

Prevalence of Chronic Kidney Disease in Asia: A Systematic Review of Population-Based Studies

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ABSTRACT

Chronic kidney disease (CKD) is an asymptomatic disease associated with high morbidity and life-threatening complications that lead to decreased life expectancy. Worldwide prevalence of CKD is escalating at an alarming rate. Large population-based representative surveys have been reported in Western countries to estimate the prevalence of the disease. However, there is paucity of data as far as developing nations are concerned. Asia is the world's largest continent accommodating maximum number of under-developed and developing countries with an unclear picture of prevalence of CKD. Current review attempts to give an insight to the prevalence of CKD in this region by combining population-based surveys. This review will assist in estimating the burden of CKD in Asia, so that appropriate control measures could be designed.

Key Words: Prevalence, Chronic kidney disease, Asia, Cockcroft-Gault formula, MDRD formula, Renal function equations.

INTRODUCTION

Chronic kidney disease (CKD) is a general term that is used to describe a number of medical complications effecting morphological structure and physiological function of the kidney. The disease progresses slowly over months or even years and symptoms do not appear until kidney function becomes one-tenth of normal or kidney failure is imminent.¹ Being asymptomatic, the disease manifests itself with a variety of non-specific symptoms. Due to silent progressive nature of disease, its diagnosis remains neglected until it reaches end-stage renal disease (ESRD), where routine dialysis or kidney transplantation is the only cure for survival. It is well-documented that ESRD is associated with increased mortality, decreased patient quality of life and extremely high risk of comorbidities such as hypertension, diabetic nephropathy, anemia and cardiovascular complications.² Early detection of CKD is crucial as both pharmacological and non-pharmacological interventions are likely to be less effective if disease progresses to advanced stages.^{3,4} Moreover, early detection of disease helps to prevent or at least delay disease progression and to reduce associated

complications. According to American Heart Association (AHA), CKD is an independent and most crucial risk factor for subsequent cardiovascular complications.^{2,5}

Currently, CKD is affecting 10-16% of adult population around the globe. Worldwide prevalence of disease is escalating with kidney diseases being 9th leading cause of death in United States causing total expenditure of more than 47.5 billion dollars in 2010.^{6,7} Annually, there are more than 100 million deaths due to lack of provision of renal replacement therapy (RRT) as a result of ESRD. The prevalence of CKD in Asia varies from 10-18%, which is not much different from other parts of the world. However, due to paucity of data in most Asian countries, the exact burden and cost associated with disease is still not clear.⁸ Due to the limited availability of resources, particularly in Asia, where most of the countries are still underdeveloped or developing, the increased prevalence of disease puts a large burden on healthcare systems and affects patients' quality of life.

Assessment of kidney function, *i.e.* glomerular filtration rate (GFR) is extremely crucial for the diagnosis and staging of kidney disease.¹ Moreover, many clinical procedures and predictive equations are also being used to assess renal function and to determine the extent of kidney dysfunction.^{9,10} However, National Kidney Foundation (NKF) recommends the use of renal function predictive equations to assess eGFR rather than direct measurement of GFR.^{11,12}

The current review aims to shed light on the prevalence of CKD in Asian countries by reviewing relevant population-based research studies on prevalence of CKD using renal function predictive equations among Asian populations.

METHODOLOGY

A systematic literature review was conducted to find out relevant studies (research and review articles) since

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2000. PubMed database, Google Scholar, and Ebscohost were used to identify potential publications. The search strategies were designed with the help of librarian; and two researchers independently reviewed and discussed relevant publications. Cross-references were also checked to identify further related publications. Following keywords were used to retrieve data: Asia, chronic renal/ kidney disease, Cockcroft-Gault formula, glomerular filtration rate, GFR, MDRD equation, prevalence, renal/kidney disease, respective names of Asians countries.

Inclusion criteria: A prospective protocol was designed by researchers for selection of studies explaining prevalence of CKD among Asian population. Studies were eligible to be included when they met following criteria: conducted among representative sample of general population; CKD was defined as creatinine clearance CrCl or GFR > 60 ml/min/1.73 m²; and use of renal function predictive equation to calculate eGFR: Cockcroft-Gault equation, MDRD equation (standardized for BSA *i.e.* body surface area), CKD-EPI equation included CG formula: creatinine clearance (ml/min) = $\{(140 - \text{age}) * \text{serum creatinine} * \text{body weight (kg)}\} / 72 * (0.85 \text{ if patient is female})$; MDRD equation: $\text{GFR/ml/min/1.73 m}^2 = 186 * (\text{serum creatinine})^{-1.154} * (\text{age})^{-0.023} * (0.742 \text{ if patient is female})$; and CKD-EPI equation: $\text{eGFR} = 141 * \min(\text{serum creatinine}/k, 1)^a * \max(\text{serum creatinine}/k, 1)^{-1.209} * 0.993 \text{ age} * [1.018 \text{ if female}] * [1.159 \text{ if Black}]$, where k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum, max indicates the maximum.

Exclusion criteria: Studies were not included in this review if they met any of following criteria: sample size of less than 100; language other than English; estimation of GFR by methods other than renal function predictive equations, full text is not available; and case control studies and meta-analyses.

Validity of selected data: Factors that can influence validity of studies were carefully studied and noted. In order to avoid repetition of data, multiple publications on the same topic, and same authors or group of authors were separated. These multiple publications were then screened individually and compared with each other before final inclusion of any study in this review.

Data extracted: The information extracted from each study for this review included study design, characteristics of study participants, sample size, duration and method used to estimate prevalence, and overall prevalence of CKD among investigated population.

Definition of kidney function: Renal function predictive equations based on serum creatinine, age, weight and/or race were used to determine kidney function. Here CKD was defined on the basis of definition published by NKF: Creatinine clearance or GFR less

than 60 ml/min/1.73 m² where 1.73 m² is the value for body surface area (BSA). All the studies included in this review expressed serum creatinine in mg/dl, weight in kg, age in years, and GFR on ml/min/1.73m².¹²

RESULTS

Literature search was undertaken to retrieve publications of potential interest. Initially, 93 publications were retrieved, of which 50 were excluded due to failure to fulfill the inclusion criteria. As a result of initial screening, 43 selected publications were subjected to detailed evaluation and 25 studies corresponding to the inclusion criteria were included in the review (Figure 1).

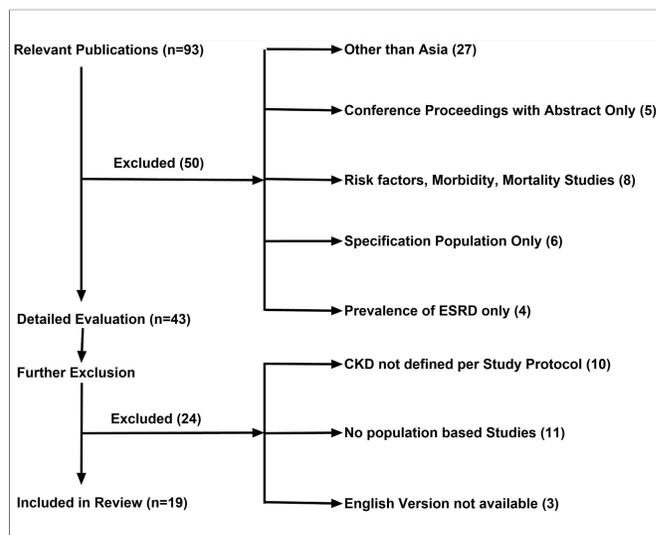


Figure 1: Flowchart summarising literature review.

General characteristics: All the studies included in this review are summarised according to location of respective country in different regions of Asia (Table I). Out of 25 studies included in the current review, seven studies were from South Asia, seven from East Asia, three from West Asia, and eight studies were from South-East Asia. Unfortunately, we did not come across any study from Central Asian regions including Tajikistan, Turkmenistan and Afghanistan.

Out of 25 extracted studies, 20 studies were cross-sectional, while 5 studies used cohort study design.¹³⁻¹⁷ Out of 20 studies using cross-sectional data in this review, two studies included data from respective National Health Surveys,^{15,18} out of which one study has used data from National Health and Nutrition Examination Survey but with four different time periods *i.e.* 1998, 2001, 2005, 2009,¹⁵ while Hooi *et al.* took data from National Health and Morbidity Survey.¹⁸ The number of participants ranged from 293 to 33,276,^{15,19} except for one study, all the participants had age ≥ 18 years.²⁰

Renal function predictive equations and prevalence of CKD: Overall, the prevalence of CKD was assessed *via* MDRD equation in most studies followed by CKD-

Table I: Prevalence of chronic kidney disease in Asia according to population-based studies.

Authors	Country	Study design, No. of participants	Participants' characteristics	Overall prevalence of CKD
Varma <i>et al.</i> 2010 ²¹	India (South Asia)	Cross sectional survey, n=3398	66% male, age above 18 years	3.02% with MDRD formula
Singh <i>et al.</i> 2013 ¹³	India (South Asia)	Prospective cohort study, n= 5588	55% male, age range of 18-98 years	5.09% with MDRD formula
Huda <i>et al.</i> 2012 ²⁰	Bangladesh (South Asia)	Cross sectional survey, n=1000	33% male, age range of 15-65 years	13.1% with MDRD 16% with CG formula
Anand <i>et al.</i> 2014 ²²	Bangladesh (South Asia)	Cross-sectional survey, n= 357	51% men with age >30 years	26% with CKD-EPI
Jessani <i>et al.</i> 2014 ²³	Pakistan (South Asia)	Cross-sectional survey n=2873	52.2% female, Age 40 years and above	12.5% with CKD-EPI formula
Imran <i>et al.</i> 2015 ¹⁹	Pakistan (South Asia)	Cross-sectional survey by arranging health campus n=293	64.5% male, age 30 years and above	25% with CKD-EPI formula
Sharma <i>et al.</i> 2013 ²⁴	Nepal (South Asia)	Community-based screening with proportionate stratification, n=1000	48% male, 52% female with age range of 20-60 years	6.3% with MDRD
Chen <i>et al.</i> 2005 ²⁵	China (East Asia)	Cross-sectional survey with random sampling, n=15540	48 % male, 52% female with age range of 35-74 years	2.5% with MDRD equation
Li <i>et al.</i> 2006 ²⁶	China (East Asia)	Community based cross-sectional survey, n=2310	49% male, 51 % female with age 40 years and above	4.9% with MDRD equation
Zhang <i>et al.</i> 2008 ²⁷	China (East Asia)	Cross-sectional survey with systematic sampling, n=13,925	Male to female ratio 1:18:1 with age range of 18 - less than 70 years	13% with MDRD equation
Ninomiya <i>et al.</i> 2005 ¹⁴	Japan (East Asia)	Prospective cohort study, n=2634	42% male, 58% female with age 40 years and above	10.3% with MDRD equation
Konta <i>et al.</i> 2006 ²⁸	Japan (East Asia)	Cross-sectional survey, n2321	44% male, 56% female with age above 40 years	28.8% with CG equation
Yi <i>et al.</i> 2010 ²⁹	Mongolia (East Asia)	Cross-sectional survey, n=4522	50% male, 50 % female with mean age of 50.3+14.3 years	12.95% with MDRD equation
Kang <i>et al.</i> 2013 ¹⁵	Korea (East Asia)	Prospective cohort survey (KNHANES) with sampling weight method, n=33276	43% men, 57% female with age above 20 years	With MDRD equation 1998: 10.3% 2001: 18.2% 2005: 17.4% 2009: 10.8 %
Hosseinpah <i>et al.</i> 2009 ¹⁶	Iran (West Asia)	Cross-sectional study with TLGS cohort, n=10063	42% male, 58 % female with age over 20 years	18.9% with MDRD equation
Sahin <i>et al.</i> 2009 ³⁰	Turkey (West Asia)	Cross-sectional study, n=1079	49% male, 51% female with age range of 18 to 95 years	5.75% with MDRD equation
Alsuwaida <i>et al.</i> 2010 ³¹	Saudi Arabia (West Asia)	Pilot community based screening, n= 491	50% male, 50% female with mean age of 37.4+ 1.3	5.7% with MDRD 5.3% with CG equation
Perkovic <i>et al.</i> 2007 ³²	Thailand (South-East Asia)	Cross-sectional survey with stratified cluster sampling, n=5146	49% male, age range of 35- over 65	13.81% with MDRD 21.04% with CG equation
Domrongkitchaiporn <i>et al.</i> 2005 ³³	Thailand (South-East Asia)	Cross-sectional study n= 2967	76% male age range of 35-55 years	6.8% with MDRD equation
Shankar <i>et al.</i> 2008 ³⁴	Singapore (South-East Asia)	Cross-sectional survey with local Malay adults n=2783	47% male, 53% female with age range of 49-80 years	20.4% with MDRD equation
Sabanayagam <i>et al.</i> 2010 ³⁵	Singapore (South East Asia)	Cross-sectional survey, n=4499	48% male, 52% female with age range of 24-95 years	5.5% with MDRD equation
Prodjosudjadi <i>et al.</i> 2009 ³⁶	Indonesia (South-East Asia)	Community-based prospective survey, n=9412	36% male, 64% female	12.5% with CG 8.6 % with MDRD
Tennille <i>et al.</i> 2013 ¹⁷	Philippines (South-East Asia)	Cohort survey (NNHeS) with stratified multi-stage cluster sampling, n=7702	With age range of 20 - 70 years	6.7 % with CKD-EPI formula
Ito <i>et al.</i> 2008 ³⁷	Vietnam (South-East Asia)	Prospective community-based survey with random sampling, n=8504	35% male, 75% female with age 40 years and above	3.1% with CG 3.6% with MDRD adjusted with Japanese co-efficient
Hooi <i>et al.</i> 2013 ¹⁸	West Malaysia (South-East Asia)	876 individuals from the National Health and Morbidity Survey	Adult (18 years and above)	9.07 with CKD-EPI formula

EPI equation while only two studies used CG equation.^{17,28} Five studies used both MDRD and CG equation.^{20,31,32,36,37} Studies that used both MDRD and CG equation, the prevalence of CKD was notably higher with CG equation as compared to MDRD equation. Study conducted by Ninomiya *et al.* reported prevalence of CKD in Japan as 10.3% with MDRD equation while one year later another study conducted elsewhere in Japan reported prevalence of CKD as 28.8% with CG equation.^{14,28} Both these studies were conducted with participants above 40 years and with almost similar sample size, *i.e.* 2,634 *versus* 2,321. The much higher reported difference in prevalence of CKD in similar population belonging to same geographical area leads to confusing results. Although we cannot compare

both studies directly because both studies used different set of population as participants but still as the characteristics of population matches; therefore, such remarkable difference of 18.5% seems unacceptable.

Age and prevalence of CKD: Nine studies included in this review assessed prevalence of CKD with respect to participants' age.^{13,15,16,21,24-27,32,34,36} In general, prevalence of CKD increased with age within same study population. For instance, the prevalence of CKD from the fourth Korean National Health and Nutrition Examination Survey (KNHANES), a prospective cohort survey representing general population of Korea, increased from 2% to 12.7% from age group 20-39 years to above 60 years.¹⁵ Trends in prevalence of CKD with respect to age are shown in Figure 2.

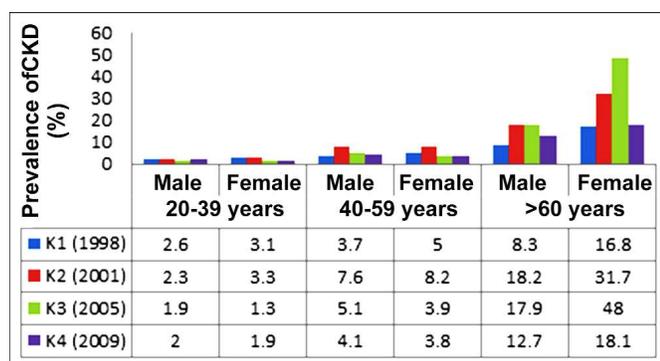


Figure 2: Trends in prevalence of CKD with respect to age in KNHANES.

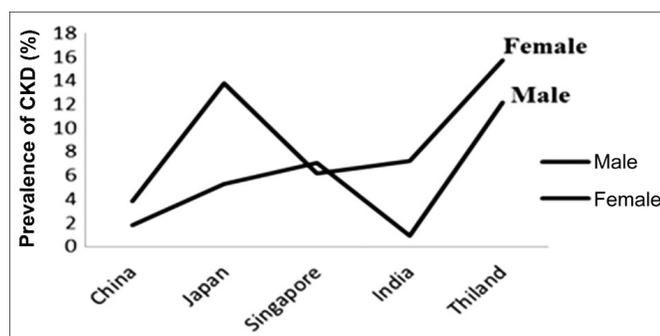


Figure 3: Trends in prevalence of CKD with respect to gender.

Gender and prevalence of CKD: CKD was more prevalent among women as compared to men. Higher prevalence of CKD among women was reported in all studies that had presented gender-specific prevalence of disease.^{15,16,21,25,26,32,36} Varma *et al.* reported remarkably higher prevalence of CKD among women as compared to men (7.23% versus 0.94%).²¹ Gender specific prevalence of CKD among different studies of this review is shown in Figure 3.

Geographical location and prevalence of CKD: Asia is the largest and the most populous continent of the world. The studies included in this review belonged to four different geographical locations in Asia. Based on the use of renal function predictive equation, highest prevalence of CKD was observed in Japan (28.8%) and Bangladesh (20.8%) by CG and CKD-EPI equation respectively.^{22,28} On the other hand, lowest prevalence of CKD was reported in Vietnam (3.1%) and India (3.02%) with CG and MDRD equation respectively.^{21,37}

DISCUSSION

Current systematic review attempts to summarise prevalence of CKD in Asia by including population-based research studies in Asia that used renal function predictive equation and standardised definition of CKD. In general, the prevalence of CKD increased with age and was more prevalent among females. Moreover, the predicted prevalence of CKD was much higher with CG equation as compared to MDRD equation. As far as

accuracy of renal function predictive equations is concerned, it is still a controversial issue. Most studies prefer MDRD over CG equation, while some studies still prefer CG equation. However, as both equations were derived from population cohort already having CKD; therefore, these equations tend to underestimate or overestimate kidney function in individuals with normal or slightly decreased kidney function. Furthermore, both equations use serum creatinine value for calculation of GFR that itself is the biggest limitation since creatinine production is effected by diet, diseases as well as certain pharmacological therapies.^{38,39} Based on NKF-KDOQI guidelines, the use of CKD-EPI equation is recommended for estimation of GFR. As compared to MDRD equation, CKD-EPI offers better sensitivity below eGFR <60 ml/min/1.73 m² and same accuracy and sensitivity as MDRD equation for eGFR >60 ml/min/ 1.73 m². Majority of the studies in current review have used MDRD equation to estimate prevalence of CKD, as MDRD equation was developed in 1999, while CKD-EPI equation was developed almost after a decade in 2009, and was adapted for use in clinical practice later.

Results of current review showed that regardless of the renal function predictive equation used and cohort under observation, prevalence of CKD increases with age. Similar results were documented in other globally (U.S, Europe) conducted studies.^{40,41} O'Hare *et al.* reported the age specific incidence of death and ESRD over a follow-up of 3 years. A total of 9,227 (4.4%) patients developed ESRD, 45,772 (21.8%) patients died before ESRD and 2,925 (1.4%) died after initiating ESRD. Irrespective of baseline eGFR, authors reported a higher risk of death with old age with almost triple risk of death with age >65 years as compared to age <45 years and lowest risk of ESRD with young age with almost double risk of ESRD with age <45 years as compared to age >65 years.⁴² In a longitudinal observational study, 3,047 patients with CKD stage 3 were followed-up for 10 years to investigate prognosis of CKD. A total of 959 (31%) patients died and 62 (2%) died at the end of observation period. Authors reported that a 10 year increment in age is associated with 2.28 HR (p<0.001) of death while a 0.75 HR (p-value: 0.0009) of incident ESRD.⁴³ Similar results have been reported by a retrospective analysis of large sample of multi-ethnic (White, South-Asians, Black, others) population.⁴⁴ It is a well-documented fact that, regardless of gender, glomerular filtration rate (GFR) decreases 1ml/min/1.73 m² in all healthy individuals after 30 years of age.^{45,46} Decline in kidney function might also be attributed to structural changes in kidney as a result of aging and presence of comorbidities. Moreover, the risk of developing CKD increases with advance age because other risk factors (hypertension, diabetes) for kidney disease are more prevalent in old people. Ageing is a non-regulatory risk factor for development of CKD that is positively

associated with arterial atherosclerotic change.²⁵ All these factors lead to decrease kidney function in elderly and explain high prevalence of CKD in elderly as compared to adults among which kidney function remains stable after infancy until late adulthood.⁴⁷

Another demographic factor that showed strong association with prevalence of CKD was gender, with CKD being more prevalent among females. The reason for this increase prevalence in females can be explained by two reasons. Firstly, creatinine that is determinant of kidney function (GFR) depends on muscle mass. Females have less muscle mass as compared to males and ultimately less creatinine that explains high prevalence among females because current renal function predictive equations use serum creatinine values to estimate GFR.⁴⁸ Also, these equations include a correction factor for females (0.85 for CG & 0.742 for MDRD). An inaccurate correction factor may also lead to over estimation of prevalence rate among females. Moreover, structure of glomerulus, hormonal balance and metabolic rate of females is different from males.⁴⁹

The results of the review showed that the highest prevalence of CKD is estimated to be in Japanese population. Apart from increase in life expectancy, there are various genetic (short stature, low muscle mass, low nephron number, increase survival of CVD patients), environmental (high salt intake, obesity, metabolic syndrome) and social factors (luxury acceptance for dialysis) that put Japanese population at higher risk of CKD and subsequent risk of ESRD.⁵⁰

Limitations: Although efforts were made to give an unbiased overview of prevalence of CKD in Asia, but the prevalence rate depicted in this review might be underestimated or overestimated as presence of comorbidities and risk factors were not included in this review. Moreover, biomarkers (proteinuria, albuminuria) for assessing kidney damage were not considered. Due to heterogeneity of data, it was not possible to include all above mentioned factors. We were unable to find studies with mentioned inclusion criteria in many countries of this region such as Sri Lanka, Jordan, Syria, Kuwait and Afghanistan etc. Most of the studies in these countries calculated prevalence of CKD by estimating creatinine clearance via 24-hour urine collection; therefore, such studies were not included.

CONCLUSION

Currently, both researchers and clinicians are facing challenges in detecting and managing CKD in Asian countries due to limited availability of resources and paucity of health data on national level. Furthermore, disparities in prevalence of CKD owing to different predictive equation further necessitates need of national health registries (NRRs) for early stages of CKD and a uniform criteria to estimate burden of disease. The first

and foremost step in addressing this challenge involves development of NRRs for maintaining record of population health data by conducting extensive population-based studied on national level. This would ultimately help to record extent of disease prevalence and would help to control disease by designing and implementing relevant strategies.

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