

Value of Cystatin C Based Equations for Assessment of Glomerular filtration rate In Relation To Renal Pathology

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَقُلْ اَعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
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List of Abbreviations

AKI	: Acute kidney injury
AUC	: Area under the curve
BTP	: B trace protein (Prostaglandin D2 synthase)
BUN	: Blood urea nitrogen
C&G	: Cockcroft–Gault
CKD	: Chronic kidney disease.
CKD-EPI	: Chronic Kidney Disease Epidemiology Collaboration
CRP	: C reactive protein
CSF	: Cerebrospinal fluid
CVD	: Cerebrovascular disease.
DTPA	: 99mTc–diethylenetriamine penta-acetic acid
e GFR	: Estimated GFR
FDA	: US Food and Drug Administration
GFR	: Glomerular filtration rate
GN	: Glomerulonephritis
HBP	: High blood pressure
HCV	: Hepatitis C virus
m GFR	: Measured GFR
MDRD	: Modification of Diet in Renal Disease
NKDEP	: National Kidney Disease Education Program
NKF-KDOQI	: National Kidney Foundation Kidney Disease Outcomes Quality Initiative
RIV	: Relative interstitial volume
ROC	: The receiver-operating characteristic
TSH	: Thyroid stimulating hormone

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Introduction

Kidney disease (CKD) is becoming a major public health problem worldwide. The current burden of disease might due to a change of the underlying pathogenicity of CKD. Glomerulonephritis was the one of the leading causes of kidney disease several decades ago. Nowadays, infections have become a less important cause for kidney disease, at least in the western world. The current evidence suggests that hypertension and diabetes are the two major causes of kidney disease worldwide (*Haroun et al., 2003*).

Given the pathogenic progression of kidney disease, patients with CKD are at high risk for progression to the end stage renal disease (ESRD) – a condition requiring dialysis or kidney transplantation to maintain patients' long-term survival. In 2001, the average annual cost for maintenance of ESRD therapy was between US \$70 and \$75 billion worldwide excluding kidney transplantation, and the predicted number of ESRD patients will reach over 2 million in 2010 (*Lysaght, 2002*).

The enormous costs of treatment lead to a large burden for the health care systems, particularly in developing countries. In addition, CKD has a complicated interrelationship with other diseases (*Snively et al., 2004*).

Recent studies have reported that CKD is an independent risk factor for cardiovascular disease (CVD) (*Mann et al., 2001*).

Therefore, kidney dysfunction should be an additional target for intervention and prevention of CVD (*De Zeeuw et al., 2005*).

In 2003, the American Heart Association (AHA) stated that persons with CKD should be regarded as the highest risk group for subsequent CVD (*Sarnak et al., 2003*).

The definition and classification for chronic kidney disease was proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and endorsed by the Kidney Disease: Improving Global Outcomes (KDIGO) in 2004.

Definition of CKD:

Chronic kidney disease was defined based on the presence of kidney damage or glomerular filtration rate (GFR <60 ml/min per 1.73m²) for more than or equal 3 months, irrespective of cause, and was classified into five stages based on the level of GFR. This framework advanced a uniform nomenclature for chronic kidney disease, objective diagnostic criteria irrespective of cause that could be assessed in most cases from readily available clinical laboratory data

Prevalence of CKD :

Age presents one of the most important factors that affect kidney function. Generally, kidney function is stable after infancy until late adulthood (*Price and Finney, 2000*).

GFR declines by 1 ml/min/1.73 m² per year after the age of 30 years in healthy persons (*Snively and Gutierrez, 2004*).

The decrease in kidney function might be due to the changes in the kidney structure associated with aging (*Lamb et al., 2003*).

In the included studies, the elderly had a markedly higher prevalence of CKD and the prevalence increased with age in all populations, particularly among elderly persons aged 70 years or older. This steep increase in the prevalence of CKD in the elderly might be partly due to related comorbidities of CKD, such as cardiovascular diseases or diabetes. Moreover, the serum creatinine concentration remains within the normal range until a significant decrease of kidney function, especially in the elderly (*Swedko et al., 2003*).

Serum creatinine is not a sensitive marker of GFR in older persons. In addition to the substantial effect of age on the kidney structure and kidney function, the same GFR level might have different pathophysiologic or non-pathophysiologic effects on kidney function in different age groups. Furthermore, a gender-different prevalence of CKD was revealed in most included studies. Females had a higher prevalence of CKD than males. Females have less muscle mass as compared to males and the muscle mass is a major determinant of serum creatinine concentration (*Zhang and Rothenbacher, 2008*).

Some risk factors for CKD are in favour of males but are unlikely to explain the difference between females and males, e.g. the prevalences of smoking and alcohol consumption, as well as the prevalence of cardiovascular diseases, which are generally higher in males than in females. The higher prevalence of CKD might partly be the result of an inaccurate correction factor for females in both equations. Additionally, the difference between females and males in glomerular structure, glomerular haemodynamics, and the hormone metabolism might play an important role in the gender disparity. However, some uncertainties about the validity of prediction equations still

remain, particularly when they are used in females (*Silbiger and Neugarten, 2003*).

Burden of chronic kidney disease: North Africa:

North Africa (NAF) is composed of six countries located in the African Sahara, namely the Western Sahara, Morocco, Algeria, Tunisia, Libya, and Egypt. Common features between these countries include similar climate, ecology, population genetics, and the socioeconomic environment. This commonality reflects on the chronic kidney disease (CKD) profile in these countries. While there are some estimates on the epidemiology of end-stage kidney disease, that of earlier stages is unknown. Several national screening programs are currently addressing this issue, such as the EGYPT-CKD project in Egypt and the MAREMAR study in Morocco. Preliminary results from the former suggest a prevalence of proteinuria in 10.6% of the relatives of patients on regular dialysis treatment. Despite the lack of reliable registries, it was possible to gather information on the etiology of CKD by direct contact with leading nephrologists in those countries. It turns out that glomerulonephritis (GN) accounts for 9–20%, diabetes 11–18%, hypertensive nephrosclerosis 10–35%, chronic interstitial nephritis 7–17%, and polycystic disease 2–3%. Compared to two decades earlier, diabetes has become more common at the expense of GN, proliferative GN, and amyloidosis regressed in favor of IgA and membranous nephropathies in Tunisian adults. Conventional schistosomal nephropathies are regressing in favor of hepatitis C viral (HCV) nephropathy in Egyptians. Focal segmental glomerulosclerosis is increasing at the expense of proliferative GNs in the region at large (*Kidney International Supplements, 2013*).

Table (1):Definition of chronic kidney disease

Definition of Chronic Kidney Disease	
Criteria	
1.	Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by <i>either</i> : • Pathological abnormalities; or • Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2.	GFR < 60 mL/min/1.73 m ² for ≥ 3 months, with or without kidney damage

(National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S000, 2002 (suppl 1))

Table (2):Stages of chronic kidney disease

Introduction and Aim of The Work

GFR (mL/min/1.73 m ²)	Definition and Stages of Chronic Kidney Disease			
	With Kidney Damage*		Without Kidney Damage*	
	With HBP**	Without HBP**	With HBP**	Without HBP**
≥90	1	1	"High blood pressure"	"Normal"
60–89	2	2	"High blood pressure with ↓ GFR"	"↓ GFR" ^a
30–59	3	3	3	3
15–29	4	4	4	4
<15 (or dialysis)	5	5	5	5

Shaded area represents chronic kidney disease; numbers designate stage of chronic kidney disease.

* Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

** High blood pressure is defined as ≥140/90 in adults and >90th percentile for height and gender in children.

^a May be normal in infants and in the elderly.

(National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 39:S1-S000, 2002 (suppl 1))

Table (3): Classification and management of comorbid conditions in chronic kidney disease

Classification and Management of Comorbid Conditions in Chronic Kidney Disease		
Type of Comorbid Condition	Examples	Management Goals
Diseases causing CKD	Diabetes High blood pressure Obstruction of the urinary tract	Improve CKD, Improve functioning and well-being, Integration of care with management of CKD
Diseases unrelated to CKD	Chronic obstructive pulmonary disease, Gastroesophageal reflux disease, Degenerative joint disease, Alzheimer's disease, Malignancies	Improve functioning and well-being, Integration of care with management of CKD
Cardiovascular disease (CVD)	Atherosclerotic CVD Coronary heart disease Cerebrovascular disease Peripheral vascular disease Left ventricular hypertrophy Heart failure	Evaluation and management of traditional and CKD-related CVD risk factors, Possibly improve CKD, Improve functioning and well-being, Integration of care with management of CKD