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COVID-19 and kidney: role of SARS-CoV-2 infection in the induction of renal damage

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Abstract. – OBJECTIVE: SARS-CoV-2 causes acute respiratory disease, interstitial and alveolar pneumonia, and involves numerous organs and systems such as the kidney, heart, digestive tract, blood, and nervous system. We aimed to evaluate the incidence of renal manifestations in patients diagnosed with COVID-19 infection.

PATIENTS AND METHODS: We performed a monocentric, cross-sectional, observational study, conducted on 114 patients with SARS-CoV-2. Clinical and laboratory parameters [renal function, serum electrolytes, inflammatory state, blood gas analysis, Interleukin 6 (IL-6) and urinalysis] were evaluated. The same values were checked out after two months (T1), however after negativization.

RESULTS: We enrolled 114 patients (59 males) with a mean age of 63.8 ± 13.9 years. We found hematuria in 48 patients (55.8%), proteinuria in 33 patients (38.4%), leukocyturia in 61 patients (70.9%), acute kidney injury (AKI) in 28 patients (24.6%), AKI in chronic kidney disease (CKD) in 24 patients (21.1%). Moreover, we found a significant increase of inflammatory indexes as C Reactive Protein (CRP), lactic dehydrogenase (LDH), alpha 1 and alpha 2 globulins with a subsequent reduction at T1 ($p = 0.016$, $p < 0.001$, $p = 0.005$, $p = 0.007$; respectively). Hemoglobin and erythrocyte values significantly decreased ($p < 0.001$, $p = 0.003$, respectively), and we found lymphopenia ($p < 0.001$). Also, we found elevated levels of the D-Dimer ($p < 0.001$) and a significant increase in the International Normalized Ratio (INR) ($p = 0.038$). We also showed a significant improvement after negativization in oxygen partial pressure ($p = 0.001$) and oxygen saturation ($p < 0.001$) and a significant increase in pH ($p = 0.018$) and bicarbonate concentration ($p = 0.042$). Moreover, we found a significant increase in IL-6 ($p = 0.004$). Also, we reported mild hyponatremia and hypokalemia with subsequent significant recovery ($p < 0.001$, $p < 0.001$, respectively) and mild hypochloremia with a recovery to the limits of statistical significance ($p = 0.053$). At the entrance, we found an increase in serum glucose with a significant reduction during recovery ($p < 0.001$).

CONCLUSIONS: The prevalence of AKI and/or CKD and/or abnormal urinalysis in patients diagnosed with COVID-19 on admission seems to be high and appears as a negative prognostic factor. Urinalysis appears to be very useful in unveiling the potential kidney impairment of COVID-19 patients; therefore, urinalysis could be used to reflect and predict the disease severity. We also recommend a careful evaluation of metabolic alterations, inflammatory states, and electrolytic disorders in COVID-19 patients.

Key Words:
COVID-19, Renal damage, SARS-CoV-2 infection, Chronic kidney disease, Inflammation.

Abbreviations

Angiotensin-converting enzyme 2 (ACE-2), acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), chronic kidney disease (CKD), Interleukin 1βeta (IL-1β), Interleukin 1 Receptor Antagonist (IL-1Ra), Fibroblast

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Growth Factor (FGF2), Granulocyte Colony-Stimulating Factor (G-CSF), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Interferon gamma (IFNγ), Human Interferon Inducible Protein 10 (IP10), Monocyte Chemoattractant Protein-1 (MCP1), Macrophage Inflammatory Proteins (MIP)1αlfa, MIP1β, Platelet Derived Growth Factor subunit B (PDGFB), Tumor Necrosis Factor (TNF)-α, Vascular Endothelial Growth Factor A (VEGFA), C-X-C Motif Chemokine Ligand 10 (CXCL10), C-C Motif Chemokine Ligand 2 (CCL2), estimated Glomerular Filtration Rate (eGFR), lactic dehydrogenase (LDH), International Normalized Ratio (INR), C-reactive protein (CRP), prothrombin time (PT) activated partial thromboplastin time (aPTT) neutrophil-lymphocyte ratio (NLR), modification of diet in renal disease formula (MDRD).

Introduction

The SARS-CoV-2 virus has caused a worldwide pandemic with a major impact on healthcare systems and economies[1]. Although COVID-19 presents primarily as a lower respiratory tract infection, increasing data suggest[1-3] multiorgan involvement in infected patients. This systemic involvement is postulated to be mainly related to the SARS-CoV-2 virus binding on ACE-2 receptors, located on several different human cells[2-3]. In fact, coronaviruses induce cell and tissue damage both by direct cytopathic effect, being able to induce both apoptosis and cell lysis, and by immune-mediated mechanisms. Following the entry into the host cell, ACE-2 is down-regulated, determining an overproduction of angiotensin II by ACE, which stimulates the receptors (type 1a), causing an increase in pulmonary vascular permeability, enhancing the disease at this level[4,5]. The immune response, essential for the resolution of SARS-CoV-2 infection, can potentiate the severity of the disease, in fact, the progression to ARDS is preceded by an increase in inflammatory chemokines and cytokines, in particular: IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, FGF2, G-CSF, GM-CSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNF-α, VEGFA, CXCL10, and CCL2. In fact, the inflammatory response to infection consists mainly of the massive release of the long series of inflammatory cytokines, causing a phenomenon called "cytokine storm", which can lead to the main complications of the infection up to the exitus. The SARS-CoV-2 infection, determining the onset of the COVID-19 pathology, is responsible for the induction of a systemic inflammatory state causing, primarily, lung pathology but potentially responsible for a large number of manifestations in other organs presenting receptors for the microorganism (ACE-2), including the kidney[1,6]. However, the exact mechanism of kidney involvement remains unclear: sepsis-related cytokine storm[7] or direct cellular injury induced by the virus[8]. The human ACE-2 receptor has been identified as the functional receptor for SARS-CoV-2 and is highly expressed in kidneys[9,10], therefore, the kidney might be a target of SARS-CoV-2.

We aimed to evaluate the incidence of renal manifestations in patients diagnosed with COVID-19 infection, such as AKI, CKD, proteinuria, hematuria, and leukocyturia.

Patients and Methods

Study Design and Subjects

We performed a cross-sectional observational, single-center study on 114 patients aged at least 18 years with diagnosis of SARS-CoV-2 with positive test by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) at the moment of hospital admission at the University Hospital "Policlinico Umberto I" in Rome, Sapienza University of Rome, between March 2020 and June 2020. We evaluated renal function, serum electrolytes, inflammatory state, blood gas analysis, serum IL-6, and urinalysis at baseline (T0) and after about 2 months (T1), however after negativization from SARS-CoV-2. The study protocol was approved by the Clinical Research Ethics Committee of Sapienza, University of Rome, Italy, and we obtained the written consent of each patient enrolled.

Laboratory Measurements

We have performed the following tests with standard technique: serum glucose (mmol/L), creatinine (mg/dL), serum nitrogen (mg/dL), serum electrolytes (mEq/L), LDH (mg/dL), serum protidogram, INR, CRP (μg/L), PT (sec), aPTT (sec), D-Dimer (ng/ml), hemoglobin (g/dL), white blood cells (10^3/mL). We also evaluated serum IL-6, blood gas analysis, urinalysis, and NLR. The eGFR was evaluated according to the MDRD. We evaluated patients with a positive SARS-CoV-2 test by RT-PCR at the moment of hospital admission. The negativization of SARS-CoV-2 testing was determined with at least two consecutive RT-PCR negative results[8].

Statistical Analysis

Data management and analysis were performed using SPSS® Statistics 22.0 for Windows®

software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk method for normal distributions was used to test the normality of variables. Continuous variables were expressed as average ± standard deviation; categorical variables were expressed as percentages. The hypothesis testing was performed through univariate analysis. The following tests were used when appropriate: Chi-squared test (χ^2), *t*-student, analysis of variance (ANOVA), and Bivariate Correlation (Pearson's r); values of $p < 0.05$ were considered statistically significant.

Results

Patients' characteristics are shown in Table I. A total of 114 patients (59 males), with a mean age of 63.8 ± 13.9 years, with a confirmed diagnosis of COVID-19 infection, were consecutively included. In our study, we showed hematuria in 48 patients (55.8%), proteinuria in 33 patients (38.4%), and leukocyturia in 61 patients (70.9%). We found AKI in 28 patients (24.6%), AKI on CKD in 24 patients (21.1%) with significant alteration of serum creatinine, nitrogen, and eGFR ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Moreover, we found a significant increase of inflammatory indices as CRP, LDH, alpha 1 and alpha 2 globulins with a subsequent reduction ($p = 0.016$, $p < 0.001$, $p = 0.005$, $p = 0.007$, respectively). Hemoglobin and erythrocyte values significantly decreased ($p < 0.001$, $p = 0.003$, respectively), and we found a lymphopenia, both in absolute and percentage value, ($p < 0.001$, $p < 0.001$, respectively), observable also at T1 ($p < 0.001$, $p = 0.001$, respectively). We found, also, elevated levels of D-Dimer both at T0 ($p < 0.001$) and at T1 ($p < 0.001$), and a significant increase of INR ($p = 0.038$). We also showed a significant improvement in oxygen partial pressure ($p = 0.001$) and oxygen saturation ($p < 0.001$) and a significant increase in pH ($p = 0.018$) and bicarbonate values ($p = 0.042$) at T1. Moreover, we showed a significant increase in IL-6 ($p = 0.004$). Also, we reported mild hyponatremia and hypokalemia with subsequent significant recovery ($p < 0.001$, $p < 0.001$, respectively) and mild hypochloremia with a recovery to the limits of statistical significance ($p = 0.053$). At the entrance, we found an increase in serum glucose with a significant reduction during recovery ($p < 0.001$).

Discussion

The SARS-CoV-2 virus presents primarily as a lung infection, but the multisystemic nature of the disease is now known, particularly for the tropism of the virus to ACE-2 receptors, including the kidney[11,12]. For this reason, we evaluated the incidence of some renal manifestations such as AKI, found in 24.6%, AKI over CKD, showed in 21.1% of the sample, as reported by Brienza et al[2] and Cui et al[13], even if the incidence of renal damage reported in the literature is highly variable from 0.5% of Guan et al[14] to 88.2% of Kudose et al[15]. Several studies[16,17] have reported the expression of the cellular receptor for SARS-CoV-2 in the kidney, as in the proximal tubule, in the intercalary ducts, in the collecting ducts, in the distal tubule, and in the glomerular epithelium. In addition, virus-like particles were

Table I. Patients' characteristics.

Parameters	T0	T1	p-value
Serum sodium mEq/L	136.5 ± 4	138.7 ± 4	< 0.001
Serum potassium mEq/L	3.99 ± 0.5	4.36 ± 0.7	< 0.001
Serum glucose mg/dL	121.2 ± 46.5	106 ± 41.3	< 0.001
pH	7.47 ± 0.04	7.45 ± 0.04	0.018
SpO_2%	95.4 ± 2.7	98 ± 1.0	< 0.001
PO_2 mmHg	81.09 ± 16.5	98 ± 25.1	0.001
PCO_2 mmHg	33.8 ± 5.5	38 ± 4.2	< 0.001
serum bicarbonates mmol/L	25.6 ± 4	26.5 ± 3	0.042
CRP µg/mL	66,819 ± 66,460	55,340 ± 70,249	0.016
LDH U/L	299 ± 110	248 ± 96.2	< 0.001
ALFHA 1%	5.6 ± 1.3	7.2 ± 1.7	0.005
ALFHA 2%	12.7 ± 3	15.8 ± 3.1	0.007
IL-6 pg/mL	8.66 ± 7.6	45.9 ± 51.8	0.004

CRP, C Reactive Protein; IL, Interleukin; LDH, Lactate dehydrogenase.

found in podocytes and renal tubular epithelial cells, suggesting the possible presence of a direct cytopathic effect by the virus, which could be responsible for renal damage[17]. In fact, in our study, we also showed proteinuria in 38.4% of the examined sample, as reported by other authors[14,18,19]. Moreover, we found hematuria in 48% of patients, similar incidences have been reported in the literature, albeit with great variability[20-23]. Some studies[15-17] showed that the genes coding for ACE-2 and transmembrane serine proteases are co-expressed by the cells of the proximal renal tubule and by the podocytes; the presence of the receptor for the virus and of the protease necessary for its entry into the cell, could allow the replication of the microorganism within these cells and the resulting damage would explain the presence of both hematuria and proteinuria, described in many subjects with COVID-19 disease. In our study, we also showed an incidence of leukocyturia of 70.9%, an incidence higher than that reported in the literature, even if the studies[22] that report this data are not many. These data appear particularly relevant as numerous authors reported these renal alterations as negative prognostic factors in patients affected by COVID-19. Marand et al[22] reported that hematuria and leukocyturia were strong negative prognostic factors in admitted COVID-19 patients. Also, Gross et al[23] showed kidney disease associated with disease severity, complications, and in-hospital death[24-26]. Moreover, Zhou et al[27] showed that urinalysis is better in unveiling potential kidney impairment of COVID-19 patients than blood chemistry tests, and urinalysis could be used to reflect and predict the disease severity[28]. Portolés et al[24] also reported that the prevalence of AKI and CKD on admission and in-hospital AKI is higher tha previously reported in Wuhan and is associated with high in-hospital mortality[29]. In our study, significant changes in the concentration of serum electrolytes, such as sodium, potassium, and chlorine, were reported, hypothesizing possible renal tubular damage, as reported by other authors[30]. Although hyponatremia is common in COVID-19 patients and the cause appears to be outside the kidneys, the occurrence of the syndrome of inappropriate antidiuretic hormone has been well characterized by Ravioli et al[26]. Moreover, in accordance with ACE-2 receptors expression predominantly in proximal tubular cells and the finding of viral particles within these cells, some authors reported some tubular function abnormalities like Fanconi syndrome[30,32,33]. Electrolyte modifications have been described in the literature, in fact, in addition to a direct infection of the renal tubule cells by the virus, the inflammatory response caused by the cytokine storm would contribute to tissue damage[34,35]. In our study, we showed a significant metabolic improvement in blood glucose values and blood gas analytical parameters at T1 (oxygen partial pressure, oxygen saturation, pH, and bicarbonates concentration) as reported by other authors[15,17,34]. Also, Hirsch et al[20] showed how AKI is more frequent in patients with respiratory failure, showing a probable correlation between the two manifestations[36]. We also found lymphopenia, as reported in previous articles[14,32,37]. The authors attribute lymphopenia to the necrosis or apoptosis of lymphocytes caused by invasive viral particles, suggesting that the severity of lymphocytopenia reflects the severity of COVID-19[38], in fact, Zhang et al[32] reported that blood leukocyte/lymphocyte count and procalcitonin level could increase the risk of poor clinical outcomes. As known in the literature, inflammation seems to be the basis of the pathogenetic mechanism of systemic and renal damage[39]. In fact, in our study, we found a significant increase in CRP, LDH, alpha 1, alpha 2 globulins, and IL6. LDH is a general indicator of acute or chronic tissue damage and is considered an inflammatory marker[40], it has been described to be increased during acute and severe lung damage, and elevated LDH values could predict respiratory failure in COVID-19 patients[41]. IL-6 is perhaps the most important cytokine in "cytokine storm", the immune dysregulation that occurs in some patients infected with SARS-CoV-2. It has been found that in patients infected with SARS-CoV-2, elevated levels of IL-6 correlate with the development of ARDS, adverse clinical outcomes and death, therefore, elevated levels of IL-6 are a sign of severe disease and could be associated with increased mortality[42]. Increased coagulation activity, with an increased D-Dimer concentration, has a reported association with increased mortality[41]. Inflammation and endothelial damage further increase procoagulant factors, causing further ulterior endovascular damage and potentially eventual thrombosis and ischemia[42,43], which could promote kidney damage and the development of AKI[44]. In fact, also in our study, we found a significant increase in D-Dimer concentration.

Conclusions

The prevalence of AKI and/or CKD and/or abnormal urinalysis in patients diagnosed with COVID-19 infection on admission seems to be

high and could be a negative prognostic factor. Urinalysis appears to be very useful in unveiling potential kidney impairment of COVID-19 infection patients, therefore, urinalysis could be used to reflect and predict the disease severity. We, therefore, recommend paying more attention to urinalysis and kidney involvement of COVID-19 infection patients with a careful evaluation of inflammatory indices, electrolytic and metabolic disorders.

Infomed Consent
Informed consent was obtained from all subjects involved in the study.

Ethics Approval
The study protocol was approved by the Local Clinical Research Ethics Committee, Sapienza University of Rome with Ethics Approval acceptance number 298/2020. The study conforms to the principles outlined in the Declaration of Helsinki.

Conflicts of Interest
The authors declare no conflict of interest.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions
Conceptualization, SL, AMP. and SR; methodology, AMP, AG, CL, and MM; software, AG and LB; validation, SR, SM, PP and CMM; formal analysis, APM, SR, FE and PM; investigation, SR, CL and FT; data curation, MRC, RC and LB; writing-original draft preparation, SL, SS and PP; writing-review and editing, SL and AMP; visualization, SS and MM and AMC; supervision, SL, SM, and RC; project administration, SL.

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