ORIGINAL ARTICLE

Prevalence of Augmented Renal Clearance (ARC), Utility of Augmented Renal Clearance Scoring System (ARC score) and Augmented Renal Clearance in Trauma Intensive Care Scoring System (ARCTIC score) in Predicting ARC in the Intensive Care Unit: Proactive Study

Girish Kanna[1], Sristi Patodia[2], Rajeev A Annigeri[3], Nagarajan Ramakrishnan[4], Ramesh Venkataraman[5]

Received on: 19 April 2023; *Accepted on:* 17 May 2023; *Published on:* 31 May 2023

Abstract

Objectives: We aimed to study the prevalence of augmented renal clearance (ARC) and validate the utility of ARC and ARCTIC scores. We also aimed to assess the correlation and agreement between estimated GFR (eGFR-EPI) and 8-hour measured creatinine clearance (8 hr-mCL_{cr}).

Study design and methodology: This was a prospective, observational study done in the mixed medical-surgical intensive care unit (ICU) and 90 patients were recruited. 8 hr-mCL_{cr}, ARC, and ARCTIC scores and eGFR-EPI were calculated for all patients. ARC was said to be present if 8 hr-mCLcr was ≥ 130 mL/min.

Results: Four patients were excluded from the analysis. The prevalence of ARC was 31.4%. The sensitivity, specificity, and positive and negative predictive values of ARC and ARCTIC scores were found to be 55.6, 84.7, 62.5, 80.6, and 85.2, 67.8, 54.8, and 90.9 respectively. AUROC for ARC and ARCTIC scores were 0.802 and 0.765 respectively. A strong positive correlation and poor agreement were observed between eGFR-EPI and 8 hr-mCL_{cr}.

Conclusion: The prevalence of ARC was significant and the ARCTIC score showed good potential as a screening tool to predict ARC. Lowering the cut-off of ARC score to ≥5 improved its utility in predicting ARC. Despite its poor agreement with 8 hr-mCL_{cr}, eGFR-EPI with a cut-off ≥114 mL/min showed utility in predicting ARC.

Keywords: ARC score, ARCTIC score, Augmented renal clearance, Creatinine clearance.

Indian Journal of Critical Care Medicine (2023): 10.5005/jp-journals-10071-24479

Highlights

Augmented renal clearance (ARC) is a phenomenon wherein the kidneys display a creatinine clearance (CL_{cr}) ≥130 mL/min/1.73 m^2. In this prospective, observational study, we aimed to study the prevalence of ARC, the utility of ARC/ARCTIC scores and correlation/agreement between 2021 CKD-EPI creatinine formula and 8-hour measured CL_{cr}.

Background and Objectives

Augmented renal clearance (ARC) is a pathologic phenomenon wherein the kidneys display increased glomerular filtration beyond what is expected under normal physiological conditions of renal function.[1] Patients in this state often have a creatinine clearance (CL_{cr}) of ≥130 mL/min/1.73 m^2.[1]

Increased cardiac output and enhanced blood flow to major organs have been postulated to be major reasons for ARC in patients admitted to the intensive care unit (ICU).[2,3] Severe trauma, infection, inflammation, burns, surgery, and pancreatitis can all potentiate a systemic inflammatory response syndrome, which results in increased cardiac output and vasodilatation, both of which lead to amplified renal blood flow and increased renal clearance of hydrophilic medications.[2] Administration of crystalloids or vasopressors may also contribute to ARC by increasing preload and thus cardiac output.[2,4]

Commonly identified risk factors for ARC include trauma, young age, male sex, and less severe illness.[1,5] Elevated CL_{cr} has been reported in patients with burns, traumatic brain injury,

[1,2,4,5]Department of Critical Care Medicine, Apollo Hospitals, Chennai, Tamil Nadu, India

[3]Department of Nephrology, Apollo Hospitals, Chennai, Tamil Nadu, India

Corresponding Author: Ramesh Venkataraman, Department of Critical Care Medicine, Apollo Hospitals, Chennai, Tamil Nadu, India, Phone: + (044) 28296517, e-mail: ccmramesh@gmail.com

How to cite this article: Kanna G, Patodia S, Annigeri RA, Ramakrishnan N, Venkataraman R. Prevalence of Augmented Renal Clearance (ARC), Utility of Augmented Renal Clearance Scoring System (ARC score) and Augmented Renal Clearance in Trauma Intensive Care Scoring System (ARCTIC score) in Predicting ARC in the Intensive Care Unit: Proactive Study. Indian J Crit Care Med 2023;27(6):433–443.

Source of support: Nil

Conflict of interest: None

poly-trauma, sepsis, and ventilator-associated pneumonia.[5,6] Other factors associated with ARC are a higher initial glomerular filtration rate (GFR), absence of diabetes, and nil to low-dose vasopressor requirement as opposed to a higher dose.[3,7]

Augmented renal clearance, if present, can potentially lead to inadequate treatment due to sub-optimal antimicrobial dosing, development of resistance to antimicrobials, increased risk of treatment failure, and increased in-hospital mortality in critically ill patients.[8–10]

Augmented renal clearance scoring system (ARC score) and augmented renal clearance in trauma intensive care scoring system (ARCTIC score) (Appendix I) have been proposed as tools to predict the likelihood of ARC in patients admitted to the general mixed ICU and to the trauma ICU respectively.[4,11] Cutoff scores of ≥7 for ARC score and ≥6 for ARCTIC score suggest a high risk for the occurrence of ARC. Augmented renal clearance can be ascertained only by measuring the creatinine clearance (CL_{cr}) of a patient. However, estimated GFR (eGFR) calculated using formulae such as Cockcroft – Gault, modification of diet in renal disease (MDRD), 2009 chronic kidney disease epidemiology collaboration (2009 CKD – EPI), etc., perform well in non-critically ill patients with a steady state serum creatinine, but are inaccurate in the critical care setting.[12–17] Prior studies have found a poor correlation and/or agreement between eGFR calculated using the above-mentioned formulae and the measured CL_{cr} (mCL_{cr}) using continuous urinary collection methods.[12–17] Though a consensus regarding the most accurate duration for continuous urine collection for measuring CL_{cr} does not exist, an 8-hour urine collection measurements, seems to provide a good balance between accuracy and feasibility in clinical practice.[18]

The prevalence of ARC in Indian ICUs is unknown and we sought to assess the prevalence of this phenomenon in our mixed medical-surgical ICU. We chose the 8-hour-measured creatinine clearance (8 hr-mCL_{cr}) as the primary estimate of GFR in order to ascertain ARC. In addition, we sought to explore the utility of ARC and ARCTIC scores in predicting ARC in our mixed medical-surgical ICU. In order to compare estimated GFR (eGFR) with 8 hr-mCL_{cr}, we chose the "Refit 2021 CKD-EPI Creatinine" formula to calculate the eGFR, which is in accordance with the current recommendations of the NKF-ASN task force.[19,20] To the best of our knowledge, among all the studies done previously comparing eGFR and mCL_{cr} in the critically ill, none have employed the "Refit 2021 CKD-EPI Creatinine" formula for calculating eGFR.

Methodology

Study Design and Setting

This is a prospective, observational, single-center study done between July 2021 to April 2022, in the 24-bed mixed medical-surgical ICU of Tertiary Care Hospital, in Chennai, India. The approval for our study and a consent waiver was obtained from the Institutional Ethics Committee prior to the commencement of the study. An institutional grant/aid was obtained from the finance department of our hospital in order to estimate urinary creatinine, thereby avoiding an addition to the patients' cost burden.

Sample Size Estimation

In the study done by Andrew A Udy et al.,[6] the prevalence of ARC was found to be 65.1%. Using the following formula $n = Z^2pq/d^2$, where $Z = 1.96$ (standard normal variate value with 95% CI), $p = 65.1\%$ (prevalence of ARC), $q = 34.9\%$ (1 – p) and $d = 10\%$ (clinical allowable error), the required sample size was calculated to be 90.

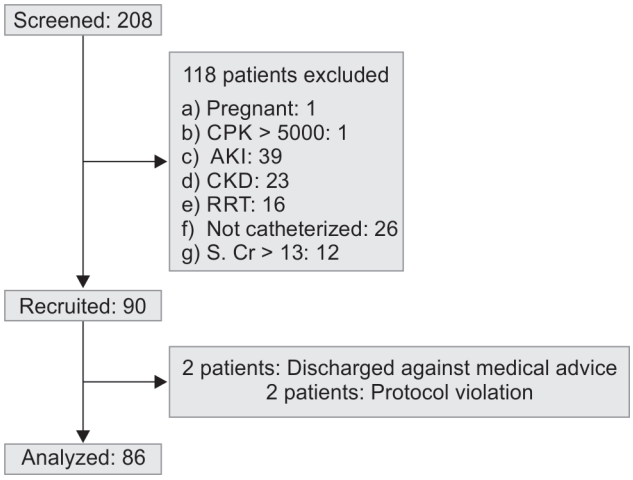


Fig. 1: Screening, recruitment and analysis of patients

Study Population

Patients above the age of 18 years and those who were expected to stay in the ICU for more than 24 hours were included in the study. The exclusion criteria for patients were as follows: (A) Pregnancy; (B) Clinical suspicion of rhabdomyolysis or an admission creatinine kinase of >5000 IU/L; (C) Patients with a baseline creatinine of greater than 1.3 mg/dL; (D) Acute Kidney Injury of any stage according to KDIGO criteria; (E) Patients requiring renal replacement therapy; (F) Diagnosis of chronic kidney disease (CKD); and (G) Patients without an indwelling urinary catheter.

A total of 208 patients were screened and 90 patients were recruited into the study (Fig. 1).

Data Collection and Calculations

Data collection began within 48 hours of admission to the ICU. Data including age, sex, admission diagnosis, co-morbid conditions, Modified SOFA score (Appendix II) and Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores (Appendix III), presence/absence of mechanical ventilation and requirement of vasopressors/inotropes were recorded. The cumulative vasopressor index (Appendix IV) was calculated for patients who were on vasopressor/inotrope infusion.

An 8-hour measured creatinine clearance (8 hr-mCL_{cr}) was the primary method of assessing the GFR of all patients inducted into the study. Urine was collected from the indwelling urinary catheter over 8 hours and the volume of urine collected over this duration was noted down prior to sending the sample to the biochemistry lab for estimation of urinary creatinine. Concurrent plasma creatinine levels were also estimated by collecting blood samples immediately after the completion of the 8-hour urine collection period. Eight hour measured creatinine clearance (8-hr mCL_{cr}) was calculated by the formula: $8\text{ hr–}mCL_{cr}(mL/min) = U_{cr} \times V / P_{cr} \times 480$,

wherein:

U_{cr}: Urine creatinine

P_{cr}: Plasma creatinine after the 8 hr urine collection period

V: Volume of urine collected in 8 hours

Augmented renal clearance and ARCTIC scores were calculated immediately prior to or during the 8-hour urine sample collection. Use of diuretics and nephrotoxic agents (mainly radiocontrast agents and antibiotics), prior to or during the 8-hour urine collection

period were documented. Augmented renal clearance was said to be present when the 8 hr-mCL_{cr} was more than or equal to 130 mL/min. Patients with an ARC score of ≥7 and/or ARCTIC score of ≥6 were said to be at a higher risk for developing ARC.

Estimated GFR using the "Refit 2021 CKD-EPI Creatinine" formula was calculated for all patients (eGFR-EPI):[19,20]

$142 \times (S.Cr/A)^{B} \times 0.9938^{age} \times (1.012$ if female) where A and B are the following:

Female	Male
S. Cr ≤ 0.7	S. Cr ≤ 0.9
A = 0.7	A = 0.9
B = –0.241	B = –0.302
S. Cr > 0.7	S. Cr > 0.9
A = 0.7	A = 0.9
B = –1.2	B = –1.2

The same value of plasma creatinine was used for the calculation of both 8-hr mCL_{cr} and eGFR-EPI.

Statistical Analysis

Continuous variables were tested for the normality using Shapiro-Wilk's test and were expressed as mean ± standard deviation or median ± inter quartile range based on the normality of their distribution. Categorical variables were represented as percentages. Sensitivity, specificity, positive and negative predictive values of ARC score (cut-off ≥7), ARCTIC score (cut-off ≥6), and eGFR-EPI (cut-off ≥ 130 mL/min) were calculated. ROC curves were drawn to find the optimal cut-off values to predict the occurrence of ARC for each score. Correlation between measured 8 hr-mCL_{cr} and eGFR-EPI was assessed using Spearman correlation coefficient (rho) and degree of agreement, using the Bland Altman plot and linear regression analysis. Data entry was done on Microsoft Excel 2016 spreadsheet and data analysis was carried out on IBM SPSS Statistics for Windows V26.0. All '*p*' values <0.05 were considered statistically significant.

Results

A total of 90 patients were recruited, of which four were excluded from analysis and the data of 86 patients was available for analysis (Fig. 1). The baseline characteristics of patients included for analysis are shown in Table 1. The age of patients ranged from 18 to 86 years, with a median age of 57 years (IQR: 38–68) and the gender distribution was almost equal with 44 females (51.2%) and 42 males (48.8%). The most common reasons for ICU admission were sepsis (33.7%), post-operative care (20.9%), cerebrovascular accident (11.6%), trauma (11.6%), and subarachnoid hemorrhage (7%). Among the 86 patients, 67 (77.9%) were discharged after treatment while 8 (9.3%) had expired. Ten patients (11.6%) were discharged against medical advice and the hospital outcome data for one patient was unavailable.

While the overall 8-hr mCL_{cr} was 91.7 mL/min (IQR: 55.2–141.4), the median 8-hr mCL_{cr} in patients with and without ARC was 168 mL/min (IQR: 146.7–200) and 66.2 mL/min (43.6–95.1) respectively ($p < 0.05$). The prevalence of ARC was 31.4% (27 out of 86 patients). It was observed to be highest in patients with trauma (40%) followed by sepsis (34.5%). The median age of patients who exhibited ARC was 33 years (IQR: 24–43) as opposed to 64 years (IQR: 55–72) in patients who did not exhibit ARC ($p < 0.05$) (Fig. 2). Among patients who required vasopressors, the median cumulative vasopressor index was 2 (IQR 2–3) in patients who manifested ARC while it was 4 (IQR 3–4) in those who did not ($p < 0.05$) (Fig. 3).

ARC score (cut-off of ≥7) predicted a high risk for the development of ARC in 24 out of 86 patients (27.9%) and ARCTIC score (cut-off ≥6) predicted the same in 42 out of 86 patients (48.8%). The sensitivity, specificity, and positive and negative predictive values of ARC and ARCTIC scores are mentioned in Table 2.

ROC curves for ARC and ARCTIC scores were plotted, in order to estimate their utility in predicting ARC (Fig. 4). The AUROC of ARC and ARCTIC scores were 0.802 (95% CI, 0.695–0.908) and 0.765 (95% CI, 0.663–0.866) respectively. Based on the ROC curves, the optimal cut-offs of ARC and ARCTIC scores for predicting augmented renal clearance were found to be five and six respectively. A cut-off of five for the ARC score improved its sensitivity to 81.5% while the specificity was 83.1%.

eGFR-EPI (cut-off ≥ 130 mL/min) predicted the occurrence of ARC in 14 out of the 86 patients (16.3%) and median eGFR- EPI was 103 mL/min (IQR: 87–119.25). The true positives identified by eGFR-EPI were 12 out of 27 (44.4%). Its sensitivity, specificity, and positive and negative predictive values in predicting ARC are mentioned in Table 2. ROC curve plotted for eGFR- EPI in relation to the occurrence of ARC revealed an AUROC of 0.899 (95% CI, 0.832-0.965) (Fig. 4) and a cut-off of 114 mL/min was shown to predict ARC with a sensitivity of 81.5% and specificity of 84.7%.

Spearman correlation coefficient (rho) between eGFR-EPI and 8 hr-mCL_{cr} was found to be 0.733, suggesting a strong positive correlation ($p < 0.05$) (Fig. 5). However, a Bland-Altman plot drawn between the two variables revealed a bias of –2.29 mL/min with the 95% limits of an agreement being +100.61 mL/min and –105.19 mL/min. This revealed a wide variation between eGFR- EPI and 8 hr-mCL_{cr} (Fig. 6). In addition to this, linear regression analysis done between the two variables detected the presence of a proportional bias, indicating a poor agreement between eGFR- EPI and 8 hr-mCL_{cr}.

Discussion

A wide range has been reported in literature, with regard to the prevalence of ARC, ranging from 28 to 67%. Multiple studies have also found an increased prevalence of ARC in younger patients and in patients with trauma.[4–6,11,13] Stéphanie Ruiz et al.[13] reported an ARC prevalence of 33% among 360 patients admitted to their ICU with its prevalence being more common among trauma patients. The overall mean age of patients in their study was 50 years, while patients exhibiting ARC were found to be significantly younger than the rest (mean of 39 years vs 55 years). Yasumasa Kawano et al.[21] and Campassi ML et al.[22] reported an ARC prevalence of 38% (among 111 patients) and 28% (among 363 patients) respectively. Yasumasa Kawano et al. found ARC to be most prevalent among trauma patients (62.5%). Patients manifesting ARC were noted to be significantly younger than those who did not, in the studies conducted by both Yasumasa Kawano et al. (median of 55 years vs72 years) and Campassi ML et al. (mean of 48 vs 65 years). Our study found similar results with the prevalence of ARC being 31.4% and patients manifesting ARC were found to be significantly younger too. ARC was also most commonly noted among patients admitted with trauma and sepsis.

A few studies have reported a higher prevalence of ARC. Udy AA et al.[4] noted the prevalence of ARC to be 57.7% among 71 septic and trauma patients admitted to their general adult ICU. Jeffrey F Barletta et al.[11] in 2016, reported the presence of ARC in 67% of

Table 1: Demographic data

Variable(s)	*All patients (n = 86)*	*Patients with ARC (n = 27)*	*Patients without ARC (n = 59)*	*p-value*
Age in years (median, IQR)	57 (38–68)	33 (24–43)	64 (55–72)	**0.000**
Gender (females/males)	44 (51.2%)/ 42 (48.8%)	14 (51.8%)/ 13 (48.2%)	30 (50.8%)/ 29 (49.2%)	0.931
Measured CL_{cr} (mL/min) (median, IQR)	91.7 mL/min	168 (146.7–200)	66.2 (43.6–95.1)	**0.000**
APACHE 4 (mean ± SD)	34.4 (14.1)	30.56 (13)	36.15 (14.3)	0.08
mSOFA (median, IQR)	3 (1–6)	3 (2–5)	3 (1–6)	0.360
Intubation	38 (44.2%)	13 (48.1%)	25 (42.4%)	0.617
Vasopressor requirement	30 (34.9%)	11 (40.7%)	19 (32.2%)	0.441
Cumulative vasopressor index (median, IQR)	3 (2–4)	2 (2–3)	4 (3–4)	**0.002**
Nephrotoxic agents	24 (27.6%)	7 (25.9%)	17 (28.8%)	0.782
Diuretics	9 (10.3%)	2 (7.4%)	7 (11.9%)	0.531

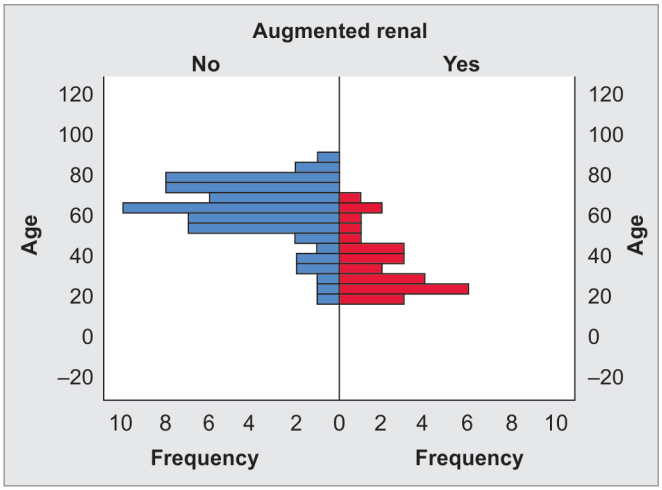


Fig. 2: Age characteristics of patients with and without ARC; $p < 0.05$

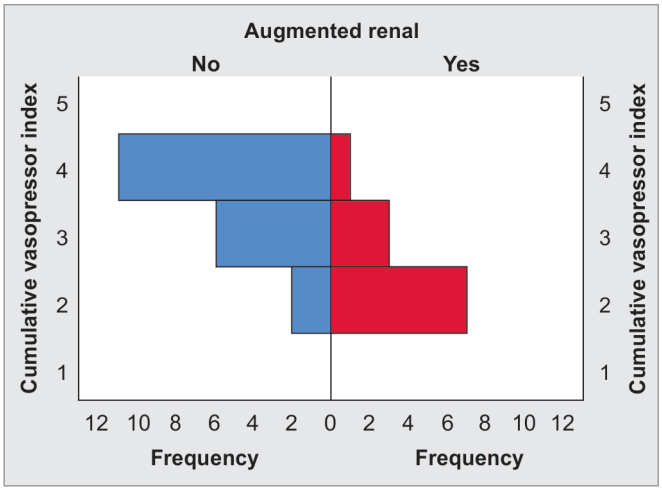


Fig. 3: Cumulative vasopressor index of patients with and without ARC; $p < 0.05$

133 patients admitted to their trauma ICU. The higher rates could be related to differences in patient characteristics (lower age), disease types (predominantly trauma patients), and/or severity. In contrast

Table 2: Sensitivity, specificity, PPV and NPV of ARC score, ARCTIC score and eGFR-Epi

Score	*Sensitivity*	*Specificity*	*PPV*	*NPV*
ARC	55.6%	84.7%	62.5%	80.6%
ARCTIC	85.2%	67.8%	54.8%	90.9%
Refit 2021 CKD-EPI creatinine derived eGFR-EPI	44.4%	96.6%	85.7%	79.2%

to these studies, our study had slightly older patients and only 11.6% of the patients recruited were trauma patients.

Udy AA et al.[4] put forth the ARC scoring system and observed that patients with an ARC score of ≥7 had the highest risk of developing ARC. Augmented renal clearance score predicted the occurrence of ARC in 45 out of 71 (63.3%) patients with 36 of them being true positives (sensitivity of 87%) and ROC curve analysis for ARC score revealed an AUC of 0.89 in their study. Conversely, in our study, ARC score ≥7 predicted a high risk for the occurrence of ARC in fewer patients (24 out of 86 patients), and only 15 were found to be true positives (sensitivity of 55.6%). Age and the presence of trauma are two important components of the ARC score and the lower predictive ability of the ARC score in our population might likely be from the higher age and lower proportion of trauma patients in our study. Akers et al.[23] assessed the utility of the ARC score (cut-off ≥7) in patients admitted to their trauma/surgical ICU and extrapolated this to evaluate antibiotic clearance rates with higher ARC scores. Augmented renal clearance score of ≥7 in their study, was found to have a sensitivity, specificity, PPV, and NPV of 100%, 71.4%, 75%, and 100% respectively, in detecting increased antibiotic clearance, increased volume of drug distribution and sub-therapeutic plasma antibiotic levels. The results they had reported with regard to the sensitivity and negative predictive value of ARC score could be unreliable due to the very low sample size of their study ($n = 13$) and also due to a high proportion of trauma patient recruitment (>60%).

Barletta et al.[11] developed the ARCTIC score based on a study conducted in a trauma ICU among 133 patients and put forth that the score predicted the occurrence of ARC with a sensitivity, specificity, PPV, and NPV of 84.3%, 68.2%, 84.3%, and 68.2% respectively. The optimal cut-off for the ARCTIC score was proposed to be ≥6. In addition, they reported the AUC to be 0.813 for the ARCTIC score using ROC curve analysis. In our study, the sensitivity,

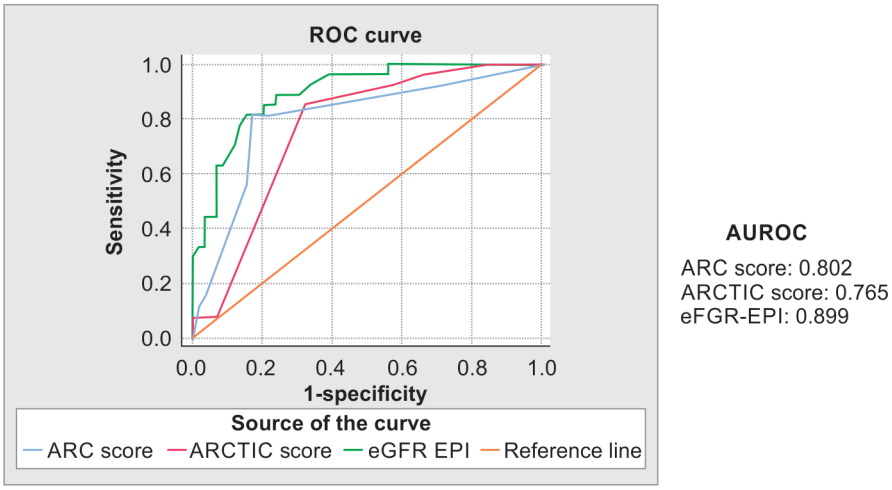


Fig. 4: ROC curves for ARC score, ARCTIC score and "2021 CKD-EPI Refit" eGFR-Epi

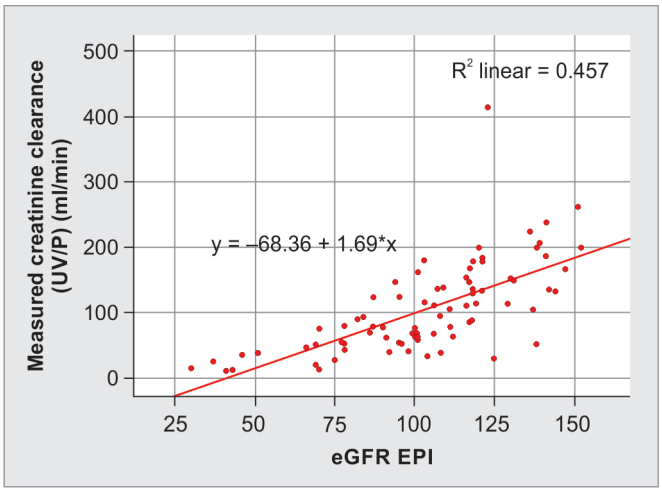


Fig. 5: Correlation between eGFR-Epi and mCL_{cr}

displayed high sensitivity (85.2%) and negative predictive value (90.9%) in our study. To the best of our knowledge, no other study has assessed the validity of the ARCTIC score in predicting ARC among patients admitted to a mixed medical-surgical ICU. ARCTIC score, unlike the ARC score, incorporates baseline serum creatinine which may intrinsically make it a more effective score considering patients with a normal serum creatinine have a higher predisposition to augmented renal clearance.

Literature is replete with studies that have compared the eGFR calculated using various formulae such as Cockcroft-Gault (CG), MDRD, and CKD-EPI, with measured CL_{cr} estimated by collecting urine over various time durations (8 hours, 16 hours, or 24 hours).[12–17] Udy et al.[14] evaluated the correlation and agreement between 8-hr mCL_{cr} and eGFR calculated using CKD-EPI and CG formula in a Tertiary Care ICU. Despite finding a moderate correlation, further analysis revealed poor agreement between 8-hr mCL_{cr} and eGFR (using both CKD-EPI and CG formula) due to a significant bias with a presence of a proportional error. Stéphanie Ruiz et al.[13] compared

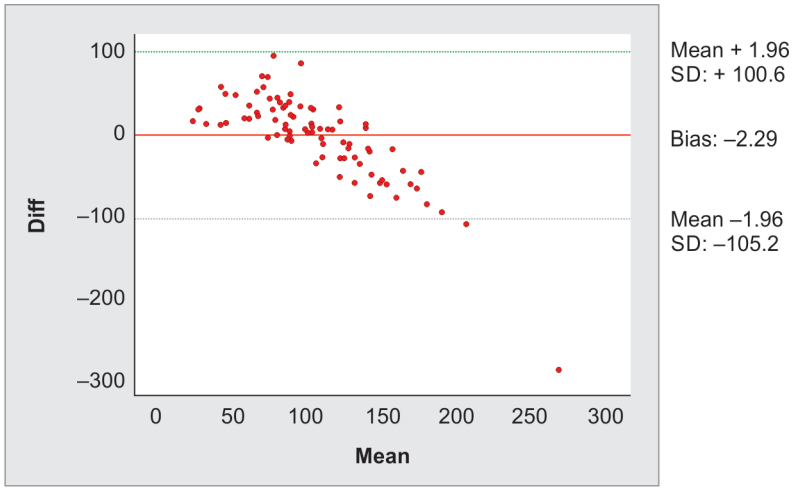


Fig. 6: Bland-Altman plot to measure the degree of agreement between eGFR-Epi and mCL_{cr}

specificity, AUROC, and cut-off for the ARCTIC score were similar to the results reported in this study. The ARCTIC score with a cut-off ≥6, which has been validated only in the setting of a trauma ICU, 24-hr mCL_{cr} with eGFR calculated using CKD-EPI among 360 patients admitted to their ICU and found a poor agreement between the two values. While screening for ARC, they reported an AUC of

0.79 for the CKD-EPI formula with an optimal cut-off of 108.11 mL/min/1.73 m^2 to predict ARC with a sensitivity and specificity of 75% each. In concordance with the previous studies, in our study, we found a strong correlation but a poor agreement between 8-hr mCL_{cr} and eGFR-EPI. However, ROC analysis revealed an AUC of 0.899 for eGFR-EPI, and a cut-off of 114 mL/min was found to predict ARC with a sensitivity of 81% and specificity of 84%.

Though CKD-EPI derived eGFR has been compared with measured CL_{cr} in the above-mentioned studies, they have utilized the original "2009 CKD-EPI" formula put forth by Levey et al.[24] We used the "Refit 2021 CKD-EPI Creatinine" formula as per the current recommendation of the NKF-ASN.[19,20] None of the previous studies comparing eGFR with measured CL_{cr} have used the "Refit 2021 CKD-EPI Creatinine" formula in their methodology and hence, no comparison can be made between our study results comparing eGFR and 8-hr mCL_{cr} with those done previously.

Our trial is among the first to evaluate the prevalence of ARC in an Indian ICU setting. Moreover, we have assessed the utility of the ARCTIC score and "2021 Refit CKD-EPI" derived eGFR in predicting ARC in a mixed medical-surgical ICU setup. To the best of our knowledge, this association has never been studied previously. Our study was conducted robustly and patients were screened consecutively for enrollment.

There were a few limitations to our study. This was a single-center study that had a limited number of patients recruited for the study. Prevalence of ARC was not assessed beyond 48 hours from the time of admission of a patient, despite its occurrence having been reported beyond this time duration in previous studies.[6,13] The gold standard for the estimation of GFR is by assessing the clearance of an exogenous substance like inulin.[30] Instead, we utilized the 8-hr mCL_{cr} as a surrogate of GFR to identify ARC, due to its ease of measurement. This could have overestimated the GFR marginally due to increased tubular secretion of creatinine. GFR calculated both by 8-hr mCL_{cr} and eGFR- EPI was not corrected for the body surface area of patients in our study.

Our study has important clinical implications. Recognizing augmented renal clearance (ARC) is of utmost importance as it has been associated with sub-therapeutic levels of medications, sub-optimal treatment, and failure to attain pharmacodynamic targets, resulting in treatment failure and increased risk of anti-microbial resistance.[9,23,25] Antibiotic activity is either a function of time or concentration.[26] Antibiotics that display time-dependent activity (e.g., β lactams) do so as a function of time spent at a concentration above the MIC of the causative organism [%fT > MIC]. Concentration-dependent (e.g., Vancomycin) antibiotic goals are expressed in terms of a ratio between the maximum achieved concentration and the MIC (C_{max}/MIC) or the area under the concentration curve and the MIC (AUC/MIC). Achieving these targets in patients exhibiting ARC has proven to be difficult and increased mortality has been noted in patients with sub-therapeutic plasma antibiotic levels.[8,9,22,27–29]

Conclusion

The prevalence of ARC in patients with preserved GFR was significant at 31.4%, within the initial 48 hours of admission to our ICU. ARCTIC score with a cut-off score of ≥6, displayed high sensitivity and negative predicting value in our mixed medical-surgical ICU and showed good potential for use as a screening tool to predict the risk of ARC. Lowering the cut-off of the ARC score to 5 increased its sensitivity and seemingly improved its utility in predicting ARC. eGFR-EPI calculated using the "Refit 2021 CKD-EPI Creatinine" formula showed poor agreement with 8-hr measured creatinine clearance, yet shows potential for use as a screening tool to predict ARC if its cut-off were to be lowered to 114 mL/min.

Orcid

Girish Kanna https://orcid.org/0000-0002-3531-6983
Sristi Patodia https://orcid.org/0000-0002-9604-6374
Rajeev A Annigeri https://orcid.org/0000-0001-5282-3592
Nagarajan Ramakrishnan https://orcid.org/0000-0001-5208-4013
Ramesh Venkataraman https://orcid.org/0000-0003-1949-3979

References

1. Bilbao-Meseguer I, Rodriguez-Gascon A, Barrasa H, Isla A, Solinís MÁ. Augmented renal clearance in critically ill patients: A systematic review. Clinical pharmacokinetics 2018;57(9):1107–1121. DOI: 10.1007/s40262-018-0636-7.
2. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J. Augmented renal clearance. Clinical pharmacokinetics 2010;49(1):1–6. DOI: https://doi.org/10.2165/11318140-000000000-00000.
3. De Waele JJ, Dumoulin A, Janssen A, Hoste EA. Epidemiology of augmented renal clearance in mixed ICU patients. Minerva Anestesiol 2015;81(10):1079–1085. PMID: 25697881.
4. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: Identifying at-risk patients. Critical Care 2013;17(1):1–9. DOI: 10.1186/cc12544.
5. Baptista JP, Martins PJ, Marques M, Pimentel JM. Prevalence and risk factors for augmented renal clearance in a population of critically ill patients. Journal of intensive care medicine 2020;35(10):1044–1052. DOI: 10.1177/0885066618809688.
6. Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L, et al. Augmented renal clearance in the ICU: Results of a multicentre observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Critical care medicine 2014;42(3):520–527. DOI: 10.1097/CCM.0000000000000029.
7. Tsai D, Udy AA, Stewart PC, Gourley S, Morick NM, Lipman J, et al. Prevalence of augmented renal clearance and performance of glomerular filtration estimates in indigenous Australian patients requiring intensive care admission. Anaesth Intensive Care 2018;46(1):42–50. DOI: 10.1177/0310057X1804600107.
8. Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ. Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 2013;28(5):695–700. DOI: 10.1016/j.jcrc.2013.03.003.
9. Roberts JA, Kruger P, Paterson DL, Lipman J. Antibiotic resistance—what's dosing got to do with it?. Crit Care Med 2008;36(8):2433–2340. DOI: 10.1097/CCM.0b013e318180fe62.
10. Saran S, Rao NS, Azim A. Drug dosing in critically Ill patients with acute kidney injury and on renal replacement therapy. Indian J Crit Care Med 2020;24(Suppl 3):S129–S134. DOI: 10.5005/jp-journals-10071-23392.
11. Barletta JF, Mangram AJ, Byrne M, Sucher JF, Hollingworth AK, Ali-Osman FR, et al. Identifying augmented renal clearance in trauma patients: Validation of the augmented renal clearance in trauma intensive care scoring system. J Trauma Acute Care Surg 2017;82(4):665–671. DOI: 10.1097/TA.0000000000001387.
12. Al-Dorzi HM, Alsadhan AA, Almozaini AS, M Alamri A, Tamim H, Sadat M, et al. The performance of equations that estimate Glomerular filtration rate against measured urinary creatinine clearance in critically ill patients. Critical Care Research and Practice 2021;18:2021. DOI: https://doi.org/10.1155/2021/5520653.
13. Ruiz S, Minville V, Asehnoune K, Virtos M, Georges B, Fourcade O, et al. Screening of patients with augmented renal clearance in ICU:

taking into account the CKD-EPI equation, the age, and the cause of admission. Annals of intensive care 2015;5(1):1–9. PMC4681181.
14. Udy AA, Morton FJ, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J, et al. 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 nephrology 2013;14(1):1–7. DOI: https://doi.org/10.1186/1471-2369-14-250.
15. Martin JH, Fay MF, Udy A, Roberts J, Kirkpatrick C, Ungerer J, et al. Pitfalls of using estimations of glomerular filtration rate in an intensive care population. Internal Medicine Journal 2011;41(7):537–543. DOI: 10.1111/j.1445-5994.2009.02160.x.
16. Kharbanda M, Majumdar A, Basu S, Todi S. Assessment of accuracy of Cockcroft-Gault and MDRD formulae in critically ill Indian patients. Indian J Crit Care Med 2013;17(2):71–75. DOI: 10.4103/0972-5229.114820.
17. Adnan S, Ratnam S, Kumar S, Paterson D, Lipman J, Roberts J, et al. Select critically ill patients at risk of augmented renal clearance: Experience in a Malaysian intensive care unit. Anaesthesia and intensive care 2014;42(6):715–722. DOI: 10.1177/0310057X1404200606.
18. Cherry RA, Eachempati SR, Hydo L, Barie PS. Accuracy of short-duration creatinine clearance determinations in predicting 24-hour creatinine clearance in critically ill and injured patients. J Trauma. 2002;53(2):267–271. DOI: 10.1097/00005373-200208000-00013.
19. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine-and cystatin C–based equations to estimate GFR without race. N Engl J Med 2021;4;385(19):1737–1749. DOI: 10.1056/NEJMoa2102953.
20. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A unifying approach for GFR estimation: Recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. Am J Kidney Dis 2022;79(2):268–288. DOI: 10.1053/j.ajkd.2021.08.003.
21. Kawano Y, Morimoto S, Izutani Y, Muranishi K, Kaneyama H, Hoshino K, et al. Augmented renal clearance in Japanese intensive care unit patients: A prospective study. Journal of intensive care 2016;4(1):1–7. DOI: 10.1186/s40560-016-0187-7.
22. Campassi ML, Gonzalez MC, Masevicius FD, Vazquez AR, Moseinco M, Navarro NC, et al. Augmented renal clearance in critically ill patients: Incidence, associated factors and effects on vancomycin treatment. Revista Brasileira de terapia intensiva 2014;26(1):13–20. DOI: 10.5935/0103-507x.20140003.
23. Akers KS, Niece KL, Chung KK, Cannon JW, Cota JM, Murray CK. Modified Augmented Renal Clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients. Journal of Trauma and Acute Care Surgery. 2014; 77(3 Suppl 2):S163–S170. DOI: 10.1097/TA.0000000000000191.
24. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604–612. DOI: 10.7326/0003-4819-150-9-200905050-00006.
25. Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, et al. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study. Int J Antimicrob Agents 2015;45(4):385–392. DOI: 10.1016/j.ijantimicag.2014.12.017.
26. Asín-Prieto E, Rodríguez-Gascón A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. J Infect Chemother 2015;21(5):319–329. DOI: 10.1016/j.jiac.2015.02.001.
27. Spadaro S, Berselli A, Fogagnolo A, Capuzzo M, Ragazzi R, Marangoni E, et al. Evaluation of a protocol for vancomycin administration in critically patients with and without kidney dysfunction. BMC Anesthesiol 2015;15(1):1–7. DOI: 10.1186/s12871-015-0065-1.
28. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, et al. Subtherapeutic initial β-lactam concentrations in select critically ill patients. Chest. 2012;142(1):30–39. DOI: https://doi.org/10.1378/chest.11-1671.
29. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E, et al. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used?. Crit care. 2013;17(3):1–9. DOI: 10.1186/cc12705.
30. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med 2006;354(23):2473–2483. DOI: 10.1056/NEJMra054415.

APPENDIX I

ARC AND ARCTIC SCORES[4,10]

ARC SCORE[4]

PARAMETERS	SCORE
Age ≤ 50	6
Trauma	3
Modified SOFA ≤ 4	1

Interpretation: 0–3: Low Risk; 4–6: Intermediate Risk; ≥ 7: High Risk

ARCTIC SCORE[10]

PARAMETERS	SCORE
Age < 56	4
Age b/w 56 - 75	3
S.Cr < 0.7 mg/dL	3
Male patient	2

Interpretation: ≥ 6: Increased risk for augmented renal clearance

APPENDIX II

Modified SOFA Score

Modified Sequential Organ Failure Assessment (MSOFA) Score

Organ System	0	1	2	3	4
Respiratory SpO2/FiO2	>400	≤400	≤315	≤235	≤150
Liver	No scleral icterus or jaundice			Scleral icterus or jaundice	
Cardiovascular, hypotension	No hypo-tension	MAP <70 mm Hg	dopamine≤5 or dobutamine any dose	dopamine>5 epinephrine≤0.1 norepinephrine≤0.1	dopamine>15 epinephrine>0.1 norepinephrine>0.1
CNS, Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal, Creatinine mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0

MAP=mean arterial pressure

dopamine, dobutamine, epinephrine, and norepinephrine doses in micrograms per kilogram per minute

CNS=central nervous system

Interpretation	
mSOFA Score	30-day mortality
0-7	4%
8-11	31%
>11	58%

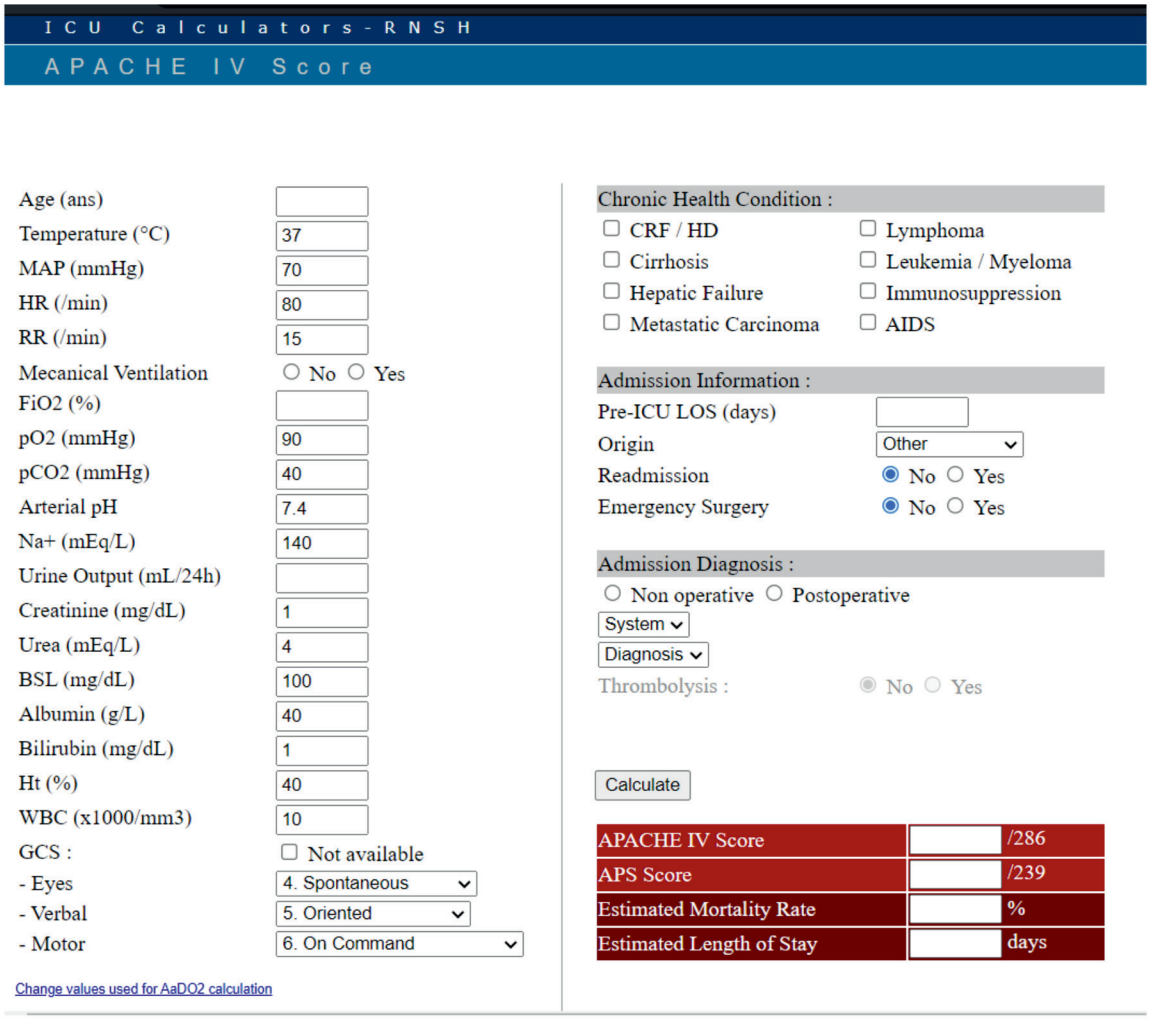
Reference

1. Grissom CK, Brown SM, Kuttler KG, Boltax JP, Jones J, Jephson AR, et al. A modified sequential organ failure assessment score for critical care triage. Disaster Med Public Health Prep 2010;4(4):277–284. DOI: 10.1001/dmp.2010.40.

APPENDIX III

APACHE IV score

The APACHE IV score for all patients using the APACHE IV calculator available on https://intensivecarenetwork.com/Calculators/Files/Apache4.html. The estimated mortality rate and estimated length of stay in ICU would therefore be calculated using the APACHE IV scores.



Reference

1. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute physiology and chronic health evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. Critical Care Medicine 2006;34(5):1297–1310. DOI: 10.1097/01.CCM.0000215112.84523.F0.

APPENDIX IV

Cumulative Vasopressor Index

Vasoactive Agent	Dose Range			
	1 point	2 points	3 points	4 points
Dopamine	0 < dose ≤ 5	5 < dose ≤ 10	10 < dose ≤ 15	>15
Epinephrine	---	0 < dose ≤ 0.05	0.05 < dose ≤ 0.1	>0.1
Norepinephrine	---	0 < dose ≤ 0.05	0.05 < dose ≤ 0.1	>0.1
Phenylephrine	---	0 < dose ≤ 0.4	0.4 < dose ≤ 0.8	>0.8
Vasopressin	---	---	---	Any dose

All doses in mcg/kg/min except vasopressin, which is U/min

Reference

1. Vallabhajosyula S, Jentzer JC, Kotecha AA, Murphree DH, Barreto EF, Khanna AK, et al. Development and performance of a novel vasopressor-driven mortality prediction model in septic shock. Ann Intensive Care 2018;8(1):1–9. DOI: 10.1186/s13613-018-0459-6.