Model comparison of estimated glomerular filtration rate for acute kidney injury in intensive care unit

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Model comparison of estimated glomerular filtration rate for acute kidney injury in intensive care unit

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Abstract. Acute kidney injury (AKI) is common in critically ill patients and often associated with higher mortality. It is commonly diagnosed using plasma creatinine, a fluid excreted by glomerular filtration. In this study, we analysed the highly nonlinear and complex behaviour within human systems of estimating glomerular filtration rate in critically ill patients to estimate AKI outcome by developing an application program that describes various numerical mathematical models estimated glomerular filtration rate (eGFR). The program was developed to collect numerous clinical patient data and perform computations of the governing equations that may provide clinicians with rapid estimation of GFR which allow prediction of recovery or worsening of renal function at bedside. Data collection using the application program was conducted at the intensive care unit in Kuantan, Malaysia from January to August 2016. It was found that the eGFR by CKD-EPI shows the best correlation with kinetic GFR (keGFR) equations compared to other mathematical methods for Malaysian ICU patients. It is endeavoured that more patient data would be collected using this mobile application, to develop a more accurate GFR estimation model suitable for Asian populations since creatinine based equations are often derived based on white populations.

Keywords. Modelling and simulation; Nonlinear analysis; Biomechanical engineering; ICU; Acute kidney injury; Mobile application.

1. Introduction

Acute kidney injury (AKI) remains an important clinical problem as it is often associated with the development of chronic kidney diseases, increased morbidity and mortality and enhanced risk of end-stage renal disease [1]. Diagnosis of AKI relies on accurate assessment of kidney function in critically ill patients, however there is no widely accepted approach to either definitely and rapidly diagnose the injury or determine the extent of its severity. The complexity in assessing the kidney function is due to the highly nonlinear and complex behaviour within human systems. This poses a big challenge to

physicians as successful patient outcomes require rapid and accurate diagnosis leading to early intervention and effective therapeutic strategies.

One method used for renal function assessment is urinary clearance (CrCl). This is obtained from a timed urine collection and blood sampling for serum creatinine [2]. Nevertheless, this method requires a steady state situation which is often not met by critically ill patients.

Another method that can be used for AKI assessments are often done by estimating glomerular filtrations rate (GFR) which measures the rate of plasma filtered through glomeruli. Current GFR methods are based on serum creatinine. However, in acute and chronic illnesses, GFR estimates remain relatively imprecise owing to rapid changes and variations in non-GFR determinants of serum creatinine [3]. Factors that may influence the accuracy of serum creatinine as a marker of kidney function in critically ill patients with AKI include fluctuations in: (1) creatinine metabolism as a result of immobilization, malnutrition or catabolic illnesses (2) true kidney function and (3) fluid balance such as increase in total body water which consequently increases the distribution volume of creatinine resulting in an attenuation in the increase in serum creatinine [4]. Furthermore, therapeutic drugs used to treat critically ill patients are known to affect the serum creatinine concentration rendering it as a poor marker for AKI [5]. GFR measured using exogeneous substances such as chromium-ethylenediaminetetraacetic acid (51Cr-EDTA), diethylene triamine pentaacetic acid, inulin and iohexol as filtration markers, is considered as the gold standard for renal function assessment [6]. These methods however are complex and expensive making them unsuitable for routine use.

A promising method for GFR estimation is by implementing estimating numerical models, also known as estimation glomerular filtration rate (eGFR), which have been developed in population studies which includes patients with stable serum creatinine and acutely changing plasma creatinine [1, 3, 7]. To overcome the limitations associated with using serum creatinine alone, these equations incorporate variables such as sex, age, body weight and race in addition to serum creatinine as a substitute for muscle mass. The development of GFR estimating equations meet the important clinical needs as it overcomes the tedious, time-consuming, and expensive techniques currently available. This technique allows the estimation of GFR at bedside techniques which is often desirable by physicians.

Due to its potential, there are several GFR estimation software applications currently available on the market. These are often web-based application which are limited to calculating the estimated GFR output and does not store any data. Hence, the user is neither able to retrieve previous calculations of estimated GFR values nor save patient readings necessary to obtain the eGFR output which is of paramount importance in improving estimating formulae which are based on population studies. Furthermore, there is still a need to develop a program application to calculate kinetic estimates of GFR (keGFR) as it has been shown to result in more accurate estimates of GFR in critically ill patients with rapidly changing kidney function [8].

Furthermore, the current system in Malaysian hospitals rely heavily on manual hard copy input of patient data [9]. The difficulty is compounded by the fact that the data set for the patient readings are large, complex and time dependent. Human error in transferring the data from the patient report as digital inputs to the equations may affect the accuracy of the model. The development of an application will allow for a larger volume of patient data which will significantly improve GFR estimations.

The purpose of this study is to describe the development of the program application used to collect and store patients' clinical and biometric data pertinent to computing the glomerular filtration rate for different estimation equations. The application provides medical experts with an easy to use user interface for efficient and accurate input of patient data and outputs calculated results of GFR estimations to provide clinicians with the ability to predict recovery or worsening of renal function at bedside. We evaluated the best method for eGFR estimation that correlates with the kinetic estimates of GFR. This is beneficial for clinicians as it will allow for rapid identification and determination of the extent of injury, provide prognostic information and allowing for early intervention and accurate therapeutic treatment. It is endeavored that the application will create a supportive ecosystem for the development of clinical research, specifically to improve the accuracy of the available GFR estimation models in the Asian context [10].

2. Mathematical model and governing equations

For serial measurement of creatinine, a database was developed to store the patient readings and the calculated glomerular filtration rate value based on the various models available for estimation.

2.1. Modified diet in renal disease (MDRD)

The Modification of Diet in Renal Disease (MDRD) equation was developed by Levey et al. [11] for prediction of GFR from serum creatinine concentration. The eGFR by MDRD equation for males is given by equation (1),

$$\mathrm{eGFR_{male}} = \frac{170 \times \mathrm{Alb}^{0.318}}{\mathrm{P_{Cr}^{0.999}} \times \mathrm{age}^{0.716} \times \mathrm{S_{UN}^{0.170}}} \tag{1}$$

For females, the estimated GFR by MDRD is given by equation. (2),

$$\mathrm{eGFR_{male}} = 0.762 \times \frac{170 \times \mathrm{Alb}^{0.318}}{\mathrm{P_{Cr}^{0.999}} \times \mathrm{age}^{0.716} \times \mathrm{S_{UN}^{0.170}}} \tag{2}$$

where $\mathrm{P_{Cr}}$ is serum creatinine concentration (mg/dL), $\mathrm{S_{UN}}$ is serum urea nitrogen concentration (mg/dL) and Alb is the serum albumi concentration (g/dL).

2.2. Cockcroft- Gault estimated glomerular filtration rate

Estimated glomerular filtration rate may also calculated using the well-known equation described by Cockcroft-Gault [12] using serum creatinine, $\mathrm{S_{Cr}}$ (μmol/L), which includes the variables age, gender, weight for reasonable prediction. For males, the eGFR by Cockcroft- Gault equation is given by equation (3):

$$\mathrm{eGFR_{male}} = \frac{\mathrm{Weight} \times (140\text{-Age})}{0.815 \times \mathrm{S_{Cr}}} \tag{3}$$

The eGFR by by Cockcroft-Gault [12] for females is given by equation (4),

$$\mathrm{eGFR_{female}} = 0.815 \times \frac{\mathrm{weight} \times (140\text{-age})}{0.815 \times \mathrm{S_{Cr}}} \tag{4}$$

2.3. Chronic kidney disease epidemiology collaboration estimated glomerular filtration rate

The Chronic Kidney Disease Epidemiology Collaboration Estimated Glomerular Filtration Rate (eGFR by CKD-EPI) model derived by Levey et al. [13] was shown to improve accuracy of the previously used Modification of Diet in Renal Disease (MDRD) equation across a wide range of clinical conditions and variety of population where S_{Cr} (μmol/L), is the serum creatinine. The eGFR by CKD-EPI is given in table 1 below:

Table 1. CKD-EPI Equation for estimating GFR [13].

Gender	S_{Cr} (μmol/L)	eGFR by CKD-EPI
Male	≤ 80	$141(\mathrm{S_{Cr}}/0.9)^{-0.411}(0.993)^{\mathrm{Age}}$
	< 80	$141(\mathrm{S_{Cr}}/0.9)^{-1.209}(0.993)^{\mathrm{Age}}$
Female	≤ 62	$144(\mathrm{S_{Cr}}/0.7)^{-0.329}(0.993)^{\mathrm{Age}}$
	< 62	$144(\mathrm{S_{Cr}}/0.7)^{-1.209}(0.993)^{\mathrm{Age}}$

2.4. Kinetic estimated glomerular filtration rate (keGFR)

In order to improve early prediction of delayed graft function (DFG) to facilitate patient management after kidney transplantation, Pianta et al. [8] modified the kinetic estimated glomerular filtration rate (keGFR) method developed by Chen [7] to include plasma cystatin C (pCysC). This is an advantage since studies have shown that plasma cystatin C outperforms serum creatinine (S_Cr) for DGF

prediction [14, 15]. Results from this study demonstrated that the formula is accurate in predicting 4 hours of renal transplantation.

The keGFR equation derived by Pianta et al. [8] is given is given by equation. (5):

$$\text{keGFR}= \frac{B_C \times \text{eGFR}}{\text{Mean}(B_C)} \times \left(1- \frac{24 \times \Delta B_C}{\Delta t_{(\text{hours})} \times \text{Max}(\Delta B_C/\text{Day})}\right) \quad (5)$$

where B_C is the circulating biomarker concentration (Serum creatinine or plasma cystatin C), eGFR is the unadjusted $\text{eGFR}_{\text{CKD-EPI}}$ in table 1, $\text{Mean}(B_C)$ is the mean of two consecutive values of B_C, ΔB_C is the change in biomarker concentration in $\mu\text{mol/L}$; for example S_{Cr} $(\mu\text{mol/L})$, $\Delta t_{(\text{hours})}$ is the interval in hours between two consecutive biomarkers and $\text{Max}(\Delta B_C/\text{Day})$ is the maximum theoretical increase in the biomarker concentration that occurs in a day when GFR is zero. According to Chen [7] and Pianta et al. [8] $B_C \times \text{eGFR}$ should only be calculated once for the renal episode. To ensure consistency, the biomarker for every 4 hours is used such that given equation (6),

$$B_C \times \text{eGFR} = B_C(4\text{h}) \times \text{eGFR} \times 1.44 \quad (6)$$

Thus, the maximum increase in the biomarker can be expressed as equation (7):

$$\text{Max}(\Delta B_C/\text{Day}) = \frac{B_C(4\text{h}) \times \text{eGFR} \times 1.44}{V_d} \quad (7)$$

where $V_d = 0.6 \times \text{weight}_{(\text{kg})}$ for serum creatinine [7] and $V_d = 0.2 \times \text{weight}_{(\text{kg})}$ for plasma cystatin C [16]. Since eGFR may not be less than 0, a value of 0 will be assigned to any negative computed values of keGFR following Pianta et al. [8]

3. Results and discussion

3.1. Technical details of the program application

The application was developed in Swift 4.0 programming language on Xcode 9.2 to run on all iOS devices. Minimum hardware requirements are Apple A6 Chipset, RAM 1GB, free 1GB internal memory since the available physical resources in the ICU we worked with are iOS devices.

It uses the Model View Controller to retrieve data from the core data and update the user interface based on the user input. The Core Data Model framework is used to manage data and is responsible in organizing data elements, defines structure of objects and standardizes how the elements relate to each other. By taking advantage of this built-in module, it is able to track data, filter data and save data on the disk. Here, Core Data uses SQLite as the persistent backing store where the actual data is stored. The advantage of using these modules together is that it allows the maintenance of offline user sessions and preferences of the application. Access to data in the persistent store is implemented via the persistent store coordinator. In the context of the application being developed, the patient forms the patient entity while the attributes consist of patient details, reading entries and calculated GFR data.

User-friendliness was one of the major goals of the design as clinicians in Intensive Care Units require quick data input and rapid results. In contrast, it was necessary that the learning time to use the program was reduced. Thus, for this purpose, many objects in UI Segmented Control, UI Picker Class, UI Alert Controller for example were used which allows for segmentation control for details such as gender and ethnicity and rotating wheels for date and time to ensure accurate yet rapid creatinine readings for patients.

3.2. Main modules of the program application

The main modules of this mobile application are:

- The **database module**, which is used for displaying and storing patient data records in figure 1(a).
- The **add new patient module**, which is used to add new patient and record their information and key in the first creatinine reading for the patient in figure 1(b).

- The **maintenance module**, which is used to edit and update serial readings of creatinine for the patient in figure 1(c).
- The **results module**, which produces data reports of the serial calculations of the GFR estimations in figure 1(d).

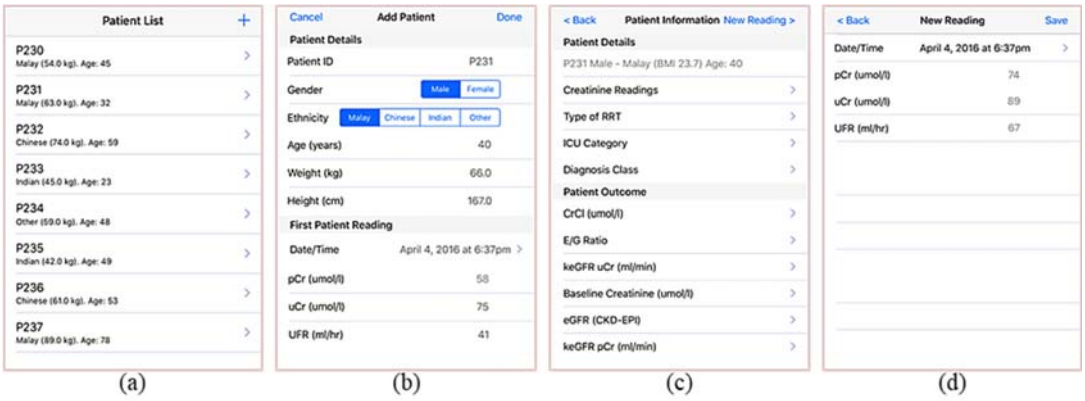

Figure 1. User interface for the developed mobile application for data collection (a) Database Module (b) Add New Patient Module (c) Maintenance Module (d) Results Module.

3.3. Data collection and validation of the program application

To control the accuracy and the accuracy of the application calculations, the program was tested against manual calculations using available patient records and virtual patient data provided by the anesthetists from the ICU. Furthermore, the user interface was also rigorously tested by the developers and the medical practitioners to ensure ease of use, check usability conditions and verify data integrity, all navigations, date field and numeric formats. The user-interface of the application was improved based on the feedback obtained from the testing.

3.4. Study Population and calculation of Glomerular Filtration Rate (GFR)

Data were recorded into the mobile application from a total of 140 adult patients admitted to the Intensive Care Unit of Hospital Tunku Ampuan Afzan, Kuantan, Malaysia from January 2016 to August 2016. A total of 31/140 (22.15%) patients died. The demographics of the patients is given in table 2. The study was registered with the Malaysian National Medical Registry (NMRR 14-1897-21447).

Table 2. Baseline characteristics of 140 patients included in the study. Identification of Acute Kidney Injury (AKI) is determined by KDIGO (Kidney disease: Improving global outcomes) [17]. Data are presented as mean ± standard deviation or number (%).

	No AKI in ICU	AKI in ICU
Number of patients	57 (40.71%)	83(58.29%)
Mortality	13 (9.29%)	18 (12.86)
Female/Male	20/37	29/54
Age (years)	45.33 ± 17.39	54.80 ± 15.48
BMI (kg/m^2)		
< 18.5 (Underweight)	3 (2.14%)	6 (4.29%)
18.5 - 24.9 (Normal)	28 (5.71%)	31 (22.14%)
≥ 25 (Overweight)	26 (18.57%)	46 (32.8%)

Table 2. Continued.

	No AKI in ICU	AKI in ICU
Ethnicity		
Malay	42 (30.00%)	66 (47.14%)
Chinese	8 (5.71%)	8 (5.71%)
Indian	3 (2.14%)	1 (0.71%)
Others	4 (2.86%)	8 (5.71%)
Type of Renal Replacement Therapy (RRT)		
Intermittent Hemodialysis	2 (1.43%)	16 (11.43%)
Continuous RRT	0 (0.00%)	8 (5.71%)
Continuous Venovenous Hemodiafiltration (CVVH)	0 (0.00%)	1 (0.71%)
Peritoneal Dialysis	0 (0.00%)	8 (5.71%)
ICU Category		
Medical	21 (15.00%)	14 (10.00%)
Surgical	36 (25.71%)	69 (49.29%)
Baseline Creatinine	92.99 ± 1.76	89.35 ±12.15
Diagnosis Class		
Cardiovascular	2 (1.43%)	9 (6.43%)
Connective Tissue/Autoimmune	2 (1.43%)	2 (1.43%)
Gastointestinal/ Hepatobiliary/ Pancreatic	5 (3.57%)	8 (5.71%)
Infection	5 (3.57%)	14 (10.00%)
Neurological	8 (5.71%)	8 (5.71%)
Renal	1 (0.71%)	3 (2.14%)
Respiratory	20 (14.29%)	31 (22.14%)
Trauma	12 (8.57%)	8 (5.71%)
Endocrine/Metabolic	1 (0.71%)	0 (0.00%)

The study has been approved by the Medical Ethics and Research Committee (MREC) and International Islamic University Ethics Committee (IREC). The study has also been approved to run by the Head of Department and Director of Hospital Tengku Ampuan Afzan Kuantan. The data for hospitalization days and records for creatinine readings were recorded throughout the patient's stay in the ICU. The mobile application automatically calculates the estimated glomerular filtration rate for the different models. The values output from the estimation models were then compared for further analysis.

3.5. Results and discussion

A total of 140 adult patients from the intensive care unit in Kuantan, Malaysia from January to August 2016 were evaluated, of which 83 patients (58.29%) were found to have developed AKI. To study the AKI outcome for each patient, the clinical and biometric data were input and computed by the kinetic estimates of GFR (keGFR) equation, Chronic Kidney Disease Epidemiology Collaboration (eGFR by

CKD-EPI), GFR by Cockcroft Gault equation and Modified Diet in Renal Disease (eGFR by MDRD) equation. The AKI outcome is determined by KDIGO [17] and labelled as 'AKI' for patients with AKI or 'No AKI' for patients with no AKI. Figure 2 shows the application of the 4 creatinine-based equations for calculating GFR for female and male. The slope of the CKD-EPI equation was similar to that of the MDRD and Crock-Gault equation. In line with the findings by Chen et al.[7] when the creatinine level was > 0.8 mg/dL and > 1.5 mg/dL in female and male, respectively, but less steep below the knots, which leads to less overestimation of GFR by the CKD-EPI equation at a lower Scr level. The KeGFR equation tended to estimate a higher value of GFR in male patients for all creatinine values. Higher GFR estimate by KeGFR equations were also observed for female patients for when creatinine level was > 2.0 mg/dL.

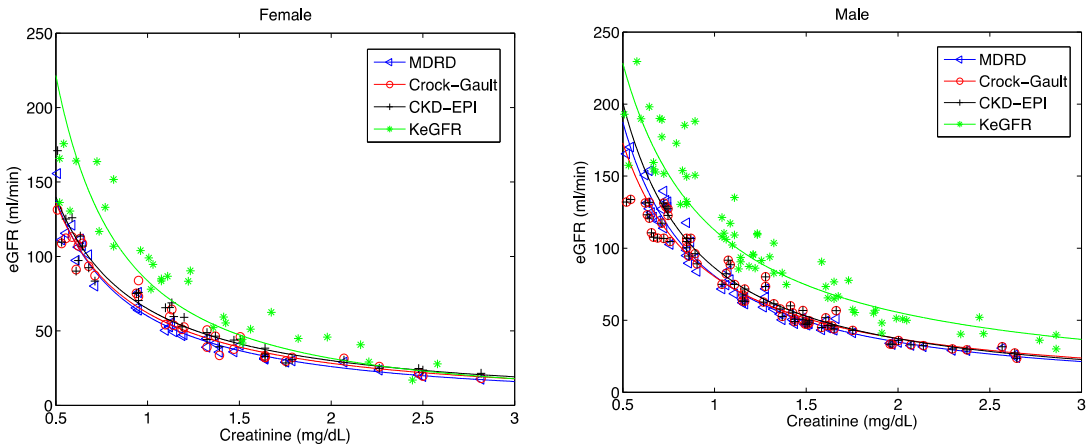

Figure 2. Estimated glomerular filtration obtained by MDRD, Crock-Gault, CKD-EPI and KeGFR for male and female creatinine readings.

The correlation between kinetic estimates of keGFR with eGFR by CKD-EPI, GFR by Cockcroft Gault equation and eGFR by MDRD for AKI and no AKI in female patients and male patients are shown in figure 3(a), (b) and (c) respectively. Estimation glomerular filtration rate methods, eGFR by CKD-EPI in figure 3(a) shows good correlation with keGFR equations for patients with and without acute kidney injury. The other methods correlate well with keGFR equations only for patients with acute kidney injury, see figure 3(b) and 3(c). These results are consistent for both male and female patients. This shows that keGFR correlates well with eGFR by CKD-EPI calculations compared to other equations regardless of the gender and AKI status. The plot shows that eGFR by CKP-EPI in figure 3(a) has the greatest precision and eGFR by MDRD, figure 2(c) has the least bias.

The differences between each mathematical model may be explained by the fact that these numerical models differ in variables and were developed based on population studies, often from patient database from the United States. It is known that variables such as ethnicity, diet and demographics will affect the serum creatinine concentration [18].

The application developed here allows for storage of all the calculated eGFR values computed based on several GFR estimation equations for more efficient monitoring of GFR. It is endeavoured that the collected data will be used in the future to develop a more accurate GFR estimation model suitable for Asian populations. This may be done by setting up a cloud data store in which the information from the mobile application is then retrieved and stored. A machine learning algorithm will then be developed based on the gathered data to estimate AKI outcome for the patient within 8-12 hours of ICU admission.

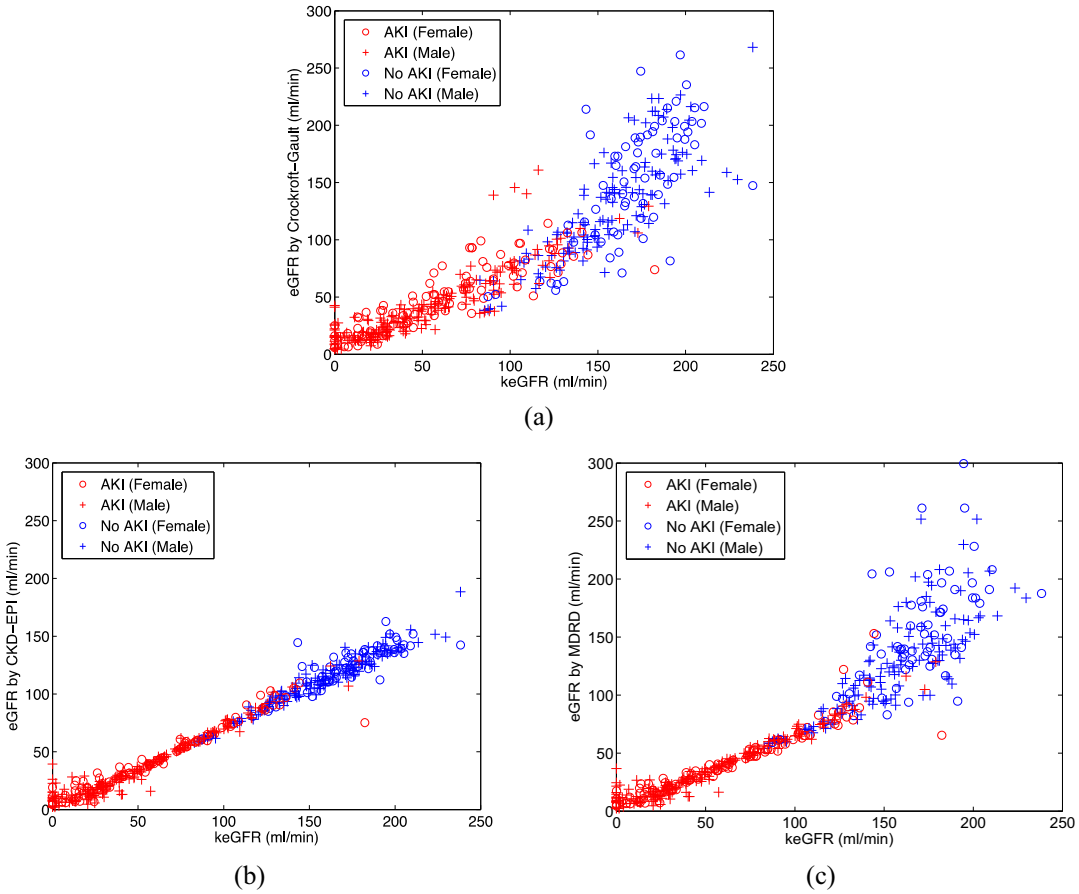

Figure 3. Correlation analysis between kinetic estimates of GFR (keGFR) with (a) Chronic Kidney Disease Epidemiology Collaboration (eGFR by CKD-EPI) equation (b) Cockcroft Gault equation and (c) Modified Diet in Renal Disease (eGFR by MDRD) equation for AKI and No AKI in female patients and male patients.

4. Conclusion

The complexity in assessing the kidney function due to the highly nonlinear and complex behavior within human systems has made estimation of glomerular filtration rate, which is highly important in determining acute kidney injury, extremely difficult. This study took advantage of the various published numerical models used for GFR estimation by developing a program application to model the AKI outcome based on clinical data.

It was found that the estimation glomerular filtration rate methods, eGFR by CKD-EPI shows the best correlation with keGFR equations compared to other methods, regardless of AKI status. Other methods correlate well with keGFR equations only for patients with acute kidney injury. These results are consistent for both male and female patients. Computations obtained by eGFR by CKD-EPI and eGFR by MDRD results in the greatest precision and least bias respectively. These mathematical models were developed based on population studies which may suggest why there are differences in the outcome. Variables such as ethnicity, diet and demographics will affect the serum creatinine concentration [18]. It is endeavored that the collected data in this study will be used in the future to develop a more accurate GFR estimation model suitable for Asian populations to significantly improve GFR estimations.

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