BRIEF RESEARCH COMMUNICATION

Direct Measurement of Creatinine Clearance over a Short Interval in Intensive Care Settings

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Abstract

Background: The definition of acute kidney injury (AKI), based on serum creatinine and urine output, bears significant limitations in intensive care units (ICUs). Serum creatinine has significant lag-time as it needs to be accumulated and stabilized at a new level whereas urine output is affected by diuresis, antidiuresis, and antinatriuresis. Direct measurement of creatinine clearance ($CrCl_{direct}$ = urine creatinine × urine flow rate/serum creatinine) over a short interval (3–6 hours) was explored to identify patients with AKI.

Materials and methods: We reanalyzed a previous published dataset. We included 11 patients who had serial daily urine collections over 0 to 3 days of stay in ICU and baseline (day -1) serum creatinine levels.

Result: The ratio of $CrCl_{direct}$ on day 0 to baseline creatinine clearance predicted the progression of AKI over the subsequent 1 to 3 days of ICU stay [area under receiver operating characteristic curve = 0.933 and 95% confidence interval (CI) = 0.780–1.000].

Discussion: $CrCl_{direct}$ over a short interval may be an alternative marker of kidney function. Future studies may explore its use to identify patients with AKI who may benefit from early renal replacement therapy.

Keywords: Acute kidney injury, Biomarkers, Critical care, Glomerular filtration rate, Measure creatinine clearance.

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Background

There has been an ongoing debate about the appropriate timing of initiating renal replacement therapy (RRT) for intensive care patients with acute kidney injury (AKI) but without metabolic disorders or fluid disturbance.[1-5] The current evidence favors the delayed strategy, or namely, the conventional strategy. Except for a single-center clinical trial,[5] other multicenter trials did not find significant survival benefit for the early strategy.[1-3] One of the caveats is that the definition[6] of AKI, based on serum creatinine and urine output, bears significant limitations in intensive care settings. During the state of AKI, serum creatinine lags behind the actual drop of the glomerular filtration rate (GFR).[6] Also, the production of creatinine is likely reduced in intensive care settings due to immobilization and reduced absorption from diet. On the other hand, urine output as an estimate of kidney function is confounded by multiple factors. Kidneys physiologically concentrate urine through antidiuresis and antinatriuresis so urine output may decrease due to postglomerular reabsorption without a drop in GFR.[7] Conversely, severe tubular dysfunction or diuretics causes a "normal" urine output despite reduced GFR.[7] These situations occur commonly in intensive care settings.[7]

Direct measurement of creatinine clearance in short intervals (3–6 hours) may be a potential alternative to identify patients with AKI. The conventional measurement of creatinine clearance is based on 24-hour urine collection to mitigate the physiological diurnal variation of creatinine clearance, urine output, serum creatinine, and urine creatinine.[8-10] However, in intensive care settings, the fluctuation of the true creatinine clearance due to rapidly changing clinical course (possibly >50%) may supersede its physiological diurnal variation (8–25%[8-10]). Previous studies have demonstrated direct measurement of creatinine clearance to be sensitive to temporal variations as short as 3-hour intervals.[10]

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Materials and Methods

Reanalyzing Previous Published Data

We reanalyzed the dataset published by Waikar, Sabbisetti, and Bonventre.[11] We included the 11 patients who had serial daily urine collections over 0–3 days of stay in intensive care units (ICU). The extracted variables were age (years), gender, ethnicity, weight (kg), length of ICU stay (days), duration of urine sample collection (hours), baseline and current serum creatinine (mg/dL), hourly urine output (mL/hour), and urine creatinine concentration (mg/mL). Baseline (day-1) serum creatinine was the latest level of creatinine prior to the acute crisis. We adopted the definition of AKI from the Kidney Disease Improvement Global Outcomes (KDIGO) guidelines.[6] The outcome was the progression of AKI stages according to the KDIGO guidelines on day 1–3 days of ICU stay from the stage of AKI on day 0 of ICU stay.

We calculated the creatinine clearance according to the direct measurement ($CrCl_{direct}$)[8-10] for day 0–3 of ICU stay,

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Urine creatinine concentration (mg/dL)} \times \text{Urine flow rate (mL/min)}}{\text{Serum creatinine concentration (mg/dL)}}$$

However, baseline (day-1) creatinine clearance was computed according to the Cockcroft–Gault Equation[12] ($CrCl_{CG}$) as there was no baseline data for urine output and urine creatinine prior to admission to the intensive care unit. Cockcroft–Gault Equation was applicable to the calculation of baseline creatinine clearance as serum creatinine was assumed to be stabilized at non-AKI states.

The area under curve (AUC) of the receiver operating characteristic curve was computed by SPSS 21. The AUC of $CrCl_{direct}$ (day 0), $CrCl_{CG}$ at baseline (day-1), and their ratio ($CrCl_{direct,day0}$/$CrCl_{CG,baseline}$) were calculated against the outcome, any progression of stages of AKI from day 0 of ICU stay. The statistically significant value was set at $p < 0.05$. CI of 95% was shown.

Result

Eleven patients (54% female; mean ± SD age, 59.9 ± 9.7 years; mean ± SD weight, 84.7 ± 35.5 kg) had complete records of serum and urine creatinine as well as urine output throughout the stay of ICU. The mean ± SD of length of ICU stay was 1.8 ± 0.8 days. The mean ± SD of $CrCl_{direct,day0}$ and $CrCl_{CG,baseline}$ were 86.1 ± 66.1 and 60.5 ± 52.9 mL/minute, respectively. The mean ± SD of duration of urine collection on day 0 was 5.5 ± 0.8 hours.

We found that the AUC of $CrCl_{direct,day0}/CrCl_{CG,baseline}$ ratio was 0.933 (95%CI = 0.780–1.000 and $p = 0.018$) in predicting the progression of AKI. The AUC of $CrCl_{direct,day0}$ and $CrCl_{CG,baseline}$ were 0.833 (95%CI = 0.535–1.000 and $p = 0.068$) and 0.600 (95%CI = 0.247–0.953 and $p = 0.584$), respectively.

Discussion

In this small reanalysis of previous published data, the $CrCl_{direct,day0}$/$CrCl_{CG,baseline}$ ratio was a significant predictor of the progression of AKI in ICU stay. $CrCl_{direct,day0}/CrCl_{CG,baseline}$ ratio represents the acute change of creatinine clearance at the state of AKI against the baseline creatinine clearance. The possible explanation was that the direct measurement of creatinine clearance provided the spot estimation of GFR over a short interval (3–6 hours) and it did not depend on the duration of oliguria (at least 12 hours to diagnose stage 2/3 of AKI[6]) or the accumulation of serum creatinine (to be stabilized over 24–48 hours[6]). This method may identify a subgroup of patients who are at risk of progression to higher stages of AKI and benefit from early RRT. The alternative explanation was that the fulfillment of the criteria of AKI according to KDIGO[6] was de facto delayed due to various reasons aforementioned. Instead of predicting, the $CrCl_{direct,day0}/CrCl_{CG,baseline}$ ratio provided a more "real-time" estimation of the change of GFR and subsequently revealed by the stages of AKI according to the KDIGO[6] definition.

Hourly urine output is thought to be the only "online" marker of kidney function whereas serum biomarkers have significant lag-time to be accumulated and stabilized at a new level.[6,13,14] Direct measurement of creatinine clearance in short intervals may be an alternative "online" marker of kidney function. It is more robust than urine output alone because diuresis, antidiuresis, and antinatriuresis theoretically affect the urine volume by postglomerulus modifications but not the amount of creatinine excreted in urine, which is mainly governed by the process of glomerulus filtration.[14] Furthermore, direct measurement of creatinine clearance provides an estimated value of GFR for medication dosage adjustment whereas serum creatinine and urine output fail to do so. Cockcroft–Gault equation and other serum creatinine-based equations do not apply during the state of AKI and likely overestimate the real GFR (due to the delayed accumulation of serum creatinine in AKI). There is no formula linking urine output to an estimated GFR value.

While serum creatinine is affected by absorption from diet and release from muscles, direct measurement of creatinine clearance is theoretically not affected. Whenever serum creatinine is changed for any reasons, the creatinine filtered in the glomerulus will change proportionally and instantaneously. However, direct measurement of creatinine clearance is still susceptible to the influence from the tubular secretion of creatinine as the amount of creatinine excreted is the sum of creatinine filtered by the glomerulus and creatinine secreted from the renal tubules. Medications that suppress tubular secretion of creatinine, for example, cimetidine and trimethoprim-sulfamethoxazole, would add further variability to this effect.

Furosemide stress test[15,16] was well studied to predict the progression of AKI and requirement for RRT. However, patients with frank hypovolemia may not tolerate intravenous furosemide and the efficacy was not well validated for patients with late chronic kidney disease,[16] whereas direct measurement of creatinine clearance theoretically do not pose these limitations. Furthermore, the furosemide stress test cannot be used for continuous monitoring due to its intrinsic limitation for repeated testing.

Limitations

First, the diurnal variation of serum creatinine concentration is often neglected in clinical practice due to convenience. The reported diurnal variation of serum creatinine concentration ranged from 8 to 25%, which is indeed comparable to the diurnal variation of directly measured creatinine clearance, from 9 to 25% for normal healthy individuals.[8-10] The drop in creatinine clearance was believed to be at 2000 to 0800 hours.[8-10] As long as the interpretation of the measured creatinine clearance in the right context like blood glucose which also has significant diurnal variation, a direct measurement of creatinine clearance may be meaningful.

Second, hourly urine output requires indwelling urinary catheter. Sampling urine creatinine concentration and recording the hourly readings are also labor intensive. Nevertheless, these frequent measurements could be still acceptable in critical care setting.

Third, creatinine clearance is a product of three different measured parameters, which means the errors may add up. The error of measuring serum and urine creatinine concentration was cited to be about 4–5%.[17] The error for visual urine output was estimated to be 26%.[7] According to the propagation of error, assuming the errors do not correlate with each other,

$$R = \frac{xy}{z},$$

$$\left(\frac{\partial R}{R}\right)^2 = \left(\frac{\partial x}{x}\right)^2 + \left(\frac{\partial y}{y}\right)^2 + \left(\frac{\partial z}{z}\right)^2,$$

$$0.27^2 \quad 0.05^2 + 0.05^2 + 0.26^2.$$

The expected error of the direct measurement of creatinine clearance is about 27%, which is also comparable to the error of eGFR, cited as 30% in previous studies.[18] As the urine output

contributes most of the error variance, improvement in measuring urine output would substantially increase the accuracy, for example, automatic measurement with a dedicated device.

Forth, the direct measurement of creatinine clearance wound be inaccurate if any of the composite parameters are inaccurate. For example, urine output would be inaccurate if there is a blockage in the urinary system or the urine collecting system; isopropyl alcohol intoxication may affect some of the creatinine assays.[19] Nevertheless, these confounding factors would affect the accuracy of KDIGO AKI definition and kinetic GFR also.

Fifth, creatinine clearance slightly overestimates GFR due to a small amount of renal tubular secretion of creatinine.[20] This overestimation is more pronounced at night and this paradoxically reduces the diurnal variation of creatinine clearance than the inulin clearance.[10] This applies to all estimations based on creatinine.

Sixth, the empirical comparison was performed on a small sample from a past dataset. Some patients had multiple measurements. Future studies with larger and more representative samples are warranted.

Conclusion

Direction measurement of creatinine clearance may be an alternative method to identify patients with AKI and to guide the initiation of RRT in intensive care settings.

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References

1. STARRT-AKI Investigators, Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, United Kingdom Critical Care Research Group, Canadian Nephrology Trials Network, Irish Critical Care Trials Group, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med 2020;383(3):240–251. DOI: 10.1056/NEJMoa2000741.
2. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med 2018;379(15):1431–1442. DOI: 10.1056/NEJMoa1803213.
3. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med 2016;375:122–133. DOI: 10.1056/NEJMoa1603017.
4. Wald R, Adhikari NK, Smith OM, Weir MA, Pope K, Cohen A, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney Int 2015;88(4):897–904. DOI: 10.1038/ki.2015.184.
5. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN randomized clinical trial. JAMA 2016;315(20):2190–2199. DOI: 10.1001/jama.2016.5828.
6. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2(1):1–138. DOI: 10.1038/kisup.2012.1.
7. Legrand M, Payen D. Understanding urine output in critically ill patients. Ann Intensive Care 2011;1(1):13. DOI: 10.1186/2110-5820-1-13.
8. Pasternack A, Kuhlbäck B. Diurnal variations of serum and urine creatine and creatinine. Scand J Clin Lab Invest 1971;27(1):1–7. DOI: 10.3109/00365517109080181.
9. Sirota JH, Baldwin DS, Villarreal H. Diurnal variations of renal function in man. J Clin Invest 1950;29(2):187–192. DOI: 10.1172/JCI102245.
10. Koopman MG, Koomen GCM, Krediet RT, De Moor EAM, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. Clin Sci 1989;77(1):105–111. DOI: 10.1042/cs0770105.
11. Waikar SS, Sabbisetti VS, Bonventre JV. Normalization of urinary biomarkers to creatinine during changes in glomerular filtration rate. Kidney Int 2010;78(5):486–494. DOI: 10.1038/ki.2010.165.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41. DOI: 10.1159/000180580.
13. Sunder S, Jayaraman R, Mahapatra HS, Sathi S, Ramanan V, Kanchi P, et al. Estimation of renal function in the intensive care unit: the covert concepts brought to light. J Intensive Care 2014;2(1):31. DOI: 10.1186/2052-0492-2-31.
14. Kassirer JP. Clinical evalution of kidney function: Glomerular function. New Engl J Med 1971;285:385–399. DOI: 10.1056/NEJM197108122850706.
15. Rewa OG, Bagshaw SM, Wang X, Wald R, Smith O, Shapiro J, et al. The furosemide stress test for prediction of worsening acute kidney injury in critically ill patients: a multicenter, prospective, observational study. J Crit Care 2019;52:109–114. DOI: 10.1016/j.jcrc.2019.04.011.
16. Chen JJ, Chang CH, Huang YT, Kuo G. Furosemide stress test as a predictive marker of acute kidney injury progression or renal replacement therapy: a systemic review and meta-analysis. Crit Care 2020;24(1):202. DOI: 10.1186/s13054-020-02912-8.
17. Joffe M, Hsu CY, Feldman HI, Weir M, Landis JR, Hamm LL, et al. Variability of creatinine measurements in clinical laboratories: results from the CRIC study. Am J Nephrol 2010;31(5):426–434. DOI: 10.1159/000296250.
18. Luis-Lima S, Porrini E. An overview of errors and flaws of estimated GFR versus true GFR in patients with diabetes mellitus. Nephron 2017;136(4):287–291. DOI: 10.1159/000453531.
19. Killeen C, Meehan T, Dohnal J, Leikin JB. Pseudorenal insufficiency with isopropyl alcohol injection. American Journal of Therapeutics 2011;18(4):e113–e116. DOI: 10.1097/MJT.0b013e3181c960cb.
20. Fernandez-Prado R, Castillo-Rodriguez E, Velez-Arribas FJ, Gracia-Iguacel C, Ortiz A. Creatinine clearance is not equal to glomerular filtration rate and Cockcroft-Gault equation is not equal to CKD-EPI collaboration equation. Am J Med 2016;129(12):1259–1263. DOI: 10.1016/j.amjmed.2016.08.019.