ORIGINAL ARTICLE

Estimates of Glomerular Filtration Rate in Critically ill Patients with Sepsis: Comparisons of Different Equations

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ABSTRACT

INTRODUCTION: Accurate assessment of glomerular filtration rate (GFR) is important in the critically ill. Kinetic estimate of GFR (keGFR) considers the changes of creatinine, creatinine production rate, and volume of distribution hence postulated to be a more accurate estimate of GFR, where there are rapidly changing kidney functions. We evaluated the association of the estimated GFR by established equations and keGFR with creatinine clearance (CrCl) measurement. **MATERIALS AND METHODS**: This is a prospective observational study of critically ill patients. Inclusion criteria were patients older than 18 years old with sepsis (clinical infection and increase in SOFA score>2), and plasma procalcitonin>0.5ng/ml. Plasma creatinine and Cystatin C (CysC) were measured on admission and 4 hours later, and the eGFR was calculated by the Cockcroft Gault (CG), MDRD, CKD-EPI, and keGFR equations, and compared to the CrCl measurement. **RESULTS**: A total of 70 patients were recruited. eGFR by all 4 equations strongly correlates with CrCl. keGFR had the least bias depicted by the mean differences nearest to zero (-18ml/min). Similarly, $keGFR_{CysC}$ had less bias than $eGFR_{CysC}$, with a mean difference of -21ml/min. $eGFR_{CG}$ had the greatest precision depicted by the narrower SD lines, however, the precision of both keGFR were not much different compared to those of $eGFR_{CG}$. **CONCLUSIONS**: In critically ill patients with sepsis, $keGFR_{Cr}$ and $keGFR_{CysC}$ had the least bias and fair precision when compared to creatinine clearance measurement. In the absence of creatinine clearance measurement, keGFR calculations are useful as a surrogate for kidney function.

Keywords
Glomerular Filtration Rate, Creatinine Clearance, Sepsis, Critical Illness

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INTRODUCTION

Accurate assessment of glomerular filtration rate (GFR) in critically ill patients is very important for diagnostic and therapeutic intervention.[1,2] GFR is best calculated using inulin or radioactive markers, such as ^{51}Cr-EDTA[3,4] or ^{99m}Tc-DPTA,[5] however this is cumbersome and not routinely available in the clinical setting. Most clinicians use plasma creatinine as a surrogate by estimating GFR using various equations including Cockcroft Gault equation,[6] Modified Diet in Renal Disease (MDRD)[7], or Chronic Kidney Disease Epidemiology (CKD-EPI)[8] equations. However, these equations have various limitations to be used in the ICU. Kinetic estimate of GFR (keGFR) has been shown to be a more accurate estimate of GFR in acute settings, where there are rapidly changing kidney functions.[9–12] Since then, many studies have shown the utility of keGFR in diagnosing acute kidney injury (AKI), staging severity, predicting renal recovery, medication dosing, and in cardiac surgical patients [13–17]

Estimates of GFR and keGFR have also been developed for plasma Cystatin C (CysC), a novel functional marker for the kidney.[10,18] Creatinine clearance (CrCl) is determined from a timed urine collection, ideally 24 hours, however durations as short as 2 hours to 4 hours have been used, and it has been the most common method used to measure GFR.[19] Limitation of this method is the tubular secretion of creatinine that

may overestimate GFR by 10 to 20%, furthermore, its measurement needs a continuous collection of urine, hence cumbersome to be used in daily clinical practice.[2,20]

We investigated which methods of eGFR and keGFR estimations best correlate with CrCl. We evaluated the association of the estimated GFR by conventional method and keGFR for creatinine and CysC with creatinine clearance measurement. This is useful for practising clinicians in the intensive care unit, as the estimation-based calculation can be used helpfully as a surrogate for creatinine clearance.

MATERIALS AND METHODS

This was a prospective observational study at the ICU of Hospital Tengku Ampuan Afzan, Kuantan and IIUM Medical Centre. The study was registered under the Malaysian National Medical Research Register (NMRR-14 -1897-21447). Ethical approval was obtained from the Malaysian Medical Ethics and Research Committee (MREC Number P15-1597). Consent from a legally-accepted representative was obtained. All patients admitted to the ICU during the study period were screened for inclusion and exclusion criteria. Inclusion criteria include age more than 18 years old who stayed in the ICU longer than 48 hours, Sepsis: defined clinical infection and acute increase in SOFA score of more than 2 organs, and Plasma procalcitonin (PCT) >0.5 ng/ml. Exclusion criteria include already having severe AKI on admission: defined as needing dialysis, creatinine three times the baseline, or urine output of less than 0.3 ml/kg/h.

Plasma creatinine and Cystatin C were measured on admission and 4 hours later. Plasma creatinine was analysed using the Olympus AU2700™ chemistry-immunoanalyser *(Olympus, Philadelphia, USA).* Estimates of GFR (eGFR) were calculated using the Cockcroft-Gault,[6] MDRD,[7] CKD-EPI formula.[8] Plasma Cystatin C was measured using FineCare Cystatin C Rapid Test (Wondfo Biotech). $eGFR_{CysC}$ was calculated using the CKD-EPI formula.[18] Kinetic estimates of GFR (keGFR) was calculated using a formula by Chen and Pickering.[9,10] Urine creatinine was assayed using Olympus AU2700™ chemistry-immunoanalyser *(Olympus, Philadelphia, USA).* Four-hour creatinine clearance was calculated for each patient.[19]

Statistical Analysis

Results are presented as mean ± SD for normally distributed variables or median (inter-quartile range) for non-normally distributed variables. Comparison of variables between the two groups was analyzed using the independent t-test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Categorical variables were compared with the Chi-Square test. Correlation between the methods was analysed using Spearman correlation analysis. The agreement of the methods was analysed using the Bland-Altman plots. The Bland-Altman plot the difference against the mean between eGFR and CrCl. Bias was shown as the total mean differences between eGFR and CrCl with zero. Precision is shown as the ± 1.96 standard deviations of the mean differences. Differences between the two methods were analysed using Wilcoxon sign rank tests.

RESULTS

Demographic and clinical characteristics

A total of 70 patients were recruited. Eight patients (11.4%) needed dialysis, and 15 (21.4%) died. Table I shows the demographic, clinical characteristics, and outcome of these patients.

Correlation Analyses

Scatter plots of association between eGFR by CG, MDRD, and CKD-EPI and CrCl were shown in Figure 1. eGFR by all 4 equations strongly correlates with CrCl, with all $p<0.0001$. Correlation between the methods was analysed using the Spearman correlation analyses (Figure 1). The correlation coefficient ranges from 0.71 to 0.96.

Table I: Demographic and clinical characteristics

Variables	n=70
Age (years)	51 ± 18
Ethnicity	
Malay	59 (84.3)
Chinese	4 (5.7)
Indian	2 (2.9)
Orang Asli	3 (4.3)
Others	2 (2.9)
Gender (Male)	42 (60.0)
Weight (kg)	66 ± 17
Height (cm)	161 ± 8
SOFA score	5.6 ± 3.2
APACHE II score	14.3 ± 5.6
Admission Category	
Medical	51 (72.9)
Surgical	19 (27.1)
Primary Admission Category	
Neurological	2 (2.9)
Respiratory	26 (37.1)
Infection	7 (10.0)
Hepatobiliary	3 (4.3)
Renal	2 (2.9)
Cardiovascular	6 (8.6)
Gastrointestinal	13 (18.6)
Trauma	3 (4.3)
Endocrine/Metabolic	4 (5.7)
Haematology	1 (1.4)
Connective Tissue	3 (4.3)

Data expressed as mean ± SD, n (%), or median (lower quartile – upper quartile). APACHE II Score: Acute Physiological and Chronic Health Evaluation II Score. SOFA Score: Sequential Organ Failure Assessment.

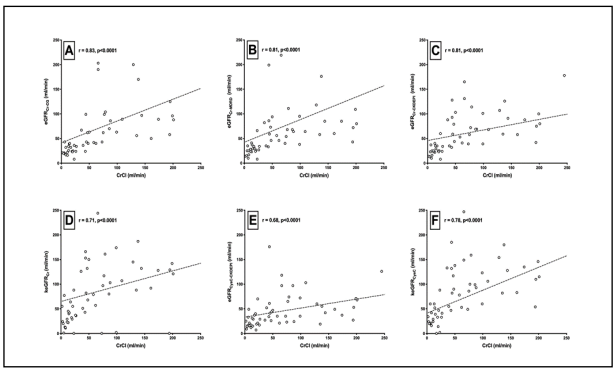

Figure 1: Scatter Plots of association between creatinine clearance with of GFR by (A) Cockcroft Gault ($eGFR_{Cr\text{-}CG}$), (B) Modified Diet in Renal Disease ($eGFR_{Cr\text{-}MDRD}$) (C) Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{Cr\text{-}CKDEPI}$), (D) $keGFR_{Cr}$, (E) $eGFR_{CysC}$ and (F) $keGFR_{CysC}$. eGFR, estimated glomerular filtration; CG: Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; keGFR: kinetic estimates of glomerular filtration rate; Cr: Creatinine; CysC: Cystatin C

Differences in distribution

The differences in the distribution of eGFR and keGFR and CrCl were analysed using Wilcoxon rank analysis (Table II). There were no differences in the distribution of eGFR by CG, MDRD, keGFR for both creatinine and CysC with CrCl. However, the distribution differed significantly for eGFR by CKD-EPI equations for both creatinine and CysC (p=0.04 and 0.001, respectively).

Table II: Wilcoxon analysis of eGFR and keGFR with creatinine clearance (CrCl)

	p-value
$eGFR_{Cr\text{-}CG}$	0.29
$eGFR_{Cr\text{-}MDRD}$	0.60
$eGFR_{Cr\text{-}CKDEPI}$	0.04
$keGFR_{Cr}$	0.61
$eGFR_{CysC\text{-}CKDEPI}$	0.001
$keGFR_{CysC}$	0.74

eGFR, estimated glomerular filtration; CG: Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; keGFR: kinetic estimates of glomerular filtration rate; Cr: Creatinine; CysC: Cystatin C

Agreement between eGFR and CrCl

The agreement between eGFR by these methods was further evaluated by Wilcoxon signed-rank the Bland Altman plots (Figure 2). $keGFR_{Cr}$ had the least bias depicted by the mean differences nearest to zero (-18 ml/min). Similar to creatinine-based eGFR, $keGFR_{CysC}$ had less bias than $eGFR_{CysC}$ when compared to CrCl, with a mean difference of -21 ml/min (Table III). $eGFR_{Cr\text{-}CG}$ had the greatest precision depicted by the narrower SD lines, however, the precision of both $keGFR_{Cr}$ was not much different compared to those of $eGFR_{Cr\text{-}CG}$.

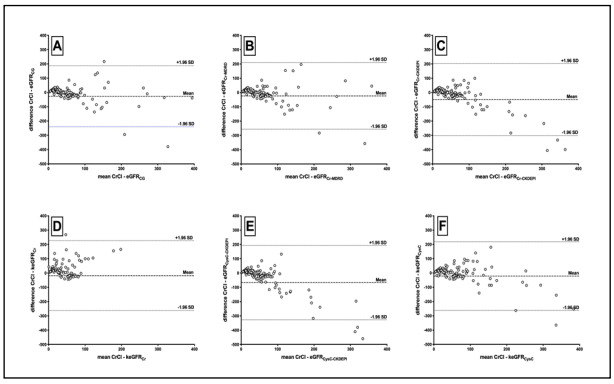

Figure 2: Bland Altman Plot of the differences and mean between creatinine clearance (CrCl) with (A) Cockcroft Gault ($eGFR_{Cr\text{-}CG}$), (B) Modified Diet in Renal Disease ($eGFR_{Cr\text{-}MDRD}$) (C) Chronic Kidney Disease Epidemiology Collaboration ($_{eGFRCr\text{-}CKDEPI}$), (D) $keGFR_{Cr}$, (E) $eGFR_{CysC}$ and (F) $_{ke}GFR_{CysC}$. eGFR, estimated glomerular filtration; CG: Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; keGFR: kinetic estimates of glomerular filtration rate; Cr: Creatinine; CysC: Cystatin C

Table III: Mean Differences and SD eGFR and keGFR with creatinine clearance (CrCl)

	Mean Differences	SD
$eGFR_{Cr-CG}$	-26.7	108.7
$eGFR_{Cr-MDRD}$	-23.8	119.8
$eGFR_{Cr-CKDEPI}$	-50.0	130.0
$keGFR_{Cr}$	-18.6	125
$eGFR_{CysC-CKDEPI}$	-67.6	133.8
$keGFR_{CysC}$	-21.7	124.0

eGFR, estimated glomerular filtration; CG: Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; keGFR: kinetic estimates of glomerular filtration rate; Cr: Creatinine; CysC: Cystatin C

DISCUSSION

We evaluated the association of the estimated GFR by conventional method and keGFR with creatinine clearance measurement. Estimated GFR by all four equations studied strongly correlates with CrCl. Kinetic estimates of GFR had the least bias depicted by the mean differences nearest to zero (-18 ml/min). Similarly, $keGFR_{CysC}$ had less bias than $eGFR_{CysC}$, with a mean difference of -21 ml/min. $eGFR_{CG}$ had the greatest precision depicted by the narrower SD lines, however, the precision of both keGFR was not much different compared to those of $eGFR_{CG}$.

Sepsis is the leading admission cause in our ICU, and most contributing to the development of AKI.[21,22] Hence, accurate assessment of GFR to identify high-risk patients for AKI is of utmost importance to enable early supportive and therapeutic intervention. Clinically, eGFR is evaluated using the existing eGFR equations, including the Cockcroft-Gault,[6] MDRD,[7] and CKD-EPI[8] equations. The limitation of these equations was that they were developed from the data of CKD patients, hence are not accurate in critical settings with rapidly changing kidney functions.[9,23]

Kinetic estimate of GFR (keGFR), proposed by Chen[12] in 2013 considers the quantitative changes of creatinine over time, creatinine production rate, and the volume of distribution, hence, this estimate is suggested to be more useful in the critically ill.[14] The utility of keGFR in diagnosing AKI has been shown to be useful in the critically ill,[14] cardiac surgery patients[17] and kidney transplantation.[10] However, the limitation of calculation of keGFR needs serial measurement of creatinine, and it involves assumptions and its accuracy, and complex calculation involving the time differences, creatinine production, and maximum creatinine produced.[9,13] Nevertheless, there are now various applications that have been developed to assist clinicians in using keGFR as a bedside tool.[24]

We showed that in critically ill patients with sepsis, keGFR creatinine had the least bias than all the other creatinine-based eGFR equations when compared to measured CrCl. Compared to the MDRD equation, keGFR better predicted AKI and dialysis in 107 critically ill patients.[14] In a large study involving a database of 13,284 ICU patients,[25] the worst keGFR value within seven days of ICU admission was associated with the hard outcome of dialysis and mortality, similar to another study of 60 paediatric ICU patients.[26] However, in 3760 critically ill patients aged 90 days to 25 years old, keGFR was not independent with AKI.[27] Dewitte et al., (2015)[16] showed that the addition of keGFR to novel biomarkers predicts AKI recovery and major adverse kidney events in 245 ICU patients. It has also been shown to assist in medication dosing in 946 critically ill patients.[15]

Cys C is a better marker of filtration due to its shorter half-life and is unaffected by muscle mass and diet.[28] Cys C-based eGFR and keGFR had been developed using a similar methodology.[10,18] There were conflicting results in the utility of CysC based eGFR in predicting outcome.[29–32] Whereas, CysC based keGFR has been shown to improve prediction of delayed graft function in 56 kidney transplant cases.[10] We showed that similar to creatinine-based keGFR and eGFR, Cys C-based keGFR has less bias compared to its eGFR counterpart.

In this study we used CrCl as the comparison, hence limitations occur as CrCl overestimates GFR due to contribution from secreted creatinine in the proximal tubules.[2] In addition, the method is confounded by variation of urine output due to the pathophysiological and intervention, and accuracy of time collection of urine

output, especially in a longer duration of collection. In this study, we used a 4-hour CrCl collection as a shorter timed collection of four hours has been shown to be accurate to the longer duration of collection.[19] Future studies comparing both creatinine and CysC based eGFR and keGFR with measured GFR using inulin or radioactive clearance in critically ill patients is warranted.

LIMITATIONS OF THE STUDY

First, it is a small study involving sepsis patients only. Hence, unable to generalise to other critically ill patients. Second, we did not measure the gold standard of GFR measurement using Inulin or radioactive clearance. Third, four-hour creatinine clearance was measured rather than 24 hours. However, a previous study has shown that four-hour clearance is accurate as 24 hours.[19]

CONCLUSION

In critically ill patients with sepsis, $keGFR_{Cr}$ and $keGFR_{CysC}$ had the least bias and fair precision when compared to creatinine clearance measurement. In the absence of creatinine clearance measurement, keGFR calculations are useful as a surrogate for kidney function. Its easiness of use and the low cost involved should encourage more clinicians to incorporate its use in daily clinical practice.

CONFLICT OF INTEREST

None

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