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Short Communication

Augmented renal clearance in critically ill COVID-19 patients: Forewarned is forearmed

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1. Introduction

The majority of patients with Sars-CoV-2 infection are asymptomatic or have mild to moderate disease but approximately 14% have severe COVID-19 disease and 5% have critical illness [1]. The hallmark sign of severe COVID-19 disease and critical illness is the rapid progression of respiratory failure with severe hypoxemia. Signs of organ dysfunction, such as acute kidney injury (AKI), are common in these patients [2]. However, critically ill patients may also experience augmented renal clearance (ARC), defined as a creatinine clearance (CL_{CR}) > 130 mL/min. ARC can be associated with subtherapeutic concentrations of renally eliminated drugs and poorer clinical outcome [3-5]. The underlying mechanism of ARC in critically ill patients is not entirely clear but it is likely that changes in the intra-glomerular filtration pressure play an essential role [6]. ARC is frequent (20–65%) in ICU patients but incidence reports in COVID-19 disease are scarce [3]. Nevertheless, many patients with COVID-19 disease receive drugs, such as β-lactam antibiotics or low-molecular weight heparins (LMWH), that have a significant renal elimination and for which achieving therapeutic drug levels is important [3,7].

1.1. Objective

To describe the incidence of ARC in adult COVID-19 patients admitted to the ICU of the Ghent University Hospital.

2. Materials and methods

This prospective observational study was conducted in the Department of Critical Care Medicine of Ghent University Hospital (Ghent, Belgium). Ethical approval was obtained from the Ghent University Hospital Ethics Committee (registration number BC-09353). Patients were eligible for inclusion if they were diagnosed with COVID-19 disease and were admitted to the surgical or medical ICU between 11/3/2020 and 7/1/2021. Patients younger than 18 years or patients requiring renal replacement therapy during their ICU stay were excluded. Demographic and biometric data, co-morbidities, need for organ support and outcomes were recorded. Daily creatinine clearance was determined by measuring urinary creatinine concentrations from an 8-h urinary collection using an indwelling urinary catheter. ARC was defined as an 8 h CL_{CR} > 130 mL/min. The Wilson score interval was used to compute the 95% confidence interval of the proportion of ARC patients and the proportion of ARC days in relation to the number of ICU days [8]. A mixed model with random intercept was used to estimate 8 h CL_{CR} and 95% confidence interval (CI) in patients with and without ARC. Negative binomial regression was used to calculate the ARC incidence rate and 95% CI. To calculate ARC incidence, patients were considered at risk until ICU discharge, death or the first day of ARC.

3. Results

129 patients admitted were included in the study. Table 1 summarizes the patient characteristics. Overall, 93 patients had at least one 8 h CL_{CR} > 130 mL/min, corresponding to a proportion of 0.72 (0.64–0.79). The proportion of ARC days was 15.6 (14.1–17.3) per 100 ICU days. The median (IQR) number of ARC days per patient was 2 (1–4) and the median first day of ARC was day 2 (3–5) of ICU stay (Fig. 1). Patients with ARC were significantly younger than patients without ARC. The 8 h CL_{CR} estimate and 95% CI for patients in the ARC group was 142.08 (136.04–148.13) mL/min as compared to 40.92 (38.09–43.6) mL/min in the non-ARC group. ARC incidence rate and 95% CI in ICU patients with COVID-19 per 100 person days was 20.47 (15.38–27.09).

4. Discussion

ARC in COVID-19 ICU patients is frequent, however the number of ARC days per 100 ICU days is lower when compared to a general ICU population (15.6 vs 36.6 per 100 ICU days) [9]. The pathophysiology of COVID-19 kidney disease, i.e. cytokine-mediated injury as well as effects related to an adaptive immune response, are likely different from the general ICU population which may explain differences in ARC incidence [10].

Our results indicate that ARC occurs early during the course of ICU stay, which is in line with previous findings in non-COVID-19 ICU patients [3] but is opposed to the findings of Beunders, et al. [11], who

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Table 1
patient characteristics, comorbidities, organ support and outcome data.

	No ARC (n = 36)	ARC (n = 93)	p-value
Patient characteristics and comorbidities			
Age in years (median, IQR)	68 (62.5–73.25)	60 (53–69)	<0.0001
Male, n (%)	24 (66.66%)	67 (72.04%)	0.5479
ICU length of stay in days (median, IQR)	7.5 (3–15.5)	12 (6–23)	0.0658
BMI (mean, sd)	29.07 (5.39)	29.80 (5.78)	0.4992
Smoking[1], n (%)	12 (33.33%)	15 (16.13%)	0.0312
Pulmonary disease[2], n (%)	6 (16.66%)	19 (20.43%)	0.6276
Cardiovascular disease[3], n (%)	24 (66.66%)	43 (46.23%)	0.0372
Liver disease[4], n (%)	4 (11.11%)	2 (2.15%)	0.0508
Diabetes mellitus[5], n (%)	14 (38.88%)	27 (29.03%)	0.2809
Rheumatologic disease, n (%)	1 (2.77%)	3 (3.23%)	1
Neurologic disease[6], n (%)	0	6 (6.45%)	0.1848
Chronic kidney disease, n (%)	10 (27.77%)	2 (2.15%)	<0.0001
Malignant neoplasm, n (%)	6 (16.66%)	7 (7.53%)	0.1219
HIV/AIDS, n (%)	0	1 (1.08%)	1
Malnutrition, n (%)	0	1 (1.08%)	1
Tuberculosis, n (%)	1 (2.77%)	1 (1.08%)	0.4818
Organ support			
Invasive ventilation			
Number of patients[7], n (%)	17 (47.22%)	61 (65.59%)	0.0556
Number invasive ventilation days/total number of ICU days, % and 95% CI	71.19% (0.71–0.8)	78.42% (0.75–0.8)	0.4419
Vasopressors			
Number of patients[7], n (%)	10 (27.77%)	43 (46.74%)	0.0560
Number vasopressor days/total number of ICU days, % and 95% CI	42.33% (0.37–0.49)	47.17% (0.41–0.47)	0.5312
Extracorporeal membrane oxygenation, n (%)	2 (5.55%)	11 (11.83%)	0.5143
Outcome data			
ICU mortality, n (%)	4 (11.11%)	15 (16.13%)	0.5856

[1] Previous as well as active smoking.
[2] Chronic pulmonary disease including asthma.
[3] Chronic cardiovascular disease including hypertension.
[4] Liver disease (mild, as well as moderate to severe); Mild = cirrhosis without portal hypertension; Moderate = cirrhosis with poral hypertension; Severe = cirrhosis with portal hypertension and with a history of variceal bleeding.
[5] Diabetes type 1 and 2, with and without complications.
[6] Chronic neurologic disease including dementia.
[7] The percentage of patients requiring invasive ventilation or vasopressor therapy during their ICU stay.

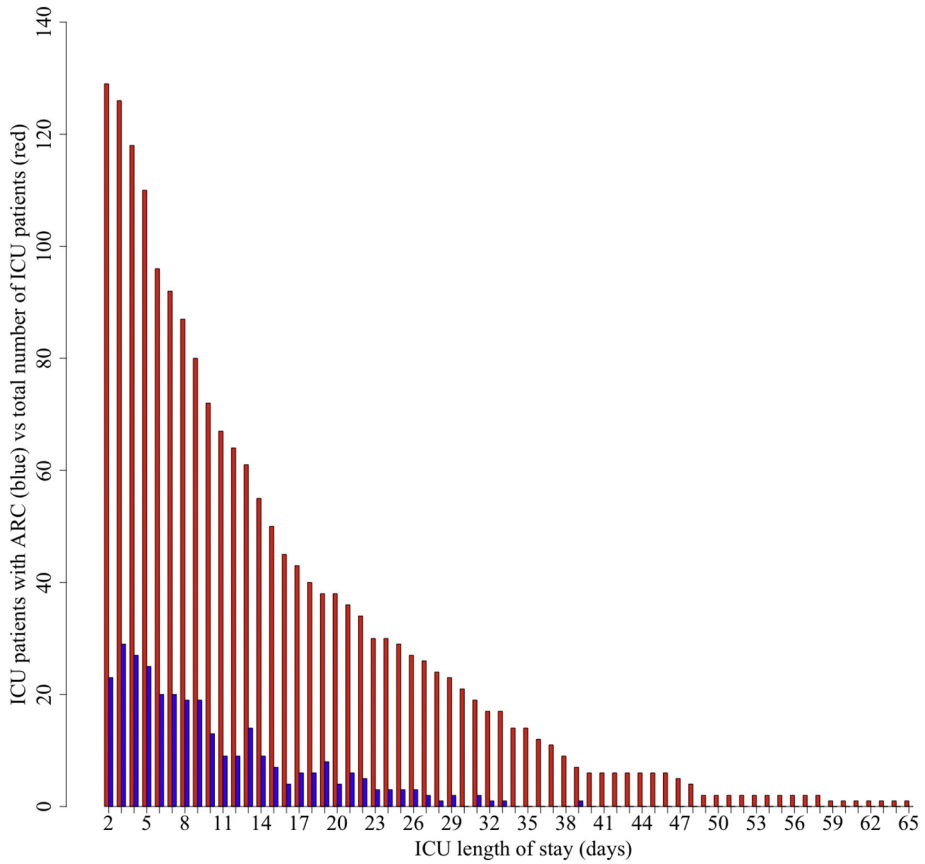

Fig. 1. Number of patients with ARC in relation to the total number of COVID-19 ICU patients per ICU admission day.
Total number of COVID-19 ICU patients (red) and number of COVID-19 ICU patients with ARC (blue) (y-axis) per day of ICU admission (x-axis).

detected ARC on average at day 28 after ICU admission. Also, younger COVID-19 patients are at increased risk of ARC [12]. Awaiting validated β-lactam and LMWH pharmacokinetic data in ICU patients with COVID-19, acknowledgement of ARC is important as it may result in undertreatment of our sickest patients. Therefore, a low threshold for measuring the CL_{CR} and, if available, therapeutic drug monitoring of renally eliminated drugs in critically ill COVID-19 patients is advisable.

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Declaration of Competing Interest

None.

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