



Case Report

COVID- 19 and Augmented Renal Clearance in Critically Ill Patients

Teresa Maria Tomasa-Irriguible^{1*}, Ana Campos-Gómez¹, José Maria Manciéo-Contreras¹, Màrius Sánchez-Satorra¹, Viridiana Philibert¹, Lara Bielsa-Berrocal¹, Yaiza Rovira-Anglès¹, Josep Roca-Antonio²

¹Intensive Care Department, Germans Trias i Pujol Hospital, Spain

²Epidemiology Department, Germans Trias i Pujol Hospital, Spain

***Corresponding author:** Teresa María Tomasa Irriguible, Intensive Care Department, Germans Trias i Pujol University Hospital, Autònoma de Barcelona University, Carretera del Canyet s/n, 08916 Badalona, Barcelona, Spain

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Abstract

Background: COVID-19 disease is accompanied by frequent thrombo-embolic episodes that increase mortality, as well as bacterial infections. Augmented renal clearance is a phenomenon that occurs frequently in critical patients and can provoke a therapeutic failure of renal elimination drugs.

Methods: Observational epidemiological study, retrospective, in the setting of Covid-19 through the analysis of blood and urine to determine the GFR. The objectives of the study were to determine ARC incidence in the critical patient with COVID-19, compare that to a group of critical non- COVID patients and analyze the concordance of the estimation Chronic Kidney Disease Epidemiology Collaboration formula and the Glomerular Filtrate Rate calculated in 24 hour urine.

Results: Eighty-two patients were included, 35 with COVID-19 and 47 without. The ARC incidence in the patients with COVID-19 was 37% and 23.4% in the non-COVID group (P=0.179). The IC mortality was similar in the COVID and non-COVID groups (17.14% vs. 23.4%). The concordance analysis between the GFR estimated by the CKD-EPI formula and that calculated through 24 hour urine illustrated that there is not a good concordance between the GFR estimated by the CKD-EPI formula and the gold standard calculated from 24 hour urine, in such a way that the CKD-EPI value sub estimates the GFR by 39% in those with ARC.

Conclusions: ARC is a very frequent occurrence in the critical patient with COVID-19 and can pass unnoticed because neither the creatinine level nor the estimation formulas detect it correctly. An excessive GFR could accompany an infra exposure to drugs designed for renal elimination such as some b-lactams and LMWH. Given that COVID-19 is a pro thrombotic disease and is also associated with infections, the 37% of COVID-19 patients could be at risk of therapeutic failure from these complications.

Keywords: Augmented renal clearance; B-lactam; Critically ill patient; Chronic kidney disease epidemiology collaboration formula; Glomerular filtrate rate; Incidence

Abbreviations: ARC: Augmented Renal Clearance; GFR: Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration Formula

Introduction

Severe Acute Coronavirus-2 Respiratory Syndrome (SARS-CoV-2) poses an emerging global threat that is exhausting the world's capacity to provide adequate medical attention. As of

27 May 2020, the disease caused by SARS-CoV-2 (COVID-19) has been responsible for more than 340,000 deaths worldwide, with 100,000 of these in the United States alone [1,2]. This disease is accompanied by frequent thromboembolic occurrences that increase its morbid mortality [3,4]. An adequate dose of anticoagulants is essential to improve prognosis in these patients. It is important to adequately dose them when renal insufficiency exists, as in those cases in which renal function is augmented. These patients can be admitted with a concomitant bacterial infection or develop infectious complications during hospital admission, and therefore an antibiotic treatment with beta-lactam, and other renal elimination antibiotics can be compromised in Augmented Renal

Clearance (ARC) situations [5-7].

ARC is a phenomenon that often occurs in critical patients and can provoke the therapeutic failure of renal elimination drugs [8]. A clear association exists between ARC and infra therapeutics of beta-lactam plasma levels [9]. ARC is defined as a creatinine clearing over 130 ml/min/1.73 m² in men and 120 ml/min/1.73 m² in women, with an ARC incidence of around 30% [10]. Patients with severe neurologic lesions, sepsis, traumatism and burns have been identified as groups at risk for ARC. The exact ARC physio-pathological mechanisms are unknown at present, as well as its causes and the magnitude of the consequences [11]. Contributing factors include an increase in temperature, cerebral lesion and the syndrome of Systemic Inflammatory Response (SIRS), factors encountered in patients with infections and traumatic sepsis, TCE, pancreatitis, autoimmune alterations, ischemia and major surgery, among others [12].

To estimate the glomerular filtration in normal clinical practice a concentration of serum creatinine is employed, or estimations centered on equations based on the creatinine level, gender, age, race, etc. However these estimations are not adequately adjusted to the case of the critical patient [13]. The GFR is the relation between the value of plasmatic creatinine and that of urinary creatinine collected in a determined volume of urine at a specified time, ranging between 2 and 24 hours [14]. The purpose of performing this epidemiological study was to determine the ARC incidence in the critically ill COVID-19 patient and to analyze the concordance of GFR estimation by the CKD-EPI formula and the GFR calculated in 24hour urine.

Material and Methods

Study Design

Observational epidemiological study, retrospective, single center in the setting of critically ill COVID-19 patients, to determine the incidence of patients with ARC and become familiar with its characteristics.

Objectives

1) To determine the incidence of ARC during the COVID-19 pandemic; 2) To compare the characteristics of the ARC and non-ARC groups; 3) To analyze the concordance between the calculated GFR and the estimated GFR using the CKI-EPI formula.

Inclusion Criteria

All those patients over 18 years of age admitted to the Intensive Care Department with COVID-19 during the pandemic.

And a previous series of non-COVID patients recorded during the same period of time (March to April), registered last year (2019).

Exclusion Criteria

Anuric patients; patients undergoing vesical lavage; patients without urinary catheterization; and patients under Renal Replacement Therapy (RRT), continuous or intermittent.

Ethical Approval

The study was approved by the ethical committee. In order to be able to carry out the data study, the anonymized database prepared by the hospital's information systems department was requested. As it was a retrospective study of routine data from analytical samples taken in anonymized form, and there was no prospective follow-up at hospital discharge, the Center's Clinical Research Ethics Committee agreed on a favorable opinion considered the need not to request informed consent afterwards.

Methods

In the ICU we routinely perform a complete analysis with a nutritional profile and 24-hour urine once a week. The ARC diagnosis is made based on a diagnostic test of common clinical practice such as the GFR determination through creatinine clearance. The necessary blood and urine analysis for the study are routine tests that follow the standard of care in the management of this type of patient and respect established ethical norms. In this way, as we normally do in normal clinical practice, COVID-19 patients had 24-hour urine collected to calculate GFR. GFR was determined based on a blood and urine sample and calculated through the relation between the creatinine found in urine with respect to plasma, in a volume of urine collected at an established time and adjusted to the corporal surface.

Formula

$$= \frac{C_o \times V_{\text{minute}} \times C_x}{C_p}$$

Where;

Cx corresponds to the creatinine clearance

Co corresponds to the concentration of creatinine in urine

Cp corresponds to the concentration of creatinine substance in plasma

Vminute corresponds to the volume of urine collected in 24 hours expressed in mL/min

$$\begin{aligned}
 & \text{Volume of urine (collected in 24 hours) } V_{\text{minute}} \\
 & = \frac{\text{-----}}{1440 \text{ min}} \\
 & C_o \times V_{\text{minute}} \times \text{ASC } C_x \\
 & = \frac{\text{-----}}{C_p \times 1.73 \text{ m}^2}
 \end{aligned}$$

The result of Creatinine Clearance (Cx) is adjusted to the Body Surface Area (BSA) of the patient by 1.73 m².

Study Variables

ARC is considered when GFR is over 130 mL/min/1.73m² and non- ARC when the GFR is maintained between 90-130 mL/min/1.73m². The patients with GFR <90 mL/min/1.73m² were not comparatively analyzed with the other two groups, ARC and non-ARC, because of being a group of worse prognosis. Regarding the quantitative variables, we recorded: Age, creatinine in both blood and urine, urine volume in 24 hours, stay in the ICU and in the hospital. Regarding the qualitative values, we recorded: Gender, mortality in the ICU and in the hospital.

Statistical Analysis

Descriptive Analysis: The qualitative variables are described through their frequency distribution and their IC 95%. The normality of quantitative variables is analyzed by means of the Shapiro-Wilk test. The normal quantitative variables are described through their mean and IC 95% and the quantitative ones that did not follow a normal distribution through their mean and IC 95%.

Univariate Analysis: The qualitative variables were compared by Student’s t test or by the Mann- Whitney u test according to

whether they followed a normal distribution or not, respectively. A type 1 error below 0.05 (p< 0.05) was considered statistically significant. For the concordance analysis the tests of Passing-Bablok and Bland Alman were carried out.

Results

The study included 82 patients, 35 COVID-19 patients admitted in the ICU during the months of March and April 2020 and 47 non-COVID ones admitted in the ICU during the same time period in 2019. These had a median age of 58.8 (18-83) and were predominantly males (80.5%). The incidence of chronic renal insufficiency was 10.98%. Acute kidney injury was recorded in 55.56%. The median CKD-EPI estimated by the laboratory was 95 (10,167) mL/min/1.73 m². The median GFR calculated from 24hour urine was 96.5 (0.8, 285) mL/min/1.73 m². Of these patients, 47.56% had a GFR < 90 mL/min/1.73 m², 23.17% had a GFR between 90-130 mL/min/1.73 m² and 29.27% had GFR > 130 mL/min/1.73 m². The need for mechanical ventilation was 90.12% and 7 (8.54%) required Extracorporeal Membrane Oxygenation (ECMO). The median ICU stay was 25 (2- 78) days. Mortality in the sample occurred in 17 patients (20.73%).

The comparative analysis between the COVID-19 patients and the non-COVID ones only showed differences in gender, with more men in the COVID-19 group. We found no differences in the remaining variable analyzed: Not in age, GFR, ARC, CKD, AKI, need of MV, ECMO, nor in mortality (Table 1). On one hand, the incidence of ARC in patients with COVID-19 was 39.13% and 25.53% in the non-COVID group. One the other hand, the incidence of GFR < 90 mL/min/1,73m² in patients with COVID-19 was 36.96%, and 55.32% for the non-COVID group, that was not statistically significant either. Mortality in the ICU was also similar between the groups with COVID-19 and those without, being 17.14% vs. 23.4%.

	Non-COVID [n 47]	COVID-19 [n 35]	P value	OR (IC 95%)	P value
Age [median (min-max)]	57 (18-83)	59 (38-71)	0,750	1,01 (0,975-1,05)	0,613
Male Sex [n (%)]	34 (72.34)	32 (91.42)	0,061	4.08 (1.18-19)	0.041
GFR [median (min-max)]	85,86 (3,45-284,59)	111,80 (0,81-204,33)			0,646
GFR (3 groups):					0.195
GFR < 90 [n (%)]	26 (55.32%)	17 (36.96%)			
GFR 90-130 [n (%)]	9 (19.15%)	11 (23.91%)			
GFR > 130 [n (%)]	12 (25.53%)	18 (39.13%)			
Urine creatinin [median (min-max)]	50 (16-150)	54 (17-156)	0.192		
Urine creatinin [median (min-max)]	0.87 (0.26-4.92)	0.78 (0.32-5.52)	0.775		

CKD-EPI [median (min-max)]	94 (11-167)	99 (10-143)	0.792		
CKD [n (%)]	4 (8.51%)	5 (14.29%)	0.638	1.79 (0.439-7.77)	0.413
AKI [n (%)]	25 (53.19%)	20 (58.82%)	0.782	1.26 (0.517-3.1)	0.615
MV [n (%)]	38 (82.61%)	35 (100%)			0.026
ECMO [n (%)]	5 (10.64%)	2 (5.71%)	0.697	0.509 (0.07-0.44)	0.437
Mortality [n (%)]	11 (23.4%)	6 (17.14%)	0.677	0.677 (0.211-2)	0.491

GFR: Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration Formula; ARC: Augmented Renal Clearance; CKD: Chronic Renal Disease; AKI: Acute Kidney Injury; MV: Mechanical Ventilation; ECMO: Extracorporeal Membrane Oxygenation

Table 1: Comparative analysis between COVID patients and non-COVID ones.

Concordance Analysis: The concordance between the GFR estimated by the CKD-EPI formula and that calculated through 24hour urine brought to light that there is not a good concordance between the GFR. Only when the values are below 100 mL/min is an acceptable concordance found, while when the CKD-EPI is over 100 the concordance is poor, and if the CKD-EPI surpasses 150-175 mL/min there is none. In such a fashion the CKD-EPI value underestimates GFR by 39% (Figures 1 and 2).

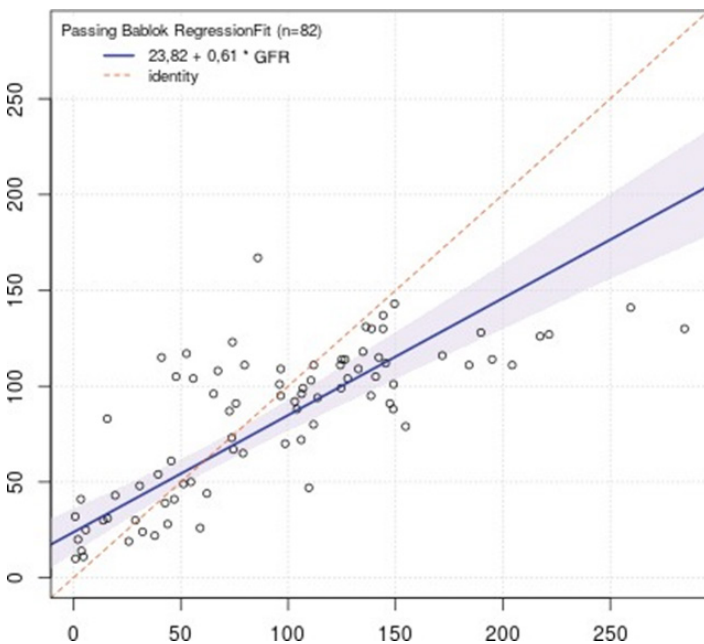


Figure 1: Concordance analysis: Bland-Altman Agreement.

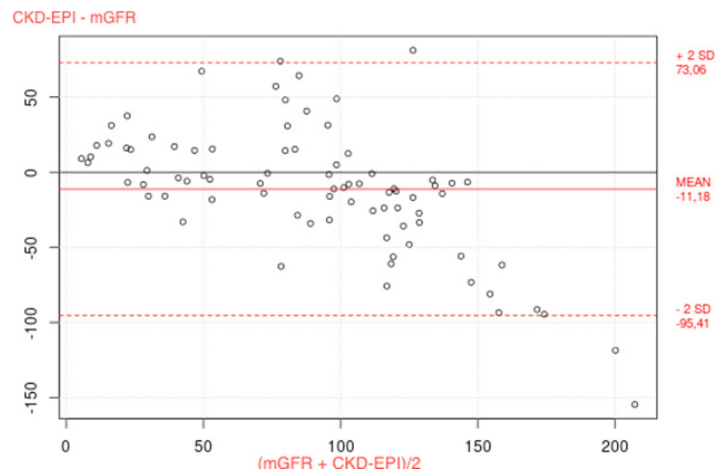


Figure 2: Concordance analysis: Passing Bablock Regression line.

Discussion

Recent studies of COVID 19 warn of a sizeable proportion of renal failure in these types of patients and highlight the well-known fact that when this occurs in a critical patient the prognosis worsens [15]. Nevertheless no study published to date mentions the opposite situation, that in which the critically ill patient has an Augmented Glomerular Filtration (ARC) and can therefore be compromised in the effectiveness of the drugs administered. This study highlights that ARC is a very frequent occurrence in COVID-19 patients, with an incidence of 39%. This article demonstrates the incidence of augmented renal clearance in critically ill patients with COVID-19 infection and compares it to the incidence of ARC in a similar group of critically ill patients

without COVID-19 enrolled during the same months time period in 2019. ARC occurs in a substantial portion of critically ill COVID-19 patients, but not at a significantly higher rate than the non-COVID-19 patients.

Since the majority of COVID-19 literature focuses on acute kidney injury and disregards ARC and its impact on medication (antibiotics, anticoagulants, anti-arrhythmics, etc.) dosing the findings demonstrated here could impact COVID-19 critical care practice. Thus, the premise and findings in this manuscript advance the critical care field.

The main problem stems from the diagnosis of these patients with ARC, given that the concentration of plasmatic creatinine is apparently normal and usually passes unnoticed. Furthermore, the formulas that estimate glomerular filtration (CKD-EPI, MDRD, CG), do not have a good concordance with the calculated GFR, and in the case of ARC are not validated to do so [16-18]. In this study we have been able to determine that there is no concordance between the GFR estimated by the CKD-EPI formula and GFR calculated through urine sample.

This fact is of great importance in that it can pass unnoticed and COVID-19 is a disease that is in part associated with other co-infections, and many of the beta- lactams administered in conventional doses may not be enough to maintain the Minimum Inhibitory Concentration (MIC), the lowest concentration (in $\mu\text{g} / \text{ml}$) of an antibiotic that inhibits the growth of a certain bacterial strain [19]. Additionally, COVID-19 is associated with multiple thrombo-embolic episodes that are generally treated with LMWH, and in patients with ARC the administration of conventional doses could provide a poor prophylaxis or insufficient treatment. Compared to non-ARC's, both DVT and PE were higher in ARC (44% vs. 31%) and (33% vs. 10%, $P = 0.025$), respectively. We also analysed 2 patients with DVT plus ARC who were receiving 150 mg daily of enoxaparin (1.5 mg/kg/day) and the antiXa activity was 0.27 and 0.28 UI/mL, respectively, when the effective range comprises 0.4-1.1 UI/mL [20].

Limitations

As this is an observational study the results obtained should be viewed with caution, given that this type of study is unable to control potentially confusing variables. Nonetheless the results observed highlight the relevance of this phenomenon in COVID-19 patients and warn of its potential consequences.

Conclusions

This study addresses a clinically novel problem, as compared to acute kidney injury; augmented renal clearance in ICU patients is a comparatively understudied problem. This study raises two

very intriguing and exciting questions: whether COVID-19 related critical illness is associated with ARC, and if the estimates routine used (CKD-EPI formula) can correctly measure ARC vs. the gold standard renal creatinine clearance calculation based on 24 Hr urine collection. The implications of ARC are very significant (facilitated drug clearance for several key drugs beta lactams, LMWH) and may have direct relationship with morbidities observed in COVID and in critical illness in general. This study demonstrates that ARC is a very frequent occurrence in the critical patient with COVID-19 and can pass unnoticed because neither the creatinine level nor the estimation formulas detect it correctly. An excessive GFR could accompany an infra exposure to drugs designed for renal elimination such as some b- lactams and LMWH. Given that COVID-19 is a pro thrombotic disease and is also associated with infections, the 37% of COVID-19 patients could be at risk of therapeutic failure from these complications.

Disclosures

The author(s) read and approved the final manuscript. Name: Ana Campos-Gómez, Ph.D, MD.

Contribution: This author collected the data and prepared the manuscript. Name: José M. Mancíño-Contreras, Ph.D, MD.

Contribution: This author collected the data and prepared the manuscript. Name: Màrius Sánchez-Satorra, MD.

Contribution: This author helped design the study and prepared the manuscript. Name: Viridiana Philibert, MD.

Contribution: This author helped design the study and prepared the manuscript. Name: Lara Bielsa-Berrocal, MD.

Contribution: This author helped design the study and prepared the manuscript. Name: Yaiza Rovira-Anglès, MD.

Contribution: This author helped design the study and prepared the manuscript. Name: Josep Roca-Antonio, MD, PhD

Contribution: This author helped design the study and analysed the data.

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Conflicts of Interest

The authors declare no competing interests.

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