Augmented renal clearance in Chinese intensive care unit patients after traumatic brain injury: a cross-sectional study

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To the Editor: Augmented renal clearance (ARC) refers to an enhanced elimination of circulating solutes, including drugs, by the kidneys at a rate statistically higher than normal. On the first day of intensive care unit (ICU) admission, ARC occurrence may predict continued creatinine clearance (CrCl) elevation for 1 day to several weeks.[1] ARC has a substantial adverse effect on renally cleared antibiotics' pharmacokinetics/pharmacodynamics. Treatment failure or worse outcomes are more frequent in ARC patients. Thus, a "one size fits all" approach to drug dosing in ARC patients is inappropriate; dosing requires adjustment for some variables.

The incidence of ARC in Australian traumatic brain injury (TBI) patients has been reported to be as high as 85%.[2] China has more TBI patients than most other countries in the world, making this condition a significant public health concern. Unfortunately, no studies have focused on ARC in Chinese TBI patients to date. The incidence of ARC, risk factors, and tools for aiding diagnosis are also unknown in these patients, not to mention the adjustment of antiinfection drug dosages after ARC. Therefore, the primary aim of this study was to explore ARC incidence in Chinese TBI patients while assessing the accuracy of four commonly used formulas and the augmented renal clearance in trauma intensive care (ARCTIC) scoring system in identifying ARC with normal serum creatinine (Scr) levels. The secondary aim was to determine risk factors that could contribute to recognizing ARC in these patients. This prospective, singlecenter, cross-sectional study was conducted in a 24-bed ICU ward at the 2209-bed University Hospital in Gansu Province, China, from October 1, 2018, to September 30, 2019. The ethics committee of First Hospital of Lanzhou University (No. LDYYLL2018-153) approved this study. Informed consent was obtained from all participants, and the patients were selected following the procedure shown in Supplementary Figure 1, http://links.lww.com/CM9/A613. ARC was defined as 24-h CrCl ≥130 mL/min. Patient characteristics and clinical features were extracted from the medical records. All statistical analyses were performed using IBM-SPSS (version 26.0, IBM Corp, Armonk, NY, USA) and MedCalc (version 19.0.4, MedCalc Software, Ostend, Belgium)) statistical software, and differences were considered statistically significant at $P < 0.05$ (two-sided). The bias and precision of different formulas compared with the measured CrCl were evaluated according to the previous study.[3]

Residual plots were used to analyze the agreement between the individual estimated glomerular filtration rates (eGFRs) and 24-h CrCl and eGFRs calculated by the Cockcroft-Gault equation (CG), modified chinese modification of diet in renal disease study equation, chronic kidney disease epidemiology collaboration equation for Asian people (CKD-EPI-Asian), or Japanese eGFR equations according to the Bland and Altman method.

We enrolled 54 patients in this study; their characteristics are shown in Supplementary Table 1, http://links.lww.com/CM9/A608. Of these, 27 patients (50%) presented ARC. ARC occurred less frequently in patients with a medical history of hypertension (MHHT) (3/16) in comparison with the overall incidence of 50% (27/54). The dose of mannitol used for hyperosmolar therapy did not show a difference between the two groups. The ARC group had a lower Scr concentration 56 (interquartile range [IQR] 48.0–66.0) than the patients without ARC 65 (IQR, 58.0–76.0). The mean 24-h CrCl of patients with ARC was significantly higher: 175.13 *vs.* 101.35 mL/min per 1.73 m^2 in patients without ARC ($P < 0.001$).

The eGFR of patients with ARC was significantly higher than that of patients without ARC ($P < 0.01$) [Figure 1A–D], except for the eGFR calculated by the CKD-EPI-Asian

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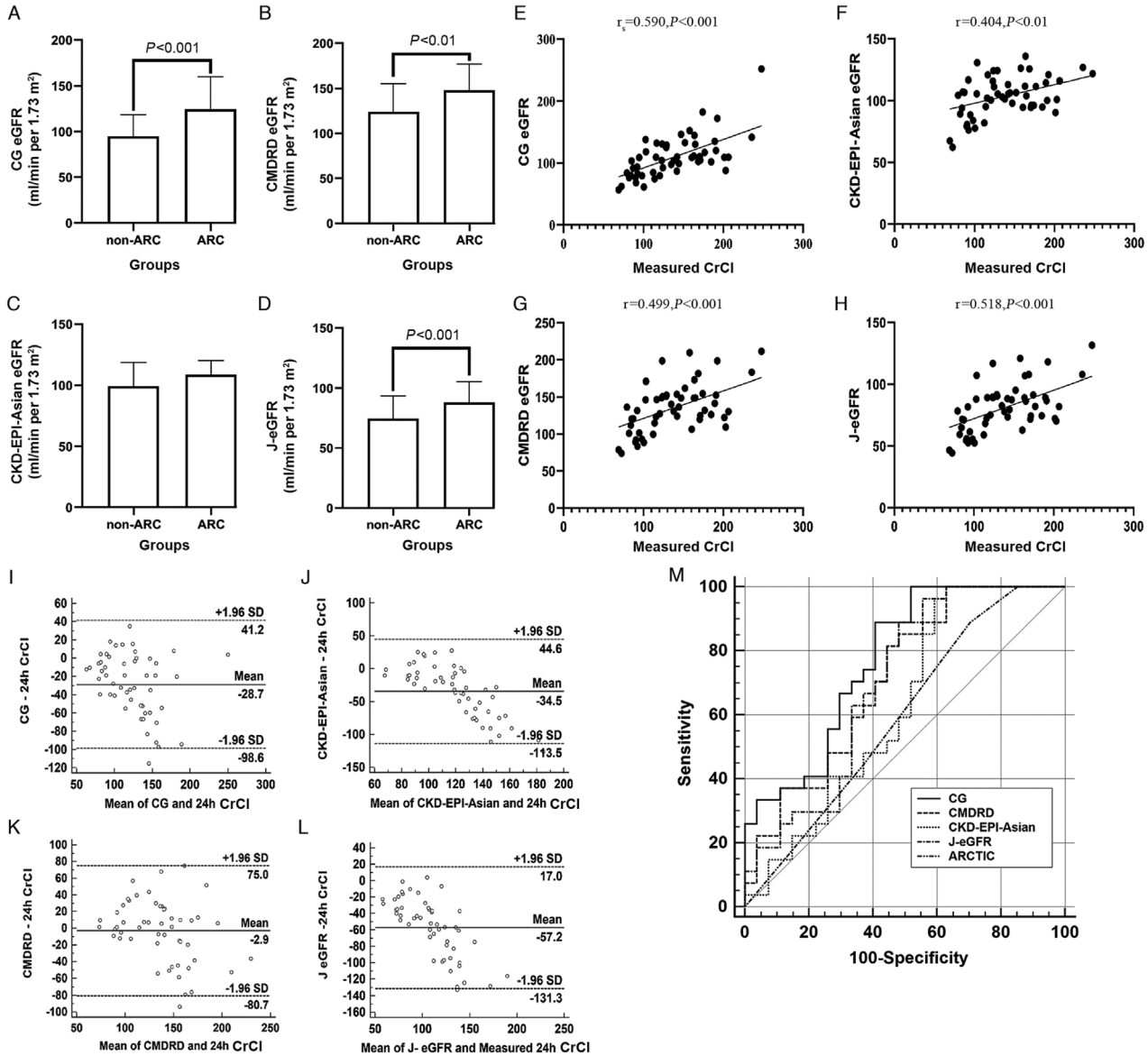

Figure 1: Comparison of the eGFR using CG (A), CMDRD (B), CKD-EPI-Asian (C), and Japanese eGFR (D) equation in patients with and without ARC. Correlation between the measured 24-h CrCl and eGFR (E–H). Measures of agreement between the 24-h CrCl and eGFR by CG, CMDRD, CKD-EPI-Asian, and Japanese eGFR equation (I–L). Comparison of ROC curves of four eGFR formulas and ARCTIC to detect ARC (M). 24-h CrCl: 24-h creatinine clearance; ARC: Augmented renal clearance; CG: Cockcroft-Gault equation; eGFR: Estimated glomerular filtration rate; J-eGFR: Japanese eGFR; CMDRD: Modified Chinese Modification of Diet in Renal Disease Study equation.

formula. Correlation analysis found a moderate correlation between measured 24-h CrCl and four calculated eGFRs [Figure 1E–H]. In the ARC subgroup, each formula underestimated CrCl. A more significant bias and a lower precision were observed in the ARC group [Supplementary Table 2, http://links.lww.com/CM9/A609]. The different formulas tended to overestimate the CrCl for low eGFR values and underestimate the CrCl for normal and high eGFRs [Figure 1I–L].

We also tested the ARCTIC score, a predictive model used to screen for ARC among trauma patients. The results showed a weak positive correlation of 0.269 ($P < 0.010$) between CrCl and ARCTIC scores. The scoring system's sensitivity was as high as 88.9%, but the specificity was only 29.6% [Supplementary Table 3, http://links.lww.com/CM9/A610].

Receiver operating characteristic (ROC) analysis was performed to evaluate the predictive ability of eGFR and ARCTIC score for ARC. The CG formula had the highest positive predictive value (PPV) (68.59%), and the J-eGFR had the highest negative predictive value (NPV) (92.31%). Only the CG formula presented an area under curve (AUC) >0.75 to detect an ARC, with a cutoff value of 95.69 mL/min per 1.73 m^2 [Supplementary Table 3, http://links.lww.com/CM9/A610]. Comparison of ROC curves of the four estimated formulas showed no difference between CG, chinese modification of diet in renal disease, and Japanese eGFR AUCs [Figure 1M], but revealed a significant difference between the AUCs of CG and CKD-EPI-Asian ($P < 0.05$).

The following variables were significantly different between patients with and without ARC: Scr (56.0 *vs.*

65.0, $P < 0.05$) and MHHT rate (5.6% *vs.* 24.1%, $P < 0.01$). Although there was no significant difference in age and body mass index (BMI) between the two groups, the difference approached significance (*P* value below or close to 0.1). Multiple logistic regression analysis was performed for five variables (age, gender, BMI, SCr, and MHHT). The results showed that male sex, BMI, SCr, and no MHHT were independent risk factors for ARC (odds ratio, 8.6, 1.3, 0.9, and 0.1, respectively) [Supplementary Table 4, http://links.lww.com/CM9/A611]. The results demonstrate that male patients who do not have MHHT, have lower Scr, and higher BMI may have an increased risk of suffering from ARC. The model was constructed by the four variables with sensitivity, specificity, PPV, and NPV all above 70% [Supplementary Table 5, http://links.lww.com/CM9/A612].

We further tested logistic regression models with significant covariates, especially taking the cutoff values of ARC detection by four different equations into consideration. While including the cutoff values of four eGFRs and other risk factors, such as BMI and MHHT, to construct the new models, all Nagelkerke R^2 values >0.45 indicated a good fit of the model, and all were more accurate than the eGFR alone or model A to predict the ARC. They all had good sensitivity, specificity, PPV, and NPV, especially specificity, which improved dramatically compared with eGFR [Supplementary Table 5, http://links.lww.com/CM9/A612].

To the best of our knowledge, this is the first study to investigate ARC in Chinese TBI adult patients. Our study showed that 50% of patients suffered ARC with normal SCr levels. None of the four eGFR formulas or ARCTIC scores accurately predicted the occurrence of ARC. However, multivariable analysis showed that an eGFR above the optimal cutoff values combine without MHHT and/or a higher BMI can be used as a useful tool to identify the ARC in Chinese TBI patients. The incidence of ARC among our patients was 50%, which is lower than that in the cohort of 20 patients described by Udy *et al*,[3] who found ARC in 85% of cases. The most likely reason is the different ethnicities and brain injury severity among patients in our and other scholars' studies (patients' Glasgow coma scale scores in our research were relatively higher). Because measuring 24-h CrCl is labor-intensive and not routinely performed in ICU patients, we attempted to assay the ARC identification ability of four generally used mathematical equations in Chinese physicians. However, none showed acceptable sensitivity and specificity. Considering the pathophysiological changes in TBI patients and eGFR formulas are essentially designed for non-critically ill patients, the result is not surprising.

In a previous study, the ARCTIC scoring system was constructed by Barletta *et al*[4] as a helpful tool to facilitate the identification of ARCs in people with traumatic injuries. However, our results demonstrated that the ARCTIC score was not accurate when used to recognize ARC in Chinese TBI patients. A possible explanation is the different patient populations and various injury mechanisms of patients included in Barletta's[4] and our study found that male sex, higher BMI, lower Scr, and no MHHT were independent predictors of ARC. The relatively young age of patients has been confirmed by other researchers to be closely related to the occurrence of ARC among critically ill patients. However, it did not differ significantly between our ARC group and the non-ARC group. The discrepancy may be because the patients in our study were much older. We also found that a higher BMI was an independent risk factor for ARC, which is exactly the opposite of the previous result.[5] A probable reason is that a considerable portion of the patients included in our study were construction workers. Therefore, a high BMI does not mean that these patients are obese; instead, they may have high muscle content and good kidney preservation. Patients with MHHT had ARC less frequently, perhaps because hypertension harms the kidney, reducing the glomerular filtration rate and renal tubule excretion. However, because of the limited number of patients with MHHT in our study, the results should be interpreted carefully.

To conclude, ARC is frequently observed in Chinese TBI patients. Neither eGFR nor the ARCTIC score could be directly used as a screening tool to identify high CrCl. However, if we regard the cutoff value of eGFR as a risk factor and combine it with other characteristics, such as lack of MHHT and/or higher BMI, it could be used as a helpful tool to screen for ARC in TBI patients.

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Conflicts of interest

None.

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