Online Supplementary Material

A SYSTEMATIC REVIEW OF RENAL PATHOLOGY IN CHRONIC KIDNEY DISEASE OF UNCERTAIN ETIOLOGY

Item S1 – Supplementary Table S1: Characteristics of studies

Item S2 – Prisma Checklist

Item S1

Supplementary Table S1: Characteristics of the studies

Study Country & Number of biopsies	Aim of the study	Study period	Patients selected from	Study design	Case selection criteria	Inclusion criteria	Exclusion criteria
				Sri Lanka			
Athuraliya et al. 2011[26] **SL cohort;** **n=26**	Population survey to study epidemiology of CKDu	2003	Medawachchiya, Anuradhapura	Population survey with community-based screening Random Cluster Sampling	Proteinuric-CKD patients with no definitive aetiology identified through household screening and referred for biopsy.	Presence of persistent proteinuria, ≥+1 (≥30 mg/dl), detected by dipstick in a spot urine sample.	
Nanayakkara et al. 2012[27] **SL cohort;** **n=57**	To describe the histopathological features of CKDu with the objective of finding possible pathogen/s.	2008-2009	General Hospital, Anuradhapura	Cross sectional descriptive study	Clinically diagnosed CKDu patients undergoing renal biopsy :		Diabetes, malignant hypertension, urological disease, SLE, IgA nephropathy
Wijetunge et al. 2013[28] **SL cohort;** **n=211**	To study the early histopathological changes in CKDu and	2007-2010	Patients referred for biopsy at tertiary hospitals of	Retrospective analysis of biopsy samples	Asymptomatic individuals living in CKDu endemic regions for more than 5 years, detected to have CKD on screening	Positive albuminuria ≥+1 and proteinuria >500 mg/24 hrs, or proteinuria <500 mg/24 hrs with haematuria, or renal insufficiency.	Diabetes, long standing hypertension, end stage renal failure, IMF positive lesions on biopsy

	correlate the findings with GFR and age of the patients.		Anuradhapura and Kandy				
Wijetunge et al. 2015[29] SL cohort; n=251	To describe the histological findings in advanced disease and correlate them with the clinical (KDIGO) stages	2003-2007	Renal biopsies received by the Department of Pathology, Faculty of Medicine, University of Peradeniya from the Nephrology Units of the Teaching Hospital Kandy and General Hospital Anuradhapura	Retrospective analysis of biopsy samples	Symptomatic and asymptomatic patients living in endemic areas for > 5years with histologically proven primary interstitial renal disease.	Interstitial renal disease not secondary to a glomerular disease or systemic disease, no specific primary or secondary glomerular disease, no IMF deposits	Diabetes, long standing hypertension, end stage renal failure
Badurdeen et al. 2016[30] SL cohort; n=46 (59 recruited for study)	To analyze the clinicopathological profile in patients from CKDu endemic regions presenting with acute symptoms and renal dysfunction.	Not mentioned	North Central Region	Prospective cohort study	Previously apparently healthy patients presenting with acute symptoms and having persistently elevated serum creatinine for up to 2 weeks.		Clinically identifiable causes for the renal dysfunction, small-sized kidneys, immune-complexes on IMF, identifiable primary or secondary renal pathology on biopsy
Selvarajah et al. 2016[31] SL cohort; n=125	To link the histopathological features with clinical, epidemiological and laboratory findings to develop a clinicopathological model for CKDu.	2008-2012	Teaching Hospital Anuradhapura	Prospective study of consecutive patients	Patients fulfilling the criteria developed by the Scientific Committee of the National Research Programme for CKDu (MOH-WER 2009 Vol36:49-REF 106)		Diabetes mellitus, chronic or severe hypertension, snake bite, GN, urological diseases, contraindications for biopsy

Wijkström et al. 2018[32] SL cohort; n=11	To assess renal pathology of CKDu in Sri Lanka and to compare with MeN	Not mentioned	General Hospital Polonnaruwa	Prospective study of patients with CKDu undergoing renal biopsy over 1 week	Patients clinically diagnosed to have CKDu	20-65 years of age and plasma creatinine 100-220 µmol/L or eGFR 30-80ml/min/1.73m^2	Diabetes mellitus, uncontrolled hypertension, albuminuria >1g/24h, other known renal disease
Anand et al. 2019[33] SL cohort; n=87 ***(Only PTKD group; n=43 were described)***	To identify if routinely measured clinical features are associated with histopathological confirmation of tubulointerstitial kidney disease, particularly for the purpose of patient selection for case-control studies in CKDu.	2016-2017	Teaching Hospital, Kandy	Prospective study on new CKD patients recommended for biopsy and subsequently confirmed as CKDu according to the presence of PTKD	Patients with unexplained abnormal urine sediment or elevated serum creatinine.	IMF predominantly negative. Inflammation and tubulointerstitial change predominant rather than glomerular or vascular pathology.	Small kidneys
Vervaet et al. 2020[38] SL cohort; n=18	To define the etiology of CINAC	Not mentioned	SL, ES, India and France	Study of biopsy material from patients diagnosed with CINAC, MeN, CKDu	CINAC/MeN/CKDu renal biopsy samples from patients meeting 4 of the 5 following clinico-epidemiologic criteria: patients with CKD living in agricultural environment; living in a CINAC-endemic region; no trace proteinuria; no diabetes; no high blood pressure		
Nicaragua							
Wijkström et al. 2017[36] NCG cohort; n=19 (only 16 considered as representative)	Replicate study of Wijkström 2013 in a cohort from a different region	2014	Research Center of Health, Work and Environment, National Autonomous, Leon	Prospective study of males with CKDu and a history of sugarcane work who had been to a medical visit during a 12-month period	Clinically diagnosed men with CKDu who had a history of sugarcane work	Age 20 to 65 years, SCr of 100 to 220 micro mol/L or eGFR of 30 to 80 mL/min/ 1.73 m2.	Proteinuria >3 g/24 h, uncontrolled hypertension, diabetes mellitus or other known kidney disease.

Fischer et al. 2017[37] NCG cohort; n=11	To describe the renal pathology in patients at the onset of the disease to facilitate clinical diagnosis and propose a mechanism of injury	2016	Chichigalpa, Chinandega	Prospective study on young AKI patients with previously normal SCr.	Patients 18 to 39 years of age with elevated serum creatinine and acute symptoms without any known causes for kidney disease	Elevated SCr (>1.3 mg/dl for males; >1.1 mg/dl for females; ≥0.3 mg/dl or ≥1.5-fold greater than baseline), leukocyturia (≥10 cells/field), and leukocytosis/neutrophilia	Hypertension, diabetes, or heart condition, <2 functional kidneys, blood thinners within 7 days, positive urine culture results, or return to normal SCr after 24 hours of intravenous fluids.
El Salvador							
Wijkström et al. 2013[34] ES cohort; n=8	To report clinical features and renal morphology in selected CKDu patients	Not mentioned	Hospital Nacional Rosales, San Salvador, El Salvador	Prospective study on selected patients	Male plantation workers with CKDu and clinical suspicion of MeN.	Age 20-65 years, SCr - 120 to 220 μmol/L or eGFR of 30 to 60 mL/min/ 1.73 m2.	Nephrotic range proteinuria (>3.5 g/24h), uncontrolled hypertension, diabetes
Lopez-Marin et al. 2014[35] ES cohort; n=46	To characterize the histopathology, describe renal damage according to disease stage and assess associations between histopathology and socio-demography of CKDu patients from Salvadoran agricultural communities.	2013	11 agricultural communities of 4 regions - Usulután, San Miguel, Ahuachapán and Chalatenango	Prospective descriptive cross-sectional study	Clinically diagnosed CKDu patients identified through population screening	CKD stage 2 to 3b	Diabetes mellitus, hypertension, glomerulopathy, polycystic kidney disease, obstructive kidney disease, HIV
Vervaet et al. 2020[38] ES cohort; n=11	To define the etiology of CINAC	Not mentioned	SL, ES, India and France	Study of biopsy material from patients diagnosed with CINAC, MeN, CKDu	CINAC/MeN/CKDu renal biopsy samples from patients meeting 4 of the 5 following clinico-epidemiologic criteria: patients with CKD living in agricultural environment; living in a CINAC-endemic region; no trace		

		proteinuria; no diabetes; no high blood pressure

Abbreviations: M:F, Male: Female ratio; SL, Sri Lanka ; ES, El Salvador ; NCG, Nicaragua; CKD, chronic kidney disease; CKDu, chronic kidney disease of uncertain etiology; CINAC, chronic interstitial nephritis in agricultural communities; MeN, Mesoamerican nephropathy; SCr, Serum Creatinine; eGFR, estimated glomerular filtration rate; IMF, Immunofluorescence; AKI, Acute kidney injury; GN, glomerulonephritis; PTKD, Primary tubulointerstitial kidney disease; SLE, Systemic lupus erythematosus; HIV, Human immunodeficiency virus

Item S2

PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page - 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3,4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	N/A
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-13; Table 1; Table 2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18-20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23