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ORIGINAL ARTICLE

Augmented renal clearance: a common condition in critically ill children

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Abstract

Background Augmented renal clearance (ARC), an increase in kidney function with enhanced elimination of circulating solute, has been increasingly recognized in critically ill adults. In a pediatric intensive care setting, data are scarce. The primary objective of this study was to investigate the prevalence of ARC in critically ill children. Secondary objectives included a risk factor analysis for the development of ARC and a comparison of two methods for assessment of renal function.

Methods In 105 critically ill children between 1 month and 15 years of age, glomerular filtration rate (GFR) was measured by means of a daily 24-h creatinine clearance (24 h Cl_{Cr}) and compared to an estimated GFR using the revised Schwartz formula. Logistic regression analysis was used to identify risk factors for ARC.

Results Overall, 67% of patients expressed ARC and the proportion of ARC patients decreased during consecutive days. ARC patients had a median Cl_{Cr} of 142.2 ml/min/1.73m^2 (IQR 47.1). Male gender and antibiotic treatment were independently associated with the occurrence of ARC. The revised Schwartz formula seems less appropriate for ARC detection.

Conclusions A large proportion of critically ill children develop ARC during their stay at the intensive care unit. Clinicians should be cautious when using Schwartz formula to detect ARC. Our findings require confirmation from large study cohorts and investigation of the relationship with clinical outcome.

Keywords Pediatric intensive care · Critically ill children · Renal function · Glomerular filtration rate · Augmented renal clearance · Risk factors

Introduction

Over the past decade, augmented renal clearance (ARC) described as an enhanced renal function, has been increasingly recognized in critically ill adults. The reported prevalence in this setting is variable, ranging from 18 to 80% depending on the chosen cutoff for definition and the study population [1–14].

Although the pathophysiology is not completely understood, ARC is suggested to result from a cascade of physiological changes in the critically ill. Triggered by a systemic inflammation response, the cardiac output in these patients increases resulting in an enhanced blood flow to the major organs, including the kidneys. This hyperdynamic circulation is further maintained by intensive care procedures like intravenous fluids suppletion and treatment with vasoactive agents. The increased renal blood flow leads to glomerular hyperfiltration (GHF) and subsequently the augmented clearance of substitute by the kidneys, or ARC [15–18].

Both GHF and ARC are defined by an increased glomerular filtration rate (GFR), although altered tubular function might also contribute to ARC [19]. In case of renally eliminated drugs, like some frequently used antibiotics, the use of standard dosage regimens in patients with ARC might result in lower plasma levels and therefore in treatment failure [3, 16, 20].

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In critically ill children, little is known about the occurrence of ARC. In this study, the prevalence of ARC in a pediatric intensive care population was investigated using an age-dependent definition. As secondary objectives, we evaluated factors associated with the development of ARC and compared two frequently used methods for GFR assessment in critically ill children.

Materials and methods

Study design

This prospective observational study was performed at the pediatric intensive care unit (PICU) and the cardiac intensive care unit (CSICU) of Ghent University Hospital, a tertiary care hospital with 14 PICU and 2 pediatric CSICU beds. Data were collected over a 10-month period. This study was approved by the institutional ethics committee and written informed consent was obtained from the parents or legal representatives and from the patients older than 12 years. Patients between 1 month and 15 years of age admitted to the intensive care unit (ICU) were enrolled, if having a urinary bladder catheter in place. Indications for placement of an indwelling urinary catheter were as follows: sedation with opiates, post-operative conditions, and strict fluid balance monitoring (e.g., shock, hemodynamic instability, acute kidney injury, hyperhydration). Patients with impaired renal function were excluded.

Assessment of renal function

Renal function was determined by a 24-h measured urinary creatinine clearance (24 h Cl_{Cr}), using the following equation:

$$\begin{aligned} Cl_{Cr}\left(\mathrm{ml/min/1.73m^2}\right) = {} & [\text{urinary volume } (U_v, \mathrm{ml}) \\ & \times \text{urinary creatinine } (U_{Cr}, \mathrm{mg/dl}) \times 1.73] \\ & /[1440\ \mathrm{min} \times \text{serum creatinine } (S_{Cr}, \mathrm{mg/dl}) \\ & \times \text{body surface area } (\mathrm{BSA}, \mathrm{m^2})] \end{aligned}$$

BSA was calculated according to Du Bois and Du Bois. Timed urinary collections were obtained via an indwelling bladder catheter starting as soon as possible after ICU admission for a maximum of 4 days or until bladder catheter removal or discharge from the ICU. Besides this, GFR was estimated daily using the revised Schwartz formula [21].

Serum and urine creatinine concentrations were measured within the 24 h collection period using a rate-blanked alkaline picrate method (limit of quantification (LOQ) for S_{Cr} 0.17 mg/dl, coefficient of variation 1.6%). GFR was calculated following the correction of the S_{Cr} results for interfering total protein concentrations, according to Speeckaert et al., in order to make them interchangeable with enzymatic creatinine values [22].

Threshold values for ARC were based on GFR values in children and adolescents without renal disease determined by inulin clearance (preferably) or ^{51}Cr-EDTA clearance for children under 2 years of age [23–25]. Subsequently, ARC was defined as a 24 h Cl_{Cr}-based eGFR exceeding GFR age-adjusted reference values plus two standard deviations. Threshold values increased steeply from 70 ml/min/1.73 m^2 at 1 month of age to 150 ml/min/1.73 m^2 for all children aged 2 and older.

Impaired renal function covers both severe acute kidney injury (AKI) and chronic kidney disease (CKD), according to the pRIFLE criteria and the NKF-K/DOQI criteria, respectively. Severe AKI was defined as "renal injury", i.e., a GFR < 50% compared to the patient's baseline, or if individual baseline values were not available, to the reference values for age [26]. Chronic renal failure refers to all patients with CKD stage 3, 4, and 5, i.e., GFR < 60 ml/min/1.73 m^2 for ≥ 3 months [27].

Study variables

Besides renal function variables, the following data were recorded for each patient: demographic data (gender, age, weight, height, body surface area (BSA)), biochemical data (serum total protein concentration, C-reactive protein (CRP)), requirement for mechanical ventilation, treatment with antibiotics, diuretics and vasopressor agents, and the daily amount of administered intravenous (iv) fluids. The main reason for admission, length of stay (LOS), ICU mortality, pediatric risk of mortality (PRISM II) score at admission, and a daily pediatric logistic organ dysfunction (PELOD-2)-score were also registered [28, 29].

Categorical data were presented as counts (%), continuous data as mean (standard deviation, SD) if normally distributed, and otherwise as median (interquartile range, Q1–Q3).

Statistical analysis

A Mann–Whitney *U* test was used for comparison between two groups for continuous data and a chi square or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was performed to assess variables associated with the development of ARC. The following variables were evaluated in the univariate analysis: gender, age, age category, weight, length, BSA, reason for admission, PELOD and PRISM II scores, LOS, amount of administered iv fluids, presence of mechanical ventilation, and administration of diuretics, vasopressor drugs, and antibiotics. All variables had a clinical plausibility and those with an a priori determined p value < 0.10 in univariate analysis were entered in the stepwise multivariate regression analysis (i.e., sex, admission after cardiac surgery, and treatment with antibiotics and diuretics).

Goodness-of-fit was evaluated with the Hosmer–Lemeshow statistic, colinearity between variables was assessed by means of a scatter plot and Pearson correlation coefficient (r). The agreement between 24 h Cl_{Cr} and eGFR using the revised Schwartz formula was quantified by means of a graphical Bland–Altman plot. A scatter plot with quadratic regression line and coefficient of determination (R^2) was used to visualize the colinearity between 24 h Cl_{Cr} and Schwartz-based GFR.

A p value of less than 0.05 was considered as indicating statistical significance. All statistical analyses were performed using SPSS statistics 24 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Data were collected from 105 patients. Of these, 13 patients were excluded due to impaired renal function (severe AKI in 8 patients, CKD stage 3–5 in 5 patients). In total, 222 timed urinary collections were assembled (day 1 $n = 92$, day 2 $n = 59$, day 3 $n = 44$, day 4 $n = 27$). Urinary sampling started within 24 h following admission to the ICU in 48 patients (52.2%) and in 87 patients (94.6%) within 3 days.

Patient characteristics are presented in Table 1. The median age of the study population was 1.54 years (Q1 0.8; Q3 3.1) and consists of a large proportion of patients (48.9%) admitted after surgery. The surgical intervention was elective in most cases (86.7%). GFR values for all patients ranged from 65 to 270 ml/min/1.73 m^2 (using 24 h Cl_{Cr}) or 63 to 236 ml/min/1.73 m^2 (Schwartz formula). Median GFR on the first study day was 127 ml/min/1.73 m^2 (Q1 100; Q3 163, 24 h Cl_{Cr}) or 126 ml/min/1.73 m^2 (Q1 101; Q3 148, Schwartz formula).

Prevalence of ARC

Augmented renal clearance, using a Cl_{Cr}-based definition, was present for at least 1 day during the study period in 67.4% of patients (62/92), and in general in 102 of 222 measurements (45.9%). The proportion of patients with ARC generally decreased over the study period, from 51.1% on the first day to 33.3% on the fourth day. A similar overall prevalence (66.3%) was observed when using the revised Schwartz formula for GFR estimation (Fig. 1). Two out of 24 patients (8.3%) from whom four consecutive urine collections were assembled and expressed ARC continuously, whilst in 12 patients (54.2%), ARC was observed during 1 to 3 days.

Table 1 shows a comparison of patients with and without ARC at any time during the study. Patients presenting with ARC were predominantly male ($p = 0.040$) and mostly found in the group between 2 and 6 years of age. They had a lower S_{Cr} ($p = 0.050$) and a median 24 h Cl_{Cr} of 142 ml/min/1.73 m^2 (Q1 124; Q3 171) compared with 100 ml/min/1.73 m^2 (Q1 77; Q3 111) in those without ARC ($p < 0.001$). Patients in the ARC group had higher PRISM II-scores ($p = 0.046$) and were more often treated with antibiotics ($p = 0.035$) and ventilated ($p = 0.065$). However, CRP was lower compared with the non-ARC group ($p = 0.040$). Patients admitted to the PICU after cardiac surgery expressed less ARC, although this was not statistically significant ($p = 0.086$). No differences in vasopressor and diuretic treatment, fluid therapy, or length of ICU stay were seen.

Risk factors for ARC

In the univariate analyses, male gender ($p = 0.044$), treatment with antibiotics ($p = 0.038$), mechanical ventilation ($p = 0.069$), and higher PRISM II-scores ($p = 0.087$) were significantly associated with ARC, whereas patients admitted after cardiac surgery were less likely to present with ARC ($p = 0.088$). Stepwise multivariate logistic regression analysis identified male gender and treatment with antibiotics as independent risk factors for the development of ARC (Table 2).

Comparison of methods for renal function assessment

A moderate positive correlation was found between 24 h Cl_{Cr} and Schwartz formula obtained GFR values ($R = 0.662$, $p < 0.001$) (Fig. 2a). Further assessment of the actual agreement between both methods, by means of a Bland–Altman plot, showed a low mean bias of 1.5 ml/min/1.73m^2 (95% limits of agreement − 71.6;74.6) (Fig. 2b). A better agreement was observed for GFR values below 100 ml/min/1.73 m^2.

Discussion

This is the first prospective observational study investigating the prevalence of ARC in a large cohort of critically ill children, using both a 24 h Cl_{Cr} and the revised Schwartz formula for renal function assessment. Major findings from our study included a high prevalence of ARC (67%) on at least one occasion during a 4-day period following ICU admission. This observation was unexpected and remarkably higher compared with what has been recently reported by Avedissian et al. In their study, ARC was observed in only 12% of patients between 1 and 21 years of age [31]. However, substantial differences in study design, study period, ARC definition, renal function assessment method, and patient selection might explain the contrast in observed prevalence. In essence, Avedissian et al. retrospectively evaluated the occurrence of ARC using vancomycin clearance as a renal function assessment method. Patients were included if vancomycin blood levels were available, irrespective of the time after admission to the ICU. While we applied an age-dependent definition,

Table 1 Patient characteristics

Variable	All patients ($n = 92$)	ARC ($n = 62$)	No ARC ($n = 30$)	p value
Age, years, median (Q1–Q3)	1.54 (0.8–3.1)	1.75 (1.0–3.1)	1.00 (0.4–3.5)	0.129
< 2 years, *n* (%)	55 (59.8)	35 (56.5)	20 (66.7)	
2 to < 6 years, *n* (%)	25 (27.2)	20 (32.3)	5 (16.7)	
≥ 6 years, *n* (%)	12 (13.0)	7 (11.3)	5 (16.7)	
Gender, male, *n* (%)	65 (70.7)	48 (77.4)	17 (56.7)	0.040
Weight, kg, median (Q1–Q3)	11.1 (7.8–15.2)	12.0 (8.2–15.1)	8.7 (7.3–18.0)	0.218
Height, cm, median (Q1–Q3)	82.0 (68.5–97.8)	85.5 (71.9–97.3)	72.3 (67.5–98.5)	0.151
BSA, m^2, median (Q1–Q3)	0.49 (0.37–0.63)	0.51 (0.39–0.63)	0.40 (0.36–0.70)	0.195
Admission category, *n* (%)				
Postoperative monitoring	45 (48.9)	27 (43.5)	18 (60.0)	0.139
Neurosurgery	21 (22.8)	15 (24.2)	6 (20.0)	0.653
Abdominal surgery	11 (12.0)	5 (8.1)	6 (20.0)	0.167
Cardiac surgery	6 (6.5)	2 (3.2)	4 (13.3)	0.086
Orthopedic surgery	2 (2.2)	1 (1.6)	1 (3.3)	0.548
Head/neck surgery	2 (2.2)	2 (3.2)	0 (0.0)	1.000
Thoracic surgery	1 (1.1)	1 (1.6)	0 (0.0)	1.000
Urologic surgery	1 (1.1)	1 (1.6)	0 (0.0)	1.000
Plastic surgery	1 (1.1)	0 (0.0)	1 (3.3)	0.326
Neurologic disorder	18 (19.6)	14 (22.6)	4 (13.3)	0.295
Respiratory disorder	16 (17.4)	12 (19.4)	4 (13.3)	0.475
Cardiovascular disorder	5 (5.4)	3 (6.5)	1 (3.3)	1.000
Burns	4 (4.3)	2 (3.2)	2 (6.7)	0.954
Hematologic/oncologic disorder	3 (3.3)	3 (4.8)	0 (0.0)	0.548
Trauma	1 (1.1)	0 (0.0)	1 (3.3)	0.326
PELOD-score day 1, median (Q1–Q3)	10 (0–12)	10 (0–20)	6 (0–11)	0.212
PRISM II-score, median (Q1–Q3)	9 (2–14)	10 (5–15)	6 (0–12)	0.046
ICU length of stay, d, median (Q1–Q3)	7 (4–14)	7 (4–13)	5 (3–14)	0.135
Death, *n* (%)	2 (2.2)	2 (3.2)	0 (0.0)	1.000
IV fluids, ml/kg/day, median (Q1–Q3)	113 (81–143)	115 (83–146)	110 (62–140)	0.527
Use of vasopressor drugs, *n* (%)	19 (20.7)	13 (21.0)	6 (20.0)	0.914
Use of diuretics, *n* (%)	35 (38.0)	22 (35.5)	13 (43.3)	0.465
Mechanical ventilation, *n* (%)	37 (40.2)	29 (46.8)	8 (26.7)	0.065
S_{Cr} day 1, mg/dl, median (Q1–Q3)	0.17 (0.17–0.24)	0.17 (0.17–0.22)	0.21 (0.17–0.32)	0.050
24 h Cl_{Cr} day 1, ml/min1.73m^2, median (Q1–Q3)	127 (100–163)	142 (124–171)	100 (77–111)	<0.001
eGFR (Schwartz) day 1, ml/kg/1.73m^2, median (Q1–Q3)	126 (101–148)	140 (111–154)	102 (86–119)	<0.001
Antibiotic therapy, *n* (%)	68 (73.9)	50 (80.6)	18 (60.0)	0.035
CRP day 1, mg/l, median (Q1–Q3)	33.6 (10.5–111.2)	26.0 (9.8–89.5)	64.0 (22.8–131.7)	0.040

Data are presented as count (percentage) or median (Q1–Q3, interquartile range). Differences between groups (i.e., patients with ARC at any time during the study and patients not presenting with ARC) were considered statistically significant if p value < 0.05. *ARC* augmented renal clearance, *BSA* body surface area, *PELOD* pediatric logistic organ dysfunction, *PRISM* pediatric risk of mortality, *eGFR* estimated glomerular filtration rate, and *CRP* C-reactive protein. [a] Renal failure, 1. Renal injury according to the pRIFLE criteria, − 2. Chronic kidney disease based on the NKF-K/DOQI-classification [27, 30]

Avedissian et al. used the same ARC threshold for all ages, from one-year-olds to young adults aged 21. Since GFR reference values show a marked age-related dependency [23, 25], this might explain why the authors rarely found ARC in their youngest age group, thereby potentially underestimating the true prevalence. Besides, their definition of ARC (i.e., a vancomycin clearance ≥ 130 ml/min/1.73 m^2) relates to drug rather than urinary clearance. We support their assumption that this may be suboptimal and therefore may help explain their low overall prevalence [31]. To date, no other studies addressing the occurrence rate of ARC in critically ill children have been published.

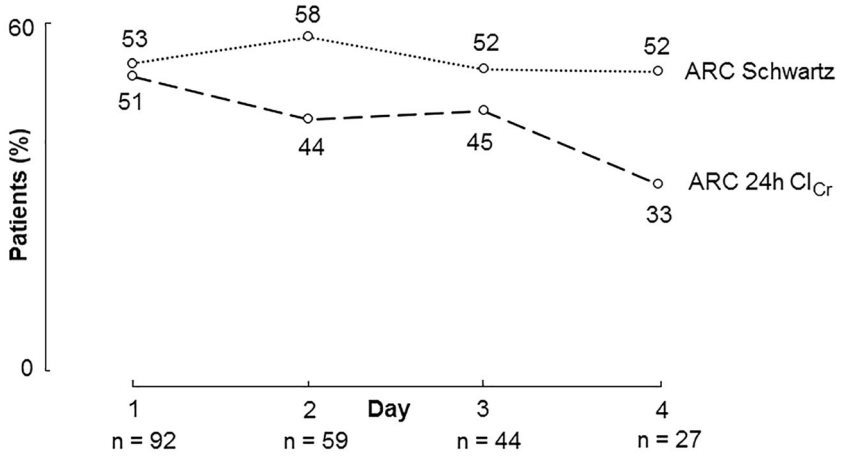

Fig. 1 Number and proportion of patients with augmented renal clearance per study day. 24 h Cl_{Cr} = 24 h creatinine clearance, Schwartz = Schwartz formula-based estimated glomerular filtration rate

The observed prevalence in our study is at the upper range of those reported in most adult ICU studies [1, 4, 6–8, 14, 15]. Udy et al. already suggested that ARC may be the result of a compensatory physiological response to a systemic inflammatory response syndrome (SIRS), whereby this physiological renal reserve decreases as patients get older [4]. This theory might illustrate why ARC in adults is repeatedly found in association with younger age [2, 3, 7, 8, 10–13, 15]. The high prevalence in our pediatric population further supports this hypothesis, suggesting that ARC in critically ill children with normal renal function may be a physiological rather than an abnormal finding.

Co-treatment with antibiotics was identified as an independent risk factor for the development of ARC in critically ill children. To the best of our knowledge, this finding has never been reported elsewhere. However, it seems plausible that most children treated with antibiotics on the ICU meet the SIRS criteria, and therefore, we believe that the systemic inflammation in these patients rather than the antibiotic treatment itself is related to the development of ARC. Another risk factor for ARC in this study was male gender. This is difficult to explain, though similar findings have been reported in several adult studies [3, 4, 12, 13, 15, 32]. This observation requires confirmation in future research since there are no differences in kidney size or excretory function between sexes in childhood. Finally, children who underwent cardiac surgery were less likely to develop ARC during the immediate postoperative period. All of our patients in this group were on cardiopulmonary bypass (CPB) during the surgical procedure. These results are consistent with the knowledge of a worsening renal function during and immediately after cardiac surgery with CPB [33, 34].

Table 2 Risk factors for augmented renal clearance

Variable	B	*p* value	OR	95% CI
Male gender	1.177	0.021	3.244	1.198–8.785
Antibiotic treatment	1.237	0.018	3.446	1.236–9.607
Constant	− 0.944	0.111	0.389	

Male gender and antibiotic treatment were identified as independent risk factors for the development of ARC (*p* value = 0.021 and 0.018, respectively). Hosmer–Lemeshow: $\chi^2 = 0.246$, df = 2, $P = 0.884$. *ARC* augmented renal clearance, *OR* odds ratio, *CI* confidence interval, *df* degrees of freedom

In our study, we evaluated the agreement between Cl_{Cr} and eGFR using the revised Schwartz formula. This formula was originally developed and validated to estimate GFR in children with chronic kidney disease [21]. As expected, a good overall agreement between both assessment methods was observed in patients with eGFR up to 100 ml/min/1.73 m^2. On the other side of the renal function spectrum, in children with high-normal to enhanced renal function, Schwartz formula usually yielded considerably lower values as compared to conventional $Cl_{Cr.}$ Therefore, clinicians should be aware of the limitations of this formula and realize that ARC can be easily overlooked using Schwartz formula alone. Similarly, the accuracy of GFR estimations in adults can also be disappointing, in particular for higher eGFR values [1]. Consequently, the Schwartz formula should be used with caution in children at risk for ARC.

In critically ill adults, ARC is well known to result in the increased elimination of renally excreted drugs and consequently in subtherapeutic plasma levels [8, 14, 35–40]. Evidence on the relationship of ARC to clinical outcome in ICU adults remains scarce and requires further exploration, as two reports already demonstrated more therapeutic failure and recurrence of infection in ARC patients receiving antimicrobial therapy [3]. In ICU children, data are limited to few observations showing the impact of enhanced renal function on the elimination of beta-lactams and glycopeptides [31, 41–43]. The true implications of ARC in daily clinical practice at the PICU remain to be established in large study cohorts.

This study has a number of limitations. First, this was a single center study, only including patients with a bladder catheter, which might limit the extrapolation of our results to

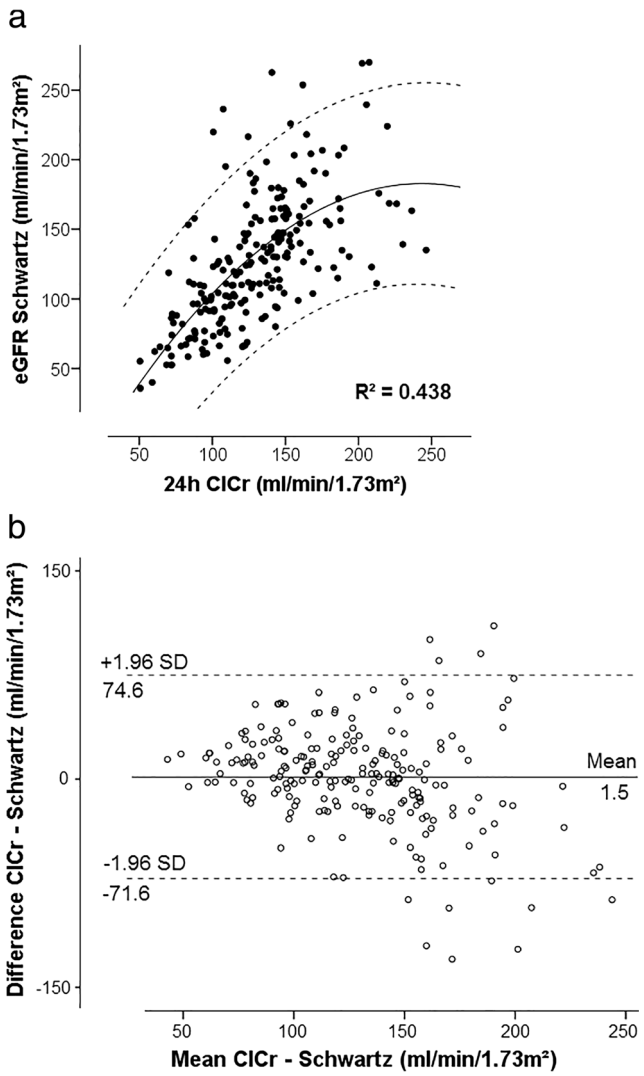

Fig. 2 Comparison of methods for renal function assessment Scatter plot (2a) showing the correlation between 24 h Cl_{Cr} and revised Schwartz formula obtained eGFR values using a quadratic model ($Y = -43.51 + 1.87*X - 0.0038*X^2$), solid line; 95% confidence interval, and dashed line; ($R^2 = 0.438$). Bland-Altman plot (2b) evaluating the agreement between both methods. Mean bias, solid line; 95% limits of agreement, dashed line. *24 h Cl_{Cr}* 24 h creatinine clearance, *eGFR* estimated glomerular filtration rate, and R^2 coefficient of determination

all PICU patients. Second, as S_{Cr} levels in infants and children are generally low, the relative error of eGFR and Cl_{Cr} is higher as compared to the situation in adults. Besides, Cl_{Cr} slightly overestimates the true GFR due to additional tubular secretion of creatinine, especially in the youngest children [24, 44, 45]. However, since measured Cl_{Cr} has been shown to be more accurate than mathematical equations for bedside GFR estimation in critically ill children, it remains a useful and inexpensive tool for rapid evaluation of renal function [46]. Finally, the time course of ARC needs further study, as a 4-day evaluation was not possible in many of our patients due to early bladder catheter removal.

Conclusions

This study demonstrates that a large proportion of critically ill children express ARC during their ICU stay, with a prevalence of 59%. Most at risk are male patients, treated with antibiotics. The revised Schwartz formula is less valid for detection of ARC in individual patients.

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Compliance with ethical standards

This study was approved by the institutional ethics committee and written informed consent was obtained from the parents or legal representatives and from the patients older than 12 years.

Conflicts of interest The authors declare that they have no conflict of interest.

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