Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Late augmented renal clearance in patients with COVID-19 in the intensive care unit. A prospective observational study

Remi Beunders, MD [a,b,c,1], Ilse H. van de Wijgert, MD [a,1], Maarten van den Berg, MD [a], Johannes G. van der Hoeven, MD PhD [a,b,c,d], Wilson F. Abdo, MD PhD [a,b,c,1], Peter Pickkers, MD PhD [a,b,c,*,1]

[a] Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
[b] Radboud Center for Infectious Diseases (RCI), Radboud University Medical Center, Nijmegen, The Netherlands
[c] Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands
[d] Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

Critically ill COVID-19 patients with respiratory failure are likely ventilated for significant periods of time and prone to show severe muscle atrophy. Therefore, plasma creatinine values may be lower [1] and renal function overestimated. Endogenous creatinine clearance is likely better to estimate glomerular filtration rate (GFR).

Augmented Renal Clearance (ARC) is an enhanced renal function which can occur during critical illness. A clearance of >130 mL/min can have a significant impact on the pharmacokinetics of drugs that are renally cleared [2]. It is unclear to what extent low plasma creatinine values in COVID-19 patients may be the consequence of muscle atrophy, or ARC. We measured endogenous creatinine clearance during different phases of the disease in critically ill COVID-19 patients with the aim to identify the occurrence of ARC.

In this prospective observational pilot study, patients diagnosed with COVID-19 admitted to the Intensive Care Unit (ICU) were eligible and enrolled. All patients or next of kin agreed with anonymous use of medical data and waste material for research purposes and the study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees. Since this is a pilot study, no formal power analysis was conducted. For the calculation of the GFR, endogenous creatinine clearance was assessed using 24-h urine collections (GFR_{ECC}) throughout ICU stay. Blood was collected in Lithium-Heparin tubes and together with the collected urine sent to the clinical chemical laboratory for determination of creatinine concentrations using hospital standards. Baseline GFR (calculated using the Modification of Diet in Renal Disease formula) and baseline plasma creatinine concentrations were collected (until a maximum of 3 months pre-admission) and used for prediction of creatinine and GFR_{ECC}. ARC was defined as GFR_{ECC} > 130 mL/min [3]. A decrease in plasma creatinine concentration was defined as lower than their baseline value. Because of the relatively limited number of patients, data are presented as median [interquartile range (IQR)]. Wilcoxon matched-pairs signed rank test was used for differences between groups. GraphPad Prism (version 5.03, California USA) was used for statistical analysis. A p-value < 0.05 (two-tailed) was considered to indicate statistical significance.

A total of 58 measurements were conducted in 24 patients, of which 6 were women (25%). Patients had a median age of 64 [56–71] years, an APACHE II score of 18 [14–24], 23 (96%) were mechanically ventilated and 10 (42%) patients developed AKI, for demographic characteristics, see Table 1. Baseline (pre-COVID) plasma creatinine concentration was 71 [63–66] μmol/L (30 [15–51] days pre-ICU), corresponding to a GFR_{MDRD} of 87 [74–104] ml/min. Following their ICU admission, 13 COVID-19 patients (54%) had a lower creatinine concentration (42 [30–49] μmol/L) compared to their baseline value. Of these 13 patients, 6 (46%) had ARC with a GFR_{ECC} of 140 [134–176] mL/min. If their baseline GFR was imputed in these patients, their plasma creatinine concentration would be 70 [56–81] μmol/L (Fig. 1A), which is not different from their baseline creatinine concentrations, indicating that creatinine concentrations are not lower due to loss of muscle mass. The time point that ARC was detected was on median [IQR] day 28 [21–42] following ICU admission. Late development of ARC was illustrated by a significant correlation between days of ICU admission and the GFR_{ECC} (normally distributed data, Pearson's $r = 0.2$, $p = 0.04$).

In our cohort with critically ill COVID-19 patients we found a high prevalence of ARC, which appeared to occur in the later phase of their ICU admission. With due consideration of the small single-center nature of study, this indicates that muscle loss may not solely contribute to low plasma creatinine concentrations in these patients. Therefore, ARC should be suspected and GFR_{ECC} measured, especially in patients with plasma creatinine concentrations that decrease below their baseline value. This is of clinical relevance, as ARC may influence the pharmacokinetics of renally excreted drugs, potentially leading to suboptimal treatment [4]. The mechanisms leading to ARC are not yet fully elucidated. However, in the better-organized ARC in bacterial sepsis patients, pro-inflammatory cytokines and increased renal blood flow in the hyperdynamic early phase of sepsis may be the driving force [2,5-8]. The occurrence of ARC in the later phases of ICU admission in critically ill COVID-19 patients may imply that the ARC is of different origin. A study that measures GFR_{ECC} serially to discover covariates that may induce ARC would be of interest. The relatively limited size of the study population signifies that confirmation of these results in a larger cohort

* Corresponding author at: Department of Intensive Care Medicine, Radboud University Medical Center, PO Box 9101, Nijmegen NL 6500 HB, The Netherlands.
E-mail address: peter.pickkers@radboudumc.nl (P. Pickkers).
[1] Shared first and last author.

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Table 1
Demographic characteristics.

Characteristics	GFR_{ECC} > 130 mL/min (n = 6)	GFR_{ECC} < 130 mL/min (n = 18)	All patients (n = 24)
Age, years	62 [59–64]	66 [57–72]	64 [56–71]
Sex			
Female	1 (20)	5 (27)	6 (25)
Male	5 (80)	13 (72)	18 (75)
Body Mass Index (kg/m^2)	27.7 [25.3–34.6]	25.4 [22.6–28.0]	25.8 [24.1–28.5]
Comorbidities			
Diabetes	0/6	5/18	5/24
Cardiovascular disease	0/6	0/18	0/24
Chronic respiratory insufficiency	0/6	0/18	0/24
COPD	0/6	1/18	1/24
Chronic renal insufficiency	0/6	1/18	1/24
Chronic dialysis	0/6	0/18	0/24
Ongoing neoplasm	0/6	0/18	0/24
Chronic haematologic malignancy	1/6	2/18	3/24
Chronic immunologic insufficiency	2/6	5/18	7/24
Chronic liver cirrhosis	0/6	0/18	0/24
APACHE II score	16 [14–25]	19 [15–24]	18 [14–24]
APACHE IV score	59 [31–80]	55 [48–66]	55 [47–67]
SOFA-score	9 [7–12]	11 [9–12]	10 [9–12]
Mechanical ventilation on day 1	6/6	17/18	23/24
Baseline plasma creatinine (μmol/L)	70 [68–79]	76 [60–96]	71 [63–88]
Baseline $eGFR_{MDRD}$ ($mL/min/1.73m^2$)	96 [74–105]	85 [73–105]	87 [74–104]
Length of stay in hospital (days)	47 [34–70]	36 [25–49]	36 [26–55]
Deceased	0/6	3/18	3/24

Data is described as median [interquartile range, n (percentage) or number of relative/total number of patients. GFR: Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; MDRD: Modification of Diet in Renal Disease.

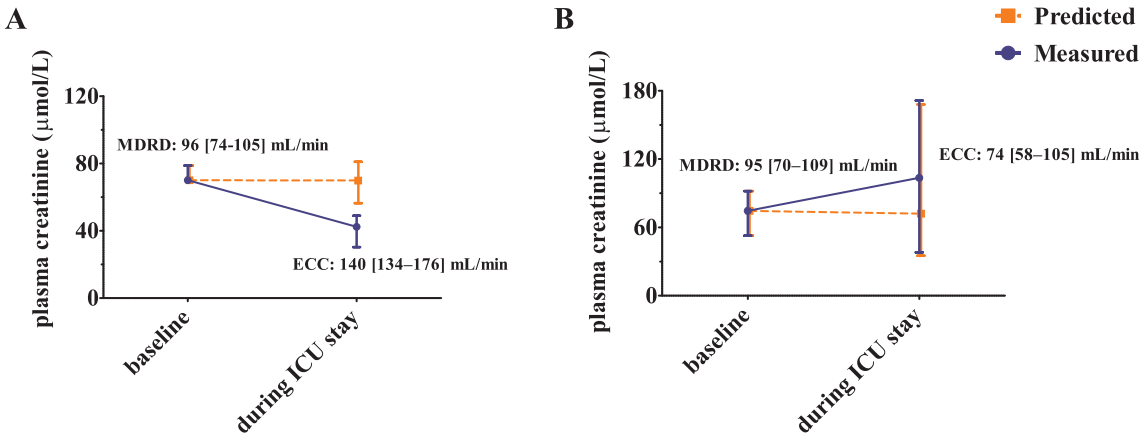

Fig. 1. Measured versus predicted plasma creatinine concentrations. Measured versus predicted plasma creatinine concentrations over time from pre-COVID baseline until the day of GFR_{ECC} measurement on the ICU. The corresponding GFR_{MDRD}/GFR_{ECC} to the plasma creatinine concentrations at the timepoints is depicted in the figures. Predicted creatinine concentrations are calculated using the baseline GFR_{MDRD} of the patients. A. In patients with Augmented Renal Clearance (GFR > 130 mL/min n = 6), measured versus predicted creatinine concentration were statistically different ($p = 0.03$). B. In patients with Normal Renal Clearance (45 < GFR < 120 mL/min, n = 8), measured versus predicted creatinine concentrations were not statistically different ($p = 0.46$). These results indicate that in patients with ARC, the augmented clearance accounts for the decrease in plasma concentrations and that creatinine concentrations are not lower due to loss of muscle mass. 10 patients had either a GFR below 45 mL/min, or between 120 and 130 mL/min and are not depicted. Baseline creatinine values were captured at 30 [15–51] days pre-ICU admission. GFR_{ECC} was conducted at day 28 [21–42] of ICU admission. Data are depicted as median and IQR and tested using a Wilcoxon matched-pairs signed rank test. GFR: Glomerular Filtration Rate; MDRD: Modification of Diet in Renal Disease; ECC: Endogenous Creatinine Clearance; IQR: Interquartile ranges.

is needed to identify possible effects of comorbidities and COVID-19 severity on the occurrence of hyperfiltration. In conclusion, ARC was diagnosed in approximately 1 out of 4 critically ill patients with COVID-19, mainly during the later phases of their disease. Especially if plasma creatinine concentrations drop below pre-COVID-19 baseline values, ARC should be suspected and excluded to prevent undertreatment of renally excreted drugs.

Ethics approval and consent to participate

The study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent. All patients or legal representatives were informed about the study details and could decline to participate.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

All authors declare to have no conflicts of interest.

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