Journal of Critical Care 52 (2019) 136–140

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Creatinine versus cystatin C based glomerular filtration rate in critically ill patients

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1. Introduction

Decreased glomerular filtration rate (GFR) is the major functional event during acute kidney injury (AKI) impairing the kidneys' ability to filter water, waste products and drugs such as antibiotics and anticoagulants. The ability to accurately quantify GFR in critically ill patients remains challenging. Plasma creatinine is the dominant endogenous marker of GFR used to diagnose and stratify AKI in the intensive care unit (ICU) setting [1]. However, in addition to reflecting GFR, plasma creatinine concentration is a function of muscle mass. This has important implications for bedridden critically ill patients. In such patients, a continuing loss of muscle mass leads to a parallel decline in plasma creatinine levels and hence a progressive overestimation of true GFR [2-5].

In contrast to creatinine, cystatin C, an alternative endogenous marker of GFR, is produced by all nucleated cells and appears less affected by muscle mass [6]. However, cystatin C is a potent inhibitor of cysteine proteases, is upregulated by corticosteroids and may therefore be upregulated in critically ill patients with the systemic inflammatory response syndrome [7,8]. Indeed, a previous study demonstrated a gradual increase in plasma cystatin C levels during ICU admission in patients with and without AKI [9]. Furthermore, Carlier et al. confirmed that cystatin C based GFR equations systematically underestimated inulin clearance in critically ill patients after a median ICU length of stay of seven days [10].

In response to concerns about the imprecision of creatinine and cystatin C based GFR estimates, equations combining both biomarkers have been developed. Compared with single biomarker estimates, validation studies on thousands of non-critically ill patients have demonstrated improved precision and accuracy with combined creatinine-cystatin C formulas [11,12]. To date, however, only three studies have compared the performance of different single marker equations and one combination equation in critically ill patients using measured GFR (mGFR) as reference [10, 13, 14].

Accordingly, we conducted a prospective observational study in critically ill patients with an extended length of stay in ICU to evaluate the performance of multiple individual and composite models for GFR estimation against measured GFR as determined by iohexol clearance.

We hypothesized that equations combining creatinine and cystatin C would outperform equations based on single markers in patients who remain in ICU for three days or more.

2. Materials and methods

This study was approved by the Regional Ethics Committee (Ethics approval number 2009/1475-31/3) and performed in compliance with the Helsinki Declaration. Written informed consent was obtained from the patients or next-of-kin before enrollment.

2.1. Patients

We prospectively included a convenience sample of patients admitted to the general ICU and the neurosurgical ICU at the Karolinska University Hospital Solna, Sweden between January 2013 and September 2014. We included patients who had been treated in ICU for at least three days and were expected to stay in ICU at least until the following day. We excluded pregnant patients, patients who had been exposed to contrast media (e.g. during radiological examinations), patients treated with renal replacement therapy (RRT), patients <18 years of age, patients undergoing aggressive fluid resuscitation, and patients in whom surgery was expected within the time of GFR measurement. We collected demographic data, comorbidities, admission diagnoses and Simplified Acute Physiology Score (SAPS-3) score.

2.2. Iohexol clearance procedure

We measured GFR from the complete iohexol concentration curve following an intravenous injection of 5 ml iohexol (Omnipaque

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https://doi.org/10.1016/j.jcrc.2019.04.007
0883-9441/

300 mg I/ml, GE Healthcare, USA). Blood samples (3.5 ml) for iohexol analysis were obtained from an indwelling arterial cannula immediately before iohexol injection (baseline, $t = 0$) and at 5, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300 and 1440 min thereafter. Exact times of iohexol injection and blood sampling were recorded. The samples were turned five times directly after filling and then left to coagulate for 30 min. Samples were centrifuged for 10 min at 3200 rpm (2000g). Serum (500 μ) was pipetted into four different aliquot tubes and stored at −80 °C. Analyses were performed in batches.

Serum iohexol concentration was determined by ultra-high performance liquid chromatography (UHPLC) separation and UV detection using the Acquity® UHPLC system (Waters Corporation, Milford, MA). The performance of the iohexol method was monitored by both internal and external controls. The external controls were from Equalis (Uppsala, Sweden) external quality assurance program for iohexol.

2.3. Creatinine and cystatin C analyses

Cystatin C was determined with a turbidimetric method (Gentian Cystatin-c UDR-Kit for Beckman-Coulter Synchron and UniCel Systems, Ref A52761, Moss, Norway). Creatinine was determined with a modified Jaffe method (CREm, Creatinine, Ref 472525).

2.4. Calculations

We calculated mGFR from the entire plasma-time iohexol concentration curve using a two-compartment model according to Sapirstein et al. [15]:

The concentration curve for serum iohexol was divided in one fast distribution phase and one slow elimination phase. After log transformation, serum iohexol concentration will fall in a straight line from approximately 2 h onward, defining the slow phase of the curve and the slope (b) and intercept (B) from the slow curve was calculated.

Then “residual” serum iohexol concentration was calculated by subtracting the measured serum iohexol concentration from the extrapolated serum iohexol concentration in the interval before 2 h, using the equation derived from the slow elimination curve.

Slope (a) and intercept (A) was derived from the linear part of the residual log serum iohexol, corresponding to the fast distribution curve.

Finally, mGFR was calculated from a, b, A and B, and given dose Iohexol (I):

$$GFR = I/(\exp A/a + \exp.B/b).$$

Body surface area was calculated according to DuBois [16] and used to normalize mGFR to ml/min/1.73 m^2.

GFR was estimated (eGFR) from plasma creatinine using the following equations: the Modification of Diet in Renal Disease ($MDRD_{CREA}$) equation, the Chronic Kidney Disease Epidemiology Collaboration ($CKD\text{-}EPI_{CREA}$) equation and the Revised Lund-Malmö ($LM\text{-}REV_{CREA}$) equation [17-19].

Additionally, we calculated eGFR from plasma cystatin C using the Caucasian, Asian, Pediatric, and Adult ($CAPA_{CYSC}$) equation and the $CKD\text{-}EPI_{CYSC}$ equation, respectively [20].

Finally, we calculated eGFR using the following combined creatinine and cystatin C equations: the arithmetic means of $LM\text{-}REV_{CREA}$ and $CAPA_{CYSC}$ ($MEAN_{LM\text{-}REV+CAPA}$), the arithmetic means of $CKD\text{-}EPI_{CREA}$ and $CKD\text{-}EPI_{CYSC}$ ($MEAN_{CKD\text{-}EPI}$) and the composite CKD-EPI equation ($CKD\text{-}EPI_{CREA+CYSC}$) [11]. These particular combination equations were chosen since they have demonstrated greater precision and accuracy than single biomarker equations across a wide range of GFR in ambulant patients [12]. A detailed list of eGFR equations is provided in Supplementary Table 1.

2.5. Clinical characteristics during iohexol study

As a measure of fluid balance stability/instability, we recorded the patients' body weight before and after the iohexol measurement period.

Patients were considered to be in a stable fluid balance state when fluid resuscitation therapy was not required and with most clinical parameters starting to normalize [21]. Supplemental Fig. 1 details individual weight diagrams as a surrogate measure of clinical stability.

2.6. Statistical analysis

We analyzed iohexol plasma-time data using Microsoft Excel™ (Redmond, WA) and Mathematica™ Wolfram Research (Champaign, IL). Statistical analyses were performed using R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing (Vienna, Austria). Continuous variables were summarized as median with interquartile range (IQR) and categorical variables as n (%). We estimated bias by calculating the median differences (with 95% confidence intervals [CI]), estimated using Efron's non-parametric bias-corrected and accelerated (BCa) method [22] with 10,000 bootstrap replications between eGFR and mGFR (eGFR - mGFR). Median difference was also reported as the percentage of mGFR. Precision was reported as the interquartile range (IQR) of the difference between mGFR and eGFR (with 95% CIs estimated using Efron's non-parametric BCa method with 10,000 replications). We assessed accuracy both as the absolute difference between estimated and measured GFR expressed in percent of measured GFR and by calculating the proportion of eGFR values within 30% (P30) and 20% (P20), respectively, of mGFR. 95% CIs were assessed using the binomial proportion Wilson score interval. A P30 of at least 75% was considered sufficient for good clinical decision-making [23].

Bland-Altman [24] plots were used to evaluate the agreement between eGFR and mGFR.

3. Results

3.1. Study patients

Characteristics of patients on ICU admission and at the time of iohexol clearance measurement are shown in Table 1. We studied 30 patients (16 females) with a median (IQR) age of 67 (54–72) years and a median SAPS-3 score of 66 (58–71). None of the included patients received steroids during their ICU admission.

3.2. Iohexol clearance measurements

The iohexol clearance measurements were performed after a median (IQR) of 16 (10−21) days after ICU admission. In the 30 study patients, we observed a median mGFR of 84.5 (64–104) ml/min/1.73 m^2.

3.3. Performance of estimated GFR equations

Table 2 shows the performance of both single and combination GFR biomarker estimates. The creatinine-based eGFR equations ($MDRD_{CREA}$, $LM\text{-}REV_{CREA}$ and $CKD\text{-}EPI_{CREA}$) overestimated mGFR while the cystatin C-based eGFR equations ($CAPA_{CYSC}$ and $CKD\text{-}EPI_{CYSC}$) underestimated mGFR. Among the single marker equations, $LM\text{-}REV_{CREA}$ demonstrated lowest bias (8.0 ml/min/1.73 m^2 [95% CI −4.17 to 16.2]) and greatest P30 accuracy (66.7% [95% CI 48.8 to 80.0]). $MDRD_{CREA}$ demonstrated the greatest bias, lowest precision and lowest accuracy.

The combined eGFR equations underestimated mGFR by a median of 7.4 to 11.5 ml/min/1.73 m^2. Compared with the single marker equations, the three combined marker equations showed consistently higher P30 (≥80%) and P20 (60%) accuracy (Fig. 1). P10 for LM rev was on par with the CDK-EPI combined equation (33%). In contrast, their precision was somewhat lower than the cystatin C based single marker equations

Table 1
Patient characteristics.

Characteristic	All patients ($N = 30$)
Female sex, n (%)	16 (53.3%)
Age, years	67 (54–72)
Highest SOFA score	12 (8–13)
SAPS 3 score	66 (58–71)
ICU	
Mixed	20 (66.7%)
Neuro	10 (33.3%)
Body weight, kg	75 (56–83)
Body mass index, kg/m^2	25 (22–28)
Length of stay in ICU, days	25 (17–31)
Time between ICU admission and GFR measurement, days	16 (10–21)
Infusion of inotropes/vasopressor at time of measurement, n (%)	29 (96.7%)
Comorbidity, n (%)	
Heart failure	9 (30%)
Diabetes	6 (20%)
Hypertension	12 (40%)
Malignancy	10 (33%)
Thyroid dysfunction	1 (3%)
Cystatin C (mg/L) at admission	0.84 (0.77–1.09)
Cystatin C (mg/L) at time of measurement	1.29 (1.03–1.62)
Creatinine (μmol/L) at admission	76 (58–114)
Creatinine (μmol/L) at time of measurement	51 (37–73)

Values are median (IQR) or n (%).
GFR: glomerular filtration rate.
SOFA: Sequential Organ Failure Assessment (system for predicting outcome based on day-to-day assessment).
SAPS: Simplified Acute Physiology Score.

(Table 2). Bland-Altman plots for the single marker and combined marker equations are shown in supplemental Fig. 2.

4. Discussion

4.1. Key findings

We compared five creatinine- or cystatin C-based single marker eGFR equations and three combined marker equations with measured GFR in critically ill patients after a median length of stay in ICU of 16 (10–21) days. We found that creatinine-based equations overestimated GFR and that cystatin C-based equations underestimated GFR. All single marker equations demonstrated low accuracy. The combined marker equations demonstrated sufficient accuracy (P30 ≥ 80%) but underestimated GFR by 8 to 14%.

4.2. Relationship to previous studies

In theory, cystatin C has several advantages over creatinine as a marker of GFR. Since the production rate of creatinine is determined mainly by muscular mass, the rate is quite variable, especially in critically ill patients. Additionally, the elimination pathways for creatinine are complex and include, besides glomerular filtration, tubular secretion and elimination via the intestine. Cystatin C, in contrast, is a direct gene product, produced at a constant rate by virtually all body tissues, and eliminated from blood almost exclusively by glomerular filtration [25,26].

Our finding that creatinine-based equations overestimate GFR may have several explanations. One explanation is the ongoing loss of muscle mass typically seen in ICU patients. In fact, a recent British study recently showed that ICU patients *on average* lose 2% of their muscle mass per day [27]. Another potential explanation comes from the fact that fluid accumulation is common in the critically ill. Owing to the large volume of distribution (total body water) for creatinine, AKI severity can easily be underestimated due to dilution and “false low” plasma creatinine [28,29]. Since emerging data indicate that fluid overload may

Table 2
Performance of single marker and combined marker equations calculated from the differences between estimated and measured GFR (estimated minus measured GFR, i.e. positive values if the estimate is higher than the measured).

Performance	Single marker equations					Combined marker equations		
	$MDRD_{CREA}$	$LM\text{-}REV_{CREA}$	$CAPA_{CYSC}$	$CKD\text{-}EPI_{CREA}$	$CKD\text{-}EPI_{CYSC}$	$CKD\text{-}EPI_{CREA+CYSC}$	$MEAN_{CAPA+LM\text{-}REV}$	$MEAN_{CKD\text{-}EPI}$
Bias								
Median difference[a], ml/min/1.73 m^2 (95% CI)	35.77 (18.1 to 47.1)	8.0 (−4.17 to 16.2)	−26 (−30.4 to −19.7)	14 (2.16 to 24.1)	−25 (−32.3 to −20.3)	−10 (−17.1 to −0.648)	−11.5 (−19.6 to −0.0541)	−7.38 (−14.7 to 4.42)
Median percentage difference (95% CI)	49.5 (24.1 to 78.9)	9.3 (−4.8 to 24.4)	−32.2 (−41.4 to −25.1)	18.7 (1.2 to 33.5)	−33.1 (−44.7 to −24.6)	−12.1 (−19.2 to −1.2)	−13.8 (−19.4 to −0.04)	−8.7 (−15.9 to 4.98)
Precision								
IQR of differences[b], ml/min/1.73 m^2 (95% CI)	45.5 (24.95 to 80.41)	31.6 (19.9 to 44.4)	18.3 (11.5 to 33.3)	35.9 (24.0 to 50.1)	18.0 (8.6 to 29.3)	20.8 (15.8 to 32.5)	22.9 (15.7 to 31.7)	25.0 (18.8 to 35.6)
Accuracy								
Median absolute percentage difference (95% CI)	49.5 (24.6 to 77.7)	17.1 (9.8 to 27.3)	32.2 (24.6 to 40.6)	19.6 (12.4 to 33.5)	33.1 (23.7 to 42.2)	14.5 (10.5 to 24.6)	17.5 (12.8 to 21.4)	16.1 (10.6 to 21.9)
p30, %[c] (95% CI)	43.3 (27.4 to 60.8)	66.7 (48.8 to 80.8)	46.7 (30.2 to 63.9)	63.3 (45.5 to 78.1)	43.3 (27.4 to 60.8)	80.0 (62.7 to 90.5)	86.7 (70.3 to 94.7)	86.7 (70.3 to 94.7)
p20, %[c] (95% CI)	23.3 (12.0 to 40.9)	56.7 (39.2 to 72.6)	23.3 (11.8 to 40.9)	53.3 (36.1 to 69.8)	20.0 (9.5 to 37.3)	60.0 (42.3 to 75.4)	60.0 (42.3 to 75.4)	60.0 (42.3 to 75.4)
P10, %[c] (95%)	6.7 (1.8 to 21.2)	33.3 (19.2 to 51.2)	6.7 (1.8 to 21.3)	23.3 (11.8 to 40.9)	10.0 (3.5 to 25.6)	33.3 (19.2 to 51.2)	26.7 (14.2 to 44.4)	23.3 (11.8 to 40.9)

CI, confidence interval; IQR, interquartile range.
Measured GFR denotes the iohexol-based measurement of GFR.
[a] Difference in estimated minus measured GFR.
[b] Interquartile rage (IQR) defined as the range between Q1 and Q3.
[c] p30, p20 and p10 refer to the percentage of GFR estimates within 30%, 20% and 10% of measured GFR, respectively.

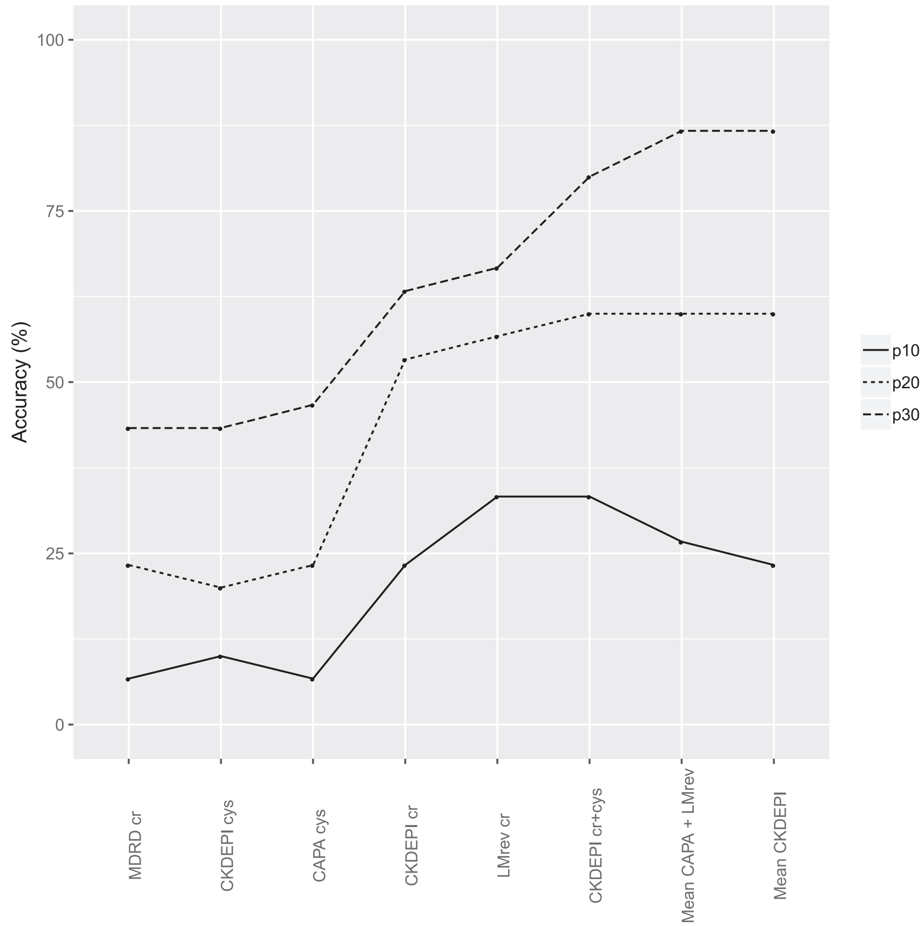

Fig. 1. Accuracy of each of the eGFR equations expressed as percentage within 10%, 20% or 30% (p10, p20, p30 respectively) of measured GFR.

contribute to the development of AKI, it is essential to understand the risks of using a marker that overestimates GFR [28-31]. For example, Prowle and co-workers showed that critically ill patients had significant falls in serum creatinine, persisting to hospital discharge, leading to a risk of inaccurate assessment of renal function, particularly in AKI survivors [5].

The practical use of cystatin C in intensive care units has been under debate. One hypothesis was that sepsis and/or inflammation would increase levels of cystatin C in plasma, but these concerns have not been confirmed [9,32]. Notably, when our group studied the impact of sepsis on cystatin C, we found that creatinine and cystatin C had differing trajectories, both in AKI and non-AKI patients [9]. In non-AKI patients, creatinine levels decreased by 25% after one week in ICU. During the same seven-day ICU stay, cystatin C increased by 25%. More recently we found that cystatin C, but not creatinine, is likely to be the superior renal function marker in patients recovering from critical illness [33]. Similar results, with a temporal decrease of creatinine in critically ill patients were demonstrated by Nejat et al. [34].

The performance of eGFR equations has previously been assessed in critically ill and postoperative patients. In a study of 21 postoperative patients following scheduled coronary bypass grafting, clearance estimations based on cystatin C were more accurate compared with estimations based on creatinine [35]. Notably, that study used a single compartment, two-sample iohexol clearance technique, which may reduce accuracy. In a subgroup ($n = 8$) of patients with an iohexol clearance <90 ml/min/1.73 m^2 the authors found cystatin C-based estimations of GFR to show a stronger correlation to measured iohexol clearance than creatinine-based estimations. In fact, estimations based on creatinine, using the MDRD- [36] and/or the Cockcroft-Gault equations [37], overestimated GFR by 30–40%. Similarly, in another study of cardiac surgery patients using (51)Cr-EDTA as a reference method, with sampling at 0, 90 and 180 min, cystatin C correlated better with the reference method than with serum creatinine or creatinine clearance [38]. In a cohort of non-surgical patients (51 non-ICU patients with various renal conditions), with varying renal function, Kyhse-Andersen and co-workers found a significantly stronger correlation ($r = 0.87$) between iohexol clearance and 1/cystatin C than with 1/creatinine ($r = 0.71$) [39]. A meta-analysis of 54 studies (non-ICU patients) found cystatin C to outperform creatinine as a marker of GFR in relation to reference standards (inulin, 51Cr-EDTA, 99Tm-DTPA, iothalamate or iohexol) of GFR [40]. A recent study on ICU patients from Belgium showed eGFR based on creatinine to have high bias and low precision and accuracy [10]. In the same study, measured urinary creatinine clearance overestimated GFR, and eGFR based on cystatin C had low bias but had limited precision and accuracy.

4.3. Implications of study findings

Our findings imply that for patients with longer treatment times in ICU (>2 weeks) there seems to be a considerable risk of overestimation of kidney function using creatinine-based equations for estimating GFR. Thus, potentially running the risk of overdosing nephrotoxic drugs. In contrast, cystatin C-based models for estimating GFR tends to under-estimate kidney function and thereby potentially jeopardize adequate treatment of e.g. infections.

Equations combining creatinine and cystatin C strengthens the accuracy considerably though it pertains the risk of under-estimating GFR.

4.4. Strengths and limitations

Our study has several strengths. It was a prospective study performed in two separate intensive care units. We used 14-point Iohexol measurements, allowing for a very detailed area under the curve measurements of GFR. Moreover, we had access to two endogenous markers of GFR, creatinine and cystatin C. Lastly, our selection process, focusing on length of stay longer than three days, with the majority of patients having a longer than average length of stay (median ICU treatment time = 25 days) ameliorates the heterogeneity of the ICU population to some extent.

The limitations of this study include the fact that critically ill patients are heterogeneous, and with only thirty patients from two ICUs generalizability is low.

5. Conclusions

In critically ill patients treated in a university hospital in Sweden, combining creatinine and cystatin C enables the best agreement between estimated and measured GFR. To determine which patients need nephrological follow-up or when prescribing drugs based on eGFR such combined eGFR methods should be considered.

Acknowledgements

This work was supported by funding from Stockholm County Council, Karolinska Institute Stockholm, Sweden.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.04.007.

References

[1] Kellum JA, Lameire N, for the KAKIGWG. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17(1):204.
[2] Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA 2015;313(8):837–46.
[3] Bell M, Granath F, Martensson J, Lofberg E, Ekbom A, Martling CR. Cystatin C is correlated with mortality in patients with and without acute kidney injury. Nephrol Dial Transplant 2009;24(10):3096–102.
[4] Patel SS, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. J Cachexia Sarcopenia Muscle 2013;4(1):19–29.
[5] Prowle JR, Kolic I, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. Clin J Am Soc Nephrol 2014;9(6):1015–23. https://doi.org/10.2215/CJN.11141113.
[6] Kashani KB, Frazee EN, Kukralova L, Sarvottam K, Herasevich V, Young PM, et al. Evaluating muscle mass by using markers of kidney function: development of the sarcopenia index. Crit Care Med 1 January 2017;45(7):e23–9.
[7] Assfalg-Machleidt I, Jochum M, Nast-Kolb D, Siebeck M, Billing A, Joka T, et al. Cathepsin B-indicator for the release of lysosomal cysteine proteinases in severe trauma and inflammation. Biol Chem Hoppe Seyler 1990;371(Suppl):211–22.
[8] Farges MC, Balcerzak D, Fisher BD, Attaix D, Bechet D, Ferrara M, et al. Increased muscle proteolysis after local trauma mainly reflects macrophage-associated lysosomal proteolysis. Am J Physiol Endocrinol Metab 2002;282(2):E326–35.
[9] Martensson J, Martling CR, Oldner A, Bell M. Impact of sepsis on levels of plasma cystatin C in AKI and non-AKI patients. Nephrol Dial Transplant 2012;27(2):576–81.
[10] Carlier M, Dumoulin A, Janssen A, Picavet S, Vanthuyne S, Van Eynde R, et al. Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med 2015;41(3):427–35.
[11] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367(1):20–9.
[12] Bjork J, Grubb A, Larsson A, Hansson LO, Flodin M, Sterner G, et al. Accuracy of GFR estimating equations combining standardized cystatin C and creatinine assays: a cross-sectional study in Sweden. Clin Chem Lab Med 2015;53(3):403–14.
[13] Delanaye P, Cavalier E, Morel J, Mehdi M, Maillard N, Claisse G, et al. Detection of decreased glomerular filtration rate in intensive care units: serum cystatin C versus serum creatinine. BMC Nephrol 2014;15:9.
[14] Kirwan CJ, Philips BJ, MacPhee IAM. Estimated glomerular filtration rate correlates poorly with four-hour creatinine clearance in critically ill patients with acute kidney injury. Crit Care Res Prac 2013;2013:1–8.
[15] Sapirstein LA, Vidt DG, Mandel MJ, Hanusek G. Volumes of distribution and clearances of intravenously injected creatinine in the dog. Am J Physiol 1955;181(2):330–6.
[16] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989;5(5):303–11 [discussion 12-3].
[17] Bjork J, Grubb A, Sterner G, Nyman U. Revised equations for estimating glomerular filtration rate based on the Lund-Malmo study cohort. Scand J Clin Lab Invest 2011;71(3):232–329.
[18] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–12.
[19] Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145(4):247–54.
[20] Grubb A, Horio M, Hansson LO, Bjork J, Nyman U, Flodin M, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. Clin Chem 2014;60(7):974–86.
[21] Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. JAMA 1998;279(18):1452–7.
[22] DiCiccio TJ, Efron B. Bootstrap confidence intervals. Stati Sci 1996:189–212.
[23] Levey AS, Coresh J, Bolton K, Culleton B, Harvey KS, Ikizler TA, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 SUPPL. 1).
[24] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307–10.
[25] Grubb A. Diagnostic value of analysis of cystatin C and protein HC in biological fluids. Clin Nephrol 1992;38(Suppl. 1):S20–7.
[26] Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. Scand J Clin Lab Invest 1985;45(2):97–101.
[27] Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA 2013;310(15):1591–600.
[28] Prowle JR, Chua HR, Bagshaw SM, Bellomo R. Clinical review: volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review. Crit Care 2012;16(4):230.
[29] Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2011;6(11):2567–72.
[30] Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordonez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009;76(8):893–9.
[31] Frendl DM, Ware Jr JE. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. Med Care 2014;52(5):439–45.
[32] Grubb A, Bjork J, Nyman U, Pollak J, Bengzon J, Ostner G, et al. Cystatin C, a marker for successful aging and glomerular filtration rate, is not influenced by inflammation. Scand J Clin Lab Invest 2011;71(2):145–9.
[33] Ravn B, Prowle JR, Martensson J, Martling CR, Bell M. Superiority of serum Cystatin C over creatinine in prediction of long-term prognosis at discharge from ICU. Crit Care Med 2017;45(9):e932–40.
[34] Nejat M, Pickering JW, Walker RJ, Endre ZH. Rapid detection of acute kidney injury by plasma cystatin C in the intensive care unit. Nephrol Dial Transplant 2010;25(10):3283–9.
[35] Bronden B, Eyjolfsson A, Blomquist S, Dardashti A, Ederoth P, Bjursten H. Evaluation of cystatin C with iohexol clearance in cardiac surgery. Acta Anaesthesiol Scand 2011;55(2):196–202.
[36] Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of diet in renal disease study group. J Am Soc Nephrol 1999;10(11):2426–39.
[37] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41.
[38] Wang QP, Gu JW, Zhan XH, Li H, Luo XH. Assessment of glomerular filtration rate by serum cystatin C in patients undergoing coronary artery bypass grafting. Ann Clin Biochem 2009;46(Pt 6):495–500.
[39] Kyhse-Andersen J, Schmidt C, Nordin G, Andersson B, Nilsson-Ehle P, Lindstrom V, et al. Serum cystatin C, determined by a rapid, automated particle-enhanced turbidimetric method, is a better marker than serum creatinine for glomerular filtration rate. Clin Chem 1994;40(10):1921–6.
[40] Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002;40(2):221–6.