The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU.

Schetz M, MD, PhD; Gunst J, MD, PhD; Van den Berghe G, MD, PhD.

Clinical Department and Laboratory of Intensive Care Medicine

Division of Cellular and Molecular Medicine

KU Leuven University

Herestraat 49, B-3000 Leuven

Belgium

Running title: eGFR for assessment of AKI recovery

Address for correspondence:

Marie.schetz@uzleuven.be

Tel 3216344021

Fax 3216344015

Abstract

Purpose: to quantify the error in evaluating recovery from acute kidney injury (AKI) with estimated GFR (eGFR) in relation to ICU stay.

Methods: secondary analysis performed on the database of the EPaNIC trial. In a cohort of patients who developed AKI during ICU stay we compared eGFR with measured creatinine clearance (Clcr) at ICU discharge. Recovery of kidney function was assessed by comparison with baseline eGFR and the accuracy of eGFR to detect "potential CKD status" defined by Clcr was quantified. The same analysis was performed in subgroups with different ICU stay. Multivariate regression was performed to determine independent predictors of the eGFR-Clcr difference.

Results: 757 patients were included. The bias (limits of agreement (LOA)) between eGFR and Clcr at ICU discharge related to ICU stay, increasing from +1.3 (-37.4/+40) ml/min/1.73m^2 in patients with short stay to +34.7 (-54.4/+123.8) ml/min/1.73m^2 in patients with ICU stay of more than 14 days. This resulted in a significantly different incidence of complete recovery with the two evaluation methods and reduced sensitivity to detect "potential CKD status" with eGFR in patients with prolonged ICU stay. Independent predictors of the bias included creatinine excretion on the last day in ICU, baseline eGFR, ICU stay, gender and age.

Conclusion: Compared to Clcr, discharge eGFR results in overestimation of renal recovery in patients with prolonged ICU stay and in reduced accuracy of "CKD staging". Since age, gender and race do not change during ICU stay the same conclusion can be drawn with regard to plasma creatinine.

Key words: critically ill - AKI – recovery – eGFR –creatinine clearance

Take home message: in patients with prolonged ICU stay recovery of AKI is significantly overestimated when assessed with eGFR

140-character tweet: using discharge eGFR instead of creatinine clearance results in overestimation of recovery from AKI in patients with prolonged ICU stay

Introduction

Acute kidney injury (AKI) is a frequent and severe complication in ICU patients. Over the past ten years consensus has been reached on how to define this syndrome, based on urine output and changes in serum creatinine compared with baseline [1]. Baseline creatinine reflects baseline glomerular filtration rate (GFR), the most commonly used parameter to describe kidney function. GFR can be measured as the clearance of endogenous (creatinine) or exogenous (inulin, ^{51}Cr-EDTA, iothalamate, iohexate) markers or can be estimated by equations that besides serum creatinine include anthropometric characteristics that account for differences in creatinine generation such as age, gender and race [2,3]. The most popular equations are the MDRD [4] and the CKD-EPI equation [5], which have been developed in patients with stable chronic kidney disease.

In an important proportion of patients with AKI kidney function will recover. A correct estimation of renal recovery has prognostic implications and is important for planning post discharge renal care [6-8]. The optimal method for determining recovery from AKI would be to compare discharge GFR with baseline GFR, both measured with a golden standard such as inulin, radioisotopes or iodinated contrast agents [2,3]. Because this is cumbersome in clinical practice recovery is usually measured by comparing discharge serum creatinine or eGFR with baseline creatinine or eGFR [9-12].

eGFR equations are not validated at high GFR levels [13,14] and do not take into account deviations from population anthropometric measurements. Small studies in critically ill patients, concentrating on the diagnosis of AKI and using creatinine clearance (Clcr) as the reference method, have shown poor correlations with eGFR equations [15-19]. Prolonged critical illness is characterized by important muscle wasting (sarcopenia) [20,21]. Reduced creatinine generation (a reflection of muscle mass) has also been demonstrated in patients with AKI [22]. In these wasted patients the use of discharge eGFR is expected to result in overestimation of GFR and thus of renal recovery. Similar restrictions can be made with regard to the use of serum creatinine.

The aim of this study was to quantify the risk of potential misclassification of renal recovery induced by using an eGFR-based assessment (derived from discharge creatinine). For this purpose we first compared the eGFR at ICU discharge with measured Clcr based on 24h urine collection. Subsequently we assessed the difference in the incidence of recovery with these two parameters by comparing both with baseline eGFR and determined the accuracy of discharge eGFR to detect discharge "CKD staging" based on Clcr. We further hypothesized that the difference between the two methods of assessing recovery relates to ICU stay and the degree of muscle wasting.

Methods

Patients

This analysis was performed on the database of the EPaNIC trial [23] comparing two nutritional strategies in a heterogeneous population of 4640 adult ICU patients that were included between August 2007 and November 2010. Written informed consent was obtained from all patients or their designated representatives. The protocol was approved by the institutional review board of the participating centers and by the Belgian authorities. The incidence of AKI was determined in the study population after exclusion of patients with end stage renal disease (ESRD), kidney transplantation or incomplete data. For this analysis we included all patients who developed AKI during their ICU stay but excluded those who died in ICU, those who were still on renal replacement therapy (RRT) at ICU discharge and those for whom Clcr on the last day in ICU was not available.

Definition of AKI and measurement of renal recovery

AKI was classified according to the KDIGO criteria and defined by the maximal stage during ICU stay (AKI_{max}). Since hourly urine output was not available in the database we only used the creatinine criteria [1]. For baseline serum creatinine we used the lowest creatinine in 3 months before ICU admission (elective admission) or the lowest creatinine from 3 months to 1 week before ICU admission (emergency admission). Serum creatinine was searched from the hospital database or manually retrieved by searching documents from referring hospitals/physicians. In case of missing values a baseline creatinine was calculated from the Modification of Diet in Renal Disease formula using an eGFR of $75 ml/min/1.73m^2$ [4].

Two methods for estimating kidney function at ICU discharge were compared: the eGFR (MDRD equation) based on the last serum creatinine in the ICU:

$$eGFR = 175 \times (P_{cr})^{-1.154} \times (\text{age, yr})^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female) ml/min/1.73m}^2$$

and the Clcr measured on a 24h urine collection on the last complete day in ICU. The Clcr measurement was part of routine care. Urine was collected over a 24h period and a mixed sample sent for analysis. For serum creatinine we used the mean of the measurement at the start and the end of the collection. All creatinine measurements were performed with an IDMS-traceable Jaffé method. Clcr was standardized to body surface area (BSA) for comparison with eGFR:

$$Clcr = (\text{urine creatinine} \times \text{urine output} \times 1.73)/(\text{serum creatinine} \times 1440 \times BSA) \text{ ml/min/1.73m}^2$$

Since muscle mass was assumed to be an important determinant of the eGFR-Clcr difference we measured creatinine excretion (reflecting creatinine generation under steady state conditions) on the last ICU day and compared this with predicted creatinine production (eG in mg/day) based on age, gender and admission weight [24].

For males: eG = (27 - 0.173 x age) x weight

For females: eG = (25 - 0.175 x age) x weight

To validate our findings, we also performed the above measurements in ICU survivors without AKI.

Recovery of kidney function was assessed by comparing discharge Clcr and eGFR with baseline eGFR. For this analysis patients in whom baseline creatinine was not available (n=179) were omitted. Complete recovery was defined as return to baseline eGFR. The above measurements were performed in all AKI patients and in subgroups with different ICU stay: short (< 8 days), medium (8-14 days) or long (>14 days). Although CKD staging [26] is not strictly applicable to the early recovery phase of AKI, we also determined the accuracy of discharge eGFR to detect “potential CKD status” (GFR<60ml/min/1.73m^2) defined by Clcr.

Statistical analysis

Continuous variables are expressed as median (IQR) and categorical variables as number and percentages. Paired continuous variables were compared with the Wilcoxon signed-rank test and unpaired variables with Wilcoxon/Kruskal-Wallis, whereas for unpaired categorical variables the Chi-square or Fisher’s exact test was used. Agreement (concordance) was assessed with Bland-Altman analysis for continuous variables and the Bowker’s test (equivalent to McNemar’s test) for categorical variables (proportion complete recovery). Subgroup analysis was performed for patients with different ICU stay. A multiple regression analysis (fit least square) with backward selection was performed to determine independent predictors of the difference between eGFR and Clcreat, including all variables that in univariate analysis had a p value below 0.1. Age, gender, baseline eGFR, malignancy, nutritional risk score (NRS), medical versus surgical admission, sepsis on admission, Apache II score, SOFA score, AKImax, creatinine excretion on the last ICU day, ICU stay and EPaNIC randomization arm were evaluated as potential predictors. We excluded colinearity amongst parameters and assured a (log)linear relationship with outcome. Statistical analysis was performed using JMP 10 software (SAS Institute, cary, NC). All tests were two-sided and a p value <0.05 was considered statistically significant.

Results

From the original study population of 4640 patients, 56 patients were excluded for ESRD, 15 for kidney transplantation and 9 for missing data on kidney function during ICU stay. AKI was diagnosed in 1296/4560 patients (28.4%). Two hundred twenty nine patients did not survive to ICU discharge, 77 were still on RRT at ICU discharge and Clcr was not available on the last day of ICU in 233 patients, leaving 757 patients to be included in the present analysis. Baseline characteristics and clinical outcomes for the whole population and for patients with short, medium or long ICU stay are shown in table 1. Maximal AKI stage was stage 1 in 439 (58%), stage 2 in 137 (18%) and stage 3 in 181 (24%).

At ICU discharge Clcr and eGFR significantly differed: 55.2 (34.6-81.8) and 60.6 (40.1-97.6) ml/min/1.73m^2 respectively (p<0.0001). Subgroup analysis showed significant and increasing differences in medium and long stay patients (Fig 1 A and Table 2). A Bland-Altman analysis (Fig 2) found an increasing bias (LOA) from +1.32 (-37.4/+40) in patients with short stay to +34.7 (-54.3/+123.8) ml/min/1.73m^2 in patients with ICU stay >14 days. In AKI patients with medium or long ICU stay, the proportion of patients who had complete recovery upon discharge was significantly higher when assessed with eGFR compared with Clcr, whereas for patients with short ICU stay the reverse effect was seen. Likewise, the sensitivity of discharge eGFR to detect “potential CKD status” defined by discharge Clcr decreased with increasing ICU stay (Table 3).

Measured creatinine excretion at ICU discharge (parameter of muscle mass) was not significantly different from the predicted creatinine production in short-stay patients. However, in medium- and long-stay patients measured creatinine excretion was significantly lower than predicted production with increasing difference with longer stay (Table 4).

The 24h creatinine excretion upon discharge, baseline eGFR, ICU stay, gender and age (in decreasing order of importance) were independent predictors of the difference between eGFR and Clcr and predicted 56% of its variation. The parameter estimate, standard error, 95% confidence intervals, standardized beta and p value of the predicting variables are shown in table 5.

To validate our findings we repeated the same analysis in the population of patients not developing AKI during ICU stay. After exclusion of 44 non-survivors and 1311 patients with unavailable data, 1952 patients were included (baseline characteristics in table 1 of the electronic supplement). As in AKI patients, discharge eGFR significantly exceeded Clcr in medium- and long-stay patients (Table 2, Fig 1 B and Fig 1 of the electronic supplement). In these no-AKI patients the same regression model explained 72% of the variability of this difference with again creatinine excretion being the most powerful predictor (details in table 5). No-AKI patients also had a decreasing discharge creatinine excretion with longer ICU stay ($p<0.0001$) which was significantly lower than predicted creatinine production with

ICU stays >7 days (p=0.02 for 8-14d and p<0.0001 for >14d) (Table 4). Another interesting observation is a decrease of discharge creatinine compared with baseline in the 1499 no-AKI patients with known baseline creatinine. The difference increased from 0.1 (-0.01-0.2) mg/dL in short stay patients (p<0.0001) to 0.21 (0.09-0.32) mg/dL in patients with long ICU stay (p<0.0001).

Discussion

In the present study we showed that, in AKI patients with an ICU stay exceeding 7 days, measuring kidney function at ICU discharge with eGFR significantly differed from the measurement with Clcr, which resulted in overestimation of renal recovery and underdiagnosis of “potential CKD status”. In patients not developing AKI during ICU stay discharge eGFR also significantly differed from Clcr. The discrepancy between eGFR and Clcr was most pronounced in long-stay patients and appears considerably explained by development of muscle wasting, gradually leading to a lower creatinine production/excretion than expected by anthropometric measures. This is supported by multiple regression analysis, in which lower creatinine excretion as parameter of lower muscle mass independently associated with a higher bias. Importantly, the inaccuracy of eGFR in long stay ICU patients is also applicable to creatinine, since the other components of the eGFR equation (age, gender and race) do not change during ICU stay.

Most clinical studies on recovery from AKI are limited to independence of RRT at some point during follow-up after RRT-requiring AKI. Few studies have evaluated the recovery from less severe forms of AKI. They use return to baseline creatinine [9,10], return to baseline eGFR [11,12] or absence of AKI criteria at discharge [27,28], all based on comparison of discharge creatinine, or the derived eGFR, with baseline creatinine or eGFR. The limitation of creatinine-based estimations of renal recovery is generally acknowledged [11,12,29] but has never before been formally quantified. Our study showed that the potential misclassification of renal recovery could be substantial in patients with prolonged ICU stay.

The most significant predictor of the difference between discharge eGFR and Clcr was creatinine excretion, a marker of muscle mass. The impact of male gender and lower age can also be related to the higher muscle mass at ICU admission (more potential for loss). ICU-acquired weakness and muscle wasting (sarcopenia) due to immobilization, disuse atrophy and systemic inflammation, is a frequent problem in prolonged critically ill patients [20,21]. The decrease of creatinine excretion with prolonged ICU stay was also present in patients without AKI, where it was an even more powerful predictor of the bias between the two GFR measurements. Another indication of important muscle wasting with prolonged ICU stay is the decrease of serum creatinine in patients without AKI. This decrease is most pronounced with prolonged ICU stay which makes fluid overload a less plausible explanation. This finding confirms the results of a recent retrospective study in critically ill patients with ICU stay of more than 5 days that found significant decreases of creatinine during hospital stay, with discharge creatinine being significantly lower than baseline, except in patients with AKI stage 3 [29].

The reduction of muscle mass is not reflected in the surrogates that are used in the MDRD equation (age, race, gender), which assumes an average relationship between these surrogates and muscle mass and used population BSA for particular age and sex groups to normalize eGFR to a BSA of $1.73m^2$ [2]. The effect of sarcopenia on the difference between estimated and measured GFR has been demonstrated in patients with neuromuscular disorders [30] or liver cirrhosis [31]. Although sepsis has also been shown to result in decreased creatinine generation [32], it was not an independent predictor of the difference between eGFR and Clcr in our analysis. Another potential explanation for overestimation of true GFR by eGFR could be dilution of creatinine by positive fluid balances, which has more effect on eGFR than on Clcr. However, dilution is expected to have more impact in the early phase of ICU when AKI develops and less in the recovery phase, especially in patients with longer ICU stay. Absence of steady state may also explain the unreliability of eGFR and could underlie the lower incidence of complete recovery with eGFR in short-stay patients whose creatinine may be decreasing at the time of discharge.

Our findings may have important implications for post-discharge care. In Belgium inclusion in a CKD program is based on the eGFR, thus excluding those patients with discrepancy between true GFR and eGFR resulting from sarcopenia. Our results also raise concern with regard to the optimal duration of follow-up after an episode of AKI, especially after prolonged critical illness. Some studies with longer follow-up time after AKI have shown improvement in kidney function [33]. Others have shown further deterioration [12,34], which could reflect true deterioration of kidney function or restoration of muscle mass after rehabilitation. Whether overestimation of recovery in the early follow-up of AKI represents one of the reasons for AKI being a risk factor for CKD [35] remains to be investigated. The important discrepancy between eGFR and Clcr also includes a substantial risk for (eGFR-based) drug overdose in patients with prolonged ICU stay.

A potential solution to the misinterpretation of renal recovery at ICU discharge may be the use of cystatin C or cystatin C-based GFR equations. Compared with creatinine cystatin C is less dependent on muscle mass [36]. Its superiority for detecting true GFR has indeed been demonstrated in patients with neuromuscular disorders [37] or chronic muscle wasting [38].

The strength of our study is the large patients number and the use of a heterogeneous population of ICU patients. On the other hand, this analysis has several limitations. First, we did not use a fixed time point for the evaluation of recovery and we realize that ICU discharge is frequently too early. However, the aim of our study was to illustrate the imperfections of assessing renal recovery with (serum creatinine-derived) eGFR and this could only be done with simultaneous measurements of eGFR and Clcr, the latter not being available after ICU discharge. In addition, the muscle weakness and sarcopenia of prolonged critically ill patients can be expected to persist long after ICU discharge [39], thus hampering the evaluation of renal recovery with eGFR also at a later time point.

Second, we did not use a golden standard (clearance of an ideal filtration marker) to determine "true" GFR. Both eGFR (MDRD) and Clcr have drawbacks. Common limitations include inaccuracies in the measurement of creatinine due to substances interfering with the Jaffé method and requirement for a steady state. A stable kidney function can indeed not be assumed to be present in critically ill patients, but the instability can be reasonably expected to be less important in patients that are considered ready for ICU discharge and in those with longer ICU stay. Absence of steady state in the recovery phase will result in underestimation of GFR, which will be more pronounced with eGFR than with Clcr and could partially explain the observed difference in short-stay patients. As already stated, the MDRD equation has been validated in patients with stable chronic kidney disease [2], underestimates GFR in healthy volunteers [13,14] and is not sufficiently accurate for the estimation of true GFR in critically ill patients, both at low and at high levels of GFR [15,16,18,19]. This inaccuracy has repeatedly been emphasized with regard to the diagnosis of AKI but less for the evaluation of recovery. Despite these recognized limitations eGFR still remains widely used in the assessment of patients with AKI.

The measurement of Clcr, especially when part of routine clinical practice, is subject to errors in urine collection. In addition, creatinine clearance may overestimate a low GFR because of intestinal elimination and tubular secretion [40], which may explain the higher discharge Clcr in short-stay patients. We acknowledge the limitations of the two GFR measurements but the aim of our study was to illustrate the inaccuracy of measuring recovery with eGFR (or serum creatinine) and the Clcr is expected to be closer to the golden standard than eGFR, especially in long-stay patients. Moreover, in these long-stay patients, the potential overestimation of the true GFR by measured Crcl would underestimate rather than overestimate the observed bias.

Third, we did not measure baseline Clcr or creatinine excretion and we did not measure body weight during ICU stay, and therefore cannot exclude that important muscle loss with difference between eGFR and Clcr already existed at baseline. However this does not invalidate the conclusion about the unreliability of eGFR or serum creatinine to evaluate recovery. In addition, the decrease of creatinine compared with baseline in long-stay patients without AKI confirms the important muscle wasting during ICU stay.

In conclusion, in patients with prolonged ICU stay recovery of AKI is significantly overestimated when evaluated with eGFR. This may result in failure to detect CKD. By analogy, this also applies to serum creatinine, since the other determinants of eGFR do not change during ICU stay. These finding have important implications for the evaluation of recovery from AKI and for post-discharge renal care.

Ethical standards

This study is a secondary analysis of the EPaNIC trial, for which written informed consent was obtained from all patients or their designated representatives. The protocol of the EPaNIC trial was approved by the institutional review board of the participating centers and by the Belgian authorities.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject of the study. GVdB, via the University of Leuven, receives structural research financing via the Methusalem program, funded by the Flemish Government (METH08/07) and holds an ERC Advanced grant (AdvG-2012-321670) from the Ideas program of the EU FP7.

References

----

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guidelines AKI: AKI definition. Kidney Intern Suppl 2:19-36.
2. Stevens LA, Levey AS (2009) Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol 20:2305-13
3. Macedo E, Mehta RL (2013) Measuring renal function in critically ill patients: tools and strategies for assessing glomerular filtration rate. Curr Opin Crit Care 19:560-6.
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461-70.
5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604-12.
6. Harel Z1, Wald R, Bargman JM, Mamdani M, Etchells E, Garg AX, Ray JG, Luo J, Li P, Quinn RR, Forster A, Perl J, Bell CM (2013) Nephrologist follow-up improves all-cause mortality of severe acute kidney injury survivors. Kidney Int 83:901-8.
7. Levin A, Stevens PE (2011) Early detection of CKD: the benefits, limitations and effects on prognosis. Nat Rev Nephrol 7:446-57.
8. Pannu N, James M, Hemmelgarn B, Klarenbach S; Alberta Kidney Disease Network (2013) Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. Clin J Am Soc Nephrol 8:194-202.
9. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, Macleod A (2007) Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 18:1292-8.
10. Kopolovic I, Simmonds K, Duggan S, Ewanchuk M, Stollery DE, Bagshaw SM (2013) Risk factors and outcomes associated with acute kidney injury following ruptured abdominal aortic aneurysm. BMC Nephrol 14:99.
11. Fortrie G, Stads S, de Geus HR, Groeneveld AB, Zietse R, Betjes MG (2013) Determinants of renal function at hospital discharge of patients treated with renal replacement therapy in the intensive care unit. J Crit Care 28:126-32.
12. Macedo E, Zanetta DM, Abdulkader RC (2012) Long-term follow-up of patients after acute kidney injury: patterns of renal functional recovery. PLoS One 7:e36388.
13. Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, Nelson RG, Rahman M, Deysher AE, Zhang YL, Schmid CH, Levey AS (2007) Evaluation of the modification of diet in renal disease study equation in a large diverse population. J Am Soc Nephrol 18:2749-57.
14. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG (2004) Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 141:929-37.
15. Udy AA, Morton FJ, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R, Starr T, Boots RJ, Lipman J (2013) A comparison of CKD-EPI

estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations. BMC Nephrol 14: 250.
16. Hoste EA, Damen J, Vanholder RC, Lameire NH, Delanghe JR, Van den Hauwe K, Colardyn FA (2005) Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant 20:747-53.
17. Bouchard J1, Macedo E, Soroko S, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease (2010) Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. Nephrol Dial Transplant 25:102-7.
18. Martin JH, Fay MF, Udy A, Roberts J, Kirkpatrick C, Ungerer J, Lipman J (2011) Pitfalls of using estimations of glomerular filtration rate in an intensive care population. Intern Med J 41:537-43.
19. Kirwan CJ, Philips BJ, Macphee IA (2013) Estimated glomerular filtration rate correlates poorly with four-hour creatinine clearance in critically ill patients with acute kidney injury. Crit Care Res Pract 2013:406075.
20. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Güiza FG, Wouters PJ, Mesotten D, Van den Berghe G (2013) Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med 41:2298-309.
21. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Padhke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE (2013) Acute skeletal muscle wasting in critical illness. JAMA 310:1591-600.
22. Wilson FP, Sheehan JM, Mariani LH, Berns JS (2012) Creatinine generation is reduced in patients requiring continuous venovenous hemodialysis and independently predicts mortality. Nephrol Dial Transplant 27:4088-94.
23. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G (2011) Early versus late parenteral nutrition in critically ill adults. N Engl J Med 365:506-17.
24. Bjornsson TD (1979) Use of serum creatinine concentrations to determine renal function. Clin Pharmacokinet 4:200-22.
25. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002; 39 (suppl 2): S1-S246
26. Macedo E, Zanetta DM, Abdulkader RC (2012) Long-term follow-up of patients after acute kidney injury: patterns of renal functional recovery. PLoS One 7:e36388.
27. Srisawat N, Murugan R, Lee M, Kong L, Carter M, Angus DC, Kellum JA; Genetic and Inflammatory Markers of Sepsis (GenIMS) Study Investigators (2011) Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. Kidney Int 80:545-52.
28. Alves SC, Tomasi CD, Constantino L, Giombelli V, Candal R, Bristot Mde L, Topanotti MF, Burdmann EA, Dal-Pizzol F, Fraga CM, Ritter C (2013)

Hypomagnesemia as a risk factor for the non-recovery of the renal function in critically ill patients with acute kidney injury. Nephrol Dial Transplant 28:910-6.
29. Prowle JR, KolicI, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunctin after AKI. Clin J Am Soc Nephrol 2014; 9: 1015-23.
30. Mirahmadi MK, Byrne C, Barton C, Penera N, Gordon S, Vaziri ND (2003) Prediction of creatinine clearance from serum creatinine in spinal cord injury patients. Am J Kidney Dis 41:269-78.
31. Sherman DS, Fish DN, Teitelbaum I (2003) Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 41:269-78.
32. Doi K1, Yuen PS, Eisner C, Hu X, Leelahavanichkul A, Schnermann J, Star RA (2009) Reduced production of creatinine limits its use as marker of kidney injury in sepsis. J Am Soc Nephrol 20:1217-21.
33. Ponte B, Felipe C, Muriel A, Tenorio MT, Liaño F (2008) Long-term functional evolution after an acute kidney injury: a 10-year study. Nephrol Dial Transplant 23:3859-66.
34. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR (2008) Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 52:262-71.
35. Chawla LS, Eggers PW, Star RA, Kimmel PL (2014) Acute kidney injury and chronic kidney disease as interconnected syndromes. New Engl J Med 371: 58-66.
36. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP (2008) Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol 3:348-54.
37. Tetsuka S, Morita M, Ikeguchi K, Nakano I (2013) Utility of cystatin C for renal function in amyotrophic lateral sclerosis. Acta Neurol Scand 128:386-90.
38. Pöge U, Gerhardt T, Stoffel-Wagner B, Klehr HU, Sauerbruch T, Woitas RP (2006) Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. Nephrol Dial Transplant 21:660-4.
39. Herridge MS (2009) Legacy of intensive care unit-acquired weakness. Crit Care Med 37(10 Suppl):S457-61
40. Perrone RD1, Madias NE, Levey AS (1992) Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 38:1933-53.

Fig 1 A. eGFR (gray boxplots) and Clcr (white boxplots) (in ml/min/1.73m^2) at ICU discharge for subgroups of AKI patients with ICU stay <7d, 7-14d and >14d. Boxplots show median and IQR, whiskers 10th and 90th percentile.

Fig 1 B. eGFR (gray boxplots) and Clcr (white boxplots) (in ml/min/1.73m^2) at ICU discharge for subgroups of no-AKI patients with ICU stay <7d, 7-14d and >14d. Boxplots show median and IQR, whiskers 10th and 90th percentile.

Fig 2. Bland-Altman analysis of the difference between Clcr and eGFR at ICU discharge A. in all AKI patients. B. in patients with ICU stay <8d. C. in patients with ICU stay between 8 and 14d. D. in patients with ICU stay >14d. The continuous line represents bias and the dashed lines the limits of agreement.

Table 1: key baseline characteristics and major clinical outcomes of AKI patients with different ICU stay. Results are presented as median (IQR) or n (%).* only in patients with known baseline creatinine (n=578). NRS = nutritional risk score, eGFR = estimated GFR, CKD = chronic kidney disease.

	Overall n=757	≤7d n=376	8-14d n=158	>14d n=223	p
ICU stay (days)	8 (4-17)	4 (3-6)	10 (9-12)	25 (19-39)	
Age (years)	69.4 (58.1-76.7)	71.2 (61.6-77.6)	69.7 (58.4-77.4)	64.6 (55.2-73.5)	<0.0001
Male gender	459 (61)	217 (58)	107 (68)	135 (61)	0.09
BMI (kg/m^2)	25.7 (22.9-29.3)	25.5 (22.8-29.1)	25.3 (22.7-29.1)	26.1 (23.4-30.0)	0.28
NRS	4 (3-4.5)	4 (3-4)	4 (3-5)	4 (3-5)	0.27
NRS ≥5	189 (25)	73 (19)	50 (32)	66 (30)	0.002
Diabetes	151 (20)	86 (23)	27 (17)	38 (17)	0.13
Malignancy	184 (24)	96 (26)	36 (23)	52 (23)	0.73
Baseline Screat (mg/dL) [µmol/L]	0.99 (0.76-1.14) [87.5]	0.98 (0.76-1.21) [86.6]	1.01 (0.78-1.16) [89.3]	0.94 (0.75-1.08) [83.1]	0.16
Baseline Screat not available	179 (24)	55 (15)	41 (26)	83 (38)	<0.0001
Known baseline Screat (mg/dL)* [µmol/L]	0.93 (0.69-1.23) [82.2]	0.98 (0.71-1.26) [86.6]	0.97 (0.70-1.28) [85.7]	0.84 (0.66-1.11) [74.3]	0.016
baseline eGFR * (ml/min/1.73m^2)	72.3 (50.8-102.4)	69.9 (50.0-95.8)	71.8 (48.9-111.0)	84.2 (58.6-106.1)	0.011
CKD (eGFR <60)*	202 (35)	122 (38)	43 (37)	37 (26)	0.046
Admission Apache II score	29 (20-36)	23 (18-32)	30 (22-37)	35 (29-40)	<0.0001
SOFA day1	9 (7-11)	8 (7-10)	9 (8-10)	10 (8-11)	<0.0001
Emergency admission	417 (55)	147 (39)	94 (59)	176 (79)	<0.0001
Surgical	714 (94)	363 (97)	143 (91)	208 (93)	0.018
Sepsis on admission	254 (34)	76 (20)	65 (41)	113 (51)	<0.0001
Screat on admission (mg/dL) [µmol/L]	1.30 (0.93-1.83) [114.9]	1.26 (0.91-1.76) [111.4]	1.40 (0.95-1.97) [123.8]	1.39 (0.93-2.00) [122.9]	0.13
AKImax stage					<0.0001
Stage 1	439 (58)	281 (75)	86 (54)	72 (32)	
Stage 2	137 (18)	55 (15)	35 (22)	47 (21)	
Stage 3 no RRT	86 (11)	35 (9)	26 (11)	25 (11)	
Stage 3 with RRT	95 (12)	5 (1)	11 (7)	79 (35)	
Screat at ICU discharge (mg/dL) [µmol/L]	1.10 (0.74-1.57) [97.2]	1.25 (0.89-1.72) [110.5]	0.99 (0.70-1.52) [87.5]	0.81 (0.57-1.35) [71.6]	<0.0001
Hospital stay (days)	27 (16-49)	18 (13-25)	28 (22-43)	54 (40-82)	<0.0001
Hospital mortality	51 (7)	14 (4)	14 (9)	23 (10)	0.003

Table 2: Discharge Clcr and eGFR and incidence of complete recovery by Clcr and eGFR at ICU discharge (only with known baseline*) for subgroups with different ICU stay.

	n	Discharge Clcreat median (IQR)	Discharge eGFR median (IQR)	p	n*	Baseline eGFR median (IQR)	Complete recovery by Clcr - n (%)	Complete recovery by eGFR - n (%)	p
AKI	757	55.2 (34.6-81.8)	60.6 (40.1-97.6)	<0.0001	578	72.3 (50.8-102.4)	163 (28.2)	205 (35.5)	0.0001
ICU stay 1-7d	376	53.4 (35.0-76.5)	51.2 (35.4-76.6)	0.86	321	69.8 (50.0-95.9)	85 (26.5)	65 (20.3)	0.003
ICU stay 8-14d	158	53.5 (34.8-88.0)	64.0 (42.5-104.2)	<0.0001	117	71.8 (48.9-111.0)	36 (30.8)	57 (48.7)	0.0002
ICU stay >14d	223	60.8 (32.2-91.0)	84.5 (48.9-137.0)	<0.0001	140	84.2 (58.6-106.0)	42 (30)	83 (59.3)	<0.0001
No AKI	1952	100.2 (75.4-130.1)	97.1 (74.8-127.4)	0.005					
ICU stay 1-7d	1604	98.1 (73.6-128.1)	92.2 (71.9-117.0)	<0.0001					
ICU stay 8-14d	184	111.3 (85.1-144.7)	117.2 (93.6-150.2)	0.005					
ICU stay >14d	164	112.4 (89.9-144.6)	147.2 (115.5-199.4)	<0.0001					

Table 3: Ability of eGFR to detect “CKD-status” by discharge Clcr (discharge ClCr <60)

	sensitivity	specificity	PPV	NPV
	% (95%CI)	% (95%CI)	% (95%CI)	% (95%CI)
ICUstay <8d (n=376)	89% (85.9-92.2)	80% (76-84)	87% (83.6-90.4)	83% (79.2-86.8)
ICU stay 8-14d (n=158)	73% (66.1-79.9)	96% (92.9-99.1)	96% (92.7-99.1)	73% (66.1-79.9)
ICu stay >14d (n=223)	64% (57.7-70.3)	96% (91.9-97.1)	95%(92.1-97.9)	74% (68.3-79.7)

Table 4: Comparison of daily creatinine excretion (in mg/day) on the last day in ICU compared with predicted creatinine production based on age, gender and admission weight in AKI and no AKI patients and in subgroups with different ICU stay.

	n	Creatinine excretion (mg/day) (median (IQR))	Predicted creatinine production (mg/day) (median (IQR))	p for difference
AKI patients	757	911 (691-1217)	1065 (878-1307)	<0.0001
ICU stay 1-7d	376	1016 (783-1331)	1027 (835-1256)	0.33
ICU stay 8-14d	158	895 (689-1158)	1042 (894-1283)	<0.0001
ICU stay >14d	223	729 (544-1040)	1132 (952-1363)	<0.0001
p for effect ICU stay		<0.0001	0.0002	
No AKI patients	1952	1162 (869-1510)	1106 (906-1362)	<0.0001
ICU stay 1-7d	1604	1205 (899-1537)	1094 (899-1345)	<0.0001
ICU stay 8-14d	184	1084 (807-1413)	1147 (944-1463)	0.02
ICU stay >14d	164	885 (670-1195)	1157 (986-1470)	<0.0001
p for effect ICU stay		<0.0001	0.0007	

Table 5: Parameter estimates of the regression analysis determining the independent predictors (in decreasing order of importance) of the difference between eGFR and Clcr in AKI and no AKI patients

variable	R^2	estimate	St Error	CI 95%	Standardized beta	p value
AKI patients	0.56					
Creatinine excretion		- 0.048	0.003	-0.053 / -0.043	-0.57	<0.0001
Baseline eGFR		0.22	0.022	0.18 / 0.27	0.27	<0.0001
ICU stay days		0.62	0.057	0.50 / 0.74	0.26	<0.0001
Gender (M)		5.94	0.993	3.99 / 7.88	0.16	<0.0001
Age		- 0.37	0.066	-0.50 / -0.24	-0.14	<0.0001
No AKI patients	0.72					
Creatinine excretion		- 0.073	0.001	-0.075 / -0.070	-0.90	<0.0001
Gender (M)		13.4	0.598	12.2 / 14.6	0.31	<0.0001
Age		- 0.52	0.037	-0.59 / -0.45	-0.18	<0.0001
ICU stay days		0.81	0.063	0.69 / 0.94	0.16	<0.0001
Baseline eGFR		0.22	0.020	0.18 / 0.26	0.14	<0.0001

Fig 1 electronic supplement. Bland-Altman analysis of the difference between Clcr and eGFR at ICU discharge A. in all no-AKI patients. B. in no-AKI patients with ICU stay <8d. C. in no-AKI patients with ICU stay between 8 and 14d. D. in no-AKI patients with ICU stay >14d. The continuous line represents bias and the dashed lines the limits of agreement.

Electronic supplementary material

Table 1

Fig 1