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ORIGINAL ARTICLE

Augmented renal clearance in critically ill patients with cancer (ARCCAN Study): A prospective observational study evaluating prevalence and risk factors

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Abstract

Augmented renal clearance (ARC) is a phenomenon that has been associated with enhanced excretion of renally eliminated drugs, such as antimicrobials, which may result in subtherapeutic levels and potentially therapeutic failure. There has been limited data on ARC in critically ill patients with cancer. This study aimed to evaluate the prevalence of ARC and to identify risk factors associated with ARC in this patient population. This was a prospective study at an oncologic intensive care unit (ICU) which included adult patients with normal renal function, defined as serum creatinine ≤1 mg/dl and urine output >0.5 ml/kg/hr. The 24-hour creatinine clearance (ClCr) study was used to determine ClCr, starting on day 1 of ICU admission, for 5 days or until ICU transfer or death. ARC was defined as ClCr >130 ml/min/1.73 m^2. Univariate and multivariate logistic regression analyses were performed to identify risk factors for ARC. Over the study period, 363 patients were enrolled who completed an average of 2.8 ± 1.5(SD) days in the study and contributed 977 ClCr measurements. The mean age was 52 ± 16(SD) years old, the majority had solid tumors (*n* = 264, 73%), mean APACHE II was 21 ± 8(SD), and the major admission diagnosis was respiratory failure (*n* = 165, 45%). ARC was reported in 116 (32%) patients on at least one of the study days. Over the study period, the incidence of ARC ranged between 15.6% and 24.3%. Age was the only risk factor significantly associated with ARC (OR 1.028, 95% CI 1.005–1.051).

KEYWORDS
augmented renal clearance, cancer, critical illness, ICU, oncology

1 | INTRODUCTION

Augmented renal clearance (ARC) is a phenomenon that is commonly described in critically ill patients and is characterized by increased creatinine clearance and enhanced renal function.[1] This condition has been described over the first 5 days of ICU admission and has been associated with increased excretion of renally eliminated drugs, such as antimicrobials, resulting in reduced levels and potentially therapeutic failure.[2-5]

The mechanism for ARC in critically ill patients is not clearly understood. It appears that the systemic inflammatory response resulting in increased cytokines and pro-inflammatory mediators,

Abbreviations: ARC, Augmented renal clearance; ClCr, creatinine clearance; ICU, Intensive care unit.

as well as the aggressive fluid and hemodynamic treatments contribute to alterations in glomerular filtration, renal tubular secretion, and tubular reabsorption observed in patients with augmented renal clearance.[5,6]

Although several studies have evaluated ARC in critically ill patients, none of the studies have specifically evaluated the critically ill patient population with cancer. Febrile neutropenia has been reported as an independent risk factor for ARC.[7] In addition, neutropenia and hematological malignancies have been associated with increased clearance of several antimicrobials, suggesting augmented renal clearance.[8-10] However, those studies had relatively small sample sizes and evaluated non-critically ill patients. In addition, the renal function was determined based on the mathematical equations for estimating renal function rather than measured creatinine clearance, which is a methodology that is recognized as being inaccurate in estimating renal function and augmented renal clearance in the critically ill patient population.[11-15]

This study aimed to evaluate the prevalence of ARC among critically ill patients with cancer, as determined by the measured creatinine clearance, and to identify predictors associated with this phenomenon.

2 | MATERIALS AND METHODS

2.1 | Setting

This was a prospective observational study conducted in the adult intensive care unit (ICU) at King Hussein Cancer Center (KHCC) between July 2017 and March 2020. KHCC is a 350-bed comprehensive cancer center in Amman, Jordan, with an oncologic ICU that treats around 800 patients per year with solid and hematologic malignancies who are admitted for the management of cancer as well as non-cancer-related critical illnesses. The ICU has a closed-unit model, with the most common admission diagnosis being respiratory failure and sepsis and an overall ICU mortality of 35%.[16]

2.2 | Ethics Approval

Ethical approval was obtained from the Institutional Review Board at King Hussein Cancer Center (research project #17KHCC22). The requirement for informed consent was waived for this study.

2.3 | Participants

The study included adult patients (≥18 years old) who had normal renal function upon admission to the ICU. Normal renal function was defined as serum creatinine of ≤1 mg/dl and urine output of ≥0.5 ml/kg/hour. Eligibility criteria included the presence of an indwelling urinary catheter within 6 hours of admission and an expected ICU length of stay greater than 24 hours. Patients with acute kidney injury were excluded, which was defined as an increase in serum creatinine of greater than 0.3 mg/dl from baseline. In addition, patients were excluded if an indwelling urinary catheter was not clinically indicated or if there was greater than 6 hours delay in inserting the catheter. In addition, on days in which the laboratory testing was not indicated for a study patient, the measured creatinine clearance (ClCr) was not performed since the serum creatinine is necessary to determine the measured ClCr. Patients who were admitted for non-critical illnesses such as observation post-surgery or observation during high-risk oncology-related therapies were also excluded.

2.4 | Study procedure and endpoints

All patients admitted to the ICU were screened on a daily basis. Patients who met the eligibility criteria had their ClCr measured, starting on day 1 of their ICU admission and for a total of 5 days or until ICU transfer or death, whichever occurred first. For patients who developed acute kidney injury during the study period, the study was terminated for that patient and no further urine samples were taken. Acute kidney injury was defined as an increase in serum creatinine of greater than 0.3 mg/dl and/or a decrease in urine output to less than 0.5 ml/kg/hr for at least 6 hours.

The 24-hour ClCr study was used to determine the patient's daily ClCr. Urine collection started within 6 hours of ICU admission. The patient's nurse recorded the time of initiating urine collection, and every 24 hours, the collected urine was sent to the hospital's laboratory to determine the ClCr. The 24-hour ClCr (ml/min) was calculated according to the following formula: [urinary creatinine (mg/dl) × urinary output (ml/min)]/ plasma creatinine (mg/dl). The plasma creatinine concentration measured on the day of the measured ClCr was used in the ClCr formula. The measured creatinine clearance was then adjusted for body surface area, using the height and weight recorded upon admission. ARC was defined as a measured ClCr >130 ml/min/1.73 m^2.

Demographics and baseline characteristics were recorded prospectively, which included age, gender, height, weight (actual and ideal), body surface area, type of malignancy, metastatic disease, Acute Physiology and Chronic Health Evaluation (APACHE) II score, admission diagnosis, thrombocytopenia, neutropenia, serum creatinine, fever, lactic acid, presence of nephrotoxic medications, mechanical ventilation, and the administration of vasopressors. In addition, we recorded ICU length of stay as well as ICU and hospital mortality.

2.5 | Statistical analysis

A priori sample size of at least 300 patients was deemed appropriate for exploratory analysis. The sample size was chosen based on the sample sizes in other similar studies as well as what was considered as a feasible sample to achieve in our setting over the study period.[5]

No assumptions were made for ClCr samples that were missed. Patients who had missing samples were still included in the study but were not counted on the days in which the creatinine clearance was not measured. For patients in whom the study was terminated due to acute renal failure, the ClCr measurements on the days prior to developing renal failure were included in the analysis but subsequent measurements, if any, were excluded.

Continuous data were reported as mean and standard deviation or median and interquartile range, while nominal data were reported as a percentage. Univariate analysis was performed to compare the characteristics of patients who developed ARC and those who did not develop ARC on the first day of ICU admission. The Student's t-test or Mann–Whitney U test was used to compare continuous data, whereas the Chi-Square test or the Fisher Exact test was used to compare nominal data. For factors that were significant in univariate analysis, multivariate logistic regression was performed to identify significant risk factors for ARC on the day of ICU admission. The goodness of fit of the regression model was performed using R-square. A two-sided p-value of less than 0.05 was considered as statistically significant, and all analyses were performed using SAS version 9.4.

3 | RESULTS

Over the study period, 363 patients were enrolled, who completed an average of 2.8 ± 1.5 (SD) days in the study, and contributed a total of 977 individual ClCr measurements. Patients who did not complete the 5 days of the study included 173 who were transferred to the floors, 47 who died, 45 who had lost samples due to accidentally being discarded by the bedside nurse, 18 patients who developed acute kidney injury, and eight who did not have serum creatinine ordered on certain days of the study.

Table 1 outlines the characteristics of the patients enrolled in the study. The mean age was 52 ± 16 (SD) years old, the majority had solid tumors (*n* = 264, 73%), mean APACHE II was 21 ± 8 (SD), and the major admission diagnosis was respiratory failure (*n* = 165, 45%). The median ICU length of stay was 3 days (IQR 2–6) and ICU mortality was reported in 115 (32%) patients.

3.1 | Prevalence of ARC

Among the enrolled patients, 116 (32%) had ARC reported on at least one of the study days. Over the study period, the incidence of ARC ranged between 15.6% and 24.3%, as demonstrated in Figure 1.

On day 1 of ICU admission, ARC was reported in 67 (18.9%) of the patients with measured ClCr, and among those patients with ARC who had additional ClCr measurements beyond day 1 (*n* = 48), 26 (54%) had at least another day with ARC. New cases of ARC were also identified on subsequent days (on day 2, 12% (*n* = 28); on day 3, 6% (*n* = 11); on day 4, 3% (*n* = 4); on day 5, 7.5% (*n* = 6)).

3.2 | Predictors for ARC

In the univariate analysis, there were statistically significant differences between patients who developed ARC and those who did not develop ARC on their first day of ICU admission in the following: age, height, ideal body weight, neutropenia upon admission, fever on day 1, seem creatinine on day 1, and mechanical ventilation during the study period. (Table 1) However, in multivariate logistic regression, only the age was significantly associated with ARC (OR 1.028, 95% CI 1.005–1.051).

4 | DISCUSSION

In this paper, we report the findings of the ARCCAN study, a prospective observational study evaluating ARC in critically ill patients with cancer. The study reports two important findings; the first being that ARC is common among cancer patients over the first 5 days of their ICU stay. The second finding is related to identifying patient-related factors and baseline characteristics that may help clinicians in predicting ARC in patients admitted to the ICU. Similar to other studies conducted in non-cancer patients, age was identified as a predictor associated with ARC in the study cohort.[5] However, the study did not identify any other predictors of ARC which makes it challenging for the clinician to predict early on, upon admission, which patients may have ARC and may potentially require higher than normal doses of antimicrobial therapy.

In the ARCCAN study, ARC was reported at least once in one-third of patients with solid and hematological malignancies over the first 5 days of their ICU stay. We are not aware of other studies that have specifically described the incidence of ARC in the critically ill cancer population, but the incidence reported in critically ill patients has generally ranged between 14% and 80%.[5,17]

Among patients who developed ARC on the first day of their ICU admission, the majority (75%) had at least one additional day with reported ARC. This is similar to what has been reported in a multicenter study which included 281 patients and 1,660 creatinine clearance measurements.[18] Over 65% of the patients manifested ARC on at least one occasion during the 7-day study period, the majority (74%) of whom had ARC reported in at least half of the creatinine clearance measurements. Other studies have reported similar findings suggesting that patients with ARC on one day are likely to have ARC on additional days.[19,20]

The literature recommends the use of measured creatinine clearance using urinary collection to identify patients with ARC since the commonly utilized formulas to calculate the creatinine clearance are imprecise in identifying ARC.[11-15,17] However, this would result in delays in identifying patients with ARC who may require higher doses of antimicrobial therapy. In the immunocompromised critically ill patient, such delay may negatively impact patient outcomes. Therefore, identifying patient-related risk factors associated with ARC is essential to predict patients who may have ARC and manage accordingly until the results of the measured creatinine clearance

TABLE 1 Patient characteristics

Variable	All Patients (n = 363)[a]	Day 1 No ARC (n = 287)	Day 1 ARC (n = 67)	p- value
Age, year, mean (SD)	52 (16)	54.2 (15.7)	44.5 (15.9)	<.001
Gender, male, n (%)	203 (56)	155 (54)	41 (61)	.287
Height, cm, mean (SD)	166 (9)	165 (9.1)	168 (9.3)	.019
Weight, kg, mean (SD)				
Actual	71 (17)	70 (18)	72 (16)	.683
Ideal	61 (9)	60 (8.8)	63 (9.8)	.034
Type of malignancy				
Solid, n(%)	264 (73)	213 (74)	44 (66)	.098
Lung cancer	61 (23)	54 (25)	7 (16)	
Genitourinary cancers	42 (16)	33 (16)	7 (16)	
Head and neck cancers	40 (15)	36 (17)	3 (7)	
Gastrointestinal cancers	40 (15)	32 (15)	6 (14)	
Breast cancer	36 (14)	25 (12)	10 (23)	
Brain tumor	21 (8)	15 (7)	6 (13)	
Sarcoma	13 (5)	9 (4)	3 (7)	
Others	11 (4)	9 (4)	2 (4)	
Hematologic, n(%)	99 (27)	74 (26)	23 (34)	
Lymphoma	44 (45)	32 (43)	12 (52)	
Acute myeloid leukemia	28 (28)	21 (28)	5 (22)	
Acute lymphocytic leukemia	11 (11)	8 (11)	3 (13)	
Chronic myelogenic leukemia	3 (3)	3 (4)	0 (0)	
Chronic lymphocytic leukemia	2 (2)	2 (3)	0 (0)	
Myelodysplastic syndrome	6 (6)	3 (4)	3 (13)	
Others	5 (5)	5 (7)	0 (0)	
Metastatic solid tumor, n (%)	147 (40)	118 (41)	28 (42)	.919
APACHE II, mean (SD)	21 (8)	21 (8)	20 (7)	.108
Admission diagnosis, n (%)				
Respiratory	165 (45)	144 (50)	19 (28)	.006
Infectious	86 (24)	64 (22)	19 (28)	
Cardiac	41 (11)	35 (12)	6 (9)	
Neurologic	28 (8)	17 (6)	10 (15)	
Hematologic	21 (6)	13 (5)	6 (9)	
Others	22 (6)	14 (5)	7 (11)	
Thrombocytopenia upon admission, n(%)	121 (33)	103 (36)	18 (27)	.156
Neutropenia upon admission, n(%)	42 (12)	27 (10)	13 (19)	.023
Serum creatinine on day 1, mg/dl mean (SD)	0.62 (0.2)	0.60 (0.2)	0.60 (0.2)	.008
Fever on day 1, n(%)	61 (17)	43 (15)	17 (25)	.041
Lactic acid on day 1, mean (SD)	2.9 (2.5)	2.9 (2.6)	2.9 (2.3)	.153
Patients on nephrotoxic medications upon admission, n(%)	272 (75)	217 (76)	49 (73)	.673
Patients on nephrotoxic medications during study, n(%)	288 (80)	225 (79)	56 (85)	.301
Mechanical Ventilation upon admission, n(%)	153 (42)	131 (46)	18 (27)	.005

(Continues)

TABLE 1 (Continued)

Variable	All Patients (n = 363)[a]	Day 1 No ARC (n = 287)	Day 1 ARC (n = 67)	p- value
Mechanical ventilation during study, n(%)	165 (45)	138 (48)	22 (33)	.030
Vasopressors upon admission, n(%)	142 (39)	117 (41)	23 (35)	.376
Vasopressors during study period, n(%)	163 (45)	133 (46)	26 (39)	.264

[a]Total number of patients with creatinine clearance measurements on day 1 was less than the total number of patients enrolled in the study. On day 1, 12 patients did not have measured creatinine clearance because samples were accidentally discarded.

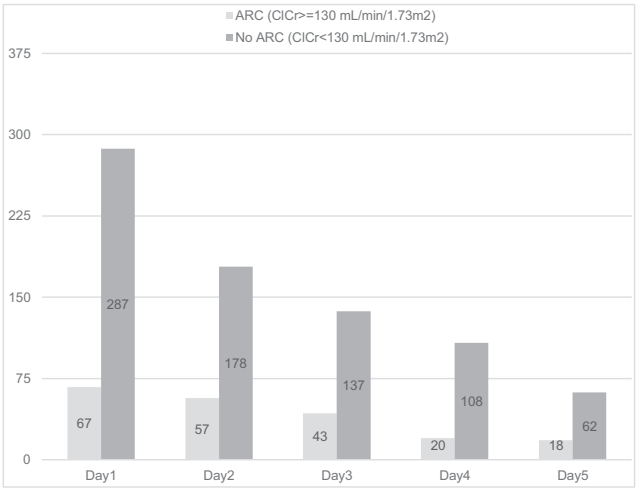

FIGURE 1 Number of patients with augmented renal clearance (ARC) versus no ARC over the study period

are available. In our study, age was the only significant predictor, but the association between age and ARC was poor. Other studies have also identified age as a predictor for ARC.[21,22]

Unlike previous studies, hematological malignancies, neutropenia, gender, and the severity of illness were not significant predictors in the ARCCAN study.[7,9,10,17,21,22] This makes it challenging for clinicians to predict who may have ARC upon admission to the ICU among a patient population in which sepsis is a common admission diagnosis and in whom the timely administration of appropriate doses of antimicrobial therapy is critical. This calls for the need of additional studies to better understand ARC in this unique population. We hypothesize that there may be other cancer-specific risk factors that may better predict ARC in this patient population, such as the specific type of malignancy, prior chemotherapy, type of chemotherapy, and performance status.

To our knowledge, this represents the first study evaluating ARC in critically ill patients with cancer. The large sample size, the prospective design of the study, and the inclusion of both solid and hematological malignancies, as well as the assessment of ARC based on the measured creatinine clearance, are strengths of the study. However, there were several limitations that should be addressed in future studies. The first was being a single-center study and therefore multi-center studies are necessary to evaluate the generalizability of the findings. We did not record certain cancer-related characteristics such as the specific stage of malignancy as well as chemotherapy and other cancer-related treatments received prior to ICU admission, which may have helped in identifying other potential risk factors for ARC. Finally, the impact of ARC on the concentrations of renally excreted medications as well as the impact on clinical outcomes was not assessed.

In conclusion, about one-third of critically ill patients with cancer had ARC at least once during the first 5 days of ICU admission. Age was identified as a significant factor associated with ARC. Future studies should aim to evaluate cancer-specific risk factors and to evaluate the impact of ARC on drug levels and outcomes in this patient population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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