Nephrol Dial Transplant (2017) 32: 97–110
doi: 10.1093/ndt/gfw070
Advance Access publication 4 May 2016

# Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies

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## ABSTRACT

**Background.** The utility of renal biopsy in patients with diabetes is highly debated. Diabetics with rapidly worsening renal disease are often 'clinically' labelled as having diabetic nephropathy (DN), whereas, in many cases, they are rather developing a non-diabetic renal disease (NDRD) or mixed forms (DN + NDRD).

**Methods.** We performed a systematic search for studies on patients with diabetes with data on the frequency of DN, NDRD and mixed forms, and assessed the positive predictive values (PPVs) and odds ratios (ORs) for such diagnoses by meta-analysing single-study prevalence. Possible factors explaining heterogeneity among the different diagnoses were explored by meta-regression.

**Results.** In the 48 included studies ($n = 4876$), the prevalence of DN, NDRD and mixed forms ranged from 6.5 to 94%, 3 to 82.9% and 4 to 45.5% of the overall diagnoses, respectively. IgA nephropathy was the most common NDRD (3–59%). PPVs for DN, NDRD and mixed forms were 50.1% [95% confidence interval (CI): 44.7–55.2], 36.9% (95% CI: 32.3–41.8) and 19.7% (95% CI: 16.3–23.6), respectively. The PPV when combining NDRD and mixed forms was 49.2% (95% CI: 43.8–54.5). Meta-regression identified systolic pressure, HbA1c, diabetes duration and retinopathy as factors explaining heterogeneity for NDRD, creatinine and glomerular filtration rate for mixed forms and only serum creatinine for DN. ORs of DN versus NDRD and mixed forms were 1.71 (95% CI: 1.54–1.91) and 4.1 (95% CI: 3.43–4.80), respectively.

**Conclusions.** NDRD are highly prevalent in patients with diabetes. Clinical judgment alone can lead to wrong diagnoses and delay the establishment of adequate therapies. Risk stratification according to individual factors is needed for selecting patients who might benefit from biopsy.

**Keywords:** diabetes, diabetic nephropathy, meta-analysis, non-diabetic nephropathy, renal biopsy

ORIGINAL ARTICLE

## INTRODUCTION

According to the WHO, in 2012 about 347 million people were affected by diabetes mellitus (DM) [1]. DM now ranks as the primary cause of end-stage kidney disease (ESKD) requiring chronic renal replacement therapy [1, 2] and the coexistence of DM and renal damage amplifies the risk of death and cardiovascular events [3].

About 30–40% of patients with diabetes with at least 10 years of history of disease usually present with a frank diabetic nephropathy (DN) [4] characterized by peculiar histological features at the glomerular level including nodular or diffuse mesangial sclerosis, arteriolar hyalinosis, micro aneurysms and exudative lesions. However, increasing evidence indicates that many patients with diabetes erroneously labelled as having progressive forms of DN are rather developing non-diabetic renal diseases (NDRD) or 'mixed' conditions where typical features of DN overlap with other kinds of histological damage.

The correct classification of such patients would be crucial to predict the natural course of their disease, thus allowing the establishment of appropriate therapeutic measures in a timely manner.

The utility of renal biopsy (RB) in patients with diabetes is currently an object of debate. As there is no overall consensus on timing and indications, the decision to perform RB is usually based on personal opinions or single-center policies [2]. RB is an invasive procedure that is not completely free from complications. Yet, in patients with diabetes presenting with rapidly worsening renal function and/or unusual clinical features (e.g. sudden appearance of heavy proteinuria in patients with short

duration of DM, haematuria, active urine sediment, no signs of other micro-vascular complications like retinopathy), RB would be crucial for identifying the presence of non-diabetic renal damage.

With this background in mind, we aimed at performing a systematic review and meta-analysis for clarifying the potential usefulness of RB in the diabetic setting by: (i) defining the cumulative epidemiology of DN, NDRD and 'mixed' forms (DN + NDRD), (ii) analysing the frequency and diagnostic likelihood of these conditions in a pooled meta-analysis and (iii) identifying factors associated with the different diagnoses by a meta-regression.

## MATERIALS AND METHODS

### Data source and search strategy

PubMed and Ovid MEDLINE were searched for articles without time and language restriction up to 15 September 2014 through a focussed search strategy (Supplementary data Table S1). References from relevant studies and reviews published on the same topic were screened for supplementary articles. The search was designed and performed by two authors (D.B. and M.F.).

### Study selection

We included any study providing prevalence data on patients with diabetes undergoing RB on: (i) DN, defined by the presence of suggestive glomerular lesions like nodular sclerosis, diffuse mesangial sclerosis, mesangial expansion, basement membrane thickening, arteriolar hyalinosis, micro aneurysms and exudative lesions [5]; (ii) NDRD, defined by any histological alteration different from the above-mentioned and suggestive of other renal diseases [e.g. IgA nephropathy, membranous nephropathy (MN), focal-segmental glomerulosclerosis (FSGS), interstitial nephritis, vasculitis, nephroangiosclerotic lesions, etc.]; or (iii) mixed forms where histological signs of DN were superimposed on NDRD. Studies dealing with both Type 1 and Type 2 DM were considered. Studies were excluded if they were (i) dealing with empirical diagnoses not made by percutaneous RB, (ii) not focussing on diabetic patients or not including diabetic subpopulations with available data on renal histology, (iii) dealing with renal biopsies only performed on transplanted patients and (iv) not providing actual numbers (percentages) on the histological pictures found. Case reports, reviews, editorials and studies performed on children (age <18 years) or animals were excluded as well. Study selection was performed by two authors (D.B. and M.F.) separately. Discrepancies in study judgment were solved collegially.

### Data extraction and meta-analysis

Data extraction and analysis were performed by two authors (M.F. and G.T.) and independently verified by another (D.B.). Single-study prevalence data were pooled in a meta-analysis using a random effect model to calculate the positive predictive values (PPVs) of clinical judgment for identifying DN, NDRD and mixed forms and the cumulative odds ratio (OR) of finding DN at RB compared with NDRD or mixed forms. Heterogeneity was assessed by $I^2$; $I^2$values of 25%, 50% and 75% were considered to correspond to low, medium and high levels of heterogeneity, respectively. Meta-regression analysis was implemented to investigate possible sources of heterogeneity. Possible publication bias was investigated by constructing the funnel plots and by applying the Egger's regression and the trim and fill tests. Statistical analyses were performed using Comprehensive Meta-analysis (Version 2.2, 2005; Biostat, Englewood, NJ, USA) and SPSS (Version 21; IBM Corporation, Armonk, NY, USA).

## RESULTS

### Search results

The flow diagram of the selection process is depicted in Figure 1. One thousand five hundred and ten potentially relevant references were evaluated for eligibility by title and abstract. A total of 1243 citations were excluded because of search overlap ($n = 100$), or because they were dealing with wrong topics or wrong populations ($n = 1143$). Among 267 studies selected for full text examination, 208 studies were excluded for not providing RB data in patients with diabetes and 11 for not providing percentage data on biopsy diagnosis. A total of 48 studies were therefore reviewed in detail and included in the quantitative analyses.

### Study and participants' characteristics

The 48 studies reviewed included a total of 4876 diabetics undergoing RB. The number of subjects enrolled in each study ranged from 16 [6] to 611 [7].Thirty-six studies had a retrospective design [6–41], eight had a prospective design [42–49] and two presented a cross-sectional design [50, 51]. We also found useful data for our analyses from two randomized, double-blind trials. Cordonnier *et al.* [52] reported biopsy data of 22 Type 2 diabetics enrolled in a randomized controlled trial testing the effects of 4 mg Perindopril on kidney structure and function. Schwartz *et al.* [53] provided information on the glomerular histology of 36 diabetics enrolled in a multicenter pilot study investigating the effects of irbesartan on renal function and urine protein excretion.

Although most studies were published in the last decade, about half of the studies reported data obtained before 2000 [27–41, 47–49, 51–53]. Twenty-seven articles focussed on Asian populations [8–11, 13, 15–20, 23–25, 27, 28, 31, 34, 36, 41–46, 48, 50], fifteen were performed in European countries [12, 14, 26, 29, 30, 32, 35, 37–40, 47, 49, 51, 52], four in north America [7, 21, 33, 53] and two studies in African regions [6, 22]. All studies included patients with Type 2 diabetes. Type 1 diabetic patients represented a small percentage of the study population in six studies (ranging from 8 to 38% of participants) [12, 18, 32, 38, 40, 41]. No studies reported data based only on patients with Type 1 diabetes. Mean age of participants was variable across studies, spanning from 46 to 62 years. Male participants were predominant in all the studies (52–94% of participants) with the exception of Nzerue *et al.* [33] (48%). Information on

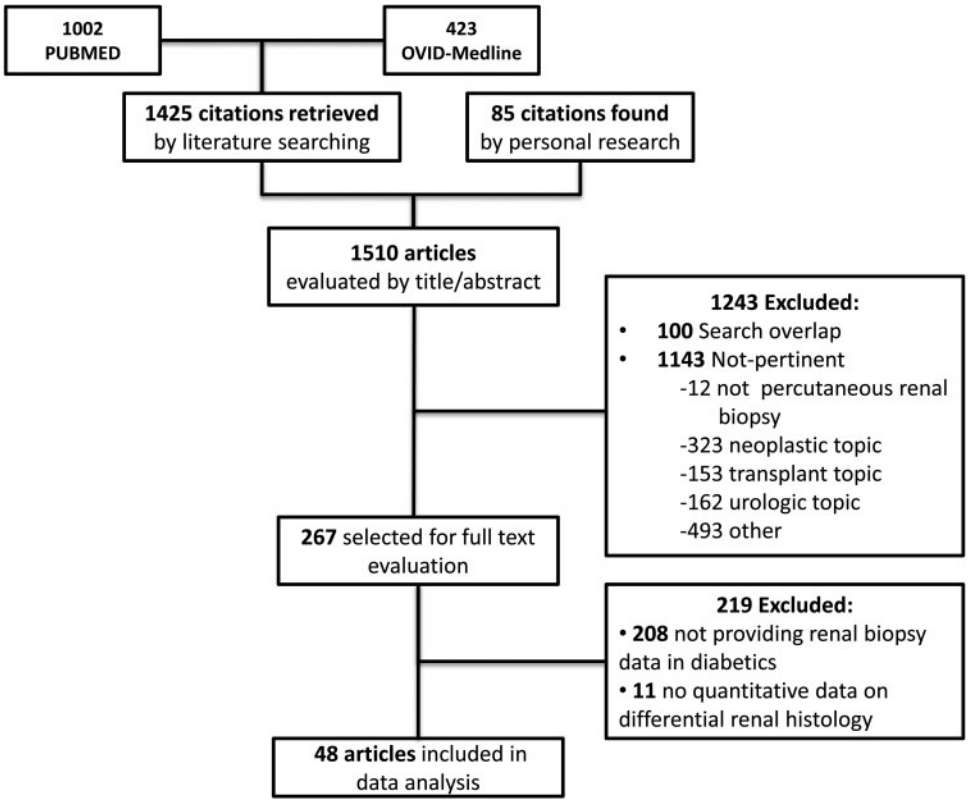


**FIGURE 1:** Flow of the study selection process.

body mass index (BMI) was provided in 12 studies only [14, 27, 28, 30, 34, 39, 42, 43, 49, 51–53]; in four studies [39, 51–53] the majority of diabetics were frankly obese (mean BMI ranging from 30.3 to 32 kg/m$^2$). Patients with diabetes undergoing RB were extremely heterogeneous with respect to renal function. Information on serum creatinine values was available in 34 studies [6, 7, 9–11, 13, 15–17, 19–21, 23–25, 27–29, 31, 33, 34, 37, 38, 42–48, 50–53]; in 10 of these studies the majority of patients had mean serum creatinine levels falling roughly within the normal range (<1.43 mg/dL) [16, 20, 25, 28, 31, 42–44, 51, 52]. In 12 studies mean values ranged from 1.44 to 3.00 mg/dL [7, 10, 13, 23, 25, 27, 29, 34, 37, 45, 47, 53] while the remaining 12 included patients with quite severely compromised renal function (serum creatinine >3 mg/dL) [6, 9, 11, 12, 15, 19, 21, 24, 33, 38, 46, 50]. Data on estimated glomerular filtration rate (eGFR) were available in 16 of the above-mentioned studies reporting information on serum creatinine [7, 10, 13, 15–17, 19–21, 28, 34, 42, 48, 51–53]. Three more studies [30, 40, 49] gave information on eGFR only. Biesenbach *et al.* [14] analysed 14 biopsies from diabetics with ESKD before their first dialysis and 70 cadaveric biopsy specimens of ESKD subjects post mortem. Mean proteinuria was reported in 36 studies [6, 7, 9, 11, 13, 15–17, 19–21, 23–31, 33–35, 37–39, 42–45, 47, 48, 50–53] and ranged from 1.07–8.9 g/24 h. Fioretto *et al.* [49] enrolled patients with a mean urinary albumin excretion rate of 44 μg/min. Glycaemic control was quite poor in the vast majority of studies where information on HbA1c was available (mean values spanning from 6.35 to 11.3%) [10, 11, 13, 14, 16, 17, 20, 23, 25, 28, 30, 31, 34, 39, 42–44, 48, 49, 51, 53]. Subjects were remarkably heterogeneous also with respect to the duration of diabetes, which ranged from 3.4 to 20 years [6–11, 13–15, 17, 19, 20, 24, 25, 27–35, 37–40, 42, 44–46, 48–51]. Data on the prevalence of retinopathy among the participants were available in 28 studies [6, 8, 11, 13, 15–17, 19–21, 23–25, 27, 30, 31, 33–35, 40, 42–46, 48, 49, 53]. In nine studies [17, 20, 27, 34, 39, 42, 48, 49, 53], the presence of diabetic retinopathy was described with different grading level according the classification of the Early Treatment of Diabetic Retinopathy Study (no retinopathy, non-proliferative and proliferative level). In three studies [18, 28, 51] none of the patients undergoing RB had signs of retinal damage. In the remaining, the prevalence of this condition ranged from 15 to 71%. Twenty-five studies [6, 9–11, 13, 15, 17, 19–21, 23–27, 30, 31, 34, 38, 39, 44, 46–48, 50] reported data on the frequency of haematuria in the analysed cohort (range 6–78%). Indications for RB in patients with diabetes were extremely variable across studies. Only five studies reported data of research-indicated RBs. In the remaining 43 studies based on clinically indicated biopsies, the major driver was represented by a clinical suspicion of NDRD defined as: (i) nephrotic-range proteinuria or renal impairment in the absence of diabetic retinopathy; (ii) nephrotic-range proteinuria or renal impairment with duration of diabetes <5 years; (iii) unexplained microscopic haematuria; (iv) unexplained acute kidney injury; (v) rapidly declining renal function in patients with previously stable renal function; or (vi) sudden onset of nephrotic-range proteinuria with normal kidney function. Other criteria less frequently adopted included sudden onset of non-nephrotic proteinuria (thresholds ranging from 0.5 to 2.5 g/24 h) or microalbuminuria [10, 16, 20, 23, 27, 28, 31, 39, 43, 44, 48–53]. Mazzucco *et al.* [29] compared a restricted biopsy policy (the

presence of haematuria, nephrotic syndrome, non-nephrotic proteinuria ≥2 g/day in the absence of diabetic retinopathy, rapidly progressive renal failure and renal insufficiency of unexplained origin) with an unrestricted policy (proteinuria > 0.5 g/day, alone or associated with haematuria and/or impairment of renal function). In five studies [6, 7, 21, 26, 41] the reasons for performing RB were not further specified. Main characteristics of the studies and participants are summarized in Tables 1 and 2.

### Prevalence of DN, NDRD and mixed forms, and pooled analyses

Prevalence data of DN, NDRD and mixed forms are summarized in Table 2. Information on the three histological pictures in the same study cohort was available in 30 papers [7–13, 17, 20, 21, 23–27, 29, 33–39, 41, 42, 45–48, 50]. Thirteen studies [6, 14, 22, 28, 30, 32, 40, 43, 44, 49, 51–53] compared only DN with NDRD while three studies [15, 19, 31] presented only diagnosis of DN or mixed forms. The prevalence of DN was extremely variable, ranging from 6.5 [8] to 94% [53] of the overall histological pictures, as well as that of NDRD (3% [35] to 82.9% [8]) and mixed forms (4% [38] to 45.5% [15]). In the study by Hashim Al-Saedi [18] all diabetics undergoing RB had histological evidence of NDRD. Differential diagnoses of NDRD were specified in 43 studies [6–11, 13–21, 23–40, 42–48, 50, 51, 53]. IgA nephropathy was the most frequent NDRD in 16 studies [6, 8, 15, 25–27, 31, 34, 35, 37, 42, 44, 47, 48, 51, 53] with a prevalence ranging from 3 [35] to 59% [48]. MN was the predominant NDRD in nine studies [13, 20, 28–30, 38, 40, 45] (7 [38] to 35% [30]). FSGS prevailed in six cohorts [12, 16, 21, 32, 33, 50], (17 [12] to 37.7% [16]). Acute interstitial nephritis was the main NDRD in four studies [9, 11, 17, 24] (18 [24] to 48.8% [11]). The analysis of the different histological pictures of NDRD according to the population background showed a significantly higher percentage of IgA diagnosis in studies on Asian populations compared with European (mean percentage of IgA diagnosis: 21.3 versus 8.2%, P = 0.003) and American studies (21.3 versus 9.4, P = 0.04). A higher frequency of FSGS was described in European studies compared with studies from the USA (mean percentage of FSGS diagnosis: 19 versus 10%, P = 0.03). Moreover, the percentage of membrano-proliferative glomerulonephritis in Asian populations was higher than that in Europeans (mean percentage: 17.6 versus 7.3%, P = 0.016). The performance of clinical judgment for correctly classifying the type of nephropathy in patients with diabetes was assessed by calculating the PPVs, i.e. the proportion of patients who are really affected by a specific nephropathy at RB among those considered as affected by DN or NDRD or by mixed forms on the basis of clinical judgment. PPVs (pooled data) of clinical judgment for identifying DN, NDRD and mixed forms were 50.1% [95% confidence interval (CI): 44.9–55.3], 36.9% (95% CI: 32.3–41.8) and 19.7% (95% CI: 16.3–23.6), respectively (Figure 2). When considering NDRD and mixed forms together, the PPV of such diagnoses was 49.2% (95% CI: 43.8–54.5) (Figure 2d). The PPV of NDRD in retrospective studies (38%, 95% CI: 32–43) was significantly higher than in prospective studies (27%, 95% CI: 20–35, P = 0.007), as well as in studies after 2000 (40%, 95% CI: 35–45) compared with PPV of studies before 2000 (26%, 95% CI: 17–37, P = 0.03). The PPVs of DN (49 versus 65%, P = 0.25) and NDRD (39 versus 25%, P = 0.18) did not differ between studies based on clinically or research-indicated biopsies; however, a higher percentage of IgA nephropathy was described in clinically indicated biopsy studies (P = 0.03). The Egger's regression test (i.e. a test indicating whether the joint distribution of standard errors and logit event rates statistically deviates from an ideal funnel plot) suggested statistical evidence of publication bias in pooled analyses of DN and mixed forms (P-values ranging from 0.003 to 0.006) (Supplementary data Figure S1). However, such a bias, although statistically significant, was not meaningful from a quantitative point of view because the Trim and Fill method (a test quantifying the potential distortion attributable to selection bias of studies in a meta-analysis) showed that the pooled PPVs for DN (0.50, 95% CI: 0.45–0.55), NDRD (0.37, 95% CI: 0.32–0.42) and mixed forms (0.20, 95% CI: 0.16–0.24) as calculated in the standard meta-analysis did not materially differ from those derived by the Trim and Fill method (DN: 0.43, 95% CI: 0.37–0.48; NDRD: 0.37, 95% CI: 0.32–0.42; mixed forms: 0.20, 95% CI: 0.16–0.24), indicating that the publication bias was not enough to introduce a distortion in the pooled estimates. There was high heterogeneity in all the three analyses ($I^2$ 90%, 88% and 86%, respectively). Meta-regression identified systolic blood pressure ($r = -0.53$, P = 0.02), HbA1c ($r = -0.49$, P = 0.02), duration of diabetes ($r = -0.36$, P = 0.04) and diabetic retinopathy ($r = -0.59$, P = 0.001) as factors explaining heterogeneity among PPVs of NDRD. The same analysis indicated serum creatinine ($r = -0.42$, P = 0.01) as the only factor underlying heterogeneity among studies for DN and creatinine ($r = 0.52$, P = 0.006) and, even more, GFR ($r = -0.73$, P = 0.007) as the only two factors elucidating heterogeneity among studies for mixed forms. Overall, the crude OR of finding DN at RB was 69% higher (OR: 1.71, 95% CI: 1.54–1.92, P < 0.001) than that of NDRD and more than four times higher (OR: 4.1, 95% CI: 3.43–4.80, P < 0.001) than that of mixed forms.

## DISCUSSION

Worldwide, roughly 3% of newly diagnosed patients with Type 2 diabetes have overt nephropathy and about 20–30% of patients with Type 1 or Type 2 diabetes develop such complications throughout their life [54]. The early identification of DN is mandatory to delay ESKD, but early biomarkers (e.g. albuminuria) often fail to predict disease course as they might not reflect the real histological damage or the possible presence of other, superimposed renal diseases. The importance of RB was studied in a large double-blind controlled trial on 285 patients with Type 1 diabetes (Renin-Angiotensin System Study, RASS), which showed the role of renin–angiotensin system (RAS) blockade on the progression of diabetic retinopathy [55]. However, most nephrologists do not advocate RB in patients with diabetes, arguing that this procedure would simply confirm the presence of DN in the majority of patients [10, 43].

Our systematic analysis of 48 studies indicates that, in patients with diabetes with suspicion of DN, the prevalence of non-diabetic renal damage is indeed seriously high (up to 82.9%

**Table 1. Main characteristics and indications for renal biopsy of the reviewed studies**

| Study | Year | Country | Design | No. of patients | Age (years) | Gender (male %) | sCr (mg/dL) | GFR (mL/min) | uPr (g/24 h) | HbA1c (%) | DM vintage (years) | DR (%) | Indications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhuo *et al.* [8] | 2013 | China | Retrospective | 216 | ~48 | – | – | – | – | – | 3.4 | 18 | Clinical renal biopsies, Type 2 DM, presence of urinary abnormalities or renal impairment |
| Sharma *et al.* [7] | 2013 | USA | Retrospective | 620 | ~62 | 61 | 2.5 | 29.1 | 4.3 | – | 9.31 | – | Clinical renal biopsies, Type 2 DM |
| Harada *et al.* [42] | 2013 | Japan | Prospective | 55 | ~58 | 67 | 1.29 | 49.83 | 2.75 | 7.69 | 10.1 | 38 | Clinical renal biopsies, Type 2 DM, presence of urinary abnormalities or renal impairment |
| Zajjari *et al.* [6] | 2012 | Morocco | Retrospective | 16 | ~60 | 81 | 4.5 | – | 4.75 | – | 6.5 | 37.5 | Clinical renal biopsies, Type 2 DM |
| Yaqub *et al.*[9] | 2012 | Pakistan | Retrospective | 68 | ~56 | 75 | 4.5 | – | 5.98 | – | 9 | – | Clinical renal biopsies, Type 2 DM, nephrotic-range proteinuria, absence of diabetic retinopathy, duration of diabetes <5 years, unexplained microscopic haematuria, unexplained acute kidney injury, rapidly declining renal function in patients with previously stable renal function |
| Oh *et al.* [10] | 2012 | South Korea | Retrospective | 126 | ~60 | 68.3 | 2.38 | 45.4 | – | 7.1 | 8.3 | – | Clinical renal biopsies, Type 2 DM, proteinuria more than 1 g/day, renal involvement without retinopathy, renal involvement within 5 years, unexplained haematuria |
| Chong *et al.* [11] | 2012 | Malaysia | Retrospective | 110 | ~53 | 58 | 3.35 | – | 7.06 | 8 | 12 | 60 | Clinical renal biopsies, Type 2 DM, uncertain cause of acute renal failure, acute or chronic renal failure, relatively short duration of diabetes or without retinopathy, heavy proteinuria (>1 g/day), and microscopic haematuria |
| Biesenbach *et al.* [14] | 2011 | Austria | Retrospective | 84 | ~60 | 53 | – | ESKD | – | 7.7 | 20 | – | Clinical renal biopsies, Type 2 DM with ESKD |
| Haider *et al.* [12] | 2011 | Austria | Retrospective | 567 | ~56 | – | – | – | – | – | – | – | Clinical renal biopsies, Type 1 and 2 DM with CKD |
| Chang *et al.* [13] | 2011 | South Korea | Retrospective | 119 | ~53 | 53.8 | 1.7 | 51.54 | 7.4 | 8.1 | 7.95 | 42.9 | Clinical renal biopsies, Type 2 DM, strong suspicion of NDRD (rapidly increasing amount of proteinuria or nephrotic syndrome), short duration of diabetes, absence of retinopathy, unexplained impaired or rapidly declining renal function, persistent haematuria |
| Bi *et al.* [15] | 2011 | China | Retrospective | 220 | ~51 | 69 | 4.37 | 38 | 3.74 | – | 9.24 | 46 | Clinical renal biopsies, Type 2 DM, with haematuria (40% of cases), rapid deterioration of renal function (19.5%), massive proteinuria without retinopathy (34.5%) |
| Zhang *et al.* [43] | 2011 | China | Prospective | 130 | ~49 | 61 | 1.3 | – | 1.8 | 6.9 | – | 41.5 | Clinical renal biopsies, Type 2 DM, microalbuminuria and/or haematuria or unexplained renal dysfunction; overt proteinuria especially heavy proteinuria; rapid progression in renal function |
| Mou *et al.* [16] | 2010 | China | Retrospective | 69 | ~53 | 52.2 | 1.34 | 57.86 | 3.74 | 6.65 | – | 42 | Clinical renal biopsies, Type 2 DM, with proteinuria over 1 g or GFR <60 mL/min |
| Lin *et al.* [17] | 2009 | Taiwan | Retrospective | 50 | ~61 | 64 | 3.15 | 34.38 | 5.07 | 7.06 | 9.97 | 48 | Clinical renal biopsies, Type 2 DM, heavy proteinuria or renal impairment, absence of retinopathy or overt neuropathy, duration of diabetes <10 years, unexplained haematuria of glomerular origin, unexplained acute renal failure |
| Ghani *et al.* [19] | 2009 | Kuwait | Retrospective | 31 | ~50 | 54.8 | 4.47 | 38.6 | 3.18 | – | 9.33 | 45.2 | Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD |
| Arif *et al.* [50] | 2009 | Pakistan | Cross-sectional | 73 | ~51 | 59 | 3.8 | – | 2.3 | – | – | – | Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD (presence of haematuria, nephrotic |

*Continued*

**Table 1. Continued**

| Study | Year | Country | Design | No. of patients | Age (years) | Gender (male %) | sCr (mg/dL) | GFR (mL/min) | uPr (g/24 h) | HbA1c (%) | DM vintage (years) | DR (%) | Indications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | syndrome, non-nephrotic proteinuria <3 g/day in the absence of retinopathy, rapidly progressive glomerulonephritis and renal insufficiency of unknown origin) |
| Hashim Al-Saedi [18] | 2009 | Iraq | Retrospective | 80 | Range 17–62 | 70 | – | – | – | – | – | 0 | Clinical renal biopsies, Type 1 and 2 DM, nephrotic-range proteinuria, absence of retinopathy |
| Zhou *et al.* [44] | 2008 | China | Prospective | 110 | ∼46 | 70 | 1.29 | – | 3.6 | 7.8 | ∼5 | 46.3 | Clinical renal biopsies, Type 2 DM, persistent proteinuria (>500 mg/day) |
| Akimoto *et al.* [20] | 2008 | Japan | Retrospective | 50 | ∼53 | 58 | 1.1 | 68.8 | 5 | 7.1 | 6.08 | 56 | Clinical renal biopsies, Type 2 DM, proteinuria >0.5 g/day, clinical suspicion of NDRD |
| Pham *et al.* [21] | 2007 | USA | Retrospective | 232 | ∼58 | 53 | 3.4 | 38.7 | 5.9 | – | – | 17 | Clinical renal biopsies, Type 2 DM |
| Huang *et al.* [23] | 2007 | China | Retrospective | 52 | ∼54 | 62 | 2.14 | – | 3.34 | 7.46 | NA | 34 | Clinical renal biopsies, Type 2 DM, overt proteinuria (>0.5 g/day), elevated sCr and/or the development of haematuria |
| Prakash *et al.* [45] | 2007 | India | Prospective | 23 | ∼53 | 65 | 2.97 | – | 3.97 | – | 6.19 | 65.2 | Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD |
| Soni *et al.* [24] | 2006 | India | Retrospective | 160 | ∼51 | 73.7 | 4.18 | – | 3.72 | – | 7.2 | 61 | Clinical renal biopsies, Type 2 DM, massive proteinuria, the absence of retinopathy, haematuria and unexplained change in renal function |
| Tone *et al.* [25] | 2005 | Japan | Retrospective | 97 | ∼53 | 59 | 1.43 | – | 3.75 | 6.35 | 5.76 | 24 | Clinical renal biopsies, Type 2 DM, short duration of diabetes (<5 years), and/or absence of diabetic retinopathy and/or presence of microscopic haematuria |
| Moger *et al.* [46] | 2005 | India | Prospective | 26 | ∼47 | 80 | Range 3.2–10.8 | – | – | – | 6.9 | 76 | Clinical renal biopsies, Type 2 DM, with documented doubling of sCr in <4 weeks or recently diagnosed advanced renal failure were identified |
| Rychlik *et al.* [26] | 2004 | Czech Republic | Retrospective | 163 | ∼58 | 65 | – | – | 8.9 | – | – | – | Not reported |
| Serra *et al.* [47] | 2002 | Spain | Prospective | 35 | ∼59 | 63 | 2.39 | – | 2.01 | – | – | – | Clinical renal biopsies, Type 2 DM, absence of diabetic retinopathy and/or presence of microhaematuria and/or presence of sudden unexpected change in renal function |
| Castellano *et al.* [30] | 2002 | Spain | Retrospective | 20 | ∼60 | 55 | – | 63.4 | 5.3 | 6.4 | 4.13 | 15 | Clinical renal biopsies, Type 2 DM, short duration of diabetes (<5 years), absence of diabetic retinopathy and/or presence of microscopic haematuria |
| Mazzucco *et al.* [29] | 2002 | Italy | Retrospective | 393 | ∼61 | 67 | 2.45 | – | 4.89 | – | 9.39 | – | Clinical renal biopsies, Type 2 DM, restricted policy (presence of haematuria, nephrotic syndrome, non-nephrotic proteinuria >2 g/day, absence of diabetic retinopathy, rapidly progressive renal failure) versus unrestricted policy (proteinuria >0.5 g/day, and/or haematuria, and/or impairment of renal function) |
| Wong *et al.* [27] | 2002 | China | Retrospective | 68 | ∼49 | 55 | 1.76 | – | 2.08 | – | 6.27 | 39.6 | Clinical renal biopsies, Type 2 DM, proteinuria 1 g/day, renal involvement, absence of retinopathy, duration of diabetes <5 years, unexplained haematuria of glomerular origin |
| Premalatha *et al.* [28] | 2002 | India | Retrospective | 18 | ∼54 | 56 | 1.39 | 76 | 4.28 | 8.5 | 8.4 | 0 | Research renal biopsies, Type 2 DM, proteinuria >1 g/day, absence of retinopathy |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Izzedine *et al.* [32] | 2001 | France | Retrospective | 21 | ~48 | 71 | – | – | – | – | 15.5 | – | Clinical renal biopsies, Type 1 (38%) and 2 (62%) DM, microscopic haematuria and/or proteinuria > 2.5 g/day without retinopathy |
| Suzuki *et al.* [31] | 2001 | Japan | Retrospective | 109 | ~48 | 67 | 1.22 | – | 1.77 | 8.82 | 7.26 | 49 | Clinical renal biopsies, Type 2 DM with proteinuria |
| Nzerue *et al.* [33] | 2000 | USA | Retrospective | 31 | ~49.5 | 48 | 4.7 | – | 4.5 | – | 10.1 | 48 | Clinical renal biopsies, Type 2 DM, severe nephrotic syndrome in three patients, suspected nephritis in nine patients and rapid deterioration of renal failure |
| Christensen *et al.* [51] | 2000 | Denmark | Cross-sectional | 51 | ~55 | 80 | 0.99 | 93.2 | 1.36 | 8.44 | 4.68 | 0 | Research renal biopsies, Type 2 DM, albuminuria > 300 mg/day, without diabetic retinopathy |
| Lee *et al.* [34] | 1999 | South Korea | Retrospective | 22 | ~51 | 63 | 1.57 | 52.8 | 3.97 | 7.79 | 4.2 | 27 | Clinical renal biopsies, Type 2 DM, nephritic syndrome or haematuria, significant proteinuria, absence of retinopathy, rapidly progressive renal failure, normal-size kidney |
| Cordonnier *et al.* [52] | 1999 | UK | RCT | 26 | ~47 | 81 | 0.93 | 123 | 1.07 | – | – | – | Research renal biopsies, Type 2 DM, proteinuria ranging from 70 to 4210 mg/day and relatively preserved GFR (creatinine clearance 60 mL/min) |
| Schwartz *et al.* [53] | 1998 | USA | RCT | 36 | ~58 | 68 | 1.53 | 65.9 | 4.68 | 8.58 | – | 71 | Research renal biopsies, Type 2 DM, proteinuria >500 mg/day, sCr <3 mg/dL, hypertension |
| Mak *et al.* [48] | 1997 | China | Prospective | 51 | ~55 | 70 | 1.9 | 86.1 | 5.26 | 11.3 | 7.23 | 58 | Clinical renal biopsies, Type 2 DM, proteinuria >1 g/day |
| Olsen *et al.* [35] | 1996 | Denmark | Retrospective | 33 | ~62 | – | – | – | 5.37 | – | 8 | 60 | Clinical renal biopsies, Type 2 DM, clinical suspicion of NDRD |
| Fioretto *et al.* [49] | 1996 | Italy | Prospective | 34 | ~58 | 76 | – | 101 | 44 µg/min | 8.5 | 11 | 67 | Research RB, Type 2 DM, microalbuminuria |
| John *et al.* [36] | 1994 | India | Retrospective | 80 | ~47 | 60 | – | – | – | – | – | – | Clinical renal biopsies, Type 2 DM, nephritic syndrome or unexplained haematuria, clinically significant proteinuria, absence of retinopathy, rapid progressive renal failure |
| Gambara *et al.* [37] | 1993 | Italy | Retrospective | 52 | ~62 | 57 | 2.65 | – | 3.1 | – | 9.72 | – | Clinical renal biopsies, Type 2 DM, proteinuria |
| Richards *et al.* [38] | 1992 | UK | Retrospective | 68 | ~52 | – | 5.45 | – | 3.07 | – | 11.05 | – | Clinical renal biopsies, Type 1 (32%) and 2 (68%) DM, severe nephrotic syndrome (25 cases), no retinopathy (18), haematuria (13), rapid decline in renal function (11), unexplained renal failure at presentation (5), no neuropathy (3) |
| Parving *et al.* [39] | 1992 | Denmark | Prospective | 35 | ~55 | 94 | – | 75.2 | 1.78 | 8.87 | 9.54 | – | Clinical renal biopsies, Type 2 DM, albuminuria > 300 mg/day |
| Kleinknecht *et al.* [40] | 1992 | France | Retrospective | 53 | ~51 | 56 | – | 51.5 | – | – | 13.2 | 53 | Clinical renal biopsies, Type 1 (34%) and 2 (66%) DM, clinical suspicion of NDRD |
| Hironaka *et al.* [41] | 1991 | Japan | Retrospective | 35 | ~49 | 60 | 1[a] | – | 6.8[a] | – | 9.2[a] | 20[a] | Clinical renal biopsies, Type 1 (8%) and 2 (92%) DM |

CKD, chronic kidney disease; DM, diabetes mellitus; DR, diabetic retinopathy; ESKD, end stage kidney disease; GFR, glomerular filtration rate; RCT, randomized controlled trial; sCr, serum creatinine; uPr, proteinuria; NA, not available.
[a]Data on 10 patients with NDRD.

**Table 2. Main histological findings of the reviewed studies**

| Study | Year | Population ($n =$ ) | Histological diagnosis | | | NDRD characteristics |
|---|---|---|---|---|---|---|
| | | | DN (%) | NDRD (%) | Mixed (%) | |
| Zhuo *et al.* [8] | 2013 | 216 | 6.5 | 82.9 | 10.7 | In patients aged 17–59 years, IgAN (29–34%), MN (11–15%), FSGS (8.8–5.4%) In patients aged >60 years, MN (25.7%), AIN (17%), MPGN (11%) |
| Sharma *et al.* [7] | 2013 | 620 | 37 | 36 | 27 | ATN (17–43%), FSGS (13–22%), hypertensive nephrosclerosis (19%), IgAN (7–11%) |
| Harada *et al.* [42] | 2013 | 55 | 54.5 | 34.5 | 10.9 | IgAN (23.6%), FSGS (5.4%), MN (1.8%) |
| Zajjari *et al.* [6] | 2012 | 16 | 62.5 | 37.5 | – | IgAN (19%), myeloma (6%) |
| Yaqub *et al.* [9] | 2012 | 68 | 31 | 52 | 17 | AIN (26.4%), post-infectious GN (10.3%), MN (5.9%), PICGN (5.9%) |
| Oh *et al.* [10] | 2012 | 126 | 39.7 | 51.6 | 8.7 | IgAN (16%), MN (11.9%), FSGS (7.6%), MPGN (4.7%) |
| Chong *et al.* [11] | 2012 | 110 | 62.7 | 18.2 | 19.1 | AIN (48.8%), hypertensive nephrosclerosis (24.4%), MCD (7.3%) |
| Biesenbach *et al.* [14] | 2011 | 84 | 78.5 | 21.5 | – | – |
| Haider *et al.* [12] | 2011 | 567 | 46.6 | 32 | 31.4 | FSGS (17%), AIN (13%), IgAN (9%), MN (3%) |
| Chang *et al.* [13] | 2011 | 119 | 36.2 | 53.8 | 10 | MN (32.9%), MCD (15.8%), FSGS (11.8%), IgAN (11.8%) |
| Bi *et al.* [15] | 2011 | 220 | 54.5 | – | 45.5 | IgAN (34%), MN (22%), mesangial-proliferative GN (14%) |
| Zhang *et al.* [43] | 2011 | 130 | 73.9 | 26.1 | – | IgAN (16.9%), MN (6.15%) |
| Mou *et al.* [16] | 2010 | 69 | 47.8 | 52.2 | – | FSGS (37.7%), IgAN (15.9%), MCD (15.9%), MN (8.7%) |
| Lin *et al.* [17] | 2009 | 50 | 48 | 22 | 30 | AIN (46%), MN (19.2%), IgAN (11.5%) |
| Ghani *et al.* [19] | 2009 | 31 | 54.8 | – | 45.2 | PICGN (21.4%), AIN (14.4%), IgAN (7.1%) |
| Arif *et al.* [50] | 2009 | 73 | 27.3 | 31.7 | 41 | FSGS/MCD (30.56%), MN (8.3%), IgAN (5.5%) |
| Hashim Al-Saedi [18] | 2009 | 80 | – | 100 | – | MPGN (40%), FSGS (25%), MN (20%), MCD (10%), amyloidosis (5%) |
| Zhou *et al.* [44] | 2008 | 110 | 54.5 | 45.5 | – | IgAN (34%), MN (22%), MPGN (14%) |
| Akimoto *et al.* [20] | 2008 | 50 | 68 | 26 | 6 | MN (8%), IgAN (6%), MPGN (6%) |
| Pham *et al.* [21] | 2007 | 232 | 27.5 | 53.2 | 19.3 | FSGS (21%), MCD (15.3%), IgAN (15.3%), MN (13.3%) |
| Huang *et al.* [23] | 2007 | 52 | 55.7 | 38.5 | 5.8 | Mesangial-proliferative GN (9.6%), MCD (7.7%) |
| Kharrat *et al.* [22] | 2007 | 72 | 34.1 | 69.5 | – | – |
| Prakash *et al.* [45] | 2007 | 23 | 56.5 | 30.5 | 13 | MN (8.7%), FSGS (8.7%) |
| Soni *et al.* [24] | 2006 | 160 | 27.5 | 42.5 | 30 | AIN (18.1%), post-infectious GN (17.2%), MN (11.2%), FSGS (7.7%) |
| Tone *et al.* [25] | 2005 | 97 | 36 | 47.5 | 16.5 | IgAN (16%), MN (13%), MCD (8%), FSGS (5%) |
| Moger *et al.* [46] | 2005 | 26 | 34.6 | 23.1 | 42.3 | Proliferative GN (27%), AIN (15.3%), PICGN (11.5%) |
| Rychlik *et al.* [26] | 2004 | 163 | 42.4 | 47.5 | 10.1 | IgAN (15%), MN (12%), PICGN (12%) |
| Serra *et al.* [47] | 2002 | 35 | 74.3 | 17.1 | 8.6 | IgAN (8%), FSGS (3%) |
| Castellano *et al.* [30] | 2002 | 20 | 45 | 55 | – | MN (35%), renal vasculitis (15%), IgAN (5%) |
| Mazzucco *et al.* [29] | 2002 | 393 | 39.7 | 43 | 17.3 | MN (23.1%), IgAN (20.3%), post-infectious GN (20.9%), MCD (12.4%), FSGS (12.4%), extra capillary GN (9.6%) |
| Wong *et al.* [27] | 2002 | 68 | 35 | 46 | 19 | IgAN (19%), nephrosclerosis (13%), MN (12%), MCD (6%) |
| Premalatha *et al.* [28] | 2002 | 18 | 50 | 50 | – | MN (33.3%), AIN (12.5%), MCD (12.5%) |
| Izzedine *et al.* [32] | 2001 | 21 | 62 | 38 | – | FSGS, IgAN, vascularnephropathy |
| Suzuki *et al.* [31] | 2001 | 109 | 73.3 | – | 26.7 | IgAN (44.8%), proliferative GN (37.9%), MN (6.9%), AIN (6.9%), FSGS (3.4%) |
| Nzerue *et al.* [33] | 2000 | 31 | 41.9 | 19.4 | 38.7 | FSGS (18%), nephrosclerosis (17%), MN (6%), PICGN (6%) |
| Christensen *et al.* [51] | 2000 | 51 | 69 | 13 | – | IgAN (8%), MPGN (4%) |
| Lee *et al.* [34] | 1999 | 22 | 36.4 | 50 | 13.6 | IgAN (22%), MN (21%), MCD (21%), AIN (5%) |
| Condonnier *et al.* [52] | 1999 | 26 | 85 | 15 | – | – |
| Schwartz *et al.* [53] | 1998 | 36 | 94 | 6 | – | IgAN (3%), MN (3%) |
| Mak *et al.* [48] | 1997 | 51 | 67 | 16 | 17 | IgAN (59%), hypertensive nephrosclerosis (24%) |
| Olsen *et al.* [35] | 1996 | 33 | 88 | 3 | 9 | IgAN (3%), mesangio-proliferative GN (3%), crio-GN (3%) |
| Fioretto *et al.* [49] | 1996 | 34 | 29.4 | 41.2 | – | – |
| John *et al.* [36] | 1994 | 80 | 18.7 | 60 | 21.3 | MCD (16%), IgAN (8%), MN (8%), AIN (6%), FSGS (6%) |
| Gambara *et al.* [37] | 1993 | 52 | 36.5 | 33 | 30.5 | IgAN, MN, FSGS, MCD, PICGN (4%) |
| Richards *et al.* [38] | 1992 | 68 | 62 | 34 | 4 | MN (7%), IgAN (2%), PICGN (2%), MPGN (2%) |
| Parving *et al.* [39] | 1992 | 35 | 77.1 | 20 | 2.9 | Mesangial-proliferative GN |
| Kleinknecht *et al.* [40] | 1992 | 53 | 64 | 36 | – | MN (14%), FSGS (14%), AIN (3%) |
| Hironaka *et al.* [41] | 1991 | 35 | 71.4 | 14.3 | 14.3 | – |

AIN, acute interstitial nephritis; ATN, acute tubular necrosis; Crio-GN, crioglobulinemic glomerulonephritis; DN, diabetic nephropathy; FSGS, focal-segmental glomerulosclerosis; GN, glomerulonephritis; IgAN, IgA nephropathy; MCD, minimal change disease; MN, membranous nephropathy; MPGN, membrano-proliferative glomerulonephritis; NA, not available; NDRD, non-diabetic renal disease; PICGN, Pauci-immune crescentic glomerulonephritis.

of the overall diagnoses). Similarly, the calculated PPVs for NDRD and mixed forms (36.9% and 19.7%, respectively) and the combined PPV (NDRD + mixed forms, 49.2%) strengthen the hypothesis that non-diabetic renal damage at RB is not as unlikely as commonly believed. Furthermore, there was high heterogeneity in the type of NDRD histologically assessed, IgA nephropathy being the most common finding (3 to 59%). The prevalence of different histological pictures of NDRD has been analysed in this systematic review and differences between population settings have been described. A higher prevalence of diagnosis of IgA nephropathy in Asian population has been described in the selected studies compared with other populations (European, American, African studies). IgA nephropathy is considered to be multifactorial disease in which pathogenesis

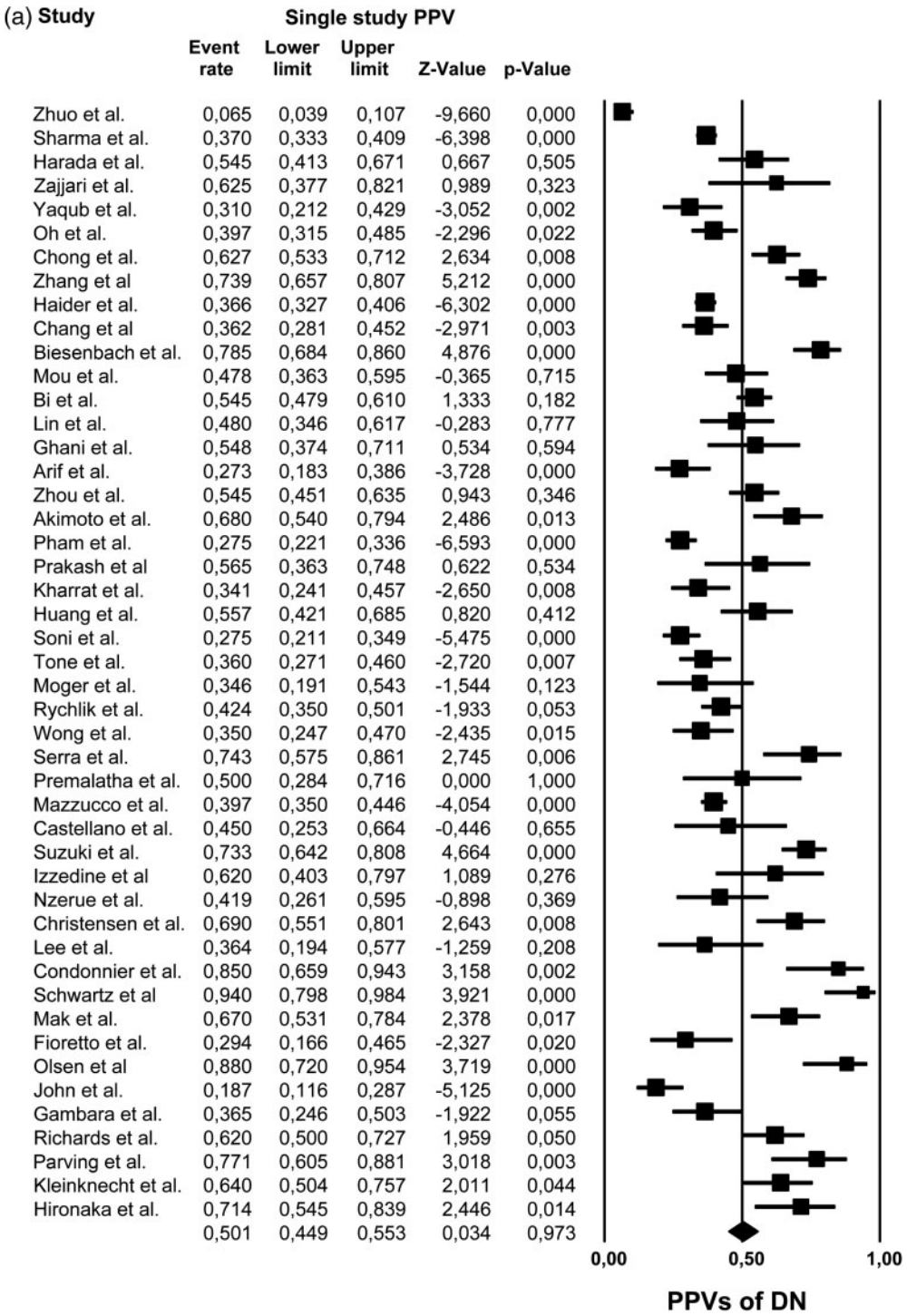


**FIGURE 2:** PPVs of clinical judgment for the diagnosis of DN (**a**), NDRD (**b**), mixed forms (**c**) and NDRD + mixed forms (**d**) from pooled meta-analysis. DN, diabetic nephropathy; NDRD, non-diabetic renal disease; PPVs, positive predictive values.

involves genetic and environmental factors. Our results are in line with the prevalence of glomerular disease in non-diabetic patients in previous studies [56, 57]. A similar prevalence of IgA nephropathy and MN was found in studies on European populations, contrary to what is reported in several RB registries [26, 58, 59].

Several factors may explain such a high histological variability. In particular, criteria used to select patients with diabetes who would benefit from RB were very different among the studies reviewed. As alluded to before, only a small number of studies evaluated research-indicated biopsies while the vast majority analysed clinically indicated biopsies. Percentages of DN and NDRD diagnoses were not statistically different between these two groups, whereas a higher percentage of IgA nephropathy was showed in clinically indicated biopsies. Although interesting, these observations may be influenced by the substantial discrepancy in the number of patients in which RB was driven by research or clinical purposes. Hence,

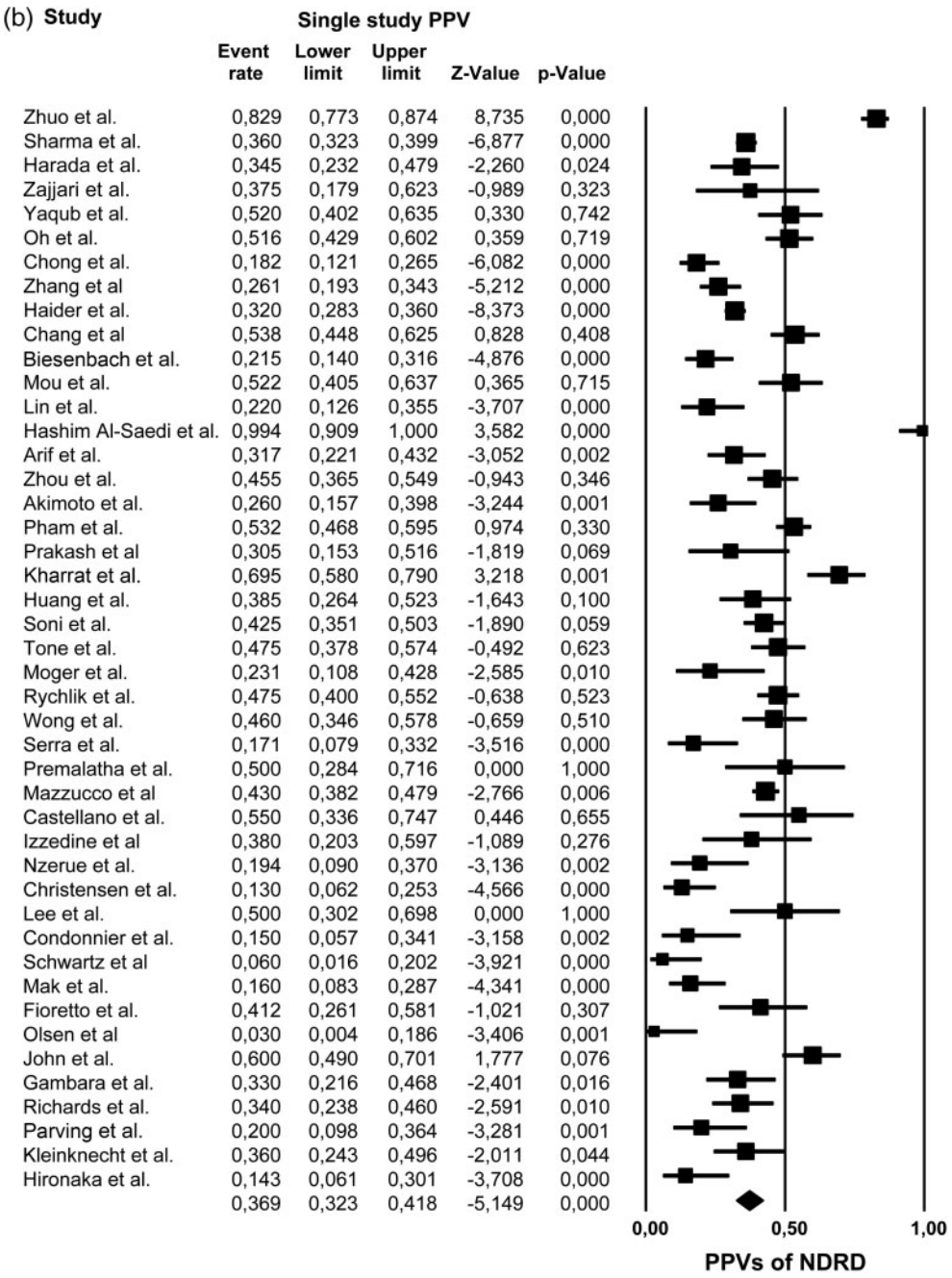


FIGURE 2: *Continued*

statistical analyses could be underpowered to detect such a significant difference in the overall percentage of diagnoses made. The most common indications were represented by a sudden onset of nephrotic-range proteinuria or renal impairment in the absence of diabetic retinopathy or in the presence of a history of diabetes <5 years, the presence of active urinary sediment, an unexplained acute kidney injury or a rapid renal function decline in patients with previously stable renal function.

The evaluation of factors explaining heterogeneity identified systolic blood pressure, HbA1c, duration of diabetes and diabetic retinopathy as inversely correlated with NDRD diagnosis. Serum creatinine was the only factor underlying heterogeneity for DN. Finally, serum creatinine and, even more, GFR elucidated heterogeneity among studies for mixed forms.

In previous studies exploring clinical predictors of the presence of DN or NDRD, Zhuo *et al.* [8] pointed at longer diabetic duration, higher systolic blood pressure, higher HbA1c and the presence of retinopathy as clinical signs highly suggestive of classic DN. The role of retinopathy was very well analysed by the RASS study [60], which described a significant association between diabetic retinopathy and preclinical histological damage in patients with Type 1 DM. Tone *et al.* [25] confirmed that diabetic retinopathy had the highest sensitivity (87%) and sensibility (93%) in predicting the presence of DN. However, the presence of proliferative retinopathy is associated with the classical nodular sclerosis of DN [49, 53], and patients with both DN and retinopathy showed a more severe renal histology than those without retinal damage [42]. Patients with other

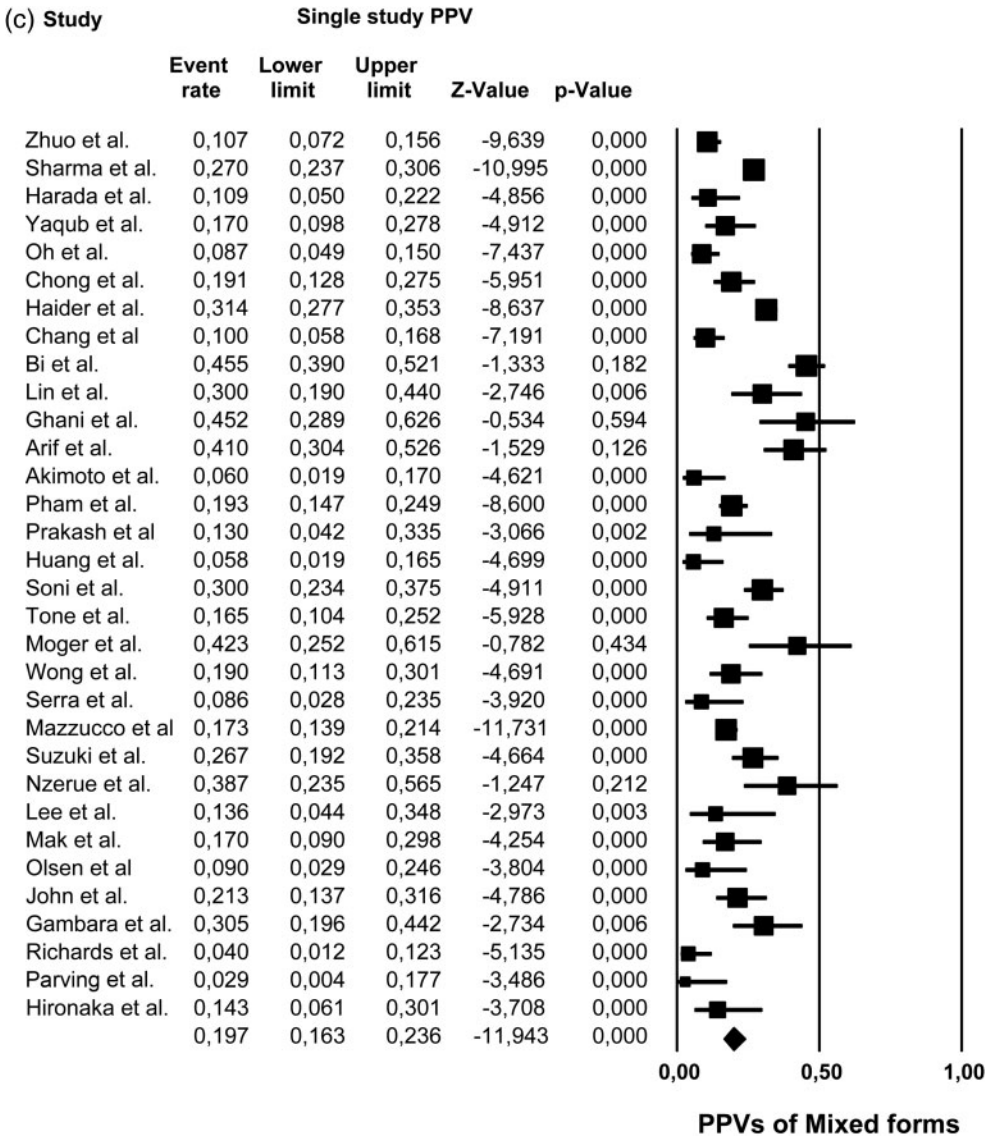


FIGURE 2: *Continued*

histological lesions more frequently have no evidence of diabetic retinopathy or only have minimal damage and none of the patients with NDRD had proliferative retinopathy [34, 39, 49, 53]. In the study by Liang *et al.* [3], the presence of dysmorphic erythrocytes and erythrocytes casts was strongly indicative of NDRD. However, in the same study the predictive role of diabetic retinopathy with respect to DN was questioned since the absence of such complication was, in some cases, associated with the presence of DN. The hypothesis that retinopathy might be a poor predictor of DN was supported by another study [45], in which DN was present in about 50% of diabetics without DR, while 40% of patients with DR had other renal diseases.

RB might be fundamental for clarifying the epidemiology of renal disease in patients with diabetes and for planning proper therapeutic management [17]. Furthermore, although this procedure is invasive, the risk profile in subjects with diabetes is comparable to that of the general population [43]. As described in a large research biopsy study on patients with Type 1 DM [55], specific histological lesions, such as thickening of glomerular basement membrane or an increase of mesangial fractional volume, can be evident early on, before the development of overt DN and initiation of treatment (such as RAS inhibition) based on clinical manifestations may be inadequate to delay the natural history of the disease. Indeed, treatment approaches for DN and NDRD may diverge: for instance, IgA nephropathy, FSGS, membranous glomerulonephritis and other primary and secondary glomerular diseases usually benefit from personalized treatments (e.g. immunosuppressive therapies) rather than from general approaches [54]. The prognostic importance of RB is another aspect that should be seriously taken into consideration [2, 10]. Oh *et al.* [10] found that ESKD occurred in 44% of DN, in 18.2% of mixed forms and in only 12.3% of NDRD. Diabetics with frank DN usually have a worse prognosis compared with patients with NDRD [13, 27] and the severity of DN correlates with histological (glomerular and tubule-interstitial damage) and clinical (eGFR, proteinuria) predictors of ESKD [10, 54]. Nevertheless, NDRD may have better outcomes, particularly if these conditions are identified early and specific treatments are predisposed [1].

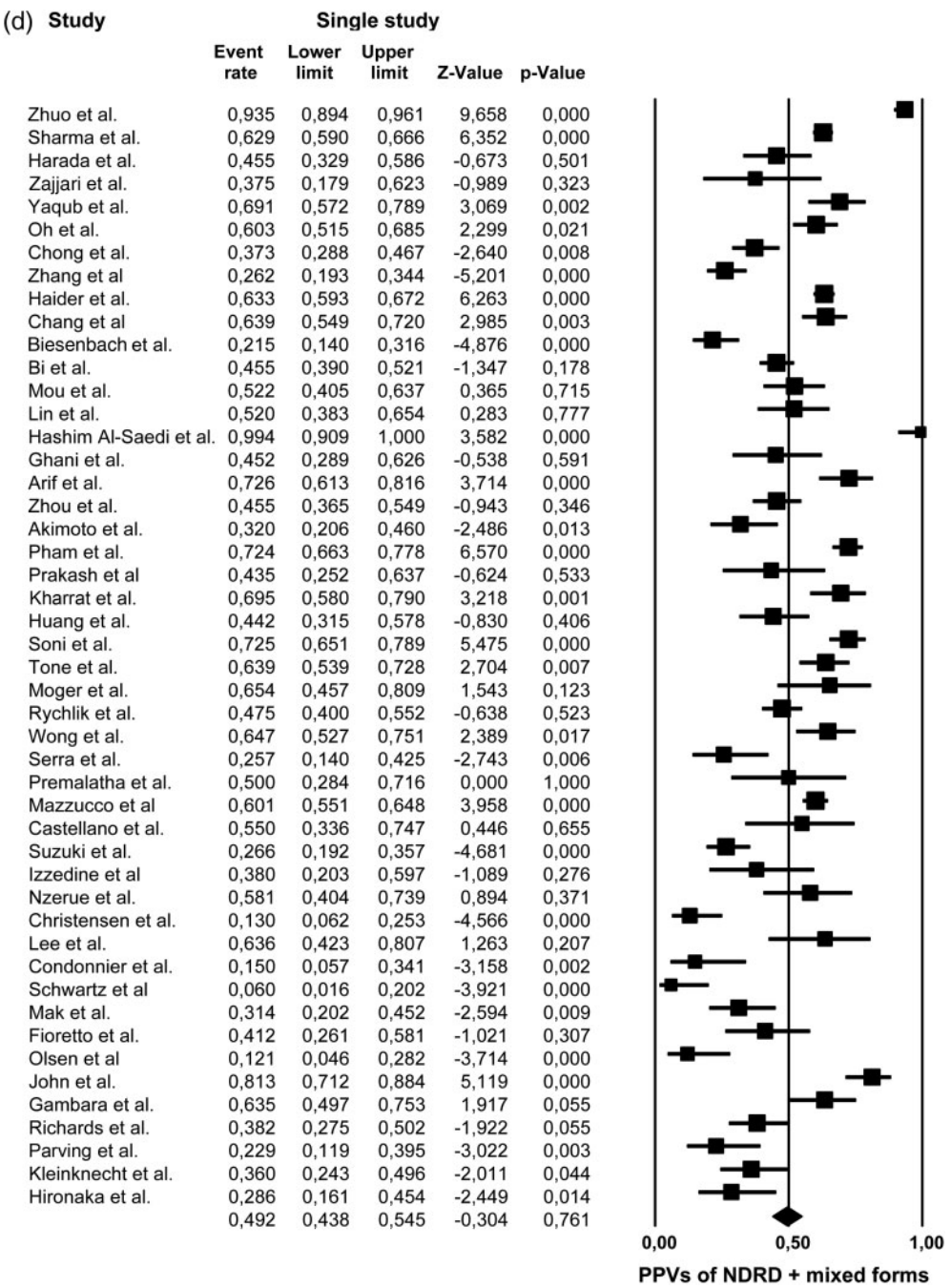


**FIGURE 2:** *Continued*

Our review has some strengths and limitations that deserve mentioning. The main strength is represented by the systematic approach to the existing literature by implementing high-sensitivity and focussed search strategies according to current methodological standards. This, however, cannot fully rule out residual publication bias. The main limitation of our findings is related to the observational nature of the included studies (most of which had a retrospective design) and the more or less evident presence of selection bias. Furthermore, as shown, there was high heterogeneity with respect to the number of subjects enrolled, the criteria used for performing RB, the degree of renal impairment, the duration of diabetes and the frequency of diabetic retinopathy; this may hamper the possibility of drawing unique and definitive conclusions and generalizing findings to the whole diabetic population.

In conclusion, our study shows proof that RB might represent an important tool in patients with diabetes, particularly for identifying subjects with NDRD who would benefit from personalized treatment for retarding ESKD. Future, well-planned studies on this issue are eagerly awaited for clarifying the exact role of this procedure in the clinical management of patients with diabetes.

## SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

## ACKNOWLEDGEMENTS

We are grateful of the European Renal Best Practice (ERBP) and ERA-EDTA Immunonephrology Working Group (both sponsored by ERA-EDTA) for the incessant support to the project. This study was financed by Italian National Health (RF09ED01: 'Prevalence and impact on total mortality of chronic kidney disease in patients with type 2 diabetes in Apulia; a paradigm for a region-based study whose data may be specifically implemented in the management of chronic metabolic and vascular diseases in a Mediterranean area') and by a grant of Italian Society of Nephrology (SIN).
The results presented in this paper have not been published elsewhere in whole or part.

## AUTHORS' CONTRIBUTIONS

M.F., D.B. and L.G. collaborated on research idea, study design, study selection and wrote the paper. V.T. helped in drafting the paper. A.P. collaborated on study selection and data collection. W.V.B. helped in full-text research and in drafting the paper. G.T. and G.D. helped in statistical analysis and data interpretation. All authors approved the final version of the submitted manuscript.

## CONFLICT OF INTEREST STATEMENT

All the authors have declared no competing interest.

(See related article by Caramori. Should all patients with diabetes have a kidney biopsy? *Nephrol Dial Transplant* 2017; 32: 3–5)

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*Received for publication: 11.7.2015; Accepted in revised form: 1.3.2016*