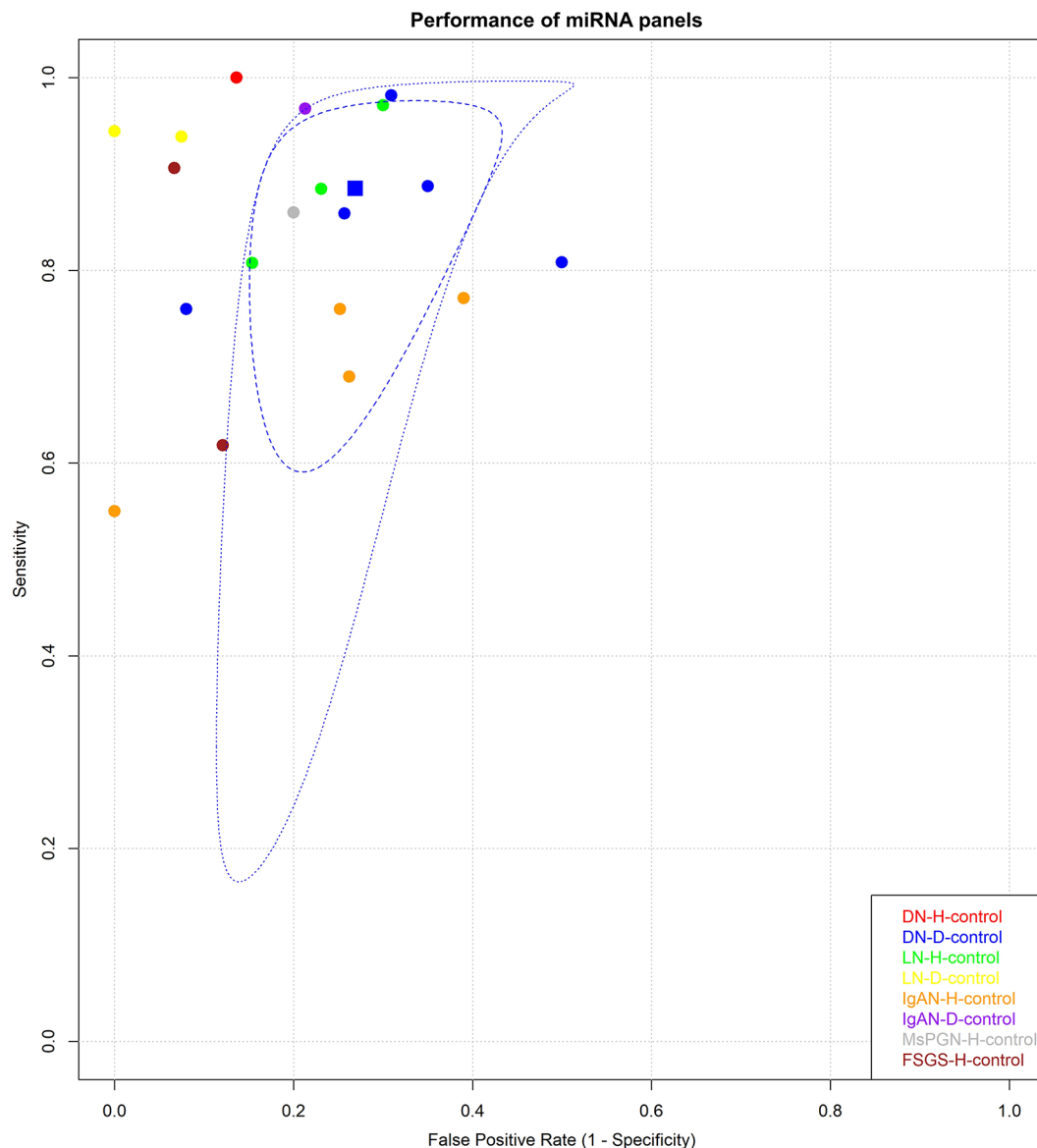
Fig. 4 The pooled sensitivity and specificity of the panel of miRNAs for CKDs. Legend: ROC curves of sensitivity and specificity for panel miRNAs are shown for kidney disease. The pooled sensitivity and specificity (≥ 4 studies) are shown for diabetic nephropathy compared to type 2 diabetes mellitus (DN-Pool2). Abbreviations: DN-Pool1, diabetic nephropathy compared to healthy controls; LN-Pool1, lupus nephritis compared to healthy controls; LN-Pool2, lcontrol, IgAN compared to systematic lupus erythematosus; IgAN-Pool2; IgA nephropathy compared to healthy controls; IgAN-Pool1, IgA nephropathy compared to chronic disease groups; NS-Pool1, nephrotic syndrome compared to healthy controls; MsPGN-Pool1, membranoproliferative glomerulopathy compared to healthy controls; FSGS-Pool2, focal segmental glomerulosclerosis compared to chronic disease group

Previous studies have confirmed that the diagnostic accuracy of a panel of miRNAs is superior to that of single miRNAs [107]. We also considered specific kidney diseases and conducted separate analyses for the healthy and chronic disease groups while considering the correlation between results from the same population. In addition, we performed a pooled analysis of the area under the curve (AUC) from each study to determine the overall diagnostic accuracy, eliminating the possibility of threshold effects.

We found that certain panels of miRNAs had higher overall AUCs when comparing DN patients, LN patients, or FSGS patients to healthy controls. These panels included miR-15b, miR-34a, and miR-636 for DN; miR-21, miR-150, and miR-423 for LN; and miR-125b, miR-186, and miR-193a-3p for FSGS. Additionally, in disease control studies, panels of miRNAs, such as miR-21 and miR-30-b-5p, had better overall AUCs for differentiating between DN patients and T2DM patients. Similarly, panels of miR-29c, miR-150, and miR-21 effectively distinguished LN from SLE patients. Another study by J. Li and

Performance of miR-192 (DN)
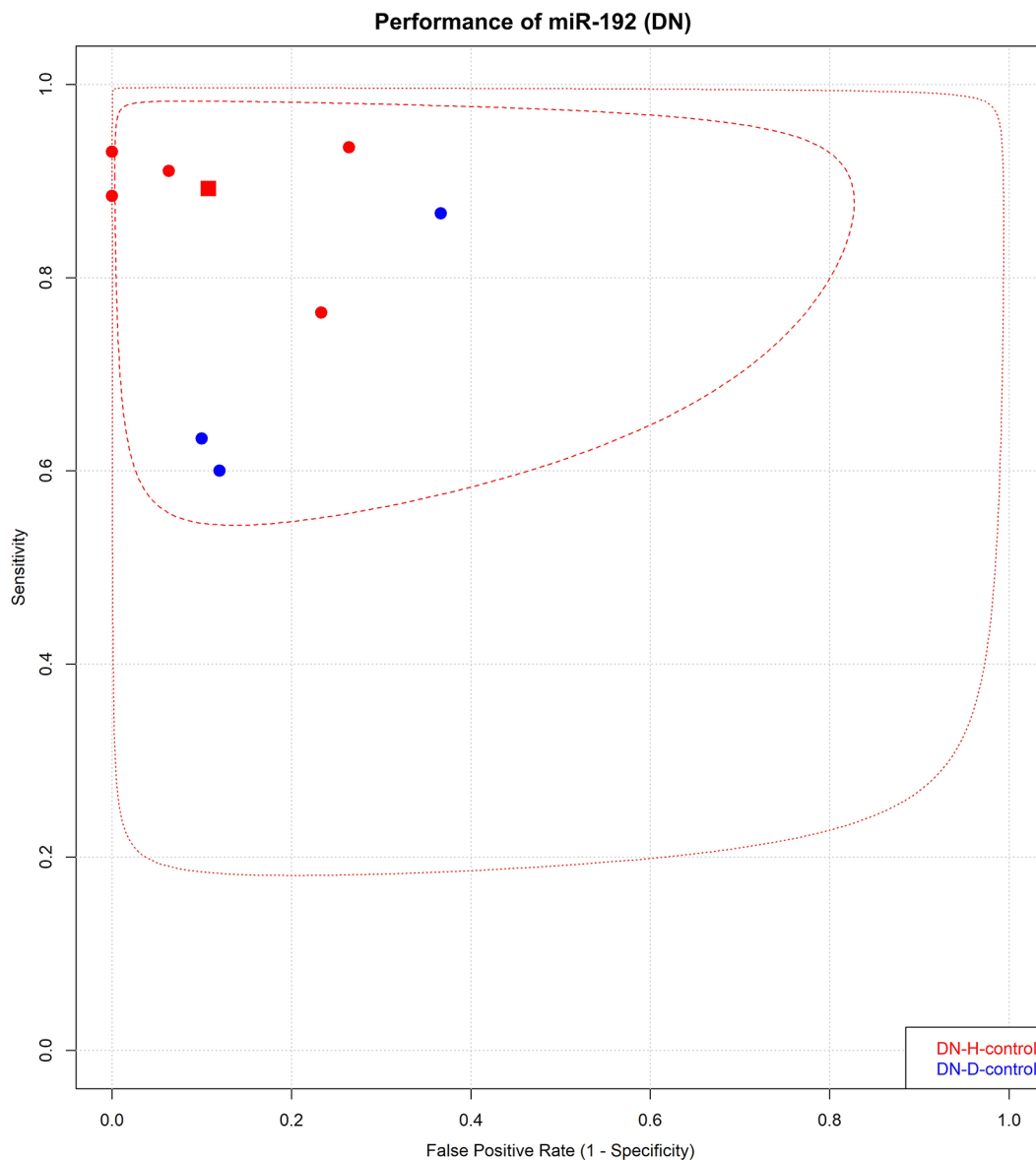
Fig. 5 The pooled sensitivity and specificity of miR-192 in diabetic nephropathy. Legend: The pooled sensitivity and specificity of miR-192 in diabetic nephropathy (DN) patients are shown. A square illustrates the summary pooled point available. Circles indicate individual sensitivity and specificity. Abbreviations: DN-Pool1, diabetic nephropathy compared to healthy control; DN-Pool2, diabetic nephropathy compared to type 2 diabetes

colleagues identified specific miRNA panels that were superior for CKD, such as miR-27b-3p and miR-1228-3p for DN; miR-21, miR-150, and miR-29c for LN; and miR-106a-5p and miR-30a-5p for mesangial proliferative glomerulonephritis (MsPGN) [107].

In comparison, our findings may differ slightly from those of J. Li and colleagues [107]; therefore, it is essential to note that our analysis included separate controls for healthy and diseased individuals with different kidney diseases (details in Supplementary Table S2). Multiple studies on cancer have shown that a miRNA panel is a more effective diagnostic marker than a single miRNA [108]. For instance, V. Bhaskaran and colleagues reported

that several miRNAs exhibit a clustered expression pattern in glioblastoma, even if they are not encoded within the same genetic locus [109]. Moreover, these studies focused on targeting several miRNAs simultaneously; as a result, coexpressed miRNAs repress epigenetic oncogenic signaling pathways and have more profound therapeutic effects than single-miRNA therapy [109]. In nephrology, it might also be helpful to consider the expression of miRNA clusters and test a miRNA panel for diagnostic purposes.

In our included studies, several miRNAs exhibited high sensitivity and specificity (over 90%). These included miR-451 for the diagnosis of DN vs. DM [25] and

miR-126 [106], miR-21 [43], miR-636 [38], and miR-192 [81, 92] for the diagnosis of DN vs. healthy controls. miR-142a-5p effectively differentiated nephrotic syndrome (NS) patients from healthy individuals [32]. In addition, J. Li and colleagues discovered that miR-133, miR-30a, and miR-126 were promising markers for the diagnosis of CKD with high accuracy levels of sensitivity or specificity above 90% [107].

These miRNAs are validated in preclinical studies, and their molecular function is reviewed by Mahtal and colleagues [110]. For example, miR-192 mediates TGF-beta/Smad3-driven renal fibrosis in a mouse model of UUO and a rat remnant kidney model [111]. miR-451 might decrease inflammation in DN by inhibiting the synthesis of the NF-κB effector proteasome subunit-β type-8 [112]. Silencing miR-21 protects animal models from DKD [113] as its overexpression is associated with mesangial cell hypertrophy by regulating Cdc25a and Cdk6, podocyte damage, and ECM accumulation by targeting Pten [113]. miR-126 supports kidney recovery after acute injury by promoting vascular integrity and association with stromal cell-derived factor 1/CXCR4-dependent vasculogenic progenitor cell mobilization [114].

While the results compared to those of healthy controls looked promising, we recommend comparing kidney disease patients with chronic disease groups. This approach could provide significant clinical benefits in distinguishing, for instance, between patients with DN and those with T2DM without nephropathy. Research on miRNAs is still in its early stages, which can lead to inconsistencies in the expression of specific miRNAs measured in laboratories within the same sample type and disease [115]. Therefore, comparing chronic disease and healthy control groups in different biological samples helps to identify potential diagnostic miRNA biomarkers.

In line with only one existing meta-analysis [107], urinary miRNAs tended to perform better than blood miRNAs in our meta-analysis, although the difference did not reach statistical significance (multivariate $p=0.06$). The quantity of miRNAs in cell-free urine is less than in plasma or urinary exosomes because of the high RNase activity present in the kidney, bladder, and urinary tract [116]. Urine miRNAs could originate from cells in the urinary tract or could be filtered from plasma, indicating kidney-related or systemic diseases. Given these points, plasma miRNAs may be more reliable for diagnosing CKD, and comprehensive cohort studies using various biological samples can yield more definitive findings. Nevertheless, urine tests might be the most applicable test in almost all clinical settings. Several urinary miRNAs had higher AUCs (0.98–0.99); in the included studies (miR-204, miR-636, and miR-146a), these miRNAs might be potential diagnostic biomarkers in CKD. Urinary miRNAs generally perform better in CKDs because

they correlate best with kidney tissue [117] and pathological consequences and are surprisingly stable [118]. Urine samples had a greater overall AUC for all kidney diseases except DN than did healthy controls. For DN patients, blood samples performed better than urine samples did, with a pAUC of 0.87 compared to 0.84. However, further investigations are needed to understand the underlying mechanisms involved.

To our knowledge, only a few studies compare the diagnostic accuracy of miRNAs with conventional markers in prospective cohort studies for CKD, but none for the overall disease course, starting from the early to late stages. They mostly reported an association between miRNA expression and conventional markers of CKD in addition to survival prediction, cardiovascular outcomes, and kidney disease progression [94, 119–121]. For example, the large cohort of 601 CKD patients showed that reduction of miR-126 and miR-223 are associated with a lower eGFR but cannot independently predict survival, cardiovascular, and kidney function decline [119].

However, combining miRNAs with clinical parameters has been suggested to be a more effective diagnostic biomarker than miRNAs alone [122]. For example, Miller and colleagues reported that a model combining urinary particle concentrations, blood lactate levels, urinary extracellular vesicles positive for PODXL, and miR-125a-5p could predict kidney injury [13].

Due to the limited number of available studies, it was not feasible to perform a meta-analysis on NS, MsPGN, or hypertensive nephropathy (HTN); only systematic reviews and visualizations were included. However, we suggest that future studies investigate the diagnostic accuracy of NS-, MsPGN-, and HTN-specific miRNAs. For instance, studies in a systematic review showed that miR-142a-5p has a better diagnostic performance than the panel miRNAs miR-30a-5p and miR-181a-5p in childhood idiopathic nephrotic syndrome [32].

Unfortunately, most of those studies did not report disease stages, so we could not analyze disease stage. Diagnostic studies must distinguish between early and late CKD stages for accurate analysis of biomarkers, particularly miRNAs. Although further research is needed to develop the most effective approach, preliminary findings show that using a miRNA panel in CKD patients can significantly enhance diagnostic accuracy.

Strengths and limitations of the study

Our analysis has several advantages that are worth highlighting. First, we attempted to determine the diagnostic accuracy of miRNAs in different types of chronic kidney diseases with various sample types. Second, by performing a subgroup analysis, we examined the potential of miRNAs in differentiating between healthy and chronic disease groups. From a statistical perspective, we can

list the following advantages of our meta-analysis of diagnostic accuracy. Given the complexity of miRNAs, the different threshold values used for background and fold change expression, we considered the area under the curve (AUC) from each study for overall diagnostic accuracy and obtained pAUC values. The threshold value does not influence these values and provides more reliable results than pooled SEN and SPE results. To avoid overestimating pooled results, we considered correlations between variables in studies that reported multiple miRNAs in the same population.

Unfortunately, we were unable to assess differences in the accuracy of miRNA detection at different CKD stages due to a lack of data. Importantly, many studies in this field are retrospective case–control studies that can potentially introduce bias in assessing the quality of patient selection domains. The miRNA detection and normalization methods varied also in the included studies in our meta-analysis. There is no universal agreement on the cutoff values of reference genes for miRNA studies, which may lead to inconsistent results in the relative quantitative analysis of miRNAs (Table S6). This limitation should be taken into account by researchers when interpreting meta-analysis results. Furthermore, it is essential to conduct large prospective cohort studies to address these limitations and expedite the integration of miRNAs into clinical applications.

Implications for practice and research

Based on our results, we propose the use of a panel of miRNAs to distinguish DN patients from T2DM patients without nephropathy and LN from SLE patients without kidney disease. To incorporate our findings into everyday medical practice [123], it is necessary to conduct prospective, well-designed cohort studies. These studies should assess the accuracy of both single and panel miRNAs for diagnosing CKDs at various stages and compare them to traditional biomarkers.

Conclusion

Analysis of miRNAs can distinguish between CKD patients, healthy individuals, and diseased patients without overt CKD, such as T2DM patients and SLE patients. Using miRNA panels for diagnosis is more effective than relying on a single miRNA. Additional cohorts should be evaluated for the diagnostic performance of miRNAs in the early and late stages of CKDs.

Abbreviations

AUC	Area under the curve
CKD	Chronic kidney disease
DN	Diabetic nephropathy
Fig: Figure	Fig. S: Supplementary Figure
HTN	Hypertensive nephropathy
IgAN	IgA nephropathy
FN	False negative
FP	False positive
FSGS	Focal segmental glomerulosclerosis
eGFR	Estimated glomerular filtration rate
MN	Membranous nephropathy
miRNAs	MicroRNAs
MsPGN	Mesangial proliferative glomerulonephritis
pAUC	Pooled area under the curve
SEN	Sensitivity, specificity
SLE	Systematic lupus erythematosus
SPE	Specificity
T2DM	Type 2 diabetes mellitus
PBMC	Peripheral blood mononuclear cell
PODXL	Podocalyxin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROC	Receiver operating characteristic
SROC	Summary receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03702-y.

Supplementary Material 1

Supplementary Material 2

Data availability
Data is provided within the manuscript and supplementary files.

Declarations

Ethics approval and consent to participate
No ethical approval was required for this systematic review and meta-analysis, as all the data were already published in peer-reviewed journals. No patients were involved in our study's design, conduct, or interpretation.

Consent for publication
Not applicalble.

Competing interests
The authors declare no competing interests.

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