Changes in renal function increase the need for advanced ventilatory support and increase the risk of mortality in critically ill patients with COVID-19

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Abstract. In addition to respiratory failure, another important outcome presented by patients hospitalized with coronavirus disease 2019 (COVID-19) is renal failure, which is related to increased severity of infection and a greater risk of mortality. Severity is often represented by the need for respiratory and/or life support, which can range from oxygen therapy to invasive mechanical ventilation. This study aimed to determine the association between the degree of renal and inflammatory impairment in patients with the need for advanced respiratory support and mortality. Included in the present study were 79 critically ill patients with COVID-19 on different days, who required a nasal cannula and/or orotracheal intubation. Data from laboratory tests, arterial blood gases and information on their clinical evolution were collected. The results obtained showed that the biochemical markers of renal function, as well as the inflammatory markers and the partial pressure of carbon dioxide, were significantly increased in patients who succumbed to the infection. Similarly, these markers were higher amongst patients who required increased respiratory assistance.

Introduction

The etiological agent of the new coronavirus disease is the SARS-CoV-2 virus, which has a high affinity for the angiotensin-2 converting enzyme (ACE2). Since this protein is abundantly expressed in the pulmonary epithelium, it facilitates colonization of the respiratory system, which is the primary system affected by the disease (1).

In addition to respiratory failure, 30% of hospitalized patients experience renal failure that usually occurs 7 to 14 days after admission. This involvement is related to a greater severity of infection, and an increased risk of mortality (2). Severity is often represented by the degree of respiratory and life support required, which can range from oxygen therapy through a nasal cannula and non-rebreather mask, to invasive mechanical ventilation, such as orotracheal intubation and tracheostomy (3). The involvement of these systems comes from direct and indirect injuries that generate a local inflammatory response, in addition to the cytokine storm that will have already occurred in critically ill patients affected by the disease (4).

To the best of our knowledge, there are no studies that have assessed the association between the biochemical parameters of renal function and the need for respiratory support and risk of mortality in patients with severe COVID. Therefore, this study aims to relate the degree of renal and inflammatory impairment with mortality, and the increased need for respiratory support.

Patients and methods

Ethical considerations. The Human Research Ethics Committee of Rio Grande do Norte State University, (Mossoró Brazil), approved the study protocol (approval no. CAAE: 36510420.6.0000.5294).

Study population. Medical records of severe COVID-19 patients were analyzed. All of the patients had a confirmed diagnosis of the viral infection by reverse transcription-PCR, and had been admitted to the Intensive Care Unit of Hospital Regional Tarcisio de Vasconcelos Maia (Mossoró, Brazil) between April and December 2020.

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Inclusion and exclusion criteria. The present study was an observational and cross-sectional study. A total of 79 severe COVID-19 patients were included (median age, 60.5 years; age range, 18-100; female/male, 25/54). The study included patients on the second day of nasal cannula use, on the second day after orotracheal intubation, and the eighth day after intubation, as these represent notably different instances of care. Patients in the prone position on the day of analysis and patients under the age of 18 years were excluded.

Data collection. Information from patients' medical records were collected. Data from laboratory tests [hemogram, alanine transferase (ALT), aspartate transferase (AST), urea, creatinine, lactic dehydrogenase (LDH), and quantitative C-reactive protein (CRP)], arterial blood gases [partial pressure of oxygen (PaO_2) and CO_2 (PaCO2)], as well as information on clinical evolution were all obtained. For evaluation purposes, the traditional reference values of the analyzed biomarkers were considered (5-8).

A leukogram was performed using a semi-automated method (9) on a BS-3000 Plus (Mindray); ALT, AST, urea, creatinine and LDH levels were measured using the Kinetic method (10) on a BS-380 (Mindray), and the CRP levels were determined using the Latex Agglutination method on Titertek Multiskan (MCC Flow Labs Inc.) (11). Arterial blood gases were measured using *Stat Profile Prime*® (Novo Biomedical).

To determine whether patients exhibited acute kidney injure (AKI), the following diagnostic criteria were used: Creatinine levels, ≥0.3 mg/dl (>26.5 μmol/l) observed within 48 h, an increase in creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or a urine volume <0.5 ml/kg/h for 6 h (12).

To consider acute kidney failure, the following diagnostic criteria were used: A threefold increase in serum creatinine levels or levels ≥350 μmol/l with an acute rise of 44 μmol/l, a decrease in glomerular filtration >75%, a urine output <0.5 ml/kg/h for over 24 h or anuria for over 12 h (13).

For evaluation purposes, two distinct aspects were considered in the patients: Mortality in the ICU (death and discharge outcomes), and the need for respiratory assistance (use of nasal cannula and/or invasive mechanical ventilation, the latter covering both patients on the second day of intubation and those on the eighth day).

Statistical analysis. To determine the distribution of the variables, a Kolmogorov-Smirnov test was performed, analyzing the asymmetry and kurtosis, which ideally should be between-2 and +2, the Gaussian curve shape, and the similarity between the mean and the median. For comparison of the data, the data were assessed based on two factors: mortality vs. discharge, and the need for use of a nasal catheter or invasive mechanical ventilation. Normally distributed data were compared using an independent samples t-test and data showing a skewed distribution were compared using the non-parametric Mann-Whitney U test. Data analyzed using a Student's t-test is presented as the mean ± SD or SEM, and data analyzed using a Mann-Whitney U test is presented as the median (IQR). $P<0.05$ was considered to indicate a statistically significant difference.

Results

A total of 79 critically ill patients affected by COVID-19 were evaluated: 29 Patients on the 2nd day of nasal oxygen cannula use, 37 on the 2nd day after orotracheal intubation, and 13 on the 8th day after intubation. There were 25 female patients (31.6%; median age, 64.0 years; age range, 18-90 years) and 54 male (68.4%; median age, 59.0 years; age range, 23-100 years), with a combined median age of 60.5 years and a combined age range of 18-100. The mean stay in the ICU was 13.3 days, where 35 patients were discharged (44%) and 44 succumbed to the disease (56%). The most-reported commonly comorbidity amongst patients was Systemic Arterial Hypertension (55%). A total of 79.5% of patients used vasoactive drugs, and 77% used sedative drugs. Of the cohort, 16 patients (20%) required hemodialysis.

The biochemical markers of renal function (urea and creatinine), as well as the inflammatory markers (CRP, LDH and leukocyte counts), and the $PaCO_2$ were significantly increased in patients who succumbed to the disease (Table I). Similarly, these markers (except for LDH) were also higher amongst patients who required more invasive respiratory assistance (Table II).

Discussion

The results of the present study showed that urea, creatinine, CRP, leukocyte counts and $PaCO_2$ were increased in patients who required increased respiratory assistance as well as in those who died. Lack of more sensitive blood markers, such as N-Gal, cystatin-C and retinol-binding protein was a limitation of this study, but markers most used in Intensive Care Units were assessed, and thus the results provided are more clinically relevant.

Once the virus binds to the ACE2 receptor, the body will fight the invading microorganism, generating a cytokine storm in the process (14). The cytokine storm is a potentially life-threatening systemic inflammatory syndrome involving elevated levels of circulating cytokines and immune-cell hyperactivation. In short, a cytokine storm involves an immune response that causes collateral damage, which may be greater than the immediate benefit of the immune response (15). However, when the inflammatory response is uncompensated, the amount of blood that would normally be directed to the glomeruli is below the normal level. Blood retention can trigger another problem: The formation of a thrombus, which is the indirect means by which SARS-CoV-2 reaches the kidneys (14,16).

Acute lung injury and AKI are complications frequently encountered in critically ill patients. Damage to the lung and/or kidneys occurs in clinical situations similar to that observed during systemic inflammatory response syndrome, shock and in the evolution of multiple organ dysfunction (17). The cytokine storm and the direct lesions present in COVID-19 generate these lesions, and the complications appear simultaneously, and a patient with renal failure is more likely to need more advanced ventilatory support (18).

Regarding kidney injury and death, there is a significantly higher in-hospital mortality rate in patients with kidney abnormalities, including elevated baseline serum creatinine, proteinuria and hematuria levels, as well as acute kidney failure (16). In addition, patients with elevated baseline serum creatinine levels have higher white blood cell counts and lower lymphocyte and platelet counts (19).

Table I. Comparison of laboratory and blood gas data in accordance with the clinical outcomes.

Analyzed parameter (Reference value)	Clinical outcome: Death, n=44, median, IQR/mean ± SD	Clinical outcome: Discharged, n=35, median, IQR/mean ± SD	P-value
Kidney function			
Creatinine (0.7-1.2 mg/dl)	1.33, 1.81[d]	0.80, 0.5[d]	0.002[c]
Urea (15-45 mg/dl)	88.00, 97[d]	54.00, 37[d]	0.003[c]
Liver function			
Aspartate transferase (12-46 U/l)	57.00, 43[d]	42.00, 34[d]	0.105
Alanine transferase (3-50 U/l)	37.00, 26[d]	44.00, 49[d]	0.082
Gasometric data			
PaO_2 (60-100 mmHg)	79.00, 36.2[d]	72.10, 28.07[d]	0.339
$PaCO_2$ (35-45 mmHg)	51.84±18.94[e]	38.46±12.04[e]	0.001[c]
Inflammatory markers			
Lactate dehydrogenase (230-460 U/l)	1,077.91±367.20[e]	929.20±388.44[e]	0.035[a]
C-reactive protein (<6 mg/l)	95.19±44.07[e]	72.95±44.2[e]	0.006[b]
Lymphocyte (21-35%)	12.00, 7.00[d]	10.00, 9.00[d]	0.768
Leukocytes (5,000-10,000/mm^3)	12,700.00, 8,500[d]	11,050.00, 5,700[d]	0.026[a]
Platelet/lymphocyte (≤2.98)	140.87, 134.40[d]	184.83, 213.25[d]	0.070
Neutrophils/lymphocytes (≤6.63)	8.71, 5.21[d]	9.54, 6.78[d]	0.756

[a]P≤0.05, [b]P≤0.01, [c]P≤0.001. [d]Median, IQR, compared using a Mann-Whitney U test; [e]Mean ± SD, compared using an unpaired Student's t-test.; Pa, partial pressure.

Table II. Comparison of laboratory and blood gas data in accordance with the need for respiratory support.

Analyzed parameter (Reference value)	Respiratory support: Mechanical ventilation, n=50, median, IQR/mean ± SD[e]	Respiratory support: Nasal cannula, n=29, median[d]/mean[e]; IQR[d]/±SD[e]	P-value
Kidney function			
Creatinine (0.7-1.2 mg/dl)	1.27, 1.7[d]	0.79, 0.39[d]	0.006[c]
Urea (15-45 mg/dl)	82.00, 103.00[d]	62.00, 41.00[d]	0.024[a]
Liver function			
Aspartate transferase (12-46 U/l)	43.00, 45.00[d]	57.00, 24[d]	0.664
Alanine transferase (3-50 U/l)	37.00, 34.00[d]	43.00, 38[d]	0.214
Gasometric data			
PaO_2 (60-100 mmHg)	74.50, 30.4[d]	71.75, 41.25[d]	0.580
$PaCO_2$ (35-45 mmHg)	52.16±17.05[e]	31.76±7.66	0.000[c]
Inflammatory markers			
LDH (230-460 U/l)	1,010.68±420.00[e]	981.82±311.02[e]	0.415
C-reactive protein (<6 mg/l)	94.49±45.32[e]	63.77±38.38[e]	0.004[b]
Lymphocyte (21-35%)	10.50, 7[d]	14.50, 10.5[d]	0.120
Leukocytes (5,000-10,000/mm^3)	12,850.00, 5,650.00[d]	9,600.00, 7,125.00[d]	0.013[a]
Platelet/lymphocyte (≤2.98)	141.71, 131.90[d]	186.35, 152.13[d]	0.162
Neutrophils/lymphocytes (≤6.63)	9.54, 5.84[d]	6.90, 5.63[d]	0.117

[a]P≤0.05, [b]P≤0.01, [c]P≤0.001. [d]Median, IQR, compared using a Mann-Whitney U test; [e]Mean ± SD, compared using an unpaired Student's t-test.; Pa, partial pressure.

The incidence of AKI is significantly higher in patients with elevated baseline serum creatinine levels than in patients with normal baseline values (19). The mentioned alterations contribute to a worse prognosis and higher mortality in patients with AKI, showing the relationship between kidney damage and disease severity (20).

Other factors that may contribute to the worsening of renal function are pre-existing diseases, such as systemic arterial hypertension and diabetes mellitus, which lead to renal vascular injury and consequent lesions. Cardiovascular changes also contribute to the patient's course of respiratory failure, the need for mechanical ventilation and the development of renal complications due to low perfusion in other organs and the use of nephrotoxic drugs (16).

In conclusion, patients who are at greater risk of AKI may require more intensive care, as they present with an increased need for ventilatory support and increased risk of mortality in the ICU. COVID-19 is a complex disease that requires attention and treatment of several bodily systems, in addition to the respiratory system.

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Availability of data and materials

The datasets generated and/or analyzed during the present study are not publicly available due to privacy requirements of the inpatients data, but are available from the corresponding author on reasonable request.

Authors' contributions

NMDM was involved in the conception of the study, data acquisition and analysis, and drafting of the manuscript. LCCDML, VDDA and MFDA were involved in data acquisition and analysis, and drafting the manuscript. EGCDN, JVF, CMB and TAADMF analyzed and interpretated the data. All authors read and approved the final manuscript. NMDM and VDDA confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was analyzed and approved by the Human Research Ethics Committee from Rio Grande do Norte State University (Mossoró, Brazil; approval no. CAAE: 36510420.6.0000.5294).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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