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Diagnosing acute kidney injury ahead of time in critically ill septic patients using kinetic estimated glomerular filtration rate

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ABSTRACT

Introduction: Accurate and actionable diagnosis of Acute Kidney Injury (AKI) ahead of time is important to prevent or mitigate renal insufficiency. The purpose of this study was to evaluate the performance of Kinetic estimated Glomerular Filtration Rate (KeGFR) in timely predicting AKI in critically ill septic patients.
Methods: We conducted a retrospective analysis on septic ICU patients who developed AKI in AmsterdamUMCdb, the first freely available European ICU database. The reference standard for AKI was the Kidney Disease: Improving Global Outcomes (KDIGO) classification based on serum creatinine and urine output (UO). Prediction of AKI was based on stages defined by KeGFR and UO. Classifications were compared by length of ICU stay (LOS), need for renal replacement therapy and 28-day mortality. Predictive performance and time between prediction and diagnosis were calculated.
Results: Of 2492 patients in the cohort, 1560 (62.0%) were diagnosed with AKI by KDIGO and 1706 (68.5%) by KeGFR criteria. Disease stages had agreement of kappa = 0.77, with KeGFR sensitivity 93.2%, specificity 73.0% and accuracy 85.7%. Median time to recognition of AKI Stage 1 was 13.2 h faster for KeGFR, and 7.5 h and 5.0 h for Stages 2 and 3. Outcomes revealed a slight difference in LOS and 28-day mortality for Stage 1.
Conclusions: Predictive performance of KeGFR combined with UO criteria for diagnosing AKI is excellent. Compared to KDIGO, deterioration of renal function was identified earlier, most prominently for lower stages of AKI. This may shift the actionable window for preventing and mitigating renal insufficiency.

1. Introduction

In the intensive care unit (ICU) the incidence of acute kidney injury (AKI) ranges from 20% in elective surgical patients to >50% in septic patients and is associated with short and long-term adverse outcomes [1,2]. AKI is a cluster of syndromes characterized by an abrupt decrease in glomerular filtration. The current gold standard for diagnosing AKI is the three-stage Kidney Disease: Improving Global Outcomes (KDIGO) group classification based on serum creatinine (SCr) and urine output (UO) [3,4].

In the early phases of AKI SCr is rapidly changing. Therefore, SCr or SCr based estimates of either creatinine clearance (eCrCl) or glomerular filtration rate (eGFR) like MDRD and CKD-EPI are not useful for the early diagnosis or prediction of AKI. These equations assume SCr is at a steady state using only one creatinine measurement. But in the early phases of AKI SCr is rapidly changing and therefore these formulas fail to

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estimate true kidney function or predict adverse acute outcomes [5,6]. It is indeed well known that up to several days may be necessary to achieve a new steady state during the development and recovery from AKI [7].

Potentially more useful estimates of GFR therefore rely on creatinine kinetics. Several formulas have been suggested that incorporate the rate of SCr change, but none of them gained wide acceptance in clinical practice [8-10]. In 2013, Chen published a kinetic GFR (KeGFR) formula that enables the estimation of kidney function in non-steady states, converting direction and rate of SCr change into information on GFR without waiting for a new steady state [11]. The KeGFR formula has been shown to impact drug dosing and predict renal outcomes and recovery more precise than eGFR and at least on par with newer biomarkers [7,12]. These studies have led to KeGFR being included in the Intensive Care Medicine Agenda on AKI and Acute Disease Quality Initiative 16 Workgroup [2,13]. However, to date, no studies have compared KeGFR with KDIGO to diagnose or predict AKI.

The goal of our study was to evaluate the performance of KeGFR to identify or predict AKI compared to KDIGO criteria. We hypothesized that KeGFR is a more rapid predictor of declining kidney function than KDIGO. We tested this hypothesis by performing a retrospective study using AmsterdamUMCdb, the first freely available European intensive care database, from which we included critically ill septic patients given their expected high incidence of AKI [14].

2. Methods

2.1. Study population

Our study was an extension of a prize-winning entry in the 2022 Critical Care Datathon by the European Society of Intensive Care Medicine and performed on the patient data available from AmsterdamUMCdb [14]. This database contains data from a 32-bed mixed surgical-medical academic ICU and a 12-bed high-dependency unit with 1 billion clinical data points related to 23,106 admissions of 20,109 unique patients between 2003 and 2016. From this database we selected critically ill patients with sepsis. Inclusion criteria were either patients diagnosed with sepsis at admission or diagnosis of other severe infections, the use of antibiotics not for prophylaxis after surgical procedures and the presence of positive blood cultures. AmsterdamUMCdb does not include all comorbidities due to deidentification, so some patients are not flagged as septic if reason for admission was, for example, a surgical admission for intestinal perforation which is flagged as "abdominal surgery". Antibiotics criteria is based on combinations of antibiotics that are often used as prophylaxis and not for empirical treatment, or antibiotics used for selective decontamination of digestive tract. For example, for patient to be flagged as septic metronidazole should be combined with another antibiotic, while others are never used prophylactically as sole antibiotic. Not to miss septic patients not flagged as sepsis for not documenting a blood culture or admitted for some other reason, this combination was used. Further inclusion criteria were length of ICU treatment over 48 h and more than one creatinine measurement during ICU admission. Exclusion criteria were missing demographic data, creatinine level of >400 μmol/L before admission, and admission for nephrectomy or kidney transplant. Patients who had been treated with renal replacement therapy (RRT) before admission and patients without more than one creatinine measurement before RRT were also excluded.

2.2. Identification and prediction of patients with acute kidney injury

The original KeGFR equation that incorporates generation, distribution and excretion of creatinine along with a time between measurements factor is as follows:

$$KeGFR = \frac{SSPCr\ x\ CrCl}{MeanPCr}\ x\left(1-\frac{24\ x \triangle Pcr}{\Delta Time\ (h)\ x\ MaxΔPCr/Day}\right) \quad (1)$$

where SSPCr is the steady state plasma creatinine, CrCl is the creatinine clearance, ΔPCr refers to the difference in the plasma creatinine concentration, ΔTime(h) is the interval in hours between two consecutive creatinine measurements and MaxΔPCr/Day is the theoretical maximal change in the plasma creatinine that can occur per day if renal function ceases completely [11]. The initial part of the formula,

$$\frac{SSPCr\ x\ CrCl}{MeanPCr},$$

is the clearance eq. (U × V/P), the product of any steady-state plasma creatinine and the corresponding creatinine clearance, and represents creatinine production rate. MeanPCr is the arithmetic mean that yields a single value suitable for use in the clearance equation. The second part of the expression,

$$\frac{24\ x \triangle PCr}{\Delta Time\ (h)}$$

incorporates the time dynamics. ΔPCr is defined as the starting creatinine subtracted from ending creatinine. The last part of the expression, MaxΔPCr/Day, addresses the mass balance principle of creatinine by embedding the volume of distribution (V_d) factor within the KeGFR equation.

To calculate the KeGFR for every patient in the cohort, we used a modification of expression (I) by O'Sullivan [15]:

$$KeGFR = \frac{Cr1\,xeGFRx1.44}{(Cr1+Cr2)/2}x\left(1-\frac{24x(Cr2-Cr1)}{\Delta\mathrm{Time(h)}x(Cr1\,xeGFRx1.44)(0.6xW)}\right) \quad (2)$$

Cr1 is the first measured SCr, eGFR the MDRD-based GFR at the same time point, Cr2 second recorded creatinine and ΔTime(h) the time in hours between the two creatinine measurements. W is the patients' weight in kilograms. For this study we approximated patients' weight from categorical data using arithmetic mean normalized for body height. 1.44 represents the conversion factor to address the difference in units, and 0.6 x W is the volume of distribution of creatinine, the whole expression normalized for the body surface area (Du Bois formula) [16].

Identification and classification of patients were performed using either KDIGO (stage 1, 2 or 3) as the current gold standard, or KeGFR with or without UO criteria adopted from the KDIGO classification (Table 1). For convenience, KeGFR cut-off values were created using weighted kappa concordance to best reflect the MDRD classification without losing specificity and sensitivity compared to KDIGO staging [17]. For analysis, patients were assigned to their worst KeGFR category according to either serum creatinine or UO criteria.

For KDIGO, we compared the lowest measured SCr within 7 days (including values available before admission) with subsequent levels. Urine output data was calculated as the rolling mean for 6-h and 12-h

Table 1
Acute kidney injury criteria used in the study.

KDIGO	
Stage 1	Increase in serum creatinine ≥26.4 mmol/L or increase of 1.5 to 2-fold from baseline, or urine output of <0.5 mL/kg/h for 6 h
Stage 2	Increase in serum creatinine 2 or 3-fold from baseline, or urine output of <0.5 mL/kg/h for 12 h
Stage 3	Increase in serum creatinine of >3-fold from baseline, or urine output of <0.3 mL/kg/h for 12 h or anuria for 12 h*
KeGFR	
Stage 1	KeGFR of 45–60 mL/min/1.73 m^2 or urine output of <0.5 mL/kg/h for 6 h
Stage 2	KeGFR of 30–45 mL/min/1.73 m^2, or urine output of <0.5 mL/kg/h for 12 h
Stage 3	KeGFR <30 mL/min/1.73 m^2 or urine output of <0.3 mL/kg/h for 12 h or anuria for 12 h

* Patients with serum creatinine >400 μmol/L were excluded; KDIGO - *Kidney Disease Improving Global Outcomes*, KeGFR – kinetic estimated glomerular filtration rate.

time windows. The most severe degree of AKI was recorded as the final KDIGO or KeGFR stage. Table 1 shows classification criteria.

2.3. Outcomes

Our primary outcome was the performance of KeGFR criteria to identify or predict patients with acute kidney injury by KeGFR criteria and KDIGO criteria. Secondary outcomes were the requirement for renal replacement therapy, length of stay in the ICU and 28-day mortality comparison between the two staging systems.

2.4. Statistical analysis

Normality of distribution of variables was tested using the Shapiro-Wilk test. The differences between quantitative variables were analyzed using *t*-test for normally distributed variables and nonparametric tests were applied to variables that were not normally distributed. Continuous variables are shown as mean ± standard deviation, or median (Q1, Q3), as appropriate. The differences between qualitative variables were compared using $\chi 2$ test or Fishers exact test (for frequencies <5), where necessary. Values are presented as number and corresponding percentage, unless specified otherwise. Agreement was calculated using Cohen's kappa with quadratic weights. Logistic regression was performed to assess the predictive value of models. All statistical analyses were two-tailed, and a *p*-value of <0.05 was considered statistically significant. For statistical analysis, Python's SciPy v.1.9.1 was used, and graphical representations were made using Python's Matplotlib v.3.2.2.

3. Results

We conducted a retrospective analysis on 25,105 patients from AmsterdamUMCdb. 3135 patients were identified as septic. After application of inclusion and exclusion criteria, 2492 patients with 202,700 creatinine measurements and 1,601,873 urine output data points were included in the final cohort. Urine output data was available for 97.8% of septic patients. Median time to achieving worse stage by creatinine measurements was 94.0 h (56.4–128.3). Patient selection process is shown in Fig. 1.

The patients were comparable by the demographic data and initial characteristics, as summarized in Table 2. By KDIGO criteria, 1560 (62.0%) patients were recognized as AKI. Combining urine output and KeGFR criteria identified 1706 (68.5%) patients with AKI.

Severity of AKI was classified into discrete KDIGO and KeGFR categories. The degree of agreement between KDIGO and KeGFR was very good (Cohen's kappa with quadratic weights = 0.77). Sensitivity of combined KeGFR and urine criteria compared to KDIGO criteria was 93.2%, specificity 73.0% and accuracy 85.7%. The concordance of each KeGFR stage and KDIGO stage is summarized in Table 3.

In each stage, KeGFR combined with urine output criteria recognized AKI onset time before KDIGO criteria. For Stage 1 of AKI, median time difference to AKI recognition was 13.2 h faster for KeGFR (KDIGO Mdn = 25.8 h [12.4, 62.7], KeGFR Mdn = 12.6 h [1.8, 36.4], $p < 0.001$) for Stage 2 7.5 h (KDIGO Mdn = 14.7 h [7.0, 31.8], KeGFR Mdn = 7.2 h [1.6, 19.7], $p < 0.001$) and Stage 3 5.0 h (KDIGO Mdn = 7.8 h [6.6, 16.6], KeGFR Mdn = 2.8 h [0.7, 7.9], $p < 0.001$).With KDIGO viewed as a golden standard, difference between medians of time to diagnosis is 5.9 h for Stage 1 (KDIGO Mdn = 18.5 h [7.0, 547.7], KeGFR Mdn = 12.6 h [1.8, 36.4], $p < 0.001$), 4.3 h (KDIGO Mdn = 11.5 h [6.6, 28.3], KeGFR Mdn = 7.2 h [1.6, 19.6], $p < 0.001$) for Stage 2 and 4.0 h for Stage 3 (KDIGO Mdn = 6.8 h [2.6, 12.3], KeGFR Mdn = 2.8 h [0.7, 7.9], $p < 0.001$). Results for paired comparisons are represented graphically in Fig. 2.

Outcomes of the patients classified to the same severity categories showed only a slight difference in LOS for all stages and 28-day mortality for Stage 1.

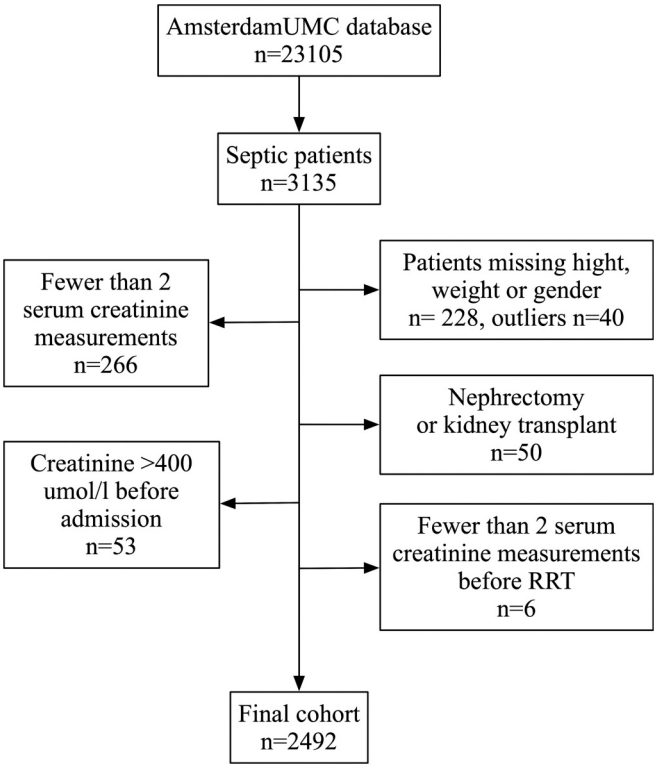

Fig. 1. CONSORT flowchart of patient selection process.

Logistic regression model for prediction of 28-day mortality between KDIGO and KeGFR stages showed a similar predictive value of KeGFR, with AUC 0.60 for KeGFR and 0.57 for KDIGO. Both models were statistically significant, $p < 0.001$. Models predicting RRT also show similar results between the two criteria. Results are graphically presented in Fig. 3.

4. Discussion

This is the first study to assess the performance of KeGFR combined with urine output criteria to predict AKI. Excellent agreement with KDIGO based AKI staging was demonstrated. Importantly, application of KeGFR formula was shown to offer a significant time advantage, especially for earlier stages of AKI. This provides a potential window of opportunity to prevent or mitigate renal insufficiency. Models show a distinct stratification for 28-day mortality risk and RRT risk based on disease stages.

Our study focused on KeGFR as a novel method of identifying AKI at an earlier time point. All previous and currently accepted AKI definitions apply the increase in serum creatinine as a central concept, from the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria in 2004, AKI Network (AKIN) classification in 2007 to their 2012 merging in KDIGO classification [4,18,19]. Creatinine is an endogenous product of enzymatic degradation of creatinine in the muscle, it is freely filtered by the glomeruli, and when renal function is normal it is completely cleared by renal excretion [20,21]. Proximal tubules in healthy individuals secrete ~10% of the excreted creatinine load, thus evaluating GFR by CrCl may result in its overestimation [21]. Although highly variable between individuals, the fraction of tubular secretion may contribute up to 50% to clearance when GFR is reduced. Reabsorption of creatinine is present in tubules in some conditions, such as decompensated heart failure and uncontrolled diabetes, which may also affect the GFR value [22].

The current consensus definition of AKI requires an at least a 33% decline in GFR resulting in an at least a 50% increase in plasma creatinine [18,23]. If only CrCl is changing and all the other determinants of

Table 2
Comparison of patient baseline values and outcomes by severity stages of AKI by KeGFR and KDIGO staging.

	No AKI			Stage 1			Stage 2			Stage 3		
Variable	KDIGO ($n = 932$)	KeGFR ($n = 786$)	p	KDIGO ($n = 466$)	KeGFR ($n = 381$)	p	KDIGO ($n = 539$)	KeGFR ($n = 522$)	p	KDIGO ($n = 555$)	KeGFR ($n = 803$)	p
Age, years	64.5 (44.5, 74.5)	54.5 (44.5, 74.5)	0.019	64.5 (54.5, 74.5)	64.5 (54.5, 74.5)	n.s.	64.5 (54.5, 74.5)	64.5 (54.5, 74.5)	n.s.	64.5 (54.5, 74.5)	64.5 (54.5, 74.5)	n.s.
Male, n (%)	609 (65.3)	381 (48.5)	<0.001	280 (60.1)	244 (64.0)	n.s.	304 (56.4)	303 (58.0)	n.s.	325 (58.6)	534 (66.5)	0.003
Surgical admissions, n (%)	284 (30.5)	244 (31.0)	n.s.	117 (25.1)	90 (23.6)	n.s.	125 (23.2)	131 (25.1)	n.s.	133 (24.0)	162 (20.2)	n.s.
Initial creatinine, umol/l	87.0 (67.0, 120.0)	75.0 (60.0, 96.0)	<0.001	98.0 (71.0, 144.2)	97.0 (73.0, 119.5)	0.025	104.0 (74.0, 140.0)	105.0 (78.0, 137.0)	n.s.	111.5 (75.0, 174.2)	136.0 (94.0, 238.0)	<0.001
Vasopressors, n (%)	634 (68.0)	486 (61.8)	0.008	375 (80.5)	284 (74.5)	0.047	481 (89.2)	461 (88.3)	n.s.	513 (92.4)	721 (89.7)	n.s.
Mechanical ventilation, n (%)	677 (72.6)	525 (66.8)	0.009	373 (80.0)	303 (79.5)	n.s.	452 (83.9)	432 (82.8)	n.s.	481 (86.7)	656 (81.7)	0.014
Initial fluid load of > 2 L within 3 h of admission	35 (3.4)	25 (3.2)	n.s.	26 (5.6)	16 (4.2)	n.s.	30 (5.6)	27 (5.2)	n.s.	45 (8.1)	58 (7.2)	n.s.
Received blood products, n (%)	320 (34.3)	248 (36.1)	n.s.	228 (48.9)	152 (39.9)	0.010	306 (56.8)	275 (52.7)	n.s.	392 (70.6)	521 (64.9)	0.026
Median time to AKI onset, hours	/	/	/	25.8 (12.4, 62.7)	12.6 (1.8, 36.4)	<0.001	14.7 (7.0, 31.8)	7.2 (1.6, 19.7)	<0.001	7.8 (6.6, 16.6)	2.8 (0.7, 7.9)	<0.001
RRT, n (%)	25 (2.7)	3 (0.4)	<0.001	6 (1.3)	1 (0.3)	n.s.	21 (3.9)	13 (2.5)	n.s.	117 (21.0)	144 (17.9)	n.s.
Length of stay, hours	60.0 (26.0, 142.0)	65.0 (28.0, 159.2)	n.s.	140.5 (46.7–304.5)	117.0 (42.0, 245.0)	0.008	200.0 (73.0, 416.0)	183.0 (65.0, 399.0)	0.022	234.5 (71.7, 498.7)	169.5 (65.0, 424.0)	0.001
ICU 28-day mortality, n (%)	417 (44.7)	312 (39.7)	0.034	251 (53.9)	178 (46.7)	0.045	303 (56.2)	278 (53.2)	n.s.	351 (63.2)	506 (63.0)	n.s.

Values are median (IQR) or n (%). Statistical tests used are Mann Whitney *U* test and Chi square test or Fishers's exact test; n.s. – not significant; AKI – Acute kidney injury, KDIGO - *Kidney Disease Improving Global Outcomes*, KeGFR – kinetic estimated glomerular filtration rate.

Table 3
Concordance of each KDIGO and KeGFR stage.

	KeGFR no AKI, n	KeGFR Stage 1, n	KeGFR Stage 2, n	KeGFR Stage 3, n	Total, n
KDIGO no AKI, n	680	132	68	52	932
KDIGO Stage 1, n	78	227	67	94	466
KDIGO Stage 2, n	18	17	370	134	539
KDIGO Stage 3, n	10	5	17	523	555
Total, n	786	381	522	803	2492

AKI – Acute kidney injury, KDIGO - *Kidney Disease Improving Global Outcomes classification*, KeGFR – kinetic estimated glomerular filtration rate.

SCr concentration are kept constant, a 50% decline in clearance from baseline value should cause a 100% rise in SCr if a steady state is assumed [9]. SCr levels will increase in a response solely to an alteration in GFR, but determining a new steady-state creatinine-based estimate of GFR will take 24–72 h (3–5 times the creatinine half-life, which rises to the same extent as GFR declines) [24]. Versatility of creatinine values would be enhanced if we could shorten the time needed to detect a change in renal function during non-steady state conditions. The latter is the fundamental principle of the KeGFR formula, which includes initial SCr, mass balance principles and change over time.

To date, studies mostly focused on agreement of KeGFR with MDRD or AKIN and RIFLE in prediction of AKI, RRT and 30-day mortality, where it was shown that the KeGFR equation can be successfully applied to in-hospital settings and ongoing AKI compared to AKIN criteria, while KeGFR predicts the need for RRT better than MDRD [15,25]. However, patients that were not detected by KeGFR in those studies were those who presented with elevated Cr level on admission. The diagnosis of AKI in this subgroup requires the incorporation of baseline creatinine, not taken into account in this study due to lack of good quality and sufficient amount of data. In our study patients with elevated creatinine were excluded, and ROC analysis showed no difference in predictive ability of classifications. A poor concurrence was reported between AKI severity and the worst achieved KeGFR by De Oliveira et al. in adult patients who met KDIGO criteria but maintained a KeGFR 70 mL/min/1.73 m^2 or KeGFR declined to 45 mL/min/1.73 m^2 while they still had no AKI or only stage 1 AKI [26]. KeGFR did not perform better sensitivity-wise over KDIGO in a study that included CKD patients [27]. Contrary to these studies, KeGFR seems to give better results if applied to children - a good agreement was reported in KeGFR and KDIGO staging [28].

All of the mentioned studies applied only creatinine criteria from KDIGO, while urine output criteria were omitted. A study on 32,045 critically ill patients showed the paramount importance of UO criteria in defining AKI, where short/term and long/term risk of death of RRT is greatest for patients who met both criteria and if those abnormalities persist for longer than 3 days [29]. It was the basis of our decision to join the UO criteria with KeGFR criteria. Use of a simplified version of the KDIGO definition that neglects UO criterion and is based only on SCr may postpone the diagnosis of AKI, thus delaying interventions, and lead to underestimation of its association with ICU mortality. Incidence of AKI stage 2 or 3 is higher and the association with ICU mortality stronger when the UO criterion is not truncated [30]. In a study on MIMIC database sepsis patients, it was shown that urine output can help clinicians identify the risk of AKI before patients meet the diagnostic criteria of AKI [31]. Including urine UO is one of the reasons concordances of KeGFR and KIDGO in disease staging is also very good in our study, and outcomes of patients staged by KeGFR and KDIGO are very similar, pointing again to at least as valuable prognostic utility of KeGFR.

Researchers have previously tried to use a potential KeGFR time advantage. One study compared KeGFR with a clinical prediction model for predicting delayed graft function in deceased donor transplant recipients and found that KeGFR equation did not outperform the clinical model but its incorporation into the model significantly improved risk

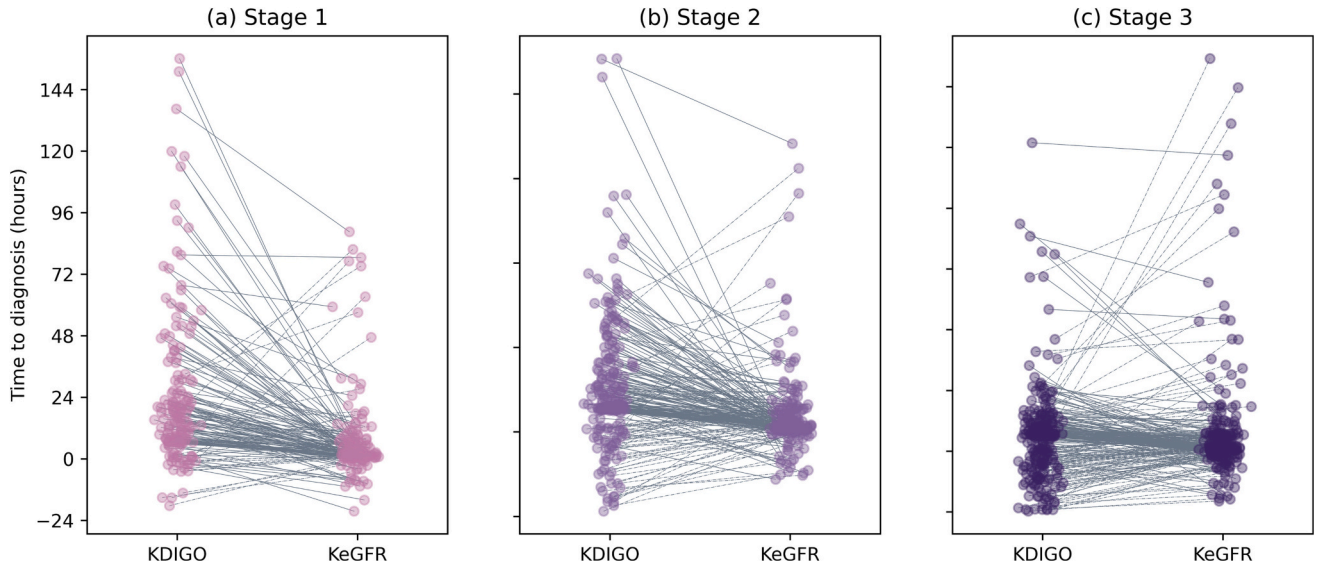

Fig. 2. Visual representation of paired differences between time to diagnosis of AKI stratified by stage between KDIGO and KeGFR in the first 7 days of ICU admission, both with urine output criteria included. AKI – Acute kidney injury; KDIGO - *Kidney Disease Improving Global Outcomes classification*; KeGFR – kinetic estimated glomerular filtration rate.

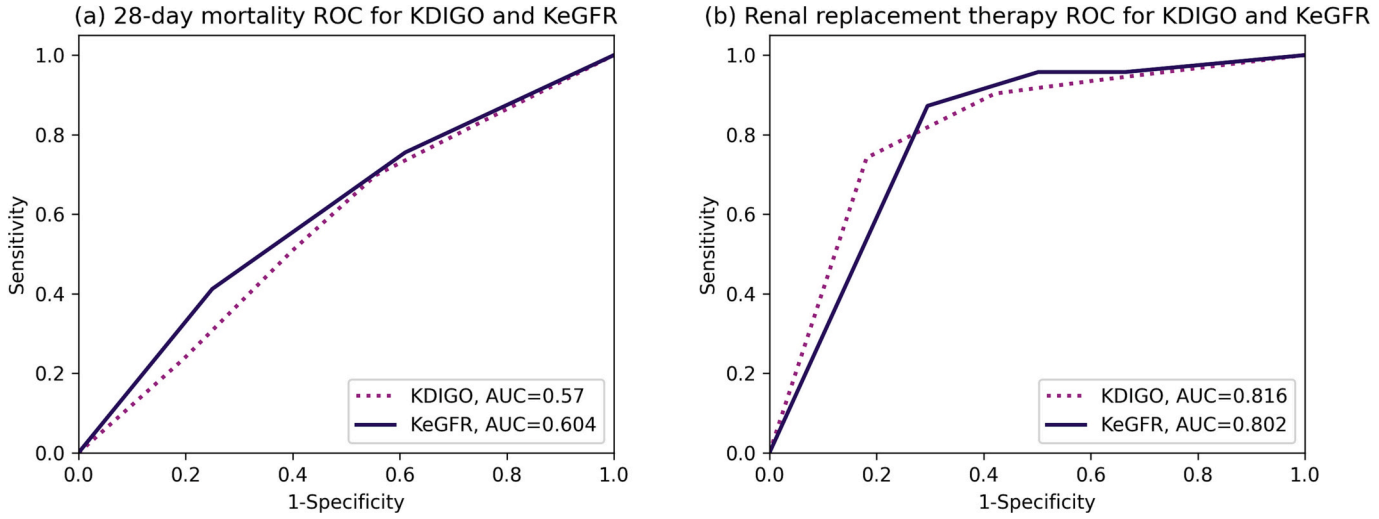

Fig. 3. Receiver operating curves (ROC) for (a) 28-day mortality and (b) renal replacement therapy between KDIGO and KeGFR*; KDIGO - Kidney Disease Improving Global Outcomes classification; KeGFR* – kinetic estimated glomerular filtration rate.

prediction for delayed graft function within 4 h of kidney transplantation [12]. A study by Hekmat et al. on patients after kidney transplant showed that KeGFR measurement, but neither the Cockcroft-Gault formula nor the MDRD formula, was able to diagnose stage 3 AKI in the 48 h after kidney donation [32]. However, in a study on a group of cardiac surgery patients, kinetic GFR modelling enabled the early detection of patients with AKI before significant incremental increases in serum creatinine were evident [33].

A different approach was taken by Kwong et al. who have shown that the use of kinetic estimates of renal function can impact medication dosing in a substantial proportion of critically ill AKI patients and its use should lower the incidence of medication toxicity as well as avoid subtherapeutic dosing during renal recovery [7]. A recent study by Dewitte et al. explored the combination KeGFR with currently available urinary biomarkers and found it may enhance their ability to predict renal recovery after AKI and improve prediction for major adverse kidney events [34]. Patients classified to same severity category by KDIGO and KeGFR systems were evaluated regarding time from hospital admission to worst AKI classification, with no clear advantage of kinetic variant, but diagnosis was classified as days after admission, not hours [27]. A study that explored percentage decrease of KeGFR difference to baseline eGFR as a prediction tool for AKI outside of ICU setting and using only creatinine criteria for KDIGO found that this it was useful for prediction of hospital-acquired AKI. This approach, using baseline eGFR, may be used to identify acute on chronic kidney failure as the KeGFR formula alone may be suboptimal for that purpose in those patients [35]. Four-hour creatinine clearance, as another measure, may also perform well in the kinetic sense for monitoring renal function in critically ill patients [36].

Utilisation of a large ICU database offers an opportunity of inclusion of a large number of patients, which is a strength of this study. This is a retrospective study on a database with limited information on comorbidities, age and weight was masked into categories due to deidentification, baseline creatinine was evaluated by the least value in the 7 days before admission and initial steady state eGFR estimation was based on it. Septic patients without serial creatinine measurements had to be

excluded, although AKI incidence in this cohort matches the assessed epidemiological incidence in other studies. Another limitation is that most of the diagnoses were made around the time of admission, probably because patients were admitted, among else, because of AKI. Finally, any ICU research is the potential for limited generalisability to other patient populations or settings.

KeGFR is a simple calculation that requires routinely collected patient demographic and laboratory data and can be readily implemented in any electronic health record, but further research is required to assess performance in different clinical situations and improve interpretability and understanding of the meaning of the results.

To assess the full potential of KeGFR formula - to maximize the time advantage it gives to a value close to theoretical maximum - a cohort should be made only from patients who developed AKI during the ICU stay, with regular creatinine measurements. Results should be confirmed on another large ICU database or in real clinical scenarios.

In conclusion, earlier diagnosis and a more precise diagnostic workup are necessary for patients with non-steady state creatinine levels, while interventions and therapies still can reverse the process of kidney injury. KeGFR formula offers that advantage and should be a complementary tool in assessing kidney function.

5. Statements and declarations

5.1. Data and code availability

AmstedramUMC database is available to researchers through credentialed access. Executed code is available from corresponding author upon reasonable request.

5.2. Consent for publication

All authors have approved this manuscript for publication.

5.3. Ethics approval and consent to participate

The Medical Research Ethics Committee of VU university medical center determined that the AmsterdamUMCdb study was exempt from their review and was not subject to the Dutch Medical Research Involving Human Subjects Act (WMO). The process of developing AmsterdamUMCdb was audited by an external team led by a member of the privacy expert group at the Netherlands Federation of UMCs. The Ethics in Intensive Care Medicine group provided external ethics review and appraisal. The use of AmsterdamUMCdb is exempt from institutional review board approval due to a combination of de-identification, contractual, and governance strategies where re-identification is not reasonably likely and can therefore be considered as anonymous information in the context of the General Data Protection Regulation (GDPR).

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CRediT author statement

LL and SP: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Writing - review, Vizualization, Formal Analysis. PE: Supervision, Writing, Rewriting and Editing, Methodology, Visualization, Resources, Project administration, Validation. PT, AE, HG, TR: Writing, Rewriting and Editing, Methodology. FH, IM and BS contributed to Conceptualization and Investigation.

Declaration of Competing Interest

none.

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