COMPARISON AND ASSESSMENT OF METHODS USED TO ESTIMATE eGFR IN CKD PATIENTS: THE ROLE OF CLINICAL PHARMACIST AND DIRECT MEDICAL COSTS

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by

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LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitors
ACR	Albumin to Creatinine Ratio
AED	Arab Emirates Dirhams
Alb	Albumin Level
ANN	Artificial Neural Network
ARB	Angiotensin Receptor Blockers
BIS	Berlin Initiative Study
CG	Cockroft-Gault Equation
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CPs	Clinical Pharmacists
51Cr-EDTA	Chromium-51 labelled Ethylene Diamine Tetra-acetic Acid
CVD	Cardiovascular Disease
DOAC	Direct Oral Anticoagulants
eCrCl	Estimated Creatinine Clearance
eGFR	Estimated Glomerular Filtration Rate
EMC	European Medicines Agency
EMEA	European Medicines Agency
ESRD	End Stage Renal Disease
FAS	Full Age Spectrum
FDA	Food and Drug Administration
GRN	Generalized Regression Network

FTE	Full Time Equivalents
IBW	Ideal Body Weight
ICU	Intensive Care Unit
IDMS	Isotope Dilution Mass Spectrometry
KDIGO	Kidney Disease Improving Global Outcomes
LMR	Lund-Malmö revised
LOSA	Length of Stay After Index Case Identification
mGFR	Measured Glomerular Filtration Rate
MDRD:	Modification of Diet in Renal Disease
MIC	Minimum Inhibitory Concentration
NOAC	New Oral Anticoagulants
PAIR	Pharmacotherapy Assessment in Chronic Renal Disease
PN	Probabilistic Networks
RSV	Respiratory Syncytial Virus
SCr	Serum Creatinine
^{99m}Tc-DTPA	^{99m}Tc-Diethylene Triamine Pentaacetic Acid
UAE	United Arab Emirates

PERBANDINGAN DAN PENILAIAN KAEDAH ANGGARAN eGFR DALAM KALANGAN PESAKIT CKD: PERANAN AHLI FARMASI KLINIKAL DAN KOS PERUBATAN LANGSUNG

ABSTRAK

Dua objektif utama bagi pemeriksaan fungsi ginjal adalah untuk menentukan peringkat penyakit buah pinggang kronik (CKD) dan kesesuaian pengdosan ubat. Parameter yang lazimnya diterima sebagai piawai emas ialah penyingkiran kencing dan kadar penapisan glomerular (GFR). Pengdosan ubat bagi CKD boleh dianggar melalui formula fungsi ginjal. Kajian ini bertujuan untuk menilai kaedah penganggaran GFR bagi pengdosan ubat bagi pesakit CKD. Simulasi yang melibatkan 1200 kes dan 22 contoh telah dijalankan untuk menilai perselisihan dalam pengdosan ubat antara pelbagai formula fungsi ginjal. Perselisihan dalam pengdosan ubat antara 5 kaedah yang dinilai adalah sebanyak 20% hingga 40%. Perbandingan anggaran penyingkiran kretinin (eCrCl) atau anggaran kadar penapisan glomerular (eGFR) secara pasangan bagi semua formula yang dinilai menunjukkan perbezaan dari segi statistic ($P < 0.0001$) kecuali pasangan antara Cockroft-Gault (CG) dan Modification of Diet in Renal Disease (MDRD) ($P = 0.5147$). Manakala Kesejajaran antara kaedah adanya serendah 55% bagi lamivudine (antara CG dan kaedah berdasarkan albumin) dan setinggi 99% bagi enoxaparin, eptifibatide dan ranitidine (antara MDRD dan kaedah CKD-EPI) dan perbezaan dos bagi meropenem dan cefepime boleh mencapai 37% dan 42% masing-masing. Di samping itu, melalui sorotan kajian secara sistematik berdasarkan pangkalan data sekunder seperti Public/Publisher Medline (PubMed) dan Elton B. Stevens Company (EBSCO), simulasi dijalankan terhadap

data daripada literatur untuk menentukan potensi bagi perbezaan klinikal yang boleh diukur antara CG dan MDRD. Seramai 8710 pesakit terlibat dalam simulasi ini dengan 2610 dan 2631 cadangan yang berbeza. Ia didapati bahawa julat signifikan bagi perubahan dalam kematian mencapai kira-kira 16% sekiranya CG digunakan dalam pengdosan ubat di kalangan populasi kajian berbanding dengan MDRD. Kesan unsur jantina terhadap pengdosan optima juga dikaji dan didapati bahawa jantina tidak menyebabkan perselisihan antara formula-formula tersebut. Satu kajian kohort pasangan-bahagian (*paired-proportion*) yang melibatkan 195 pesakit telah dijalankan di sebuah hospital tentera di Emiriah Arab Bersatu. Maklumat termasuk demografik pesakit, kreatinin serum (sCr), pengumpulan air kencing 24-jam serta sejarah perubatan yang lalu dan terkini telah dikumpulkan. Penyelarasan dos yang dijalankan oleh ahli farmasi klinikal dan pasukan nefrologi untuk mencapai respon klinikal yang dikehendaki adalah dicatatkan dalam borang tertentu. Perisian Rangkaian Saraf (neural network software) yang disahkan digunakan terhadap seluruh set data tersebut. Terdapatnya jumlah 1487 ubat yang digunakan oleh pesakit dan antaranya, hanya 785 ubat yang disingkirkan melalui ginjal diambil kira. Selain itu, sebanyak 107 perubahan pada farmakoterapi dilakukan oleh pasukan nefrologi dan multidisiplin dan 70 intervensi farmasi klinikal juga didokumenkan. Tambahan pula, daripada 94 penyelarasan dos, pasukan perubatan telah menggunakan pengdosan optima pada 81 kes, di mana 45 ialah CG dan 36 MDRD (P = 0.159). Lebih kurang 13.8% daripada kes kajian (n = 13) juga menunjukkan bahawa kedua-dua formula adalah tidak berkeupayaan untuk menjangka dos optima. Selain itu, ia didapati bahawa optimaliti formula dalam 89% daripada kes CG (40 daripada 45 kes) dan 58% daripada kes MDRD (21 daripada 36 kes) adalah berdasarkan pengiraan klinikal semata-mata tanpa bacaan GFR. Antara lima kes yang mempunyai bacaan GFR dalam kumpulan CG, empat

(80%) kes adalah sejajar dengan bacaan mGFR manakala 9 daripada 15 (60%) dalam kumpulan MDRD sejajar dengan mGFR. Untuk menilai kos perubatan secara langsung yang berkaitan dengan pengdosan ubat di kalangan pesakit CKD, kos ubat sebelum dan selepas penyelarasan rawatan dihitung berdasarkan harga dalaman. Sekiranya dos ditentukan dengan menggunakan formula yang betul, penjimatan sebanyak USD4127.89 dapat dicapai. Kesimpulannya, parameter yang berbeza bagi setiap kaedah anggaran fungsi ginjal menyebabkan kepelbagaian dalam perselisihan. Kaedah CG dan MDRD mempunyai kelebihan tersendiri bagi ubat yang berbeza dan ianya tidak boleh diganti antara satu sama lain. Antara jantina, umur, berat badan, tahap albumin dan peringkat CKD, tiga pemboleh ubah teratas yang mempengaruhi kaedah pengdosan optima ialah tahap albumin, peringkat CKD dan berat badan.

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ABSTRACT

Assessment of kidney function has dual objectives, staging of CKD and appropriate dosing of medications. Gold standard of this assessment is still urinary clearance and glomerular filtration rate. Drug dosing in chronic kidney disease (CKD) are estimated randomly by using one of the renal function equations. This study aimed to evaluate GFR estimating algorithms for medication dosing in CKD patients. Simulation of 1200 cases and 22 example of medications were conducted to evaluate the discordance of the various renal function estimated equations in medication dosing. Discordance found in dosing among 5 studied methods ranged from 20 to 40%. Pairwise eCrCl or eGFR comparisons showed that all formulas gave statistically different results ($P < 0.0001$) except for CG vs MDRD ($P = 0.5147$). Concordance ranges from as low as 55% for lamivudine (CG vs albumin– based) to 99% for enoxaparin, eptifibatide, and ranitidine (MDRD vs CKD–EPI) and dose differences in meropenem and cefepime can reach up to 37% and 42%. Moreover, Systematic review was performed by using secondary databases such as, Public/Publisher Medline (PubMed) and Elton B. Stevens Company (EBSCO), data from literature was simulated to timely quantify any potential for measurable clinical differences between Cockroft-Gault (CG) equations versus Modification of Diet in Renal Disease (MDRD). A total of 8701 patients were included with 2610 and 2631 different

recommendations in simulations. Significant margin was found of about 16% for a change in mortality if CG is used versus MDRD for dosing in this study population. Gender effect on the optimal dosing was tested, resulting in no effect of gender on the discordance between the equations. A paired-proportion cohort design was applied for 195 real patients at a flagship military hospital in the United Arab Emirate. Demographics, SCr, 24 urine collection as well as past and concurrent medical history were collected. Dose adjustments to desire clinical response done by clinical pharmacist and nephrology teams and it was recorded in standardized form. Validated neural network software on the entire data set was applied. A total of 1487 concurrent medications and 785 drugs were included with renal elimination. Moreover, there were 107 changes in pharmacotherapy done by the nephrology or multidisciplinary team and 70 documented clinical pharmacy interventions. Additionally, out of the 94 dose adjustments, the team established an optimal dosing method in 81 cases, 45 CG and 36 MDRD (P value = 0.159). Moreover, there is almost 13.8% of cases (N = 13) where neither equation was more predictive of the optimal dose. Furthermore, there was 40/45 CG cases (89%) and 21/36 MDRD cases (58%) in which the optimality of the equation was purely clinical with no measured GFR. Also, among the 5 cases with measured GFR in the CG group 4 (80%) were concordant with mGFR whereas 9 out of 15 (60%) in the MDRD group were concordant with the mGFR. To assess the direct medical costs associated with dosing in CKD patients, drug costs were calculated before and after treatment changed using internal pricing data. If we correctly dose all patients in the current study with the propar equation, we will save annually in total ~ 4127.89 USD. In conclusion**,** different parameters in each renal function estimation method explain the variability in discordance. Both CG and MDRD has their own superiority for different medications and it cannot be replaced with one another. Among

gender, Age, Weight, Albumin levels and CKD staging variables, the top three that affect the optimal dosing method are Albumin levels, CKD staging and weight.

CHAPTER 1

INTRODUCTION

This chapter introduces pertinent key concepts in kidney function estimation, the various equations used in clinical practice to estimate kidney function as well as to dose medications in chronic kidney disease (CKD) patients. It presents the rationale for the study in investigating the use of the various formulae to dose medications. One important aspect, which forms the backbone of this dissertation, is the huge economic burden of CKD. This chapter will show this burden is largely driven by hospitalization and overuse of institutional resources. Dosing is a major contributor to the challenge as well. Finally, by completing this study, the suggested strategy to resolve some of the formulating problem to dose medications will be represented.

1.1 Background

Assessment of kidney function has dual objective, staging of CKD and appropriate dosing of medications (Hudson and Nyman, 2011). Gold standard of this assessment is still urinary clearance with urine collection during a continuous infusion of inulin (Soveri *et al.*, 2014). However, this standard is cumbersome, expensive, and often impractical for most practice institutions. Therefore, clinicians rely on several markers with practically and commercially available kits to estimate renal function (Levey *et al.*, 1999; 2009; Inker *et al.*, 2012).

Traditionally, the most common such marker used for drug dosing is estimated creatinine clearance (eCrCl) by Cockcroft-Gault (CG). Most medication dosing in CKD is based on this method. Two other common methods are estimated glomerular filtration rate (eGFR) with modification of diet in renal disease (MDRD) or the CKD–Epidemiology

Collaboration (CKD–EPI). Estimate GFR with MDRD is now automatically reported by most clinical laboratories. Each one of these estimates may emerge as a better predictor of optimal dosing of medications in different populations (Hudson and Nyman, 2011). There is chaos and uncertainty among practitioners as to which of these estimates is better in a given patient.

During this study, series of research studies were conducted to answer some key questions: what equation shall practitioners' default to in dosing medications in a given population? What factors determine the optimal equation? If medication type or class is one of these factors, what medications can be dosed with CG, MDRD, or CKD-EPI? Since, most hospitals labs used MDRD equation; it was selected as a representative of all eGFR methods.

1.2 Measurement of Glomerular Filtration Rate

Direct measurement of GFR is quite impossible, because this process involves the simultaneous filtration of an endless number of molecules found in blood through millions of nephrons. As a result, researchers and clinicians usually measure the degree to which this important step in renal clearance takes place by recording the clearance of certain exogenous substances eliminated by filtration alone.

Traditionally, inulin is the gold standard substance used for the purpose of determining the measured glomerular filtration rate (mGFR) (Smith, 1951). This is a cumbersome and expensive procedure because it involves injecting the patient with continuous infusion of inulin and then collecting urine over a long period of hours. Therefore, researchers and clinicians use other exogenous substances to measure this single common step in the renal clearance of all xenobiotics. These include 51-labeled

ethylenediaminetetraacetic acid (^{51}Cr-EDTA), ^{99m}Tc-diethylene triaminepentaacetic acid (^{99m}Tc-DTPA), iohexol, and iothalamate (Soveri *et al*., 2014).

Soveri et al found that even the gold standard plasma inulin method had a parameter P10 (i.e. probability of 10% or less error) median of 72% which means that only 72% of the errors in this index measurement did not exceed 10%. The P10 for the various methods, namely ^{51}Cr-EDTA, ^{99m}Tc-DTPA, iohexol, and iothalamate, ranged from 19 to 66%. On the other hand, the P30 for all the methods ranged from 56% to 97% meaning that anywhere from 3 to 44% of errors in this index measurement did exceed 30% for the various methods (Soveri *et al*., 2014). Hence, even the most accurate exogenous substance method for mGFR has been shown to be significantly error prone. In summary, mGFR is an imperfect, cumbersome, and time-consuming activity. Practice confirms these conclusions as there are very limited numbers of patients where glomerular filtration is measured and that these cases usually must wait for results. Hence, initial empiric drug dosing based on estimates of renal function is inevitable.

1.3 Chronic Kidney Disease: Definition and Estimation of Function

The CKD is defined as a structural abnormality of the kidney or a progressive loss of kidney function that is present for more than 3 months with consequent implications for the patient's quality of life (Stevens and Levin, 2013). Objectively, in contrast to healthy and acute renal failure populations, experts consider two measures for CKD. One is a stable eGFR of less than 60 mL/min/1.73 m^2. Another is kidney damage (often indicated by the presence of proteinuria). An example marker of the latter is the albumin (Alb) to creatinine ratio (ACR) of equal or more than 30 mg/dL (Baekken *et al*., 2008).

Staging of CKD, which fall into one of six categories, takes both factors into consideration. Stages 1 and 2 consist of patients with glomerular filtration rate preserved above 60

mL/min/1.73 m^2 but with significant albuminuria. On the other hand, stages 3a, 3b, 4, and 5 may or may not co-exist with albuminuria.

One major complication of this functional decline is the dichotomy of drug suboptimal doses and toxicity (Zand *et al*., 2010; Almorza *et al*., 2017; Sorli *et al*., 2019). Although ^{51}Cr-EDTA is a gold standard method for mGFR, it is a cumbersome procedure and may in fact, overestimate the clearance of the tracer by approximately 10% (Moore *et al*., 2002). Therefore, practitioners often find themselves in a position of not only estimating the kidney function, but also being uncertain about the optimal dose to choose when the different estimates fall into different dosing tiers (Lessard and Zaiken, 2013).

Currently, there are numerous methods used to estimate GFR that employ creatinine and cystatin (Björk *et al*., 2019). This is a foggy area such that researchers keep developing new models for this daunting purpose (Liu *et al*., 2107).

1.4 Incidence and Prevalence of CKD

In the United States of America (USA), population that have CKD is 6.7% (eGFR < 60 ml/min per 1.73 m^2). Values of eGFR and rates of CKD vary significantly by ethnicity in the USA. (United States Renal Data System, 2013). Paradoxically, eGFR is found to be higher in African Americans than European Americans (Stevens *et al*., 2011). The cause of these differences may be due to environmental factors such as heavy metals, industrial chemicals, elevated ambient temperatures, and infections and genetic factors (Patzer and McClellan, 2012). In the United Arab Emirates (UAE), the prevalence of CKD has increased dramatically over the past two decades, with 13.4% of the population affected worldwide and that due to shifting from a semi-nomadic lifestyle to an urbanized civilization. Recently, it has been reported that the prevalence of these disease

stages among UAE nationals is 4.6% in males and 2.8% in females (Richards *et al*., 2015; Hill *et al*., 2016; Al Shamsi *et al*., 2016).

The incidence and prevalence of CKD is rising in the elderly age groups (United States Remal Data System, 2015). For example, the incidence of CKD in people aged 20 to 64 in the USA remains less than 0.5%. However, in those aged 65 years and above, the incidence rose from 1.8% to 4.3% between 2000 and 2008. Similarly, the prevalence of CKD stage 3 for those aged 20 to 39 remained less than 0.5% whereas it jumped for those 60 years and above from 18.8% in the late 80s and early 90s to 24.5% in 2003 to 2006. Overall prevalence of stages 1 through 5 were 5.7%, 5.4%, 5.4%, 0.4%, and 0.4 %, respectively (Centers for Disease Control and Prevention, 2007). UAE has higher rates of CKD risk factors including diabetes, hypertension, obesity, dyslipidemia, and smoking (Coresh *et al*., 2003; Fox *et al*., 2004; Yamagata *et al*., 2007; Saadi *et al*., 2007; Alhyas *et al*., 2011; Hajat *et al*., 2012; Aden *et al*., 2013; Shen *et al*., 2017). Therefore, it is expected that current prevalence of stages 3 to 5 of 4.6% in males and 2.8% in females is a huge underestimation of the real scope of the growing CKD problem in our population (Richards *et al*., 2015; Al Shamsi *et al*., 2016). At the other far end in Malaysia, there is a huge growth in scope of CKD as well. A simple statistic evidently exemplifying this is the rise in incidence and prevalence of patients with end stage renal disease (ESRD) on dialysis from 88 and 325 per million populations (pmp), respectively in 2001 to 170 and 762 pmp, respectively in 2009 (Lim *et al*., 2011).

1.5 Complications of CKD

In addition to the progression of CKD itself which eventually lead to renal failure, need for dialysis, renal transplants as well as mortality, there are many CKD

complications. These include hypertension, diabetes, dyslipidemia, cardiovascular disease, anemia, and bone and mineral disorders. There is strong evidence that controlling blood pressure and glucose as well as the use of various cardiovascular medications including angiotensin converting enzyme inhibitors and angiotensin receptor blockers slow the progression of CKD and the development of the major complications necessitating dialysis or leading to death (Yang *et al*., 2011). Determination of kidney function plays important roles for proper dosing of medication in CKD patients. In addition, estimated kidney function can vary between estimated creatinine clearance (eg, CG equation) and Glomular filtration rate (eg. MDRD) to direct measurement of kidney function. Any differences in estimated kidney function can cause misleading in drug dosing which can cause complications. Furthermore, medications with nephrotoxic effects are more susceptible to result in adverse effects in CKD patients' especially with comorbid conditions (Whittaker *et al.*, 2018). As a result, a proper estimatation of kidney function can decrease CKD complication.

1.6 The CKD Stage–Discordance of Various Equations

It has shown that there is about 15% discordance between CKD-EPI and MDRD in CKD staging, while, the discordance between CG and CKD-EPI was 45% (Parsh *et al*., 2015). Schwandt et al found that MDRD was the most accurate equation in matching mGFR in diabetic Brazilian CKD population (Schwandt *et al*., 2017). On the other hand, Veronese et al demonstrated that the accuracy of the equations differs with CKD stage and that different equations may perform better in different age, diabetes status, or CKD stage groups (Veronese *et al*., 2014). Ohsawa et al concluded in Japanese CKD patient sample that eGFR with CKD-EPI correlated better to mortality risk than eGFR derived from MDRD (Ohsawa *et al*., 2013). At the very outset, the accuracy of estimating the

glomerular filtration rate or creatinine clearance is far from being a one-size-fits-all task. This is a dynamic problem with even the best estimates varying within the CKD population being investigated.

1.7 Dosing Medication Algorithms in CKD Patients

Since 1998, the United States Food and Drug Administration (FDA) made it a requirement that new medication applications include renal dosing (US Food and Drug Administration, 1998). In 2004, the European Medicines Agency (EMEA) brought forth a similar statement in acute kidney injury patients (European Medicines Agency, Committee for Medicinal Products for Human Use, 2004). Many of the old medications still have dosing algorithms largely based on post-marketing data and the type of equation that the manufacturer company will used (Zuber *et al*., 2013). Patients with CKD face several challenges that may alter the responses to medications, and hence, may affect the optimal dosing of medications.

Some of the many factors that modify the dose-response relationships in CKD patients include; variable toxic drug levels in CKD patients, clinician's judgment, degree of acute deterioration and the stability of chronic kidney function, augmented clearance, and third fluid spacing (Zuber *et al*., 2013; Cook and Hatton-Kolpek, 2019). Clinicians end up estimating kidney function especially for initial dosing of medications in CKD patients. The USA FDA noted the CG equation in its guiding document for manufacturers, and therefore, it is this equation which is most often used during this medication dosing phase. On the other hand, the newer formulas which are used in renal function estimation guideline; namely, MDRD, Norm MDRD, and CKD-EPI generally offer a less biased and more accurate estimate of the GFR in CKD patients (Levey *et al*., 1999; National Kidney

Disease Education Program, 2010). However, this accuracy in estimating the kidney function falls short in guaranteeing a better drug dosing and that, according to studies, CG, MDRD, or CKD-EPI may derive better dosing outcomes (Wargo *et al*., 2006; Golik and Lawrence, 2008; Spruill *et al*., 2008; Hermsen *et al*., 2009; Stevens *et al*., 2009; Jennings *et al*., 2010).

Dosing of medications in CKD patients is further complicated by the very nature of the dose-response interactions for the various medications. Some medications need high peak levels for clinical responses whereas others require less fluctuation of the levels over the dosing intervals (Charpentier *et al*., 2000; Snyder and Berns, 2004; Thummel *et al*., 2011; Rocha *et al*., 2013). Aminoglycoside antibiotics are an example of the former, whereas β-lactams are representative of the latter (Stabler and Ensom, 2011; Jenh *et al*., 2011; Falagas and Vardakas, 2017; Habayeb *et al*., 2018). Another factor that modifies individualized dosing of these medications is malnutrition. In this patient population, and those with muscular atrophy or wasting, albumin may serve as a marker of kidney function and, therefore, can be used to select better dosing regimens (Spruill *et al*., 2008; Meijers *et al*., 2008).

Now, using the equations mentioned above, clinicians would normally have a calculated figure for eCrCl or eGFR that would then be used to determine the dose based on a recommendation provided in a drug monograph.

It should be noted that these monographs give sharp single point drug dosing tiers. For example, consider 54-year-old female, 60 kg, 182 cm, slender patient with alb of 3.3 g/dL, and serum creatinine (SCr) of 5.3 mg/dL who presents with hospital-acquired pseudomonas pneumonia. Normal dosing of meropenem for this patient would be 2 g

intravenously (i.v) every 8 hours. To adjust for kidney function with CG, the dose would be given at 1 g i.v every 12 hours (eCrCl ~ 11.5 ml/min). Using MDRD or Norm MDRD, this same patient would receive 1 g i.v every 24 hours (eGFR~9.0 ml/min/1.73m^2 or ml/min, respectively). Given this, clinicians would be faced with the dilemma of which dose would be a better choice for their patient.

Further complication could be resulted by the fact that most dosage forms of medications are inflexibly changed to individualize doses. For example, at our study institution, meropenem is only available as the 1 g dosage form. Therefore, it is not possible to try and give a middle 1.5 g dose in this case. Even if that was possible, it could be compromising a less biased and more accurate CG or MDRD estimate. A further elaboration with the use of antibiotics highlights, for example, the variability in their effect on organisms. To illustrate that, the concept of minimum inhibitory concentration (MIC) is considered (Rapp, 1999). MIC of antibiotic is the minimum concentration among its different concentrations that would inhibit the visible growth of the microorganisms such as bacteria. There is normally two-fold variability in this MIC value (Mouton *et al*., 2018). This means that the MIC could be, for example, 0.5 or 1 or 2 mcg/ml for a given drug-microbe combination. Obviously, adding the variability in MIC and that in the dosing tiers would further compound the dosing problem in CKD patients.

Astute researchers may find that the various renal function estimate equations can be used interchangeably in dosing medications on statistical grounds (Dinsa *et al*., 2017). The study including large samples, in addition to data with smaller groups of patients in the present study did indeed find statistical insignificance in renal function formula applications as presented in this current research. However, one would need to exercise caution in accepting such conclusions as this study alludes to these equations being far

from interchangeable at the borders of dosing tiers where one equation recommends a specific regimen while another would justify a different plan. Surprisingly, this study demonstrates in some cases that patients respond at doses totally outside of the dosing tiers recommended in well-known drug monographs.

Variability in dosing based on the different methods of renal function estimation is an intrinsic property of the equations (Fernandez-Prado *et al*., 2016). It is the factors used in each equation which comprise the different calculations that lead to dosing recommendations. However, dosing a specific patient can be guided by more than just the renal function estimate, and therefore, requires full consideration of all pertinent variables rather than mere substitution of one equation with another (Yao *et al*., 2017; Levey and Inker, 2017). Indeed, CKD alters both the pharmacokinetics and pharmacodynamics of a given medicine (Campoy and Elwell, 2005). Therefore, a better match of the GFR does not automatically translate into better drug dosing. Levey and Inker clearly discuss why the choice of eGFR or mGFR for drug dosing should be individualized for each patient. They further give basis for the Kidney Disease Improving Global Outcomes (KDIGO). (Levey and Inker, 2017).

1.8 Gender effect in Chronic Kidney Disease

Gender refers to gender identity and/or sociocultural roles, whereas sex refers to attributes that characterize biologic sex. Gender and sex each play a role in the development and progression of CKD, yet these two terms are often inappropriately used interchangeably in scientific and medical literature. In many studies, common gender identity category terms (woman and man) and sex category terms (female and male) are erroneously treated as synonymous (Ahmed et.al 2010).

Animal and experimental studies offered further explanations for gender differences in disease progression. Endogenous estrogens considered to have anti-fibrotic and anti-apoptotic effects on the kidney. Faster kidney function decline in men attributed to the specific proapoptotic and profibrotic properties of androgen gender differences in chronic kidney disease kidney blood press res 2010,33;383-392 385 gens (Carrwro.et.al 2010). Postmenopausal women on HRT had a significant reduced risk of albuminuria if compared with that not on hormone. Retrorepective study suggested an independent dose-dependent association of oral estrogen use and loss of kidney function in elderly women. In a retrospective study, the (MDRD-eGFR) was suggested to differ between sexes and to vary with age more than serum creatinine concentration dose. Incorrect GFR estimation may over/underestimate renal function, influencing results from large epidemiological studies and/or clinical decisions such as medication prescription. Higher prevalence was reported on CKD stages 3-5 in females than male , which couse ESRD statistics increased, and this may depend on the limitations of the MDRD equation.(Carrwro.et.al 2010).

1.9 Computer Simulation in Science

Computer simulation used a computer in gradually methods to explore the behavior of mathematical model, the original model contains discrete equations or the original model have the rules of evolution. In this, the computer simulation is comprehensive method study systems as an entire process. Simulation is a system, which have dynamic behavior, which is similar to such extent that it can be studied to learn about it (Holford *et. al.* 2000)

Types of computer simulation: equation based simulation and agent based simulation, it can be used for prediction, understanding and exploratory purposes. Equation based simulations: used in physical science in which the governing theory can used the

building of mathematical models based differential equations. Agent based simulations: used in behavioral, social sciences, and it represent the behavior of many discrete individuals and it is the behavior of the individuals, which is dictated by their own local rules

Multi-scale simulations: it is couple modeling elements with different description scales and it can be divided further into serial multi-scale and parallel multi scale methods. While Monte Carlo simulations: it is a computer algorithm, which use randomness to calculate properties of mathematical model in which the algorithm is not the target model feature. The purpose of simulation is for heuristic purpose, generating and understanding the data, which we have, or predicting the data we do not have. Regarding the heuristic models the simulation can be divided into usage to communicate knowledge to others or represent information to ourselves.

In addition, computer simulation can use models to predict the future or tell us about the past. To understand the systems and the way they behave simulation can help to understand generally especially if we have the data, then computer simulation can provide answers about the possibility of events and how it did occur (Vinks *et.al.,* 2015).

1.10 Clinical Pharmacist Roles in Dosing Adjustment

Clinical pharmacists are specialty trained practitioners who provide direct patient care and comprehensive medication management. There are clinical pharmacists throughout the world who are improving the care of patients of all ages and in all areas of acute and ambulatory care.There role in dose adjustment of renally eliminated drugs are crucial to prevent or decrease drug-related adverse events and eventually decrease hospitalization and costs. (Alshammari,2019). Nearly every third admitted patient had impaired renal

function. Frequent dose unadjustments increase the risk of adverse drug reactions. Clinical pharmacists can increase the rate of proper dose adjustments in patients with renal impairment. The implementation of systemically provided pharmaceutical care in hospital wards can facilitate positive treatment outcomes and increase patient safety (Papic *et.al*., 2018).

The benefit of clinical pharmacist education, monitoring and intervention was demonstrated in a prospective, randomized study of 800 heart failure or hypertension patients treated at the clinics of a large public hospital. The patients with clinical pharmacist interventions had a 34% lower risk of any adverse drug event (ADE) or medication error (ME) (risk ratio 0.66, 95% confidence interval [CI], 0.50-0.88) including a significantly lower risk of ADE, preventable ADE, potential ADE, and medication errors compared with control patients treated at the same clinics. Patients with complicated cardiovascular histories had the greatest number of medications and events. Pharmacist interaction, education, and regular communication with the rest of the team improved medication adherence, patient satisfaction, and reduced healthcare utilization and direct costs of care. A systematic review of 12 randomized trials of clinical pharmacist impact on heart failure patients showed similar benefits with a reduced rate of all-cause hospitalization (Odds ratio [OR] 0.71, 95%CI (0.54-0.94) and heart failure hospitalization rate OR 0.69, 95%CI (0.51-0.94)16. Other reviews have described additional benefits of clinical pharmacist monitoring and interventions on a variety of treatment endpoints (blood pressure, lipid profile, weight, and glycemic control). The American College of Cardiology has endorsed a strategy of team-based care, including clinical pharmacists. Clinical pharmacists on medical inpatient acute care teams have been shown to reduce preventable adverse drug events by 78%19. A clinical pharmacist who rounded with a critical care

team more effectively identified and prevented more adverse drug events than pharmacists involved in order entry and verification, and avoided the potential expenditure of over $210,000 in 4.5 months. A review of 36 studies describing the impact of clinical pharmacists on hospital inpatients suggests that the addition of a clinical pharmacist to the acute care team resulted in improved care, with no evidence of harm. Interacting with the team on rounds, interviewing patients, reconciling medications from outpatient to inpatient, patient discharge education, and follow-up all resulted in improved outcomes. Highest risk patients such as the very elderly, and the very young have been shown to benefit from the presence of and contributions of clinical pharmacists (Judith, 2016).

1.11 Economic Burden of CKD

Both direct and indirect medical costs of CKD are huge and rise as the disease progress from early stages to dialysis. The list of direct and indirect medical costs is large with hospitalizations being a significant portion of the costs. To give the reader an idea about the humongous economic burden, consider the total Medicare expenditure in USA per patient of around 20,000 US dollars for early stages rising to more than 65,000 US dollars for late stages. Nationally these correspond to a total Medicare expenditure of 125 billion US dollars for early stages mounting to more than 400 billion dollars for late stages of CKD (Wang *et al*., 2016).

In calculating medical cost for treatment, all costs, which are resource use are attributable to health care intervention or illness, called direct cost. This in turn can be divided into direct medical and non-direct costs. The cost of intervention with follow up and cost for medications in ambulatory, in-patient, and nursing care are considered direct medical costs. Other services as transportation and additional paid caregiver time considered direct non-medical costs.

1.12 External Validation of Clinical Prediction

A famous type of clinical research is the statistical models that evaluate diseases and outcomes. Predication model is one of these models that assessed, evaluate and predicate any data and find the outcomes. This model used to predict and study the patterns in data and the chances of different outcomes can occur. However, to build an accurate model, problem should be well defined and data to be collected. Followed by running and evaluating the model and solving the define problem (Riley *et. al* 2016).

External model is another model that used to validate the predication model. This model can estimate individual's probability of developing a disease or outcome in the future. It is very important to evaluate its predictive performance using a separate data set from that used for a model. External validation should not be identical to the main original data set. It should slightly differ in some parts such as data collecting timing or main study setting. Published studies evaluate prognostic models are often conducted using sample sizes that are clearly inadequate for this purpose, leading to exaggerated and misleading performance of the prognostic model. In addition, this model can be assessed using new data from the source as the derivation sample, comparing the result with observed and predicted events rates (Collins *et al.,* 2016).

1.13 Artificial Neural Network (ANN Modeling)

This section will introduce the broad specialty and modeling tool known as ANN. Reason is that the optimal renal estimate to dose medications in CKD is a heuristic problem that require a prediction tool and ANN is one of the most powerful available to do the job. ANN (Figure 1.4) are computer software and/or hardware that employ the concepts of the brain and nervous systems of intelligent species (humans) to train, test, validate and eventually predict outcomes from known inputs (Zemikow *et al*., 1998). In its

simplest form it is a group of neurons (circle or ellipses) interconnected by weights (arrows). The neurons are organized into layers; one input, one output, and one or more hidden. Each input node represents an independent variable used in the dataset. This input node takes a weight and it, and the subsequent nodes feed forward into all (completely connected) or part (partially connected) of the neurons in the subsequent layers.

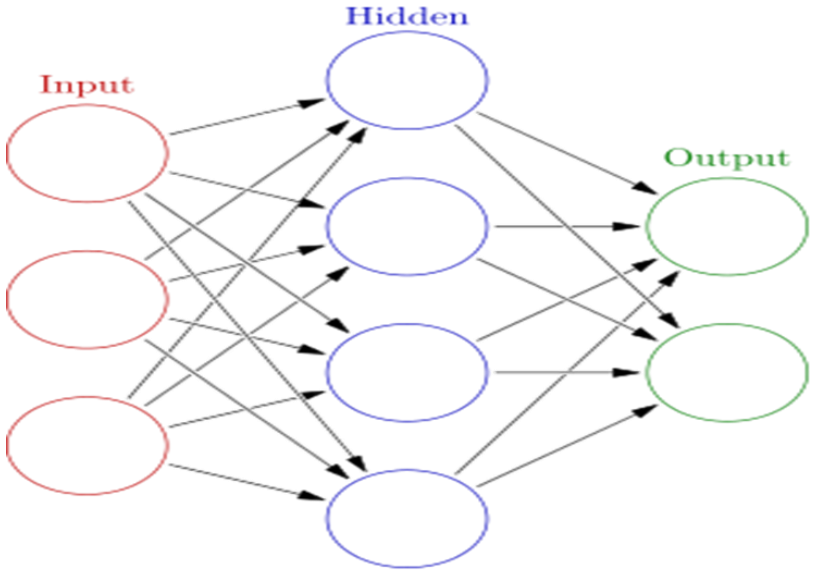

Figure 1.4 Simple Artificial Neural Network (ANN). Source:
(URL: http://uc-r.github.io/ann_fundamentals, accessed Wendsday May 20st 2020)

The ANN configurations can be broadly categorized based on the outcome variable into two main types. Probabilistic networks (PN), used for categorical outcomes, are partially connected and generate probabilities that reflect a level of confidence that the network has in each prediction it makes. For example, the network may be 99% confident in predicting risk of readmission. In addition, we can develop models that will predict, with reasonable precision and certainty, outcomes such as readmission risk associated with specific clinical decisions (Jamei *et al*., 2017).

1.14 Research questions

Given the above arguments and details around the use of GFR algorithms for medication dosing, this research aims to investigating the following general problems:

1. What factors explain the emergence of one renal function estimate as a more optimal dosing algorithm or predictor of clinical response?
2. How can this heuristic dosing problem be completely separated into its components? In other words, can we dose all CKD patients or specific groups of CKD patients with the correct renal function estimate right from the start?
3. What are the clinical and financial implications of this accurate initial empiric drug dosing?

1.15 Justification of Research

First of all, there is much confusion in selecting the best equation for drug dosing in CKD patients (Gonwa *et al*., 2004; O'Meara *et al*., 2006; Gill *et al*., 2007; Melloni *et al*., 2008; Barras *et al*., 2010; Park *et al*., 2012). Clinicians need to be more informed about how to dose each patient according to clear evidence. The best estimates for dosing seem to vary such that research teams find different methods that may be better in different populations. Second, clinical pharmacists (CPs) mostly make dosing interventions in CKD patients and this too, is largely based on specific equations in various studies (Diego *et al*., 2008; Desrochers *et al*., 2011; Craig *et al*., 2012; Dooley *et al*., 2013; Pourrat *et al*., 2015; Glatard *et al*., 2015). Rarely, do researchers correlate these adjustments of medication doses in CKD patients with clinical outcome. Therefore, one of the ultimate goals of this research is to know when to use each equation correctly. Specifically, in what situations is CG a better option and, on the other hand, in which instances can MDRD serve to provide

an optimal estimate of the correct dose. Although knowing the specialist who deals with CKD patient whether he/she (clinician) is nephrologist or clinical pharmacist, this study would shed the light on who would make a difference in the choice of the equation to dose medications. Moreover, the potential economic burden from this little informed dosing decision in CKD patients and the financial gain achieved from using an evidence-based dosing in CKD patients were elucidated.

1.15.1 Justification of Specific Research Outcomes

The specific outcomes to produce in this research are to determine, which calculated renal function estimate would be more concordant with clinical response in a real-life paired proportion cohort study design. Up to this point in time, there is lack of clinical research investigating the optimal dosing method in CKD patients in terms of the clinical response. There are many studies on the dosing errors in CKD patients and the concordance between equations and mGFR (Lesley *et al*., 2009; Farag *et al*., 2014; Saad *et al*., 2019). However, there is paucity, if at all, data about the clinical outcomes of such dosing algorithms. Therefore, in this research all consecutive CKD cases as to what dosing method or equation produced the needed clinical response of each medication in every case were evaluated.

Once again, background differences in the approaches adopted by CPs and nephrologists in handling dosing interventions in CKD patients will be determined. More specific research outcomes will include identifying factors that point to the optimal dosing method, especially those factors relating to the medication or groups of medications being studied. To clarify this further, the effect of factors such as medication or class of medication, weight, CKD stage, age, gender, ethnicity, albumin, and concomitant diseases on determining the optimal dosing algorithm will be studied. Optimality of a dosing

algorithm simply means that the equation concord with the clinically chosen dose and which match the recommendation based on that estimate. Finally, the economic impact of optimal dosing with the best renal function estimate based on this study will be determined.

1.15.2 Benefit to the Targeted Community

This is a simple business-oriented explanation of how the current research would benefit the various stakeholders of dosing medications in CKD patients. This research will firstly and ultimately benefit the patients. The random selection of dosing equations in CKD patients delays the optimal dosing and, hence achieving the subsequent needed clinical response. Therefore, this research will facilitate reaching this optimal dose more quickly and effectively in a sizable proportion of patients. As clearly shown before, this would help minimize the progression and emergence of the various complications and/or comorbidities of CKD (Yang *et al*., 2011). Our second beneficiary in current study would be the insurers and payers of care, who will, therefore, pay less to chaotic medication dose selection in CKD patient care.

The huge economic burden that would remain with the suboptimal dosing of medications used for the various CKD concomitant diseases was emphasized (Wang *et al*., 2016). Care providers would also benefit since they will be able to dose better in less time and hence would be perceived more positively by their patients and families. This can be easily understood if readers appreciate that satisfaction of patients and their families is related to optimal medication dosing in CKD care (Diamantidis *et al*., 2015). Health professions students and trainees will have better guidance on employing the various equations in dosing medications to CKD patients. Bhasin et al. hinted to how a better understanding and optimal dosing prediction tools in CKD can revolutionize the field of

nephrology just as it did in surgery and ophthalmology (Bhasin *et al*., 2013). The list is endless, as all of society should benefit from a more informed dosing activity in CKD patients.

1.16 Research Aims and Objective

The aim of this study is to evaluation medication dosing and risk factors association with dosing errors in CKD patients, and comparative assessments of different methods used to estimate eGFR. In addition, the role of clinical pharmacist and Direct Medical Costs at a flagship military hospital in Abu Dhabi, U.A.E. Specific objectives in this research study include:

1. To compare the various equations used to estimate eGFR in drug dosing and to evaluate the intrinsic factors when applied to simulated cases
2. To apply CG or MDRD formulae in dosing of medications to establish clinical differences in CKD patients
3. To measure the degree of involvement of CPs and nephology staff in adjusting medication doses in CKD patients.
4. To determine the direct medical cost of effectively achieving timely optimal dosing of medications in CKD patients.

1.17 Research Strategy

A clear research strategy to answer the above research questions posed will need to be developed. The documented research in this area points to the use of fragmented tactics and methods by various authors to study parts of the queries posed in this study. For example, some authors have focused on simulation while others have used actual data. Another important consensus in published literature which is out of context, is the insistence on using mGFR as a reference for the correctness of the doses used in practice

without paying much attention to the real end outcomes or clinical response. The reason this is a faulty consensus is multifactorial as shown in various parts of this dissertation. Outcomes in individual patients depend on many pharmacokinetic and pharmacodynamics factors that shall never be reduced to a population one-size-fit-all dose per an eGFR or mGFR. Even mGFR has significant error in degree of renal function deterioration. Consequently, in this research a systematic scientific approach will be followed in evaluating the research questions.

Firstly, a simulation will be performed to study the intrinsic nature of each equation and whether the various methods of renal function estimation concur relative to dosing. Second, a systematic review of the literature and a second simulation will be undertaken to gain insight on the potential of statistically and clinically significant consequences to discordance, if any, of renal function estimates. Thirdly, real life data will be collected to inform practitioners dosing to clinical response as opposed to dosing to match drug monographs. Fourth, using the real-life data, an attempt will be made to establish the optimal drug dosing method, and if there are any patterns for a preferential method to emerge as better. In addition, the heuristic nature of the problem of optimality of renal function estimates will be tested by developing, training, testing, and validating an ANN application that will enable discernment cases that demonstrate the optimality of a given equation over another. Fifth, the degree of involvement of CPs and nephology staff in adjusting medication doses in CKD patients was measured. Finally, direct medical cost of effectively achieving timely optimal dosing of medications in CKD patients by comparing the cost of medication before and after intervention and the decision tree analysis was determined and applied.

CHAPTER 2
LITERATURE REVIEW

2.1 Objectives of Literature Review

Globally, CKD has become of substantial health and economic burden. With decreased renal function, the pharmacokinetics of many drugs are significantly changed so that the effect of usual doses either becomes augmented or diminished (Ponticelli *et al.*, 2015). Moreover, the patient's response may be changed due to the effect on multiple organ systems, increasing the susceptibility to the effect of drugs. CKD patients undergoes to significant accumulation of drugs, accompanied with high risk of side effects and toxicities in conjunction with the use of polypharmacy to treat comorbid conditions. Inappropriate medication dosing in CKD patients can cause toxicity or ineffective therapy. This necessitates adequate renal dosing adjustments.

This review will address medication dosing in CKD patients from a different angle, and it will cover all the studies that compare the various equations used to estimate renal function, and the effect of intrinsic factors. In addition, the effect of involvement of clinical pharmacists and Nephrology staff in adjusting medication doses in CKD patients. Moreover, this chapter will review all types of studies associated with direct medical cost effect when achieving optimal dosing of medications, of particularly it will focus on the clinical response and the optimal dose.

2.2 Search Strategy for Literature Review related to Study Objectives

In this connection, the objective is to collect data from the literatures to quantify the potential of related study objectives. Google Scholar, PubMed/MEDLINE, EMBASE, Science Direct and Cochrane Library were used to search for following terms:

"Concordance CG and MDRD, estimating glomerular filtration rate, Creatinine clearance estimation, Discordant is the Various Formulas, Dosing Problem in CKD Patients, Discordance Effect on CKD Outcomes, Clinical Pharmacy or Nephrology, Factors modifying concordance, Dosing to desired response, ANN model, CKD dosing and medical cost"

2.3 How Discordant is the Various Formulas?

Models estimating glomerular filtration rate and creatinine clearance have an inherent discordance as can be shown from this research. At the very outset, the literature findings were summarized as following (Table 2.1):

Wargo et al showed that 25% of antimicrobials would have been dosed differently with CG versus MDRD (20 – 36%, $p < 0.001$) (Wargo *et al*., 2006). They assumed that one equation was used across all cases and that CG would have resulted in the maximum percentage of discordance with doses received. Using the same rationale, MDRD would have resulted in a 21% overdosing (18 – 30%). The greatest discordance was observed with the drug, meropenem, at above 35%. In our real practice, however, clinicians use these models or equations at different times and sometimes even for similar scenarios (i.e. they do not abide to one equation or another) (Spruill *et al*., 2008).

In addition, Golik et al confirmed these findings in another study where the discordance between CG and MDRD was reported as a range from 22.8% to 36.3% for the studied antimicrobials (Golik and Lawrence, 2008). Cefepime and meropenem had the greatest discordance rates at 36.3% and 32.4%, respectively. These are broad spectrum antibiotics with special value in use for resistant pathogens, including *Pseudomonas aeruginosa*.

Interestingly, the emerging literature in subsequent years clearly demonstrated a higher, yet unequivocal, mortality risk with cefepime used for various pathogens and infections (Fisher *et al*., 2009; Gomez *et al*., 2009; Mebis *et al*., 2009; Nguyen *et al*., 2009; Paul *et al*., 2009; Kim *et al*., 2010; Leibovici *et al*., 2010; Chopra *et al*., 2012). Bauer et al reduced the cefepime-increased mortality for *Pseudomonas aeruginosa* with a better dosing strategy; namely, extended intravenous infusions (Bauer *et al*., 2013). On the other hand, Alves et al reported a clear association of cefepime dose with mortality (Alves *et al*., 2014). Authors in their study assessed a homogenous population in terms of creatinine clearance. Their rationale was that cefepime would produce a mortality difference, patients with CKD be unequally distributed between cefepime usual and high doses. Therefore, discordance in dosing these antibiotics based on renal function estimation can lead to significant mortality outcome variations.

Wargo et al have also shown similar results between CG and the CKD epidemiology collaboration equation (CKD-EPI) with a discordance of 15 to 25% for selected antimicrobials (Wargo and English, 2010). Gill et al demonstrated an even more dangerous discordance with the narrow therapeutic index drug, digoxin, where 58 patients of the 179 (32.2%) would receive a higher dose with MDRD compared with CG formula. In the same study, amantadine doses would have been higher in 21.2% of patients with MDRD compared with CG. Similarly, the authors reported a huge rate of discordance In the CKD staging by the two equations where less than 40% of the patients having the same stage with CG and MDRD. To the puzzled reader, these discordant dosing recommendations are inherent in the equations themselves because these equations give different eCrCl or eGFR values and these values would all fall into different dosing tiers (Gill *et al*., 2007).

Corsonello et al showed that MDRD and CKD-EPI were highly concordant but both discorded with CG in about one third of cases (Corsonello *et al*., 2011). It is an expected higher concordance since both MDRD and CKD-EPI estimate GFR as opposed to the old CG which estimate eCrCl. On the other hand, Dowling et al recommended clearly that clinicians should refrain from using MDRD and CKD-EPI in place of CG as both overestimated creatinine clearance in contrast with both measured CrCl and CG in elderly patients (Dowling *et al*., 2013).

In another study using direct or new oral anticoagulants (DOAC or NOAC), they reported an overall population discordance of 8.5% to 11% between CG and both MDRD and CKD-EPI. This increased to 13.2% to 30.4% in elderly patients with eGFR below 60 ml/min. Clearly, apixaban had high concordance rates compared to dabigatran and rivaroxaban which is expected given the fact that dosage adjustments for apixaban are made with raw SCr levels in drug monographs (Manzano-Fernández *et al*., 2015).

Hudson et al presented another example where gabapentin dosing discorded in 27% of cases between CG and MDRD or CKD-EPI (Hudson *et al*., 2015). They noted that the greatest discordance was for drugs with more dosing tier stratifications.

Using the cystatin-based methods may improve the measurement of degree of CKD impairment but it does not decrease the dosing discordance with CG. Using a creatinine and cystatin combined equation can increase the percentage (69%) of eGFR within 20% of the actual mGFR (P20). According to this study, CG has a P20 of 38% thereby underlining a 45% dosing discordance, mostly lower dose with CG, in contrast to the combined equations (Chew-Harris *et al*., 2015). Using cystatin-based CKD-EPI reclassified 31 to 52% of patients into lower drug dosing category compared to the creatinine-based CKD-EPI, MDRD, and CG equations (Wang *et al*., 2018).