Original Article

The Utility of the Creatinine Excretion to Production Ratio and the Plasma Creatinine and Cystatin C Based Kinetic Estimates of Glomerular Filtration Rates in Critically Ill Patients with Sepsis

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Abstract

Introduction: Creatinine kinetics denotes that under steady-state conditions, creatinine production (G) will equal creatinine excretion rate (E). The glomerular filtration (GFR) is impaired when excretion is less than production. The kinetic estimate of GFR (keGFR) and E/G ratio were proposed as a more accurate estimate of GFR in acute settings with rapidly changing kidney function. We evaluated keGFR and E/G to diagnose AKI, predict recovery, death or dialysis. **Methods:** This is a prospective observational study of critically ill patients. Inclusion criteria were patients >18 years old with sepsis, defined as clinical infection with an increase in SOFA score >2, and plasma procalcitonin >0.5 ng/mL. Plasma creatinine and Cystatin C were measured on ICU admission and 4 h later, and their keGFR was calculated. Urine creatinine and urine output were measured over 4 h to calculate the E/G ratio. **Results:** A total of 70 patients were recruited, of which 49 (70%) had AKI. Of these, 33 recovered within 3 days, and 15 had a composite outcome of death or dialysis. Day 1 $keGFR_{Cr}$ and $keGFR_{CysC}$ discriminated AKI from non-AKI with AUCs of 0.85 (95% Confidence interval: 0.74–0.96), and 0.86 (0.76–0.97), respectively. The E/G ratio predicted AKI recovery (AUC: 0.81 (0.69–0.97)). The keGFRs were not predictive of death or dialysis, whereas E/G was predictive (AUC: 0.76 (0.63–0.89). **Conclusion:** keGFR was strongly diagnostic of AKI. The E/G ratio predicted AKI recovery and a composite outcome of death and dialysis.

Keywords: *Creatinine, critical illness, Cystatin C, glomerular filtration rate, sepsis*

Introduction

Acute kidney injury (AKI) is an independent risk factor that contributes to morbidity and mortality in critically ill patients. In a Malaysian population, AKI occurred in 65% of patients, mainly attributed to sepsis, higher compared to studies in other countries.[1,2] Current diagnosis of AKI is based on the surrogates of filtration function, namely creatinine and urine output.[3] It is recognized that injury biomarkers measured in the urine or plasma may provide earlier indications of AKI than plasma creatinine. However, few have reached clinical utility, and their use is complicated by the heterogeneity of the ICU population. Furthermore, they are only available at a high cost.

Kinetic estimate of GFR (keGFR) was proposed by Chen[4] to be a more accurate estimate of GFR in acute settings, where kidney function can change rapidly in the critically ill. It considers the changes in plasma (or serum) creatinine over time, creatinine production rate, and the volume of distribution. keGFR has been shown to be a better predictor of AKI and AKI recovery compared to the eGFRs.[5,6] Since then, many studies have shown the utility of keGFR in diagnosing AKI, staging severity, predicting renal recovery, medication dosing, and in cardiac surgical patients.[7–10]

In a steady state (unchanging GFR), the creatinine production rate (G) must equal the creatinine excretion rate (E). If production exceeds excretion, glomerular filtration function (GFR) is impaired.[11] On the contrary, if excretion exceeds production, it may indicate a recovering GFR following a reduction in GFR. Creatinine production cannot be measured directly, but like the estimating equations for GFR, there are estimating equations for production. The E/G ratio provides additional information

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on the state of GFR. Utilizing either the E/G ratio or keGFR may offer a cheap way to evaluate the kidney function in critically ill patients. We investigated the ability of the keGFR and E/G to diagnose AKI, predict its recovery, and predict the hard outcome of death or dialysis in the ICU. In addition, we explored the association of AKI severity stages with keGFR severity classifications.

Methods

This was a prospective observational study at Hospital Tengku Ampuan Afzan, Kuantan and Sultan Ahmad Shah Medical Center (SASMEC@IIUM). 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) and the International Islamic University Ethics Committee (IREC number: 511). Consent from legally accepted patient representatives was obtained. All patients admitted to the ICU during the study period were screened for inclusion. The inclusion criteria were patients older than 18 years, ICU stay longer than 48 h with sepsis, and plasma procalcitonin (PCT) > 0.5 ng/mL. Sepsis was defined as clinical infection and acute increase in SOFA score of more than two organs.[12] The exclusion criteria were patients who already had 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 and urinary samples were collected on admission and at 4 and 8 h on the first day, then two samples daily 4 h apart for the first 3 days of ICU admission. Urine samples were centrifuged at 2000 rpm for 5 min, and the supernatant was stored at –80°C. Blood samples were centrifuged at 3600 rpm for 15 min, and the plasma was stored at –80°C. PCT was assayed using the rapid PCT quantitative test (*Wondfo Biotech*). Plasma and urine creatinine were assayed using Olympus AU2700™ chemistry-immunoanalyzer *(Olympus, Philadelphia, USA)*, and 4-h creatinine clearance was calculated.[13] Baseline creatinine could not be obtained from clinical records; therefore, it was estimated using back-calculation of the Modified Diet in Renal Disease (MDRD) equation based on an estimated glomerular filtration rate (eGFR) of 75 mL/min.[14,15] AKI was defined as a plasma creatinine increase of greater than 26.4 umol/L or 50% of baseline within 24 h of ICU admission or urine output of less than 0.5 mL/kg/h for the past 6 h. AKI recovery (AKI_{rec}) was defined as the return of plasma creatinine to less than 1.5 times the baseline value or less than 30 µmol/L (0.35 mg/dL), or reversal of oliguria within 3 days of ICU admission.[16] Estimated GFR (eGFR) values were calculated using the Cockcroft–Gault,[17] MDRD,[18] and CKD-EPI formulas.[18] keGFR was calculated using the formula by Chen.[4,6] The excretion rate (E) was calculated using the urinary volume measured over 4 h and the urinary creatinine concentration measured from this 4-h volume.

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. Differences between the three groups were analyzed using one-way analysis of variance (ANOVA) with post-hoc least significant difference analysis. Categorical variables were compared with Chi-square test. The diagnostic and predictive performances were assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the sensitivity verse 1-specificity. The ideal cutoff point was defined as the measured quantity, which maximized sensitivity and specificity.

Table 1: Demographic and clinical characteristics and outcome

Variables	All patients (*n*=70)
Age (years)	51.0±17.6
Gender (male)	42 (60.0)
Weight (kg)	66±17
Height (cm)	162±8
Baseline SOFA Score	5.6±3.2
Baseline APACHE II Score	14.3±5.6
Category	
Medical	51 (72.9)
Surgical	19 (27.1)
Primary admission diagnoses	
Cardiovascular	6 (8.6)
Gastrointestinal/Hepatobiliary/Pancreas	13 (18.6)
Infective	7 (10.0)
Renal	2 (2.9)
Neurological	2 (2.9)
Respiratory	26 (37.1)
Trauma	3 (4.3)
Connective tissue/autoimmune	3 (4.3)
Endocrine	4 (5.7)
Hematology	1 (1.4)
Dialysis	8 (11.4)
Death at 30 days	12 (17.1)
Dialysis or Death at 30 days	15 (21.4)
Mechanical Ventilation (MV)	56 (80.0)
Length of MV (days) (*n*=46)	2.7 (1.6-6.8)
Length of ICU stay (days) (*n*=58)	4.4 (2.8-7.9)
Length of hospital stay (days) (*n*=58)	13.9 (8.7-24.6)

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

Results

Demographic and clinical characteristics

A total of 70 patients were recruited, of which 49 (70%) had AKI. Of these, 36 (51.4%) had AKI based on creatinine criteria alone, and 38 (54.3%) had AKI based on urine output criteria alone. Out of 49 patients with AKI, 33 (67.3%) recovered within 3 days. The remaining 16 (32.7%) had persistent AKI. Patients' flow is shown in Figure 1. Table 1 shows the demographic and clinical characteristics and outcomes of recruited patients. Of the 70 patients, 12 (17.1%) died within 30 days of ICU admission and eight (11.4%) needed dialysis. Fifteen patients (21.4%) had the composite outcome of death or dialysis.

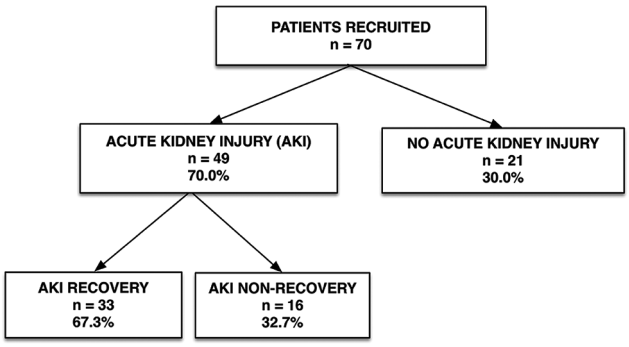

Figure 1: Patient flow

Profile of plasma Creatinine, plasma CysC, their GFR derivatives, and E/G ratio

Figure 2 shows the line graph between patients with AKI and no AKI for plasma biomarkers and their eGFR equations. Plasma creatinine and Cystatin C were higher in patients with AKI versus no AKI. Correspondingly, their GFR derivatives were lower in patients with AKI compared to no AKI.

Diagnosis of AKI

Plasma creatinine and CysC were diagnostic of AKI throughout the 3 days of ICU admission [Figure 3]. Similarly,

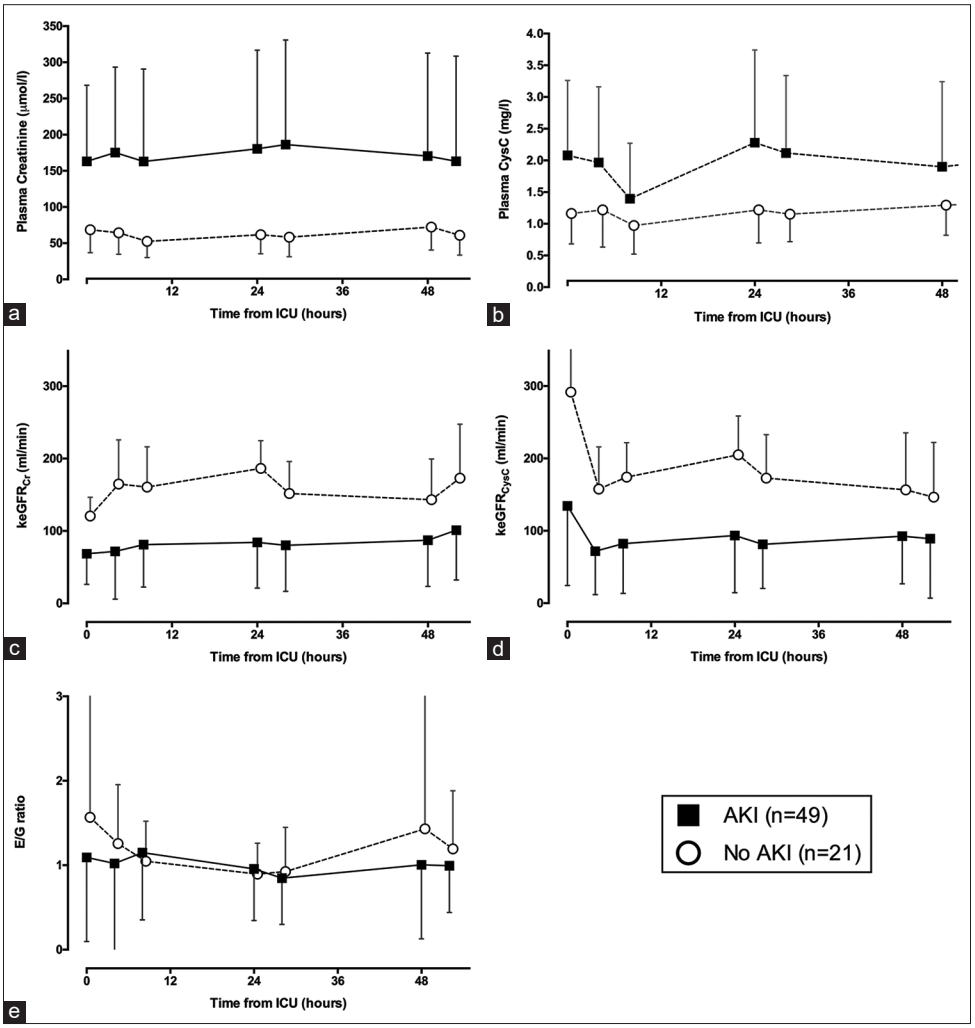

Figure 2: Line graph between AKI and No AKI for (a) Plasma Creatinine, (b) Plasma Cystatin C, (c) $keGFR_{Cr}$, (d) $keGFR_{CysC}$, and (e) E/G ratio. Each point is the mean for all patients at that time. The 95% confidence interval is shown for each data point. For clarity's sake, we display only one side of the CI

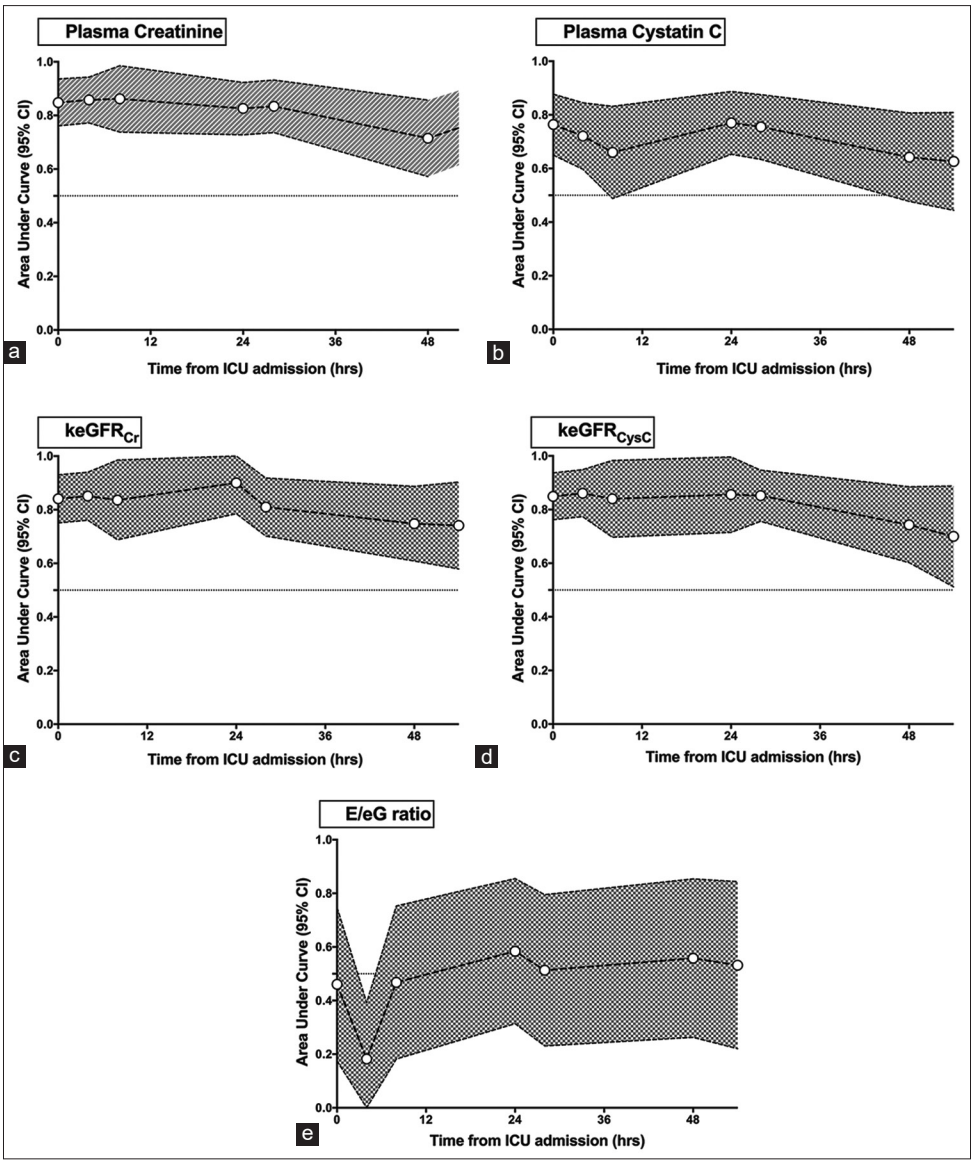

Figure 3: Time-dependent performance for the diagnosis of AKI (a) Plasma Creatinine, (b) Plasma Cystatin C, (c) keGFR$_{Cr}$, (d) keGFR$_{CysC}$, and (e) E/G ratio. The shaded area represents the 95% Confidence interval. keGFR: kinetic estimate of glomerular filtration rate, E/G ratio: production/excretion ratio of creatinine

keGFR$_{Cr}$ and keGFR$_{CysC}$ were diagnostic of AKI throughout the 3 days, whereas the E/G ratio was not diagnostic. Day 1 keGFR$_{Cr}$ and keGFR$_{CysC}$ performed best in the diagnosis of AKI, with an AUC of 0.85 (0.74–0.96) and 0.86 (0.76–0.97), and an ideal cutoff point of 103 and 100 mL/min, respectively [Table 2]. Day 1 E/G ratio was also diagnostic of AKI, but with a lower AUC of 0.69 (0.56–0.82).

Prediction of AKI recovery

In 49 patients with AKI, 33 (67.3%) recovered within 3 days. In these cases, the E/G ratio was strongly predictive of AKI recovery with the highest AUC of 0.81 (0.69–0.94) [Table 2]. The ideal cutoff point of the E/G ratio in the prediction of AKI recovery was 0.59 (representing that the excretion rate is 59% of the production rate). keGFR derivatives for creatinine and plasma CysC were also predictive, with lower AUCs.

Prediction of death or dialysis

Twelve patients (17.1%) died, eight (11.4%) needed dialysis, and 15 (21.4%) either died or needed dialysis. Plasma creatinine, CysC, and their eGFR derivatives were not predictive of death or dialysis. On the contrary, the E/G ratio was predictive, with an AUC of 0.76 (0.63–0.89) and an ideal cutoff point of 0.68.

Discussion

Seventy percent of the recruited patients had AKI based on either plasma creatinine or urine output criteria. Of these, more than half recovered within 3 days of admission. Plasma creatinine, CysC, and their keGFR measured on ICU admission were diagnostic of AKI; in contrast, the E/G ratio was not. E/G ratio was useful for the prediction of recovery in patients with AKI and in the prediction of death or dialysis.

Table 2: Performance of day 1 plasma creatinine, CysC, their keGFR derivatives, and E/G ratio for diagnosis AKI, prediction of AKI recovery, and prediction of death or dialysis

Variables	AUC (95% CI)	Ideal Cutoff Point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Diagnosis of AKI (*n*=49)						
pCreatinine	0.85 (0.76-0.94)	95 mmol/L	0.73 (0.60-0.85)	0.86 (0.71-1)	0.92 (0.84-1)	0.58 (0.41-0.75)
pCysC	0.76 (0.64-0.87)	1.5 mg/L	0.62 (0.49-0.76)	0.86 (0.71-1)	0.91 (0.81-1)	0.50 (0.34-0.66)
$keGFR_{Cr}$	0.85 (0.74-0.96)	103 mL/min	0.86 (0.71-1)	0.75 (0.62-0.88)	0.62 (0.44-0.80)	0.92 (0.83-1)
$keGFR_{CysC}$	0.86 (0.76-0.97)	100 mL/min	0.86 (0.71-1)	0.80 (0.68-0.91)	0.67 (0.49-0.84)	0.92 (0.84-1)
E/eG ratio	0.60 (0.45-0.75)	0.66	0.86 (0.71-1)	0.42 (0.28-0.56)	0.39 (0.25-0.53)	0.87 (0.73-1)
Prediction of AKI recovery (*n*=33) in patients with AKI (*n*=49)						
pCreatinine	0.79 (0.65-0.94)	175 mmol/L	0.69 (0.46 to0.91)	0.82 (0.69-0.95)	0.65 (0.42-0.87)	0.84 (0.72-0.97)
pCysC	0.70 (0.53-0.86)	1.53 mg/L	0.81 (0.62-1)	0.55 (0.38-0.72)	0.46 (0.28-0.65)	0.86 (0.71-1)
$keGFR_{Cr}$	0.74 (0.59-0.88)	55 mL/min	0.63 (0.46-0.81)	0.93 (0.81-1.1)	0.95 (0.85-1)	0.56 (0.37-0.75)
$keGFR_{CysC}$	0.79 (0.65-0.92)	47 mL/min	0.76 (0.60-0.91)	0.81 (0.62-1)	0.88 (0.75-1)	0.65 (0.44-0.86)
E/G ratio	0.81 (0.69-0.94)	0.59	0.81 (0.70-0.91)	0.83 (0.62-1)	0.96 (0.9-1)	0.48 (0.26-0.69)
Prediction of death or dialysis (*n*=15)						
pCreatinine	0.65 (0.48-0.81)	163 mmol/L	0.6 (0.35-0.85)	0.78 (0.67-0.89)	0.43 (0.22-0.64)	0.88 (0.78-0.97)
pCysC	0.58 (0.42-0.73)	1.51 mg/dL	0.6 (0.35-0.85)	0.57 (0.44-0.71)	0.28 (0.13-0.44)	0.84 (0.72-0.96)
$keGFR_{Cr}$	0.61 (0.43-0.78)	55 mL/min	0.69 (0.56-0.81)	0.64 (0.39-0.89)	0.88 (0.77-0.98)	0.36 (0.17-0.55)
$keGFR_{CysC}$	0.64 (0.45-0.83)	55 mL/min	0.69 (0.56-0.81)	0.64 (0.39-0.89)	0.88 (0.77-0.98)	0.36 (0.17-0.55)
E/G ratio	0.76 (0.63-0.89)	0.68	0.76 (0.65-0.87)	0.73 (0.51-0.96)	0.91 (0.83-0.99)	0.46 (0.26-0.66)

keGFR: kinetic estimate of glomerular filtration rate, E/G ratio: production/excretion ratio of creatinine

A high proportion (70%) of our patients had AKI. This may be due to the strict inclusion criteria of our study. Apart from using the Sepsis-3 definition, we also included PCT of greater than 0.5 ng/mL, which further specified our target population as having a bacterial infection. Many of these patients were of a high severity stage due to the presence of already two organ failures; thus, the resultant incidence of AKI was also higher compared to general ICU populations. We showed that both $keGFR_{Cr}$ and $keGFR_{CysC}$ were strongly diagnostic of AKI with an AUC of greater than 0.8. This is consistent with other studies. A study of 56 kidney transplant patients showed that keGFR was predictive of delayed graft function, whereas creatinine was not.[6] In a large study involving 4000 cardiac surgery patients, keGFR in the presence of unchanged creatinine level predicted AKI and mortality.[19] On the contrary, we showed here that keGFR had similar AUCs to that of plasma creatinine.

keGFR calculations consider the changes of creatinine over time, creatinine production rate, and the volume of distribution. Thus, in rapidly changing kidney functions as in critically ill patients, this estimate is suggested to be more useful.[4] The limitations of keGFR include its complex mathematical calculations. In addition, reductions in creatinine production associated with muscle mass loss and changes in the volume of distribution in critically ill patients may be an important confounder for its utility for a long-term outcome.[20]

About 60% of our AKI patients recovered within 3 days of ICU admission, similar to another study which showed that about 51% of their ICU patients had short-term recovery defined as resolution of plasma creatinine and oliguria within 48 h.[16] In contrast to the diagnosis of AKI, we showed that keGFR performed inferior in the prediction of AKI recovery in our cohort, with a lower AUC of 0.74 and 0.79 for creatinine and CysC, respectively, with almost similar AUCs to their plasma concentrations. A study by Dewitte *et al*.[16] showed that keGFR provided the best AUC for renal recovery with an AUC of 0.87 compared to other plasma biomarkers, that is, NGAL, TIMP-2, and IGFBP7.

Of all the derivatives, we showed that the E/G ratio performed the best for AKI recovery. In a proof-of-concept paper, Endre *et al*.[5] retrospectively analyzed the utility of the E/G ratio in 482 critically ill patients. The E/G ratio predicted AKI and its recovery defined by changes in creatinine 12 h later. The ratio was predictive in a subgroup of 66 chronic kidney disease patients. In a study of 56 renal transplant patients, both E/G and keGFR improved risk prediction for delayed graft function.[6] In this study, we showed that the E/G ratio was strongly predictive of AKI recovery with an AUC of greater than 0.8. Under steady state, creatinine production equals to creatinine excretion rate.[11] E/G ratio provides additional information on the current state of the patients' GFR in relation to the steady state. An E/G ratio of less than 1 (production exceeds excretion) indicates that the patient's GFR is falling from

the steady state, whereas a ratio of more than 1 (excretion exceeds production) indicates that the patient's GFR is recovering from a prior fall. In predicting the occurrence of death or dialysis, we showed that the E/G ratio had the highest predictive performance, whereas keGFR of both creatinine and CysC were not predictive. To the best of our knowledge, this is the first study that demonstrates this.

Limitations of the study

The study has several limitations, First, we only recruited sepsis patients with PCT greater than 0.5 ng/mL; this may limit the generalizability of the finding to the general ICU population. Second, we estimated the baseline creatinine as we did not have data on measured baseline creatinine; this may over/underestimate the number of AKI in our setting. Third, baseline creatinine could not be obtained from clinical records; therefore, it was estimated using back-calculation of the MDRD equation based on eGFR of 75 mL/min.[14,15] This has been shown to be a poor method.[15]

Conclusion

AKI occurred is common in critically ill patients with sepsis. keGFR of both creatinine and CysC was useful for the diagnosis of AKI. E/G ratio was useful for the prediction of recovery in patients with AKI, and prediction of death or dialysis.

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Conflicts of interest

There are no conflicts of interest.

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