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REVIEW

Burden of Chronic Kidney Disease by KDIGO Categories of Glomerular Filtration Rate and Albuminuria: A Systematic Review

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ABSTRACT

Introduction: The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines recommend classifying patients by glomerular filtration rate (GFR) and albuminuria to predict chronic kidney disease (CKD) prognosis. The aim of this systematic review was to explore the epidemiological burden of CKD stratified by the KDIGO 2012 categories.
Methods: MEDLINE® and Embase were searched for observational studies of patients with CKD with results stratified according to the KDIGO 2012 classification. Investigated outcomes were prevalence, incidence, and risk factors and complications of CKD, including mortality.
Results: The review included ten observational studies with 3033 to 46,949 participants, conducted in the USA, China, France, Italy and Spain. The most frequently reported outcome was the prevalence of CKD (GFR categories G3–5), ranging from 2% to 17%. Most participants were normoalbuminuric, with 0.4–3.2% macroalbuminuric, and most fell within the KDIGO 2012 low-risk or moderate-risk groups, with 0.9–5.6% in the high-risk and 0.3–4.8% in the very high-risk groups. Although scarce, data on the prevalence of comorbidities in CKD according to the KDIGO classification suggest that they increase with albuminuria severity.
Conclusions: Patients with CKD frequently have complications, but only a small proportion have severely increased albuminuria or fall within the KDIGO high-risk or very high-risk groups. These groups, however, are associated with the highest burden of disease, as comorbidities are more prevalent with increasing

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albuminuria severity. New studies framed by the KDIGO 2012 classification are needed to address key gaps in the understanding of CKD burden and outcomes.

Keywords: Albuminuria; Cardiovascular diseases; Chronic kidney disease; CKD; Diabetes mellitus; Hypertension; KDIGO; Prevalence; Renal insufficiency

Key Summary Points

Why carry out this study?

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) organisation issued a set of guidelines recommending that chronic kidney disease (CKD) be classified by both the level of glomerular filtration rate (GFR) and albuminuria.

We conducted a systematic review to explore the uptake of the guidelines (i.e. how many studies use this classification system) and the epidemiology of CKD according to these guidelines (i.e. the prevalence of patients within the GFR/albuminuria-defined risk groups).

What was learnt from the study?

A substantial proportion of the general population have CKD, but only a small fraction of patients have severely increased albuminuria or fall within the high-risk or very high-risk groups defined by the KDIGO 2012 guidelines.

These groups, however, have a high prevalence of diabetes, cardiovascular disease and hypertension, especially among those with higher levels of albuminuria.

Testing for albuminuria is therefore valuable for CKD prognosis and management.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13207706.

INTRODUCTION

Chronic kidney disease (CKD) is a substantial public health burden associated with high morbidity and mortality. It is estimated that over 850 million people are affected by kidney diseases worldwide, the majority of whom suffer from CKD [1]. The estimated global prevalence of CKD is 8–16% [2–4], with the highest rates reported in Saudi Arabia and Belgium (both 24%), Poland (18%), Germany (17%), and the UK and Singapore (both 16%) [5]. Internationally, CKD was responsible for 1.2 million deaths and 35 million disability-adjusted life-years (DALYs) in 2016 [6]. Global CKD incidence, prevalence, mortality and DALYs have all increased dramatically since 1990, driven by population growth and aging, and increased numbers of people with diabetes and hypertension [6], which, along with glomerulonephritis, are the leading causes of CKD [3, 6–8].

Kidney function is typically measured via glomerular filtration rate (GFR), with CKD diagnosed when levels are below 60 mL/min/1.73 m^2 for 3 months or more [3, 9]. GFR is also used to distinguish between different levels of kidney function, ranging from normal function to kidney failure. Common non-kidney complications of CKD also include myocardial infarction, stroke, heart failure and infections [10]. The treatment of CKD and comorbid conditions imposes a substantial economic burden [2, 11]. By itself, however, GFR may not optimally predict prognosis [9]. One of the most important predictors of the risk of CKD progression to kidney failure, dialysis, adverse events including cardiovascular risk and premature mortality is elevated albuminuria [12–14]. This has been suggested to have a higher specificity for detecting patients with grade 3/4 CKD who are most likely to progress and a greater ability of avoiding those who are less likely to progress [13]. Similarly, patients without impaired eGFR but with elevated albuminuria may also be at higher risk of adverse kidney and cardiovascular outcomes [14]. As such, the consideration of albuminuria would have substantial benefits for the early identification of such patients, proactive management of their disease and healthcare resource planning. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines recommend classifying individuals according to six GFR categories and three albuminuria categories [9] (Fig. 1). Through the combined assessment of GFR and albuminuria status, a patient can be more accurately evaluated as being at low, moderately increased, high or very high risk of worsening kidney function and other complications, facilitating improved decision-making in patient monitoring and management [9, 15, 16].

The epidemiology of CKD has been the subject of previous systematic reviews and meta-analyses [17–19], but in these studies, patients were only classified according to GFR status, making it difficult to quantify the true prevalence of a population at high or very high risk of progression to kidney failure or premature mortality. The epidemiology of CKD according to the 2012 KDIGO categories, as well as the volume of evidence on this topic, is unclear. Therefore, we conducted a systematic review to explore the uptake of the KDIGO 2012 classification system within epidemiologic studies, the relative size and clinical profile of each cohort, and a picture of CKD epidemiology according to the KDIGO 2012 classification system, based on a sample of key countries that were expected to utilise the KDIGO guidelines.

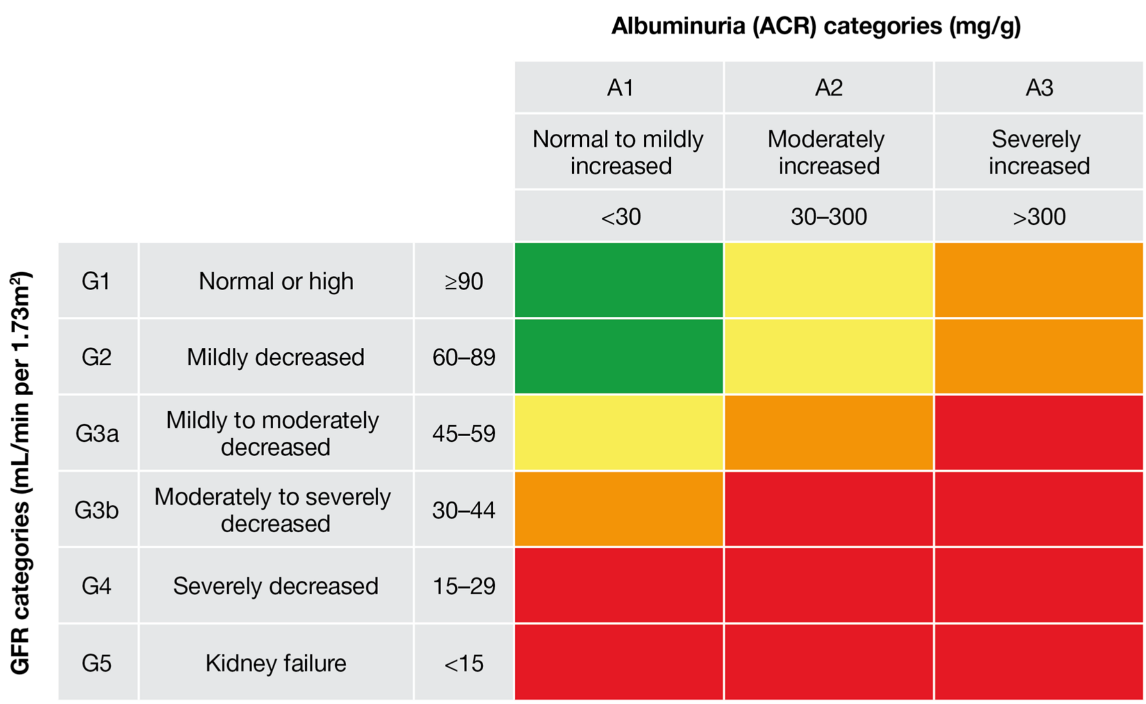

Fig. 1 Prognosis of CKD by GFR and albuminuria categories. Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression. CKD chronic kidney disease, GFR glomerular filtration rate, ACR albumin-to-creatinine ratio

METHODS

This systematic review was based on a prespecified protocol and conducted in accordance with the standards prescribed by the Centre for Reviews and Dissemination [20] and the Cochrane Collaboration [21]. MEDLINE® and Embase were searched simultaneously via the Ovid SP platform on 10 June 2019. The search terms used are provided in Table S1 in the electronic supplementary material. The bibliographies of relevant published systematic reviews were hand-searched to find additional articles that were not identified in the electronic database searches. Grey literature searches included conference proceedings of six major nephrology, cardiology and diabetes congresses held between 2017 and 2019, and three major CKD-related registries (Table S2). Expert advice was sought to identify potentially relevant articles that were not captured by the electronic database searches or supplementary searches.

Two independent reviewers (MM, DGL) screened the title and abstract of each record (stage 1), as well as the full texts of all potentially eligible records identified in stage 1 (stage 2). A third independent reviewer (AB) resolved any disagreements. Detailed eligibility criteria are given in Table 1. Eligible publications included English language articles reporting on relevant non-interventional studies involving adult patients with CKD, in which relevant outcomes were stratified according to the KDIGO 2012 guidelines or similar classification, with data stratified by albuminuria and GFR status or albuminuria status alone. Studies that stratified data by GFR status alone were excluded. Relevant articles were limited to those published in 2012 or later (i.e. since the publication of the KDIGO 2012 guidelines) and conducted in the USA, China or a European Union Five (EU5) country (France, Germany, Italy, Spain or the UK).

Relevant outcomes were the prevalence of CKD, the prevalence of CKD risk factors and complications (e.g. diabetes, hypertension, heart failure and cardiovascular disease [CVD]), and the incidence of CKD, CVD complications (e.g. myocardial infarction and stroke), hospitalisations for heart failure, and CVD-related or all-cause mortality. Data were extracted and summarised qualitatively, as ranges of prevalence; owing to the nature of this review a meta-analysis was not performed and any numbers have been given as reported in the included studies or arrived at by calculating a simple proportion (ratio of participants with a specific characteristic to the total population).

A single reviewer (MM or DGL) extracted data from the included studies into a prespecified extraction grid and assessed study quality using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies 2017 [22]. Extracted data and quality assessments were independently verified by a second reviewer (MM or DGL), with discrepancies arbitrated by a third reviewer (AB).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Study Selection

Electronic database searches yielded 4286 records. After title/abstract screening, 249 potentially relevant records were selected for full text review, of which 11 were included. A complete list of articles excluded at the full text review stage is provided in Table S3. Supplementary searches yielded 3262 records, of which two met the inclusion criteria. One article was screened on the basis of expert advice and met the inclusion criteria [23]. A total of 14 publications reporting on 10 unique non-interventional studies were included in the review (Fig. 2, Table S4). The number of articles that were excluded because of not reporting CKD epidemiology outcomes according to KDIGO classification was 1334 (Fig. 2). From this, it can be calculated that only 1.04% of articles reported such outcomes using the KDIGO

Table 1 SR eligibility criteria

Category	Inclusion criteria	Exclusion criteria
Population	Adult patients with CKD stages 2, 3a, 3b, 4, 5/ESRD, categorised according to the KDIGO 2012 classification or similar Mixed populations, if the outcomes are reported separately for the population of interest	Population does not include patients with CKD of a relevant stage or classification, or does not report results separately for this subgroup Animal/in vitro studies
Intervention/comparator	Any or none	N/A
Outcomes	Country or regional-level prevalence, incidence or mortality reported for the following health states, including but not limited to: CKD albuminuria categories, with albuminuria measured by methods including but not limited to: UACR PCR AER PER Protein reagent strip Level of overlap between CKD, T2DM and heart failure† Cardiovascular complications (e.g. MI, stroke, angina, MACE, hospitalisation for heart failure) Hypertension	No relevant epidemiological outcomes
Study type	Non-interventional studies, e.g. observational studies or population surveys of any design, including cohort studies, cross-sectional surveys, case–control studies, registry studies, chart reviews etc. Meta-analyses of relevant study designs	Any other study type, e.g. RCTs, case reports/series
Publication type	Original research studies Conference abstracts SRs of relevant primary publications (these were considered relevant at the title/abstract review stage and hand-searched for relevant primary studies, but excluded during the full-text review stage)	Irrelevant publication types including narrative reviews, commentaries, editorials

Table 1 continued

Category	Inclusion criteria	Exclusion criteria
Other criteria	Studies conducted in the USA, China or EU5 country (France, Germany, Italy, Spain, UK)	Studies conducted in any other geographical location
	Studies published in or after 2012	Studies published before 2012
	Conference abstracts published in or after 2017	Conference abstracts published before 2017
	Full text in English	Full text in any other language

AER albumin excretion rate, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *EU5* European Union Five, *KDIGO* Kidney Disease: Improving Global Outcomes, *MACE* major adverse cardiac events, *MI* myocardial infarction, *N/A* not applicable, *PCR* protein-to-creatinine ratio, *PER* protein excretion rate, *RCT* randomised controlled trial, *SR* systematic review, *T2DM* type 2 diabetes mellitus, *UACR* urinary albumin-to-creatinine ratio

† Heart failure was defined on the basis of the New York Heart Association classification [46]

classification (14/1348 × 100). Any results presented below have been reported in the included studies or calculated through a simple proportion; no quantitative synthesis has been conducted.

Study Characteristics

Table 2 summarises the characteristics of the 10 studies included in this systematic review. Five studies were conducted in the USA [24–28], one in China [29], one in the USA and China [30], one in Italy [31], one in Spain [32] and one in France [23]. Of the six studies that reported study location(s), all involved participants from multiple geographical locations, with the exception of one that was based in a single province in eastern Sardinia [31]. The earliest data collection period was 1988–1994 [26], while the most recent data were collected in 2013–2016 [23, 27]. Sample size ranged from 3033 [23] to 46,949 participants [30]. All studies involved data from cross-sectional surveys and registry analyses (6/10) or cohort studies (4/10).

In all studies, CKD was classified according to clinical test results rather than administrative codes (Table 2). Estimated GFR (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation in eight studies, the Modification of Diet in Renal Disease (MDRD) equation in one study [29], and both in another study [31]. Eight studies used urinary albumin-to-creatinine ratio (UACR) to determine albuminuria status, one used urinary protein and albumin concentrations only [31], and another used several methods, including UACR, protein-to-creatinine ratio (PCR), albumin excretion rate (AER) and protein excretion rate (PER) [23].

In seven studies, patients were recruited from the general population, whereas in three studies, patients were from specific groups or settings. Of the latter, one evaluated hypertensive patients from a Spanish primary care setting [32], another analysed a subset of patients from a larger sample of the general population who were prescribed antihypertensive medication [28], and a third involved nephrologist-referred outpatients from the French Chronic Kidney Disease–Renal Epidemiology and Information Network (CKD-REIN), a cohort study investigating the determinants of prognosis and care in patients with CKD [23].

Patient Demographics, Aetiology and Baseline Comorbidities

Patient demographics are summarised in Table 3. Average age was reported in eight studies and ranged between 42.6 years [30] and 67.5 years [28]. Gender ratio was reported in five studies and ranged from 42.3% [31] to 65% male [23]. Racial demographics were reported in

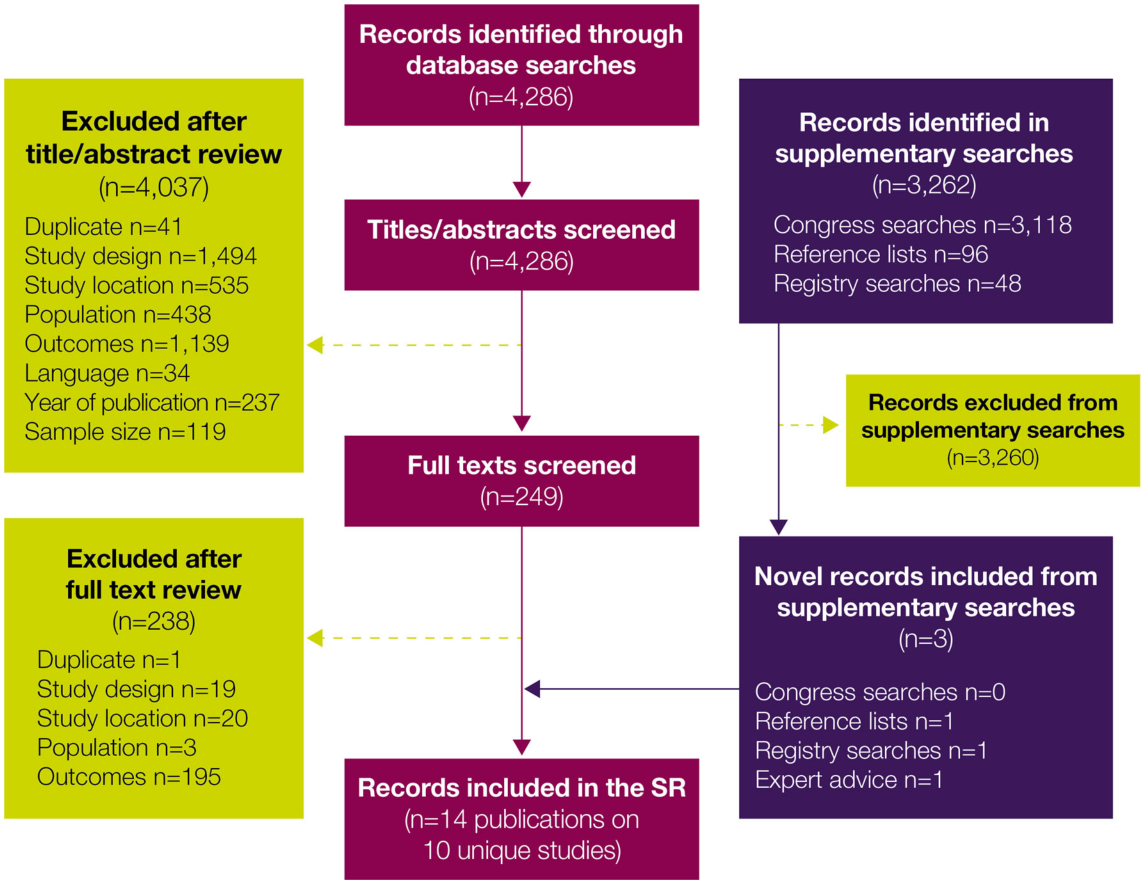

Fig. 2 PRISMA flowchart of records included and excluded in the review. Expert advice: one article was identified on the basis of advice from KT and RPF. PRISMA preferred reporting items for systematic reviews and meta-analyses, SR systematic review

four studies; black individuals comprised between 10.6% [30] and 50.1% [28] of participants.

Baseline comorbidity data are presented in Table 4. Of the seven studies that involved general population samples, four provided information on the prevalence of hypertension and diabetes at baseline, which ranged from 24.5% [26] to 47.4% [24] and 5% [30] to 16.6% [24] respectively.

Stratified Prevalence of CKD

General Population Cohorts

The most frequently reported outcome was the point prevalence of CKD in the general population, reported in seven studies across the USA, China and Italy [24, 29–31] (Fig. 3). The overall prevalence of patients with GFR categories G3–5, the clinical definition of CKD, was 2–17%. Prevalence appeared lower in China (2–3%) and Italy (3%) than in the USA (6–17%).

In individual studies, across GFR categories G2–5, the prevalence of individuals with normal albuminuria (UACR < 30 mg/g) was 27.4–56.4%, moderately increased albuminuria (UACR 30–300 mg/g) was 2.9–10.0%, and severely increased albuminuria (UACR > 300 mg/g) was 0.4–3.2%. The ranges of prevalence in GFR category G1 were 35.5–59.8%, 1.9–6.5% and 0.2–1.8% in normal albuminuria, moderately increased albuminuria and severely increased albuminuria, respectively. On the basis of the combination of GFR status (across categories G2–5) and albuminuria status (across categories A1–3), 24.8–51.4% of

Table 2 Characteristics of the included studies

Study	Registry, database or cohort	Country	Study design	Study setting	Data collection period	Sample size	GFR categories	Measure of eGFR	Albuminuria categories	Measure of albuminuria
Odden [26]	NHANES 1988–1994 and NHANES 1999–2002	USA	Cross-sectional survey	General population	1988–1994 and 1999–2002	10,956	G4 and G5 merged; G2 split into 60–74 and 75–89 mL/min/1.73 m^2; G3a and G3b subcategories presented	CKD-EPI equation	A1 split into < 10 and 10–29 mg/g subcategories	UACR
Pani [31]	SardiNIA	Italy	Prospective cohort study	General population	Start 2001; average follow-up 7 years	4842	KDIGO 2012	CKD-EPI and MDRD equation	KDIGO 2012	Urinary protein and albumin levels
Wang [30]	NHANES 2009–2010 and China National Survey of CKD 2009–2010	USA and China	Cross-sectional survey	General population	2009–2010	5557 (USA); 46,949 (China)	KDIGO 2012	CKD-EPI equation	KDIGO 2012	UACR
Levin [25]	NHANES 1999–2006	USA	Cross-sectional survey	General population	1999–2006	18,026	KDIGO 2012	CKD-EPI equation	KDIGO 2012	UACR
Hui [24, 47–49]	ARIC	USA	Prospective cohort study	General population	1996–1998 (visit 4); 2011–2013 (visit 5)	11,060	KDIGO categories but G4 and G5 merged	CKD-EPI equation	KDIGO 2012	UACR

Table 2 continued

Study	Registry, database or cohort	Country	Study design	Study setting	Data collection period	Sample size	GFR categories	Measure of eGFR	Albuminuria categories	Measure of albuminuria
Stengel [23, 33]	CKD-REIN	France	Prospective cohort study	Outpatient nephrology care (GFR category G3–4 at census; GFR category G2–5 at inclusion)	2013–2015 [23]; 2013–2016 [33]	3033	KDIGO 2012	CKD-EPI equation	A3 split into 300–1999 and ≥ 2000 mg/g subcategories	UACR (30% of patients); PCR, AER or PER (all other patients)
USRDS [27]	NHANES 2013–2016	USA	Cross-sectional survey	General population	2013–2016	NR	KDIGO 2012	CKD-EPI equation	KDIGO 2012	UACR
Tanner [28]	REGARDS	USA	Prospective cohort study	General population (analysis restricted to hypertensive patients)	2003–2007	10,700	G1 and G2 merged; G3a omitted; G3b, G4 and G5 merged	CKD-EPI equation	A1 split into < 10 and 10–29 mg/g subcategories	UACR
Ruiz-Hurtado [32]	Spanish ABPM Registry Cohort	Spain	Cross-sectional registry analysis	Primary care setting (93% hypertension patients)	2009–2014	16,546	G2 omitted; G3a, G3b, G4 and G5 merged	CKD-EPI equation	KDIGO 2012	UACR

Table 2 continued

Study	Registry, database or cohort	Country	Study design	Study setting	Data collection period	Sample size	GFR categories	Measure of eGFR	Albuminuria categories	Measure of albuminuria
Lin [29]	Zhejiang Province	China	Cross-sectional survey	General population	2009–2012	10,384	KDIGO categories but G4 and G5 merged	Simplified MDRD equation	KDIGO 2012	UACR

ABPM ambulatory blood pressure monitoring, *AER* albumin excretion rate, *ARIC* Atherosclerosis Risk in Communities, *CKD* chronic kidney disease, *CKD-EPI* CKD Epidemiology Collaboration, *CKD-REIN* CKD-Renal Epidemiology and Information Network, *(e)GFR* (estimated) glomerular filtration rate, *KDIGO* Kidney Disease: Improving Global Outcomes, *MDRD* Modification of Diet in Renal Disease, *NHANES* National Health and Nutrition Examination Survey, *NR* not reported, *PCR* protein-to-creatinine ratio, *PER* protein excretion rate, *REGARDS* Reasons for Geographic and Racial Differences in Stroke, *SardiNIA* National Institute on Aging Sardinia Project, *UACR* urinary albumin-to-creatinine ratio, *USRDS* United States Renal Data System

participants fell within the KDIGO 2012 low-risk group, 3.7–13.4% within the moderately increased risk group, 0.9–5.6% within the high-risk group and 0.3–4.8% within the very high-risk group. For the very high-risk group, prevalence was lower in China (0.3–0.4%) and Italy (0.4%) than in the USA (1.1–4.8%).

Selected Cohorts

Two studies documented the prevalence of patients per the KDIGO 2012 albuminuria categories in specific cohorts selected for CKD or hypertension. In one cohort in a French nephrology outpatient setting, eligible patients had eGFR < 60 mL/min/1.73 m^2 for at least 1 month, with no prior chronic dialysis or transplantation [23] (Fig. 4). Normal albuminuria (UACR < 30 mg/g) was observed in 23.6% of these patients, moderately increased albuminuria (UACR 30–299 mg/g) in 27.4%, severely increased albuminuria (UACR 300–1999 mg/g) in 29.0% and high-grade albuminuria (UACR ≥ 2000 mg/g) in 7.1%. The other cohort consisted primarily of individuals with hypertension (93%) in a Spanish primary care setting [32]. Among those with eGFR < 60 mL/min/1.73 m^2, 74.4% had normal albuminuria (UACR < 30 mg/g), 20.1% had moderately increased albuminuria (UACR 30–300 mg/g) and 5.5% had severely increased albuminuria (UACR ≥ 300 mg/g). There were no available data on high rates of eGFR (G1 equivalent) in the selected cohorts. This was as expected as such cohorts frequently include patients with more advanced stages of disease.

Prevalence of CKD Risk Factors and Complications

In the Spanish hypertensive cohort, the prevalence of diabetes was higher in patients with CKD that had greater albuminuria severity; among patients with eGFR < 60 mL/min/1.73 m^2, diabetes was present in 26%, 43% and 53% of individuals with normal albuminuria, moderately increased albuminuria and severely increased albuminuria, respectively (Fig S1) [32]. In the French CKD cohort, the proportion of patients with atherosclerotic CVD was higher

Table 3 Patient demographics of the included studies

Study	Age mean (SD)†	Gender % male	Race/ethnicity %	SES (income, educational level)	Geolocation (urban vs rural)	Inclusion criteria	Exclusion criteria
Odden [26]	46.8 (0.7)	49.4	77.9% white, 11.2% black, 10.9% other	Reports educational level (< high school, high school, > high school) stratified by gender and uric acid level	NR	Adults aged ≥ 20 years	Pregnant participants. Participants who did not complete both the interview and examination
Pani [31]	49.7 (16.3)	42.3	NR	NR	NR	NR	NR
Wang [30]	47.2 (SE 0.51) (USA); 42.6 (SE 0.15) (China)	49.0 (USA); 50.0 (China)	10.6% black (USA); NR (China)	≥ high school: 81.2% (USA); 31.4% (China)	Equal number of urban and rural locations	NR	Participants with missing data on serum creatinine or albuminuria, < 20 years of age or reported as being pregnant at the time of the study
Levin [25]	NR‡	NR‡	NR‡	NR‡	NR‡	NR‡	NR‡
Hui [24, 47–49]	62.8 (5.7)	NR	78% white, 22% black, 0% Hispanic, 0% Asian	NR	NR	Adults aged 45–64 at baseline	Participants reporting race other than white or black, or missing values of either kidney measure or covariates
Stengel [23, 33]	66.2 (12.9)	65	NR	Educational level: < 9 years, 15%; 9–12 years, 49%; ≥ 12 years, 36%	The study encompassed rural and urban regions (numbers NR)	eGFR < 60 mL/min/1.73 m^2 for at least 1 month. No prior chronic dialysis or transplantation. Written signed consent form	Age < 18 years old. Pregnant patients. Patients that planned to move. Patients that were unable to give informed consent or declined to participate

Table 3 continued

Study	Age mean (SD)†	Gender % male	Race/ethnicity %	SES (income, educational level)	Geolocation (urban vs rural)	Inclusion criteria	Exclusion criteria
USRDS [27]	NR	NR	NR	Reports income and educational level stratified by presence of CKD, GFR status and albuminuria status	NR	Adults aged ≥ 20 years	NR
Tanner [28]	67.5 (8.7)	NR	50.1% black	Income < 20,000 and less than high school education reported stratified by presence of treatment resistant hypertension	NR	Adults aged ≥ 45 years. Individuals with hypertension who were taking ≥ 1 class of antihypertensive medication	Individuals missing serum creatinine, urine albumin or urine creatinine, BP data or information from the pill bottle review. Participants who reported being on dialysis at baseline or were missing information on dialysis status. Participants with uncontrolled BP on one or two antihypertensive medication classes
Ruiz-Hurtado [32]	59.6 (13.6)	NR	NR	NR	NR	Patients included in the registry with valid ABPM readings and complete information for the determination of albuminuria, diabetes and CKD status	NR

Table 3 continued

Study	Age mean (SD)†	Gender % male	Race/ethnicity %	SES (income, educational level)	Geolocation (urban vs rural)	Inclusion criteria	Exclusion criteria
Lin [29]	52.9 (14.5)	43	NR	NR	Equal number of urban and rural locations	Adults aged ≥ 18 years from the Zhejiang province who completed the required questionnaire, physical examination and laboratory examination	NR

ABPM ambulatory blood pressure monitoring, *BP* blood pressure, *CKD* chronic kidney disease, *(e)GFR* (estimated) glomerular filtration rate, *NR* not reported, *SD* standard deviation, *SE* standard error, *SES* socioeconomic status, *USRDS* United States Renal Data System

† Unless otherwise stated

‡ This publication is a clinical practice guideline that reproduces data from a conference report; as such, it provides no patient demographic data

in moderately albuminuric (30.9%) and severely albuminuric (34.4%) than in patients with normal albuminuria (28.5%) [33]. In an analysis of USA-based hypertensive patients, the prevalence of apparent treatment-resistant hypertension was found to increase with both worsening GFR status and increasing albuminuria severity [28]. In hypertensive patients with eGFR 45–59 mL/min/1.73 m^2, the prevalence of apparent treatment-resistant hypertension was 17.2%, 26.9%, 32.2% and 50.7% in groups with UACR < 10, 10–29, 30–299 and ≥ 300 mg/g, respectively. In those with eGFR < 45 mL/min/1.73 m^2, the corresponding figures were 22.5%, 24.5%, 32.8% and 56.4%.

Other relevant outcomes such as the prevalence or incidence of CKD complications, heart failure, myocardial infarction, stroke, or CVD and all-cause mortality according to the KDIGO classification were not identified.

Study Quality

There was sufficient information to assess the quality of four of the ten studies, all of which were judged to be of high quality, whereas the overall quality of the remaining six studies was unclear (see supplementary data and Table S5).

DISCUSSION

This systematic review of the epidemiological burden of CKD uniquely considered both GFR and albuminuria status, consistent with the KDIGO 2012 classification system and recommendations of the recent KDIGO Consensus Conference [9, 34]. This provides a very valuable different perspective from previous work that has only classified CKD epidemiology according to GFR status and, particularly, allows delineation of the groups that are likely to be at highest risk of adverse outcomes and progression to kidney failure. Measurement of albuminuria should be a key component of risk assessment for CKD [9], in that higher levels of albuminuria are associated with a faster rate of GFR decline and higher risk of kidney failure and mortality [13, 14, 35].

Table 4 Baseline comorbidity data

Study	Hypertension %	Diabetes† %	SBP (mmHg) mean (SD)‡	BMI (kg/m^2) mean (SD)‡	History of CVD/CVD events %	History of MI %	History of stroke %	History of HF %
Odden [26]	24.5	6.2	123.9 (0.8)	27.8 (0.3)	NR	3.4	1.9	2.3
Pani [31]	32	9.1	NR	25.9 (4.7)	5.6	NR	NR	NR
Wang [30]	35.1 (USA); 30.4 (China)	10.7 (USA); 5.0 (China)	120.3 (SE 0.51) (USA); 125.2 (SE 0.18) (China)	28.7 (SE 0.13) (USA); 23.5 (SE 0.03) (China)	5.2 (USA); 2.0 (China)	NR	NR	NR
Levin [25]	NR	NR	NR	NR	NR	NR	NR	NR
Hui [24, 47–49]	47.4	16.6	127.6 (19)	28.8 (5.6)	13.9	NR	NR	NR
Stengel [23, 33]	91	43	142 (20)	29 (6)	53	NR	NR	NR
USRDS [27]	NR	NR	NR	NR	NR	NR	NR	NR
Tanner [28]	NR	34.7	132.9 (14.1)	NR	NR	19.3	10.7	NR
Ruiz-Hurtado [32]	93	25.3	NR	29.3 (4.9)	12.4	NR	NR	NR
Lin [29]	NR	NR	133.4 (24.1)	23.1 (3.99)	NR	NR	NR	NR

BMI body mass index, *CVD* cardiovascular disease, *HF* heart failure, *MI* myocardial infarction, *NR* not reported, *SBP* systolic blood pressure, *SD* standard deviation, *SE* standard error, *USA* United States of America, *USRDS* United States Renal Data System

† Diabetes subtype unspecified in all studies

‡ Unless otherwise stated.

We included 14 relevant publications reporting on 10 non-interventional studies. The modest number of relevant studies (compared with the literature focusing on GFR alone) may reflect the relative recency of the publication of the KDIGO recommendations and the time required to perform and disseminate epidemiological studies. It may also suggest that the evaluation of albuminuria status remains limited. UACR testing is still not widely practised, due to lack of awareness and coordinated initiatives to encourage implementation in healthcare systems [36], and possibly lower practicality of urine- versus blood-based diagnostics. This is despite good evidence of its prognostic value. A 2010 meta-analysis, for example, revealed that the risk of all-cause and CVD-related death both increase as UACR rises, independent of GFR [37, 38].

The prevalence of CKD in a general population sample, stratified according to the KDIGO 2012 recommendations, was reported in seven out of ten studies from the USA, China and Italy. The overall prevalence of patients with GFR categories G3–5 ranged from 2% to 17%, echoing a previous report that the global

Total Combined

GFR categories (mL/min per 1.73m²)		Albuminuria (ACR) categories (mg/g) A1 <30	A2 30–300	A3 >300
G1	≥90	35.5–59.8	1.9–6.5	0.2–1.8
G2	60–89	24.8–51.4	2.2–5.6	0.3–1.3
G3a	45–59	1.04–7.84	0.1–2.21	0.05–0.89
G3b	30–44	0.14–2.48	0.02–1.6	0.01–0.63
G4	15–29	0.02–0.3	0–0.2	0.02–0.15
G5	<15	0–0.02	0–0.04	0–0.1

USA

GFR categories (mL/min per 1.73m²)		Albuminuria (ACR) categories (mg/g) A1 <30	A2 30–300	A3 >300
G1	≥90	35.5–57.3	1.9–3.5	0.2–0.5
G2	60–89	29.8–51.4	2.2–5.6	0.3–0.93
G3a	45–59	3.6–7.84	0.7–2.21	0.1–0.89
G3b	30–44	0.6–2.48	0.3–1.6	0.06–0.63
G4	15–29	0.13–0.3	0.1–0.2	0.1–0.15
G5	<15	0–0.02	0–0.04	0–0.1

Italy

GFR categories (mL/min per 1.73m²)		Albuminuria (ACR) categories (mg/g) A1 <30	A2 30–300	A3 >300
G1	≥90	59.8	6.5	1.8
G2	60–89	24.8	2.8	1.3
G3a	45–59	2.2	0.1	0.2
G3b	30–44	0.4	0.02	0.04
G4	15–29	0.02	0	0.04
G5	<15	0.02	0	0.02

China

GFR categories (mL/min per 1.73m²)		Albuminuria (ACR) categories (mg/g) A1 <30	A2 30–300	A3 >300
G1	≥90	57.6	4.4–4.9	0.3–0.5
G2	60–89	30.8	2.66–3.5	0.3–0.44
G3a	45–59	1.04–1.8	0.29–0.4	0.05–0.09
G3b	30–44	0.14–0.17	0.07–0.1	0.01–0.04
G4	15–29	0.1	0.03	0.02
G5	<15	0.02	0.01	0.01

Fig. 3 Prevalence of each KDIGO 2012 category in general population samples. Tables informed by seven studies (total combined), five studies (USA), one study (Italy), two studies (China). Note that the number of studies does not add up to seven as one study reported data for both USA and China. Numbers represent percentage of entire sample. Totals for each row and column are not presented as the highest prevalence in one category may not come from the same study as the highest prevalence in another category, which would misleadingly lead to a summation of values across categories to result in a range where the upper value appears to be > 100%. Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression. ACR albumin-to-creatinine ratio, GFR glomerular filtration rate, KDIGO Kidney Disease: Improving Global Outcomes

prevalence of CKD is 8–16% [3]. Prevalence was considerably higher in the USA than China or Italy, consistent with existing evidence [6].

The prevalence of normal albuminuria, moderately increased albuminuria and severely increased albuminuria (across GFR categories G2–5) was 27.4–56.4%, 2.9–10.0% and

France

GFR categories (mL/min per 1.73m²)		Albuminuria (ACR) categories (mg/g) A1	A2	A3		Missing ACR Data
		<30	30–299	300-1,999	≥2,000	
G2	60–89	0.9	0.5	0.2	0.1[a]	0.4
G3a	45–59	6.0	4.4	3.3	0.5	1.3
G3b	30–44	11.2	10.8	9.2	1.7	4.6
G4	15–29	6.1	11.5	14.8	4.1	4.4
G5	<15	0.2	0.7	1.7	0.9	0.6

Fig. 4 Prevalence of each KDIGO 2012 category in a cohort of patients with CKD. Data from Stengel 2019 [23]. [a]Patients considered to be at high risk of CKD progression by the KDIGO 2012 guidelines, but very high risk by Stengel 2019 [23]. Numbers represent percentage of entire sample. Green, low risk of disease progression; yellow, moderately increased risk of disease progression; orange, high risk of disease progression; red, very high risk of disease progression; grey, patients without ACR data. ACR albumin-to-creatinine ratio, CKD chronic kidney disease, GFR glomerular filtration rate, KDIGO Kidney Disease: Improving Global Outcomes

0.4–3.2%, respectively. Across GFR categories G2–5 and albuminuria categories A1–3, 3.7–13.4% of participants fell within the KDIGO 2012 moderate risk CKD, 0.9–5.6% within the high-risk group and 0.3–4.8% within the very high-risk group. These numbers are broadly consistent with those of a recent cross-sectional study that evaluated the global prevalence of CKD stratified by the KDIGO 2012 categories based on the results of general population CKD screening programmes performed in China, Mongolia, India, Nepal, Iran, Nigeria, Moldova and Bolivia [39]. Taken together, the data imply that a significant proportion of the general population may experience CKD progression and complications [9, 15, 16], minimising their quality-of-life and chances of survival, as well as imposing a substantial burden on healthcare resources [2, 11]. Measuring albuminuria also provides an additional insight in that the prevalence of those at high and very high risk of progression is lower than the prevalence if only accounting for GFR status [40].

Since this systematic review was conducted, two further articles have been published reporting the prevalence of the KDIGO 2012 albuminuria categories from the UK, Germany, France and USA [41, 42] (Table S6). The cohorts included patients with CKD, with a higher proportion of moderately and severely increased albuminuria compared with the general population cohorts included in this systematic review. The numbers mirror those of the one study included in this systematic review that recruited patients with CKD alone [23] (Fig. 4).

Very little information has been published on the prevalence of CKD risk factors and complications in patients stratified by the KDIGO 2012 categories; only three of the included studies reported such outcomes. From the scarce data available, diabetes, apparent treatment-resistant hypertension and atherosclerotic CVD [28, 32, 33] were found to be more prevalent with increasing albuminuria severity. Further epidemiological studies are needed to confirm and expand on these initial findings, but they are consistent with evidence that albuminuria heralds CKD progression and complications [9, 15, 16, 37, 38]. These data highlight the need for the screening of both GFR and albuminuria status in populations at risk for CKD, particularly those with diabetes or hypertension, and for the regular monitoring of individuals with CKD [3, 12, 25, 43].

A notable strength of the included data is that CKD was classified according to clinical tests in every study rather than administrative codes, providing a robust appraisal of kidney function. Study quality was judged to be high in four out of ten included studies (see supplementary data and Table S5). Within the remaining six studies, some risk of bias was recognised as a result of missing methodological information but this was judged as low and unlikely to threaten internal or external data validity.

No evidence regarding the incidence of CKD, CVD complications, or CVD-related or all-cause mortality according to the KDIGO 2012 categories was identified. Moreover, data on the prevalence of CKD risk factors and complications according to albuminuria status were only obtained from studies of specific high-risk groups (i.e. CKD or hypertensive patient cohorts), which represents a major data gap to be addressed by future longitudinal studies to more completely and accurately assess CKD burden and outcomes.

We aimed to provide an overview of the uptake of the KDIGO 2012 guidelines and volume of evidence available on CKD epidemiology according to the GFR and albuminuria categories. As such, a meta-analysis was beyond the scope of this work, and the review is limited to a qualitative summary and description of the results as reported in the individual studies. To aim to provide a multinational overview in a sample of countries likely to have the highest uptake of the KDIGO guidelines, the review focused on studies performed in the USA, China or EU5 countries. As such, the results may not fully represent the international epidemiological burden of CKD, given the strong USA focus of the data and previous evidence that prevalence varies by race/ethnicity [44, 45] and geographical location [2, 6]. However, as a result of the consistent estimates reported in the studies that were identified, it is expected that these values would be fairly generalisable to other countries.

Along with further observational studies to address the current data gaps in CKD prevalence and overlapping comorbidities according to albuminuria status in general population cohorts, useful future work would include a comprehensive review that expanded the included countries to all countries and languages with published data on the epidemiology of CKD according to the KDIGO 2012 guidelines. Associations between CKD prevalence and country-specific parameters including healthcare spending and economic climate could also be useful to explore within this.

CONCLUSIONS

This systematic review identified ten studies with outcomes stratified according to GFR and albuminuria status, consistent with the KDIGO 2012 recommendations. These studies reveal that a substantial proportion of the general population have CKD, which has important implications for adverse complications, health-related quality-of-life, survival, and healthcare resource planning and utilisation. While CKD is common, a small proportion of patients have severely increased albuminuria or fall within the KDIGO high- or very high-risk groups. These groups, however, have a high presence of diabetes, CVD and hypertension, especially with higher degrees of albuminuria. As such, testing for albuminuria is valuable for CKD prognosis and management. There is also a need for comprehensive longitudinal studies to address key gaps (incidence of CKD, complications, CVD and mortality according to the KDIGO classification) in understanding the burden and outcomes of CKD defined by KDIGO 2012 recommendations.

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