PROGNOSIS OF NON-DIALYSIS DEPENDENT (NDD) CHRONIC KIDNEY DISEASE (CKD) PATIENTS AND OUTCOMES OF DIURETIC THERAPY BY USING BIOIMPEDANCE SPECTROSCOPY

by

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LIST OF ABBREVIATIONS

AASK	African American study of kidney disease and hypertension
ACEI	Angiotensin converting enzyme inhibitors
ACR	Albumin creatinine ratio
AER	Albumin excretion rate
AIPRD	ACE inhibition in Progressive Renal disease
ALLHAT	Anti-hypertensive and lipid lowering treatment to prevent heart attack
ARBs	Angiotensin receptor blockers
ARIC	Atherosclerosis Risk in Communities study
BB	Beta blockers
BCM	Body composition monitor
BIA	Bioimpedence analysis
BIS	Bioimpedance spectroscopy
BMI	Body mass index
BNP	brain natriuretic peptide
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
Ca	Calcium
CAD	Coronary artery disease
CAD	Coronary artery disease
CCB	Calcium channel blockers
CG	Cockroft and Gault
CHD	Congestive heart disease

CHEP	Canadian Hypertension Education Program
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	chronic kidney diseas-epidemiology
CKD-MBD	Chronic kidney disease associated mineral and bone disorder
CPP	Calcium phosphate prodcut
Cr Cl	creatinine clearance
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECF	Extracellular fluid
ECW	Extracellular water
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
FBS	Fasting blood sugar
Fe	Female
FGF	Fibroblast growth factor
FMT	Fluid management tool
FO	Fluid overload
FTI	Fat tissue index
GFR	Glomerular filtration rate
HF	Heart failure

HIV	Human immunodeficiency virus
HR	Hazard ratio
HRP	Hydration reference plot
HS	Hydration status
HUNT II	Second health survey of Nord-Trondelag
HUSM	Hospital Universiti Sains Malaysia
ICW	Intracellular water
IHD	Ischemic heart disease
INSIGHT	Intervention as a goal in hypertensive treatment
IQR	Inter quartile range
IVC	Inferior venacava
JEPeM	Jawatankuasa Etika Penyelidikan-Manusia
JNC	Joint National Committee
K	Potassium
KDOQI	Kidney Disease Outcome Quality Initiative
L	Liter
LDL	Low density lipoprotein
LTI	Lean tissue index
LVH	left ventricular hypertrophy
MDRD	Modification of diet in renal disease
MDTR	Malaysian dialysis and transplant registry
MI	Myocardial infarction
MICS	malnutrition-inflammation complex syndrome
MRFIT	Multiple Risk Factor Intervention Trial

Na	Sodium
Nacl	Sodium chloride
ND	Non-dialysis
NDD-CKD	non-dialysis dependent chronic kidney disease
NHANES	National health and nutrition examination survey
NICE	National Institute of Health and Clinical Excellence
NKF	National kidney foundation
NRR	National renal registry
NT-pro BNP	N-terminal pro brain natriuretic peptide
OH	Overhydration
OSA	Obstructive sleep apnea
OSA	obstructive sleep apnea
PCKD	Poly cystic kidney disease
PREVEND	Prevention of Renal and Vascular Endstage Disease
PSGN	post strepto-coccal glomerulonephritis
PWV	Pulse wave velocity
R	Correlation coefficent
RAAS	Renin angiotensin aldosterone system
RCT	Randomized controlled trial
RENAAL	Reduction of End points in Non-insulin dependent Diabetes Mellitus
RR	Relative risk
RRT	renal replacement therapy
SBP	Systolic blood pressure
Scr	serum creatinine

SD	Standard deviation
SHEP	Systolic hypertension in elderly program
SLE	systemic lupus erythematosus
Syst-Eur	Systolic hypertension in Europe
TABLE	Target Blood pressure level
TIN	Tubulointerstitial nephritis
TBW	Total body water
UO	Urine output
US	United States
USRDS	United States Renal Data System
WHO	World Health organization

PROGNOSIS PESAKIT-PESAKIT PENYAKIT GINJAL KRONIK (CKD) YANG TAK-BERGANTUNGAN DIALISIS (NDD) DAN HASIL TERAPI DIURETIK MELALUI SPEKTROSKOPI BIOIMPEDANS

ABSTRAK

Penyakit ginjal kronik (CKD) merupakan masalah kesihatan global yang mempengaruhi 10% daripada populasi dunia. Walaupun terdapat peningkatan insiden penyakit renal tahap akhir (ESRD) di Malaysia, tiada catatan mengenai kelaziman dan juga hasil pemeriksaan daripada peringkat pra-dialisis CKD. Tambahan pula, sorotan kajian awal menunjukkan peranan diuretik masih kontroversi dan beban bendalir berlebihan dalam progresi CKD. Oleh itu, satu kajian dua fasa telah dijalankan untuk menilai prognosis pesakit-pesakit CKD yang tidak bergantung pada dialisis (NDD) secara retrospektif manakala tahap kemerosotan buah pinggang dengan terapi diuretik dan hubungan antara diuretik dan beban bendalir berlebihan diperhatikan secara prospektif. Dalam fasa retrospektif, sejumlah 621 pesakit dengan anggaran kadar penapisan glomerular (eGFR) pada 15-59 ml / min / 1.73m2 (tahap CKD 3 & 4) telah dipilih dan di ikuti untuk tempoh 10 tahun atau sehingga ESRD atau kematian, yang mana terlebih dahulu berlaku. Perkembangan keseluruhan penyakit diperhatikan dalam 372 (60%) pesakit, manakala 113 (18%) pesakit telah meninggal dunia. Dalam kalangan pesakit dengan tahap 3 CKD, 21% telah berkembang ke tahap 4, 10% telah berkembang ke tahap 5ND (tidak dialisis) dan 31% untuk terapi penggantian buah pinggang (RRT) manakala kematian diperhatikan pada 16% pesakit. Sementara itu, 8% pesakit dengan tahap 4 CKD berkembang ke tahap 5ND, 31% kepada RRT dan kematian diperhatikan dalam 24% kes. Pesakit dengan penyakit kardiovaskular (CVD), tekanan darah sistolik lebih

tinggi, tahap fosfat tinggi, proteinuria berat, hematuria mikroskopik dan penggunaan diuretik lebih cenderung mengalami ESRD. Pada awalnya (apabila pesakit-pesakit dipilih), peningkatan usia, eGFR rendah, tekanan darah sistolik rendah, hemoglobin rendah dan kencing manis merupakan peramal-peramal penting bagi mortaliti manakala wanita telah didapati dapat megurangkan risiko mortaliti. Dalam fasa prospektif, sejumlah 312 pesakit NDD-CKD telah disusuli selama satu tahun. Beban bendalir berlebihan telah dinilai melalui spektroskopi bioimpedans (BIS). Sejumlah 144 subjek diprekripsikan dengan diuretik. Penggunaan diuretik telah dikaitkan secara ketara dengan penurunan eGFR dalam setiap kategori status bendalir dengan penurunan maksimum diperhatikan pada pesakit hipervolemik (-5.1 ± 2.1 ml / min / 1.73m2) yang menggunakan diuretik gabungan. Sejumlah 36 (11.5%) pesakit telah memulakan RRT manakala 2 (0.64%) kes kematian telah diperhatikan pada akhir susulan. Selain itu, telah diperhatikan bahawa utilisasi diuretik adalah rendah kalangan pesakit hipervolemik manakala lebih preskripsi diuretik diperhatikan pada pesakit-pesakit bukan hipertensi yang euvolemik dan hipovolemik. Kesimpulannya, penemuan terkini menunjukkan bahawa pesakit lebih cenderung kepada ESRD daripada kematian. Kepentingan utama harus diberikan kepada peringkat CKD yang sederhana bagi melambatkan malah mungkin dapat membalikkan perkembangan CKD. Berkenaan dengan penggunaan diuretik, dicadangkan bahawa ia adalah sebagai prediktor bagi hasil advers terhadap ginjal. Spektroskopi Bioimpedans (BIS) berupaya membantu para penjagaan kesihatan profesiona-profesional penjagaan kesihatan untuk mengenal pasti pesakit-pesakit CKD dengan bebanan bendalir berlebihan dan memberikan farmakoterapi individu mengikut keperluan-keperluan klinikal pesakit.

PROGNOSIS OF NON-DIALYSIS DEPENDENT (NDD) CHRONIC KIDNEY DISEASE (CKD) PATIENTS AND OUTCOMES OF DIURETIC THERAPY BY USING BIOIMPEDANCE SPECTROSCOPY

ABSTRACT

Chronic kidney disease (CKD) is a global health concern effecting 10% of world population. Despite escalating incidence of ESRD in Malaysia, there is no record about prevalence as well as outcomes of pre-dialysis stages of CKD. Moreover, preliminary literature search showed controversial role of diuretics and fluid overload in CKD progression. Therefore, a two phase study was conducted to evaluate prognosis of non-dialysis dependent (NDD) CKD patients retrospectively while the extent of renal deterioration with diuretic therapy and relationship between diuretics and fluid overload was observed during prospective phase of the study. In the retrospective phase, a total of 621 patients with estimated glomerular filtration rate (eGFR) of 15-59ml/min/1.73m^2 (CKD stage 3 & 4) were selected and followed up for 10 years or until ESRD or death, whichever occurred first. Overall disease progression was observed in 372 (60%) patients while 113 (18%) patient died. With respect to CKD staging, both mortality and progression to stage 5ND was more prevalent in CKD stage 4 patients. Among patients with CKD stage 3, 21% progressed to stage 4, 10% to stage 5ND (non-dialysis) and 31% to renal replacement therapy (RRT) while mortality was observed in 16% patients. On the other hand, 8% patients with CKD stage 4 progressed to stage 5ND, 31% to RRT and mortality was observed in 24% cases. Patients with cardiovascular disease (CVD), higher systolic blood pressure, elevated phosphate levels, heavy proteinuria, microscopic hematuria and use of diuretics were more likely to develop ESRD. At

baseline (when patients were enrolled), advance age, low eGFR, low systolic blood pressure, low hemoglobin and diabetes were found to be significant predictors of mortality while female gender reduced risk of mortality. In the prospective phase, a total 312 NDD-CKD patients were followed-up for one year. Fluid overload was assessed via Bioimpedance spectroscopy (BIS). A total of 144 subjects were prescribed with diuretics. Diuretics use was significantly associated with decline in eGFR within each category of fluid status with maximum decline observed in hypervolemic patients (-5.1±2.1 ml/min/1.73m^2) using combination diuretics. A total of 36 (11.5%) patients initiated RRT while 2 (0.64%) mortal cases were observed at the end of follow-up. Moreover, underutilization of diuretics was observed in hypervolemic patients while more diuretic prescriptions were noted in euvolemic and hypovolemic non-hypertensive patients. In conclusion, current findings suggest that patients are more likely to develop ESRD than death. Prime importance should be given to mild forms of CKD to retard and even reverse CKD progression. With respect to diuretic use, it is cautiously suggested that diuretic use is an independent predictor of adverse renal outcomes. Bioimpedance spectroscopy can aid health care professionals to identify CKD patients with fluid overload and provide individualized pharmacotherapy according to patient clinical needs.

CHAPTER 1

GENERAL INTRODUCTION

1.1 Background

Chronic kidney disease (CKD) is a general term used to describe heterogeneous disorders affecting structure and function of kidneys (Levey & Coresh, 2012). 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 with total expenditure of more than 47.5 billion dollars in 2010 (Kearns *et al.,* 2013; Coresh *et al.,* 2007). Globally, more than 100 countries (combined population >1 billion) have no facilities for RRT, attributing to more than 1 million annual deaths due to end stage renal disease (Ojo, 2014).

According to 22nd report of Malaysian dialysis and transplant registry (MDTR), the number of patients initiating dialysis as a mode of RRT has sharply increased from 6702 in 2000 to 31,637 in 2013 resulting in a serious economic burden on health resources. The incidence of ESRD is escalating in Malaysia yet there is no record about prevalence as well as incidence of pre-dialysis stages of CKD. Based on one population based study in West Malaysia, the prevalence of CKD is estimated to be 11.09 % which means that approximately 3.3 million of Malaysian population is at risk of developing ESRD (Hooi *et al.,* 2013). Although the results of this study needs confirmation by epidemiological data, still due to absence of latter, this population based study gives rough estimation. The alarming high incidence of ESRD is attributed to high incidence of diabetic kidney disease that accounts for 58% of new ESRD patients, the highest incidence of diabetics undergoing ESRD (Huri *et al.,* 2015).

Nearly fifteen years ago, kidney failure was considered as a public health concern due to its increasing incidence, poor outcomes and high cost. The rationale for global initiative to address increasing issues of kidney failure becomes evident with a substantially higher number of kidney disease patients with cardiovascular disease and premature death before reaching kidney failure (Levey *et al.,* 2005). Due to lack of consensus of definition to categorize such patients in terms of disease severity and paucity of clinical trials in field of nephrology, many initiatives were taken to improve the outcomes and care of CKD patients before reaching kidney failure (Eckardt & Kasiske, 2009). The first and foremost step was to define disease severity and classify CKD patients in different levels of risk to ensure appropriate treatment and prevention of disease progression towards kidney failure.

1.2 Definition

In 2002, National kidney foundation (NKF) has proposed an evidence based definition of CKD in their Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines (Levey *et al.,* 2003). According to these guidelines, the definition of CKD is based on three parameters; kidney damage, kidney function and time frame. In this definition, glomerular filtration rate (GFR) is used as a measure of kidney function. The normal value of GFR is approximately 120-130 ml/min/1.73m^2 in healthy adult. The definition of CKD has used a cut-off value of GFR<60ml/min/1.73m^2 to define loss of kidney function as this value represents loss of approximately more than half of normal adult kidney function (Assiago *et al.,* 2009).

CKD is defined as kidney damage for ≥3 months as manifested by structural or functional abnormalities of the kidney with or without decreased GFR or GFR<60ml/min/1.73m^2 for ≥ 3 months, with or without kidney damage (Levey *et al.,* 2005). The definition of CKD according to KDOQI guidelines is summarized in Table 1.1.

Table 1.1: Definition of Chronic kidney disease according to KDOQI guidelines

Structural or functional abnormalities of the kidney for > 3 months
1. Kidney damage (with or without decreased eGFR) manifested by • Pathological abnormalities (glomerular disease, vascular disease) • Markers of kidney damage o Abnormalities detected by urine (proteinuria, hematuria) o Abnormalities detected by blood (electrolyte imbalance, renal tubular syndrome) o Abnormalities detected by imaging i.e. ultrasound, CT scan, MRI (size, shape, obstruction) • Kidney transplantation
2. Decreased GFR (<60ml/min/1.73m^2) with or without kidney damage

1.2.1 Classification/ Staging

There are five stages of CKD as proposed by NKF-KDOQI. Stage 1 is the least complicated stage while stage 5 represents end stage renal disease (ESRD) with marked loss of kidney function. The KDOQI staging of CKD is shown in Table 1.2.

Since the introduction of this staging system in 2002, many proposals have been suggested for its modification. In 2009, an International controversy conference was held that proposed three main modifications: (Levey *et al.,* 2011)

1. Addition of cause of disease (if known) to CKD staging as underlying cause is of prime importance in predicting outcome and selection of appropriate treatment

2. Division of CKD stage 3 (GFR 30-59 ml/min/1.73m^2) into 3a (eGFR 45-59 ml/min/1.73m^2) and 3b (30-44 ml/min/1.73m^2)
3. Addition of albuminuria to CKD staging to assess disease severity

Table 1.2: Classification of Chronic Kidney Disease

CKD staging	GFR (ml/min/1.73m^2)	Markers of Kidney damage
1	≥90	Required
2	60-89	Required
3	30-59	Not required
4	15-29	Not required
5	<15	Not required

On the basis of these recommendations, Kidney disease improving global outcomes (KDIGO) proposed a CGA (cause, GFR, albuminuria) classification of CKD that is summarized in Table 1.3 (Levin & Stevens, 2014).

Table 1.3: KDIGO classification of chronic kidney disease

GFR category	GFR (ml/min/1.73m^2)	Level of kidney function
G1	≥90	Normal or high
G2	60-89	Mild decreased
G3a	45-59	Mild to moderate decreased
G3b	30-44	Moderate to severe decreased
G4	15-29	Severe decreased
G5	≤15	Kidney failure
Albuminuria category	**AER (mg/24 hour)**	**Level**
A1	<30	Normal to mild increased
A2	30-300	Moderate increased
A3	>300	Severe increased
Abbreviations: GFR: glomerular filtration rate; AER: albumin excretion rate		

1.3 Assessment of kidney function

Kidneys perform essential functions of eliminating metabolic waste products (urea, creatinine), reabsorption of nutrients (glucose, amino acids, water), maintaining body pH (by reabsorbing biocarbonates and excreting hydrogen ion), osmolality regulation (balance between water and electrolytes by maintaining urine concentration and water reabsorption), maintenance of blood pressure (renin-angiotensin aldosterone system) and secretion of hormones (erythropoietin, calcitriol, renin) to regulate systemic and renal hemodynamics (Hall, 2015). Assessment of kidney function is done to identify severity of disease. Based on definition and staging of CKD, the key measure to assess kidney function is glomerular filtration rate (GFR) (Stevens *et al.,* 2006).

1.3.1 Glomerular filtration rate

The GFR is the sum of filtration rate of all the functioning nephrons in glomeruli. GFR is almost equal to the total number of nephrons and size of glomeruli; therefore, in clinical practice GFR is normalized to body surface area (BSA) to take account of different body sizes. The normal value of GFR is 120 -130 ml/min/1.73m^2 in young adults (aged 25 years) after adjustment for BSA (Soveri *et al.*, 2014). There is no standardized method available for measurement of GFR. It can be measured indirectly by measurement of urinary clearance of inulin, a gold standard for measurement of GFR. Inulin is not routinely used in clinical practice as it needs continuous bolus administrations along with timed urine collection i.e. a method that is used to collect all urine samples for a specified time interval (Berg *et al.*, 2011).

1.3.2 Serum creatinine as marker of kidney function

Serum creatinine is the most widely used endogenous marker of kidney function in routine clinical practice (Rule *et al.,* 2004; Myers *et al.,* 2006). It is produced by non-enzymatic degradation of creatine in skeletal muscles and dietary intake of proteins. Although creatinine fulfills the criteria of an ideal marker by being freely filtered through glomerulus, neither reabsorbed nor metabolized by kidney but still there are some inherent limitations of using creatinine as marker of kidney function. Some of these limitations are listed below: (Coresh *et al.,* 2003; Stevens *et al.,* 2006)

- Dietary variation in creatinine production
- Creatinine production depends on muscle mass suggesting lower values in women, elderly and cachexia patients
- Approximately 40% of urinary creatinine is produced by proximal tubules so it overestimates GFR
- Decreased creatinine secretion by certain drugs such as cimetidine, trimethoprim, ranitidine
- Extra renal elimination of creatinine (degradation by intestinal flora) particularly in patients with impaired kidney function

1.3.3 Renal function predictive equation

Renal function predictive equations estimate GFR by relying upon serum creatinine, demographic variables that effect GFR and various correction factors (Florkowski & Chew-Harris, 2011). The main purpose of development of such equations is to measure extent of kidney function clinically without undergoing expensive and time

consuming procedures. Three widely accepted and clinically used renal function predictive equations are given in Table 1.4 (Earley *et al.,* 2012).

Table 1.4: Commonly used renal function predictive equations

Equation (year)	Outcome	Formula
CG equation (1976)	(CrCl)	(140 – age) × (wt in kg) × (0.85 if fe) / (72 × Scr mg/dl)
MDRD formula (1999)	eGFR	$175 \times (0.011312 \times sCr)^{-1.154} \times age^{-0.203} \times 0.742$ (if fe) × 1.212 (if black)
CKD-EPI equation (2009)	eGFR	$141 \times \min (Scr/k\ '\ 1)^{\alpha} \times \max (Scr/k\ '\ 1)^{-1.209} \times 0.993^{age} \times 1.018$ (fe) × 1.159 (black) For female: k= 0.7, α= -0.329 For male: k=0.9, α= -0.411

CG:Cockroft and Gault, CKD-EPI:chronic kidney diseas-epidemiology, CrCl: creatinine clearance, eGFR:estimated glomerular filtration rate, fe:female, MDRD:modification of diet in renal disease, min:minute, Scr:serum creatinine, wt:weight, k and α represent constants

1.3.3(a) Limitations of predictive equations

The inherent limitation associated with renal function predictive equations is the use of serum creatinine that is not a sensitive renal biomarker. It is affected by several renal and non-renal factors that are independent of both kidney function and kidney injury. Moreover, these equations tend to show variations in result among different populations. Such populations include obese, multi ethnicities, any condition leading to unusual muscle mass, pregnancy and patients with high GFR (Lin *et al.,* 2003; Froissart *et al.,* 2005). Conclusively, all estimating equations are mathematical derivations and no equation is ideal for entire population (Botev *et al.,* 2011). On the basis of data, CKD-EPI equation shows improved performance for eGFR near or above 60 ml/min/1.73m^2 and has almost similar performance to MDRD equation for low eGFR (<60 ml/min/1.73m^2) (Levey *et al*., 2009).

1.3.4 Measurement of proteinuria

Proteinuria or albuminuria is used to assess kidney damage (Table 1.5). A spot urine or dipstick proteinuria is only sensitive to assess albuminuria (excretion of low molecular weight protein) and insensitive to assess proteinuria. Ideally a 24 hour urine collection is done to assess proteinuria. Due to cumbersome nature of timed urine collection, a spot urine specimen is widely used to assess albumin to creatinine ratio as indicator of proteinuria (Eknoyan *et al.*, 2003).

Table 1.5: Measures of urinary albumin and protein

Characteristics	Albumin excretion rate (mg/day)	Protein excretion rate (mg/day)	Albumin: Creatinine ratio (mg/g)
Normal	<30 mg/day	<150 mg/day	30 mg albumin /g creatinine
Microalbuminuria	30-300 mg/day	----	30-300 mg albumin/ g creatinine
Proteinuria	>300 mg/day	500-3500 mg/day	>300 mg albumin/g creatinine
Nephrotic range	-----	>3500 mg/day	----

1.4 Prevalence of CKD in Asia

It is difficult to estimate accurate prevalence or incidence of CKD because of asymptomatic nature of disease and lack of National renal registry (NRR) for non-dialysis dependent CKD patients (stage 1-stage 4). Renal registries of most countries focus on ESRD patients receiving renal replacement therapy (RRT) i.e. dialysis or transplantation. Moreover, lack of generalizability of biomarkers and methods to estimate GFR leads to biased prevalence (Levey & Coresh, 2012).

Based on population based surveys and health screening programs, the prevalence of CKD can be estimated. The prevalence of CKD in Asia varies from 10-18 percent that is not much different from other parts of the world. However, due to paucity of data in Asian countries, the exact burden and cost associated with disease is still not clear (Hamer & Nahas, 2006). A summary of prevalence of CKD in different Asian countries is shown in Table 1.6.

Table 1.6: Prevalence of Chronic Kidney Disease in Asia

Author [Reference]	Country	Study design, no. of participants	Participants characteristics	Overall Prevalence of CKD
Ninomiya *et al.*, 2005	Japan (East Asia)	Prospective cohort study, n=2634	42 % male, 58% female with age 40 years and above	10.3 % with MDRD equation
Chen *et al.*, 2005	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
Konta *et al.*, 2006	Japan (East Asia)	Cross sectional survey, n=2321	44 % male, 56 % female with age above 40 years	28.8 % with CG equation
Li *et al.*, 2006	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
Perkovic *et al.*, 2007	Thailand (South East Asia)	Cross sectional survey with stratified cluster sampling, n=5146	49 % male, 51% female with age range of 35- over 65	13.81% with MDRD, 21.04% with CG equation
Ito *et al.*, 2008	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
Zhang *et al.*, 2008	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

Table 1.6: Continue…

Author [Reference]	Country	Study design, no. of participants	Participants characteristics	Overall Prevalence of CKD
Hosseinpanah *et al.,* 2009	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
Prodjosudjadi *et al.,* 2009	Indonesia (South East Asia)	Community based prospective survey, n=9412	36% male, 64% female	12.5% with CG, 8.6 % with MDRD
Sahin *et al.,* 2009	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
Sabanayagam *et al.,* 2010	Singapore (South East Asia)	Cross sectional survey with SPSP, n=4499	48% male, 52% female with age range of 24-95 years	5.5 % with MDRD Equation
Yi *et al.,* 2010	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
Alsuwaida *et al.,* 2010	Saudia 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
Varma *et al.,* 2010	India (South Asia)	Cross sectional survey , n= 3398	66 % male, 34 % female with age above 18 years	3.02 % with MDRD formula

Table 1.6: Continue…

Author [Reference]	Country	Study design, no. of participants	Participants characteristics	Overall Prevalence of CKD
Kang *et al.*, 2012	Kore (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 %
Huda & Alam. 2012	Bangladesh (South Asia)	Cross sectional survey, n= 1000	334 male, 666 female with age range of 15-65 years	13.1 % with MDRD, 16 % with CG formula
Singh *et al.*, 2013	India (South Asia)	Prospective cohort study,, n= 5588	55% male, 45 % female with age range of 18-98 years	5.09 % with MDRD formula
Tennille et al., 2013	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
Hooi *et al.*, 2013	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
Sharma *et al.*, 2013	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
Jessani *et al.*, 2014	Pakistan (South Asia)	Cross sectional survey, n=2873	52.2% female, Age 40 years and above	12.5% with CKD-EPI formula

Out of total 21 studies, the prevalence of CKD was assessed via modification of diet in renal disease (MDRD) equation in 12 studies while chronic kidney disease epidemiology (CKD-EPI) equation was used by three studies (Hooi. 2013; Tennille *et al.,* 2013; Jessani. 2014). Majority of the studies 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 (Delanaye *et al*., 2013). One study used only Cockroft and Gault (CG) equation (Konta *et al.,* 2013). Five studies used both MDRD and CG equation (Perkovic *et al.,* 2007; Ito *et al.,* 2008; Prodjosudjadi *et al.,* 2009; Alsuwaida *et al.,* 2010; Huda & Alam, 2013). In studies using 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 in Japan reported prevalence of CKD as 28.8% with CG equation (Ninomiya *et al.,* 2005; Konta *et al.,* 2006). Both these studies were conducted with participants above 40 years and with almost similar sample size i.e. 2634 versus 2321, respectively. 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. Disparities in prevalence of CKD owing to different predictive equation further necessitates need of NRRs for early stages of CKD and a uniform criteria to estimate burden of disease.

1.5 Risk factors of CKD

Due to asymptomatic nature of disease, CKD remains undiagnosed in 80-90% cases in its early stages (Chadban *et al.,* 2003; John *et al.,* 2004). According to World Health organization (WHO), "a risk factor is any attribute or characteristics of an individual that increases the likelihood of developing a disease" Clinical risk stratification plays an important role in early detection of CKD and ensures interventions at the earliest possible stage (WHO, 2004). Risk factors for CKD can be broadly classified into 3 main types as described in Table 1.7 (Levey *et al.,* 2005).

Table 1.7: Categorization of risk factors of CKD

Factors	Description	Type
Susceptibility factors	Factors that increase susceptibility to kidney disease	Old age, family history, obesity, ethnicity
Initiation factors	Factors that directly initiate kidney disease	Hypertension, diabetes, autoimmune disorders, urinary obstruction/stones, Toxicity of drugs, metabolic disorder
Progression factors	Factors that cause progression of kidney disease	High blood pressure, diabetes (uncontrolled), proteinuria, smoking, metabolic disorder/dyslipidaemia

A brief over-view of pathophysiology of these risk factors is discussed below.

1.5.1 Obesity as risk factor of CKD

Weisinger *et al.,* first reported the relationship between obesity and decline in kidney function as manifested by heavy proteinuria (Weisinger *et al.,* 1974). Obesity as defined by BMI > 25 kg/m^2 is associated with a three fold increase risk of CKD as compared to non-obese i.e. BMI< 25 25 kg/m^2 (Ejerblad *et al*.,2006). Obesity increases the metabolic demands of kidney leading to higher glomerular pressure and glomerular hypertrophy. This causes excretion of urinary albumin i.e. microalbuminuria initially and then proteinuria that directly damages kidney and causes ESRD (Garland, 2014). Obesity is frequently associated with hyperinsulinemia that directly damages structure of kidney by increasing depositions on kidney. This structural damage along with histological changes in kidney leads to focal segment glomerulosclerosis. Moreover, obesity also increases the risk of hypertension and diabetes, both of which are potential risk factors of CKD (Kramer, 2006).

1.5.2 Metabolic syndrome (MS) as risk factor of CKD

A metabolic syndrome (MS) is defined as concomitant presence of metabolic disturbance in glucose/ insulin metabolism and atherosclerotic risk factors (hypertension, dyslipidemia) accompanied by central obesity (Tanaka *et al.*, 2006). In normal healthy individuals, the cumulative risk of CKD development is higher in subjects with metabolic syndrome as compared to subjects without metabolic syndrome; (10.6% versus 4.8%, p-value: 0.01) (Ninomiya *et al*., 2006). There are several inter-related mechanisms that underlie the effect of metabolic syndrome on renal function. Hyperinsulinemia associated with both diabetes and obesity causes glomerulopathy (Kramer, 2006; Tanaka *et al.,* 2006). Gloermular hypertrophy, intraglomerular hypertension and hyperaldosteronism due to high blood pressure along with co-existing lipid disorders are all implicated in metabolic syndrome driven CKD (Gabbay *et al.,* 2015).

1.5.3 Hypertension as risk factor of CKD

Hypertension is not only a cause but also a complication of CKD. Like diabetes, hypertension is a well described and one of the most potential risk factor for CKD. Compared to patients with normal BP, the risk of CKD development increases with higher BP. The *HR* of CKD development is 8.8 for stage 4 hypertension while the *HR* decreases to 6.3 for patients with stage 1 hypertension (Haroun et al., 2003). High blood pressure (>140/90 mmHg) causes faster decline in kidney function, increases risk of renal failure and cardiovascular diseases. Hypertension causes vasoconstriction of glomerular afferent arterioles to maintain renal blood flow and glomerular pressure. This vasoconstriction causes further increase in pressure load to

renal vasculature resulting in mechanical stretch of glomerular capillaries thereby causing glomeulosclerosis and renal artery stenosis (Ravera *et al.,* 2006).

1.5.4 Diabetes as risk factor of CKD

Globally, diabetic kidney disease (DKD) is the leading cause of development of CKD. Diabetes mellitus (DM) not only causes CKD but it also serves as a potential independent risk factor of CKD progression. High blood sugar associated with DM directly increases glomerular permeability that results in leakage of contents from glomerulus (albuminuria, hematuria). Further DKD results in activation of RAAS that causes increase level of angiotensin II (a potent vasoconstrictor) resulting in vasoconstriction of afferent arterioles that ultimately increase albuminuria and overt nephropathy (Toth-Manikowski & Atta, 2015).

1.5.5 Smoking as risk factor of CKD

A number of biological mechanisms by which smoking causes kidney disease have been identified. Conclusively, smoking causes acceleration of renal artherosclerosis, altenates renal and systemic hemodynamics (increases glomerular permeability, enhance albuminuria) and causes endothelial dysfunctions (Shankar *et al.,* 2006; Ishizaka *et al.,* 2008).

1.5.6 Proteinuria as risk factor of CKD

Proteinuria is a widely accepted marker of kidney damage that is associated with diagnosis, prognosis as well as treatment of kidney disease. It causes increase glomerular capillary artery pressure causing increase pore size of basement

membrane effecting proximal tubule protein reabsorption (Levey *et al.,* 2009). Proteinuria is strongly associated with arterial stiffness that causes high blood pressure and endothelial dysfunction (Clausen *et al.,* 2001; Agarwal & Light, 2009).

1.5.7 Family history as risk factor of CKD

Mutation in genes that cause structural abnormalities in kidney (podocin, non-muscle myosin heavy chain) causes chronic glomerulonephritis. Moreover, genes causing sympathetic activation of nervous system (chromogranin A) leads to hypertension associated ESRD (McClellan *et al.,* 2009).

1.5.8 Advance age as risk factor of CKD

It is a well-documented fact that GFR decreases 0.75-1ml/min/1.73m^2 in all healthy individuals after 30 years of age (Berg, 2006). Moreover, the risk of developing CKD increases with advance age because other risk factors (hypertension, diabetes) for kidney disease are more prevalent in elderly. Ageing is a non-regulatory risk factor for development of CKD that is positively associated with arterial atherosclerotic change (Chen *et al.,* 2009).

1.5.9 Autoimmune disorders as risk factor of CKD

Autoimmune disorders such as systemic lupus erythematosus (SLE) and IgA nephropathy cause glomerular disease In such cases, autoantibodies are produced within body that are deposited on glomerular membrane causing inflammation (glomerulonephritis) and scarring (glomerulosclerosis) (Levey *et al*., 2005).

1.5.10 Infections as risk factor of CKD

Certain infections are associated with development of early or rapid glomerular disease. Human immunodeficiency virus (HIV) causes HIV-associated nephropathy that rapidly causes kidney failure due to massive proteinuria (Wyatt *et al*., 2008). Infective endocarditis is also associated with development of glomerular disease by causing renal lesions. Acute post strepto-coccal glomerulonephritis (PSGN) is another example of kidney damage as a result of infection. Streptococcus bacteria does not directly damages kidney rather the infection causes over production of antibodies by immune system that are then deposited on the basement membrane of kidney leading to glomerular disease (Levey & Coresh, 2012).

1.5.11 Urinary tract obstructions/ stones as risk factor of CKD

Urinary tract obstructions or severe urinary tract infections frequently cause transient renal dysfunction. In few cases, it can cause chronic renal failure. The pathological mechanism involves renal atrophy along with interstitial fibrosis and inflammation (Hong *et al.,* 2010). Moreover, hydronephrosis (swelling of kidney due to accumulation of urine) causes renal dysfunction (Levey & Coresh, 2012).

1.5.12 Drug induced nephrotoxicity as risk factor of CKD

Drug induced nephrotoxicity is common with certain drugs that are routinely used in clinical practice. As most of the drugs concentrate and reabsorb in proximal tubules cells of nephron, they cause cytotoxicity by damaging mitochondria of tubules and increase oxidative stress.This results in generation of free radicals causing acute tubulointerstitial nephritis (TIN). Such drugs include aminoglycosides, amphotericin