Proteinuria as a Biomarker for COVID-19 Severity

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Background: Renal involvement in syndrome coronavirus 2 (SARS-CoV-2) infection has been retrospectively described, especially acute kidney injury (AKI). However, quantitative proteinuria assessment and its implication in coronavirus disease 2019 (COVID-19) remain unknown.

Methods: In this prospective, multicenter study in France, we collected clinical and biological data including urinary protein to creatinine ratio (UPCR) in patients presenting with moderate to severe COVID-19. Clinical outcome was analyzed according to the level of UPCR.

Results: 42/45 patients (93.3%) had renal involvement (abnormal urinary sediment and/or AKI). Significant proteinuria occurred in 60% of patients. Urine protein electrophoresis showed tubular protein excretion in 83.8% of patients with proteinuria. Inflammatory parameters and D-dimer concentrations correlated with proteinuria level. Patients who required intensive care unit (ICU) admission had higher proteinuria ($p = 0.008$). On multivariate analysis, proteinuria greater than 0.3 g/g was related to a higher prevalence of ICU admission [OR = 4.72, IC95 (1.16–23.21), $p = 0.03$], acute respiratory distress syndrome (ARDS) [OR = 6.89, IC95 (1.41–53.01), $p = 0.02$], nosocomial infections [OR = 3.75, IC95 (1.11–13.55), $p = 0.03$], longer inpatient hospital stay ($p = 0.003$).

Conclusion: Renal involvement is common in moderate to severe SARS-CoV-2 infection. Proteinuria at baseline is an independent risk factor for increased hospitalization duration and ICU admission in patients with COVID-19.

Keywords: acute kidney injury, biomarker, COVID-19, proteinuria, SARS-CoV-2, kidney involvement, pronostic and predictive factors
INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a transmitted disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It primarily manifests itself as an acute respiratory illness but can affect multiple organs such as kidneys, heart, digestive tract, and nervous system (Wang et al., 2020). In previous reports of SARS and Middle East Respiratory Syndrome coronavirus, acute kidney injury (AKI) was described in 5 – 15% of patients and was associated with high mortality rates (60–90%) (Chu et al., 2005; Cha et al., 2015). Recent reports showed renal abnormalities in COVID-19 patients (Naicker et al., 2020), but kidney involvement has not been yet well characterized (only retrospective cohorts using urine dip-stick tests) (Pei et al., 2020; Wang et al., 2020). A recent Chinese study also reported that AKI was an independent risk factor for mortality (Cheng et al., 2020). However, the exact mechanism of kidney involvement remains unclear: sepsis-related cytokine storm (Mehta et al., 2020) or direct cellular injury induced by the virus (Sun et al., 2020). Human angiotensin-converting enzyme 2 (ACE2) receptor has been identified as the functional receptor for SARS-CoV-2 and is highly expressed in kidneys (Hoffmann et al., 2020; Walls et al., 2020). These data suggest that the kidney might be a target of this SARS-CoV-2 as highlighted in pathological examinations (Su et al., 2020). Reports about the natural course of renal complications during SARS-CoV-2 are scarce, most of them concern only AKI or specific populations (e.g., Chinese) (Cheng et al., 2020; Pei et al., 2020), or kidney transplant recipients (Akalin et al., 2020; Alberici et al., 2020; Banerjee et al., 2020). We aimed to prospectively identify renal involvement, more especially proteinuria (quantitative) at baseline and its prognosis in a French cohort with moderate to severe SARS-CoV-2 infection.

MATERIALS AND METHODS

Study Protocol
Multicenter prospective observational study.

Study Approval
Use of routinely collected health data as a current care practice study (NCT04355624).

Patient Population
Inclusion criteria: all patients aged ≥18 years-old with symptomatic proven moderate to severe COVID-19 according to the WHO classification, admitted in one infectious diseases department or in three different intensive care unit (ICU) of Nice University Hospital and Antibes Juan-les-Pins hospital general hospital, between March 15th to April 19th, 2020.

Patients with a history chronic kidney disease and pregnant women were non-included.

Patients with documented urinary tract infection at inclusion were excluded to avoid confusing results.

Data Sources
The demographic characteristics (medical history, clinical symptoms, laboratory data, and medications) were extracted from electronic medical records. Urinary data were collected on urine sample: microalbuminuria, urine protein/creatinine ratio (UPCR), urine protein electrophoresis, red blood, and white blood cells counts.

Definitions
Proven COVID-19 was defined as a positive SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) assay in nasopharyngeal swabs.

Severe COVID-19 was defined as respiratory failure or need for mechanical ventilation, shock or organ failure or need for ICU admission.

Acute kidney injury was defined according to KDIGO guidelines.

The date of disease onset was defined as the day of first symptom.

The last day of follow up was the in-hospital death or hospital discharge.

Statistical Analysis
For descriptive statistics, data are presented as median (ranges) or mean ± standard deviation. Shapiro-Wilk test was used to test for normal distribution of variable. Comparison of qualitative criteria was performed using Chi-square test or Fisher’s exact test. Comparison of quantitative variables was performed using the Student t-test or Wilcoxon-Mann–Whitney test. Spearman rank-order test was used to find correlations between continuous variables. Multivariate analysis was performed using logistic regression. The multivariate model was built by including variables that met the 20% significance threshold in univariate analysis. Choice among colinear variables was performed using Akaike Iteration Criteria. Receiver Operating Characteristic (ROC) curve was used to evaluate the performance of the test. Comparisons for survival curves were performed using Kaplan-Meier analysis. A p-value < 0.05 indicated statistical significance. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA, United States) and RStudio [RStudio Team (2019). RStudio. Inc., Boston].

RESULTS

Baseline Characteristics
A total of 45 patients were enrolled and followed for a median of 11 days (5–23 days). Twenty-two patients (49%) developed severe COVID-19 and required ICU admission. Table 1 shows the characteristics of the cohort. Prevalence of hypertension and diabetes mellitus was 37.8 and 26.7%, respectively. Less than 25% of patients were on renin-angiotensin system (RAS) blockers. Two patients died from SARS-CoV-2 infection: one in the ICU from refractory respiratory failure, one patient died from respiratory failure in conventional unit with DNR order.
# TABLE 1 | Clinical and biological characteristics of the cohort.

| Variables                              | All patients (n = 45) | Severe COVID-19 (n = 22) | Non-severe COVID-19 (n = 23) | P-value |
|----------------------------------------|-----------------------|--------------------------|-----------------------------|---------|
| **Clinical characteristics**           |                       |                          |                             |         |
| Age, years                             | 64.0 (48.5–71.5)      | 66.0 (58.8–72.0)         | 58 (47.0–68.0)              | 0.11    |
| Male patients, n (%)                   | 31.0 (68.9)           | 18.0 (81.8)              | 13.0 (56.5)                 | 0.07    |
| Respiratory disease, n (%)             | 9.0 (20.0)            | 5.0 (22.7)               | 4.0 (17.4)                  | 0.65    |
| Hypertension, n (%)                    | 17.0 (37.8)           | 9.0 (40.9)               | 8.0 (34.8)                  | 0.67    |
| Diabetes mellitus, n (%)               | 12.0 (26.7)           | 6.0 (27.3)               | 6.0 (26.1)                  | 0.93    |
| Cardiac disease, n (%)                 | 5.0 (11.1)            | 3.0 (13.6)               | 2.0 (8.7)                   | 0.60    |
| Vascular disease, n (%)                | 3.0 (6.7)             | 1.0 (45.5)               | 2.0 (8.7)                   | 0.58    |
| Active and former smokers, n (%)       | 13.0 (28.9)           | 9.0 (39.1)               | 4.0 (17.4)                  | 0.08    |
| Immunosuppression, n (%)               | 6.0 (13.3)            | 3.0 (13.6)               | 3.0 (13)                    | 0.95    |
| ACE inhibitor, n (%)                   | 1.0 (2.2)             | 1.0 (4.5)                | 0                           | 0.30    |
| ARB, n (%)                             | 8.0 (17.8)            | 2.0 (9.0)                | 6.0 (26.1)                  | 0.14    |
| BMI (kg/m²)                            | 27.8 (24.3–32.5)      | 28.9 (25.0–32.9)         | 25.8 (23.4–32.6)            | 0.47    |
| Systolic blood pressure, mmHg          | 125.0 (120.0–137.5)   | 128.5 (120.0–144.0)      | 120.0 (115.0–130.0)         | 0.03*   |
| Diastolic blood pressure, mmHg         | 75.0 (67.0–80.0)      | 80.0 (71.5–80.0)         | 70.0 (60.0–80.0)            | 0.02*   |
| Days from illness onset to admission   | 8.0 (5.0–12.0)        | 11.0 (6.0–14.0)          | 7.0 (4.0–10.0)              | 0.03*   |
| **Biological data**                    |                       |                          |                             |         |
| Leukocytes, G/L                        | 5.7 (4.4–8.3)         | 7.7 (5.0–9.3)            | 4.9 (4.0–6.9)               | 0.03*   |
| Lymphocytes, G/L                       | 0.9 (0.6–1.2)         | 0.7 (0.5–1)              | 1 (0.7–1.3)                 | 0.11    |
| Neutrophils, G/L                       | 4.7 (3.2–6.8)         | 5.9 (4.2–7.9)            | 3.4 (2.5–4.9)               | 0.008*  |
| Hemoglobin, G/L                        | 13.0 (12.2–14.2)      | 13.0 (12.1–14.2)         | 13.2 (12.2–14.2)            | 0.93    |
| Platelets, G/L                         | 205.0 (165.5–270.0)   | 255.5 (174.8–288.5)      | 203.0 (157.0–256.0)         | 0.11    |
| D-dimer, ng/ml                         | 1764.0 (779.0–5689.0) | 4944.0 (1814.0–9374.0)   | 913.0 (476.0–1422.0)        | <0.001* |
| Fibrinogen, g/l                        | 7.1 (5.8–8.7)         | 7.8 (6.8–9.7)            | 5.5 (4.8–7.4)               | 0.001*  |
| Procalcitonin, ng/ml                   | 0.2 (0.1–0.5)         | 0.4 (0.2–0.8)            | 0.1 (0.1–0.3)               | 0.002*  |
| Sodium, mmol/L                         | 137.0 (134.0–139.0)   | 135.5 (133.0–141.0)      | 138.0 (135.0–139.0)         | 0.24    |
| Potassium, mmol/l                      | 4.0 (3.7–4.3)         | 4.2 (3.8–4.5)            | 3.8 (3.6–4.1)               | 0.04*   |
| C-reactive protein, mg/l               | 23.0 (20.0–26.0)      | 22.0 (20.0–23.3)         | 24.0 (23.0–26.0)            | 0.003*  |
| Albumin, g/l                           | 28.9 (25.4–32.8)      | 27.0 (24.7–30.0)         | 30.8 (27.3–34.3)            | 0.02*   |
| BUN, mmol/l                            | 5.2 (3.9–7.3)         | 4.7 (2.8–6.3)            | 3.7 (1.7–4.6)               | 0.06    |
| Creatinine, µmol/l                     | 72.0 (57.0–87.5)      | 75.5 (59.3–94.0)         | 72.0 (55.0–82.0)            | 0.44    |
| eGFR, ml/min per 1.73 m²               | 72 (82–101)           | 69 (80–97)               | 72 (82–106)                 | 0.45    |
| **Renal involvement**                  |                       |                          |                             |         |
| AKI, n (%)                             | 12.0 (26.7)           | 8.0 (36.4)               | 4.0 (17.4)                  | 0.15    |
| KDIGO 1                                | 6/12 (50.0)           | 4/8 (50)                 | 2/4 (50)                    |         |
| KDIGO 2                                | 4/12 (33.3)           | 2/8 (25)                 | 2/4 (50)                    |         |
| KDIGO 3                                | 2/12 (16.7)           | 2/8 (25)                 | 2/4 (50)                    |         |
| RRT                                    | 2/12 (16.7)           | 2/8 (25)                 | 2/4 (50)                    |         |
| Proteinuria >0.3 g/g, n (%)            | 27 (60.0)             | 17 (77.3)                | 10 (43.5)                   | 0.02*   |
| Non-albumin proteinuria, n (%)         | 37 (82.2)             | 18 (81.8)                | 19 (82.8)                   | 0.94    |
| Microalbuminuria, n (%)                | 5 (11.1)              | 3 (13.6)                 | 2 (8.7)                     | 0.6     |
| Hematuria, n (%)                       | 21 (46.7)             | 12 (54.5)                | 9 (39.1)                    | 0.3     |
| Leukocyturia, n (%)                    | 21 (46.7)             | 13 (59.1)                | 8 (34.8)                    | 0.10    |
| Normoglycemic glycosuria, n (%)        | 0                    | 0                        | 0                            |         |
| **Treatment**                          |                       |                          |                             |         |
| Steroids, n (%)                        | 22 (48.9)             | 17 (77.3)                | 5 (21.7)                    | <0.001* |
| Antibiotics, n (%)                     | 21 (46.7)             | 17 (77.3)                | 4 (17.4)                    | 0.001*  |
| Lopinavir/Ritonavir, n (%)             | 3 (6.7)               | 3 (13.6)                 | 0                            | 0.07    |
| Hydroxychloroquine, n (%)              | 17 (37.8)             | 14 (63.6)                | 3 (13.0)                    | <0.001* |
| Tocilizumab, n (%)                     | 2 (22)                | 1 (4.5)                  | 0                            | 0.97    |

(Continued)
TABLE 1 | Continued

| Variables                      | All patients (n = 45) | Severe COVID-19 (n = 22) | Non-severe COVID-19 (n = 23) | P-value |
|--------------------------------|----------------------|--------------------------|-------------------------------|---------|
| Vasopressor, n (%)             | 12 (26.7)            | 12 (54.6)                | 12 (52.2)                     | 0.001*  |
| Invasive ventilation, n (%)    | 15 (33.3)            | 15 (68.1)                | 0                             | 0.001*  |
| Outcome                        |                      |                          |                               |         |
| Nosocomial infection, n (%)    | 15 (33.3)            | 13 (59.1)                | 2 (8.7)                       | <0.001* |
| In-hospital death, n (%)       | 2 (4.5)              | 1 (4.5)                  | 1 (4.3)                       | 0.97    |
| Length of stay, days           | 11 (5–23)            | 23 (14–32)               | 7 (5–11)                      | 0.001*  |

ACE, angiotensin-converting-enzyme inhibitor; ARBs, angiotensin II receptor blockers; BMI, body mass index; BUN, blood urea nitrogen; AKI, acute kidney injury; RRT, renal replacement therapy. *Significant, P < 0.05.

Renal Involvement
On admission, 93.3% of patients (42 of 45) presented with renal involvement.

Urine Sediment Abnormalities
Significant proteinuria (>0.3 g/g) occurred in 27 patients (60%) with a mean of 0.50 ± 0.47 g/g (77.3% patients in the severe disease group versus 43% in the non-severe group, p = 0.02). Higher UPCR was observed in patients with severe COVID-19 (0.59 ± 0.40 versus 0.42 ± 0.53 g/g, p = 0.008). Urine protein electrophoresis showed non-albumin proteinuria excretion in 77.7% of patients with significant proteinuria. Inflammatory variables, D-dimers and length of hospital stay were correlated with the level of proteinuria (Supplementary Table 1).

Acute Kidney Injury
The incidence of AKI in the overall cohort was 26.7% (12 of 45 patients) according to KDIGO definition (Table 1). Stage 1 AKI accounted for 50% (6/12 patients with AKI), stage 2 comprised 33.3% (4/12), and 16.7% (2/12) reached stage 3 and required renal replacement therapy (RRT). Among patients with AKI: proteinuria, hematuria and leukocyturia were not different compared with non-AKI patients (Supplementary Table 2). Mortality was not different between AKI and non-AKI patients. Among patients in whom AKI developed, 50% recovered.

Impact of Proteinuria in SARS-CoV-2 Infection
Patients who required ICU admission had significantly higher level of proteinuria (0.59 ± 0.40 versus 0.42 ± 0.53 g/g, p = 0.008).

Patients with significant proteinuria defined as proteinuria above 0.3 g/g had a longer hospital stay [19 days (9–31) versus 7 days (5–11), p = 0.001], a higher prevalence of nosocomial infection (48.1 versus 11.1%, p = 0.01) and acute respiratory distress syndrome (ARDS) (48.1 versus 11.1%, p = 0.01) but mortality was not significantly higher (p = 0.24) (Table 2). Using univariate and multivariate analyses, proteinuria was related to a higher prevalence of ICU admission, ARDS and nosocomial infection (Table 3). Kaplan-Meier analysis revealed a significantly longer hospitalization duration for patients with a significant proteinuria (Figure 1). For in-hospital mortality and AKI, proteinuria was not an independent predictor (Table 3).

DISCUSSION
Among the 45 patients prospectively analyzed in the present study, a high proportion presented renal involvement. Proteinuria at baseline was associated with poor outcome in SARS-CoV-2 infection. Our data are consistent with a recent retrospective study among 333 patients in China (Pei et al., 2020). Our study confirmed that kidney involvement is common in hospitalized COVID-19 patients, but not only in severe cases. AKI has been previously described as associated with in-hospital mortality in COVID-19 (Cheng et al., 2020) and renal complications in COVID-19 remains associated with poor outcome (Pei et al., 2020). To our knowledge, this is the first study using quantitative assessment of urinary protein excretion and identifying proteinuria as a factor associated with poor outcome in COVID-19 (higher prevalence of ARDS, nosocomial infection, ICU admission). Furthermore, we could show that a significant proteinuria (i.e., above 0.3 g/g) was associated with a higher risk of ICU admission, developing ARDS, requiring vasopressor, developing nosocomial infections. Proteinuria higher than 0.3 g/g was a predictor for length of stay. Similar results have been described in a retrospective cohort with bacterial community-acquired pneumonia (Spoorenberg et al., 2012) but also in non-infectious diseases such as cirrhosis (Lin et al., 2014) or lung cancer (Hsu et al., 2018).

The tubular profile of kidney involvement we describe is consistent with recent pathologic reports (Su et al., 2020). The analysis of 26 autopsies from COVID-19 patients showed diffuse proximal tubule injury with the loss of brush border, non-isometric vacuolar degeneration, necrosis; hyaline casts and microthrombi were also observed. Interestingly, in this study, some patients did not present AKI according to KDIGO definition suggesting subclinical kidney injury. Proteinuria appears as a sensitive tool, comparing to creatinine and/or BUN, for renal assessment in COVID-19, even in subclinical kidney injury.

In our study, hematuria and leukocyturia were present in almost half of the patients but we found no difference between severe and non-severe COVID-19. Our results suggest an interstitial participation in kidney. Histopathologic reports did not show interstitial inflammation but 61.5% of patients had steroids before kidney biopsy was performed (and data are not available for 23% of patients) (Su et al., 2020). Even if a case
TABLE 2 | Characteristics of patients with and without proteinuria >0.3 g/g.

| Variable                      | Proteinuria (n = 27) | No proteinuria (n = 18) | P-value |
|-------------------------------|----------------------|-------------------------|---------|
| Age, years                    | 66.0 (49.0–72.0)     | 61.0 (43.5–68.3)        | 0.18    |
| Male patients, n (%)          | 22 (81.5)            | 9 (50.0)                | 0.03*   |
| Day from illness onset to admission, days | 9.0 (5.0–11.0)   | 8.0 (5.5–12.5)          | 0.83    |
| Systolic blood pressure, mmgh | 127.0 (120.0–140.0)  | 120.0 (120.0–130.0)     | 0.40    |
| Diastolic blood pressure, mmgh| 80.0 (70.0–80.0)     | 70.0 (60.0–80.0)        | 0.54    |
| Respiratory disease, n (%)    | 7 (25.9)             | 2 (11.1)                | 0.22    |
| Hypertension, n (%)           | 11 (40.7)            | 6 (33.3)                | 0.62    |
| Diabetes mellitus, n (%)      | 10 (37.0)            | 2 (11.1)                | 0.06    |
| Cardiac disease, n (%)        | 3 (11.1)             | 2 (11.1)                | 1       |
| Vascular disease, n (%)       | 3 (11.1)             | 0                       | 0.14    |
| Active and former smokers, n (%) | 9 (33.3)           | 4 (22.2)                | 0.42    |
| ACEI, n (%)                   | 1 (3.7)              | 0                       | 0.41    |
| ARB, n (%)                    | 3 (11.1)             | 5 (27.8)                | 0.15    |
| BMI (Kg/m²)                   | 26.5 (24.3–32.9)     | 28.3 (24.1–32.6)        | 0.74    |
| C Reactive protein, mg/l      | 112.8 (75.1–168.1)   | 51.6 (81.2–104.0)       | 0.04*   |
| Procalcitonin, ng/ml          | 0.3 (0.1–0.7)        | 0.2 (0.1–0.4)           | 0.27    |
| D–Dimer ng/ml                 | 4349.0 (1701.0–6828.0) | 779.0 (472.0–1501.0)    | <0.001* |
| AKI, n (%)                    | 9 (33.3)             | 3 (16.7)                | 0.22    |
| ICU admission, n (%)          | 17 (62.9)            | 5 (27.8)                | 0.02*   |
| ARDS, n (%)                   | 13 (48.1)            | 2 (11.1)                | 0.01*   |
| Length of stay, days          | 19 (9.0–31.0)        | 6.5 (4.8–11.3)          | 0.001*  |
| Nosocomial infection, n (%)   | 13 (48.1)            | 2 (11.1)                | 0.01*   |
| In-hospital death, n (%)      | 2 (7.4)              | 0                       | 0.24    |

ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; ARDS, acute respiratory distress syndrome; BMI, body mass index; AKI, acute kidney injury; ICU, intensive care unit. *Significant, P < 0.05.

TABLE 3 | Association between significant proteinuria and outcomes.

| Variable     | Univariate analysis | Multivariate analysis |
|--------------|---------------------|-----------------------|
|              | Odds ratio          | 95% Confidence interval | P value | Odds ratio          | 95% Confidence interval | P value |
| AKI          | 2.33                | 0.57–12.02             | 0.26    | 6.89                | 1.41–53.01             | 0.02*   |
| RRT          | 5.33                | 0.48–119.84            | 0.18    | 4.72                | 1.16–23.21             | 0.03*   |
| ARDS         | 6.96                | 1.55–49.87             | 0.02*   | 12.32               | 1.83–254.97            | 0.03*   |
| ICU admission| 4.08                | 1.15–16.19             | 0.03*   | 3.75                | 1.11–13.55             | 0.03*   |
| Vasopressor  | 11.0                | 1.82–213.24            | 0.03*   |                     |                      |        |
| Nosocomial infection | 6.96          | 1.56–49.87             | 0.02*   |                     |                      |        |
| In-hospital death | 4.17            | 0.63–34.32             | 0.13    |                     |                      |        |

AKI, acute kidney injury; RRT, renal replacement therapy; ARDS, acute respiratory distress syndrome; ICU, intensive care unit. *Significant, P < 0.05.

of collapsing glomerulopathy has been reported in COVID-19 (Gaillard et al., 2020), acute tubular necrosis (ATN) with interstitial component probably remains the main cause of kidney injury. Other factors may contribute to kidney involvement: systemic inflammation and cytokine storm (Burton and Harris, 1996; Coletta et al., 2000; Gohda et al., 2001; D’Amico and Bazzi, 2003; Imai, 2003; Thorevska et al., 2003; Mäkelä et al., 2004; Wassmann et al., 2004; Kieler et al., 2005; Abbate et al., 2006; Liu et al., 2007; Delvaeye and Conway, 2009; Murugan et al., 2010; Ranganathan et al., 2013; Darmon et al., 2014, 2017; Su et al., 2017; Sarhan et al., 2018; Meissner et al., 2019; Cremoni et al., 2020; Mehta et al., 2020; Pan et al., 2020; Rossi et al., 2020; Siddiqi and Mehra, 2020; Tang et al., 2020; Vaninov, 2020; Zhang et al., 2020; Ruetschi et al., 2021), release of pathogen-associated molecular patterns (PAMPs), high levels of damage-associated molecular proteins (DAMPS) from lung injury and severe hypoxic respiratory failure (Burton and Harris, 1996; Coletta et al., 2000; Gohda et al., 2001; D’Amico and Bazzi, 2003; Thorevska et al., 2003; Mäkelä et al., 2004; Wassmann et al., 2004; Kieler et al., 2005; Abbate et al., 2006; Delvaeye and Conway, 2009; Ranganathan et al., 2013; Darmon et al., 2014, 2017; Su et al., 2017; Sarhan et al., 2018; Meissner et al., 2019; Cremoni et al., 2020; Pan et al., 2020; Rossi et al., 2020; Siddiqi and Mehra, 2020; Tang et al., 2020; Vaninov, 2020; Zhang et al., 2020; Ruetschi et al., 2021). All these factors could also lead to tissue factor release and the hypercoagulate state...
In conclusion, kidney involvement in SARS-CoV-2 infection seems multifactorial and not only due to viral infection. Last, we did not have renal histopathological data to correlate to biological data since there were no formal indication for kidney biopsy.

Nevertheless, our study is prospective and multicentric. This is the first conducted in an European population. Differences have been described between Caucasian and Asian populations in kidney disease and also in ACE2 expression (Hoffmann et al., 2020). We used quantitative urinary protein excretion that is more accurate but still an easy and inexpensive test in contrast with other urinary markers.

In conclusion, kidney involvement in SARS-CoV-2 infection is common and not only in severe forms. Renal impairment in SARS-CoV-2 infection and more precisely proteinuria is an independent predictor for length of stay and admission to the ICU. Proteinuria is an easily measurable marker to predict outcome and may be used to assess the severity of SARS-CoV-2 infection. Evidence suggest that proteinuria is a marker of chronic disease progression (Burton and Harris, 1996; Abbate et al., 2006). In SARS-CoV-2 infection, quantitative proteinuria should be monitored at admission and during follow-up, even in patients without AKI or severe disease to assess long-term implication of SARS-CoV-2 infection.
DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

COLLABORATORS

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AUTHOR CONTRIBUTIONS

HO, SB-S, and JD designed the study and drafted and revised the manuscript. HO, LM, JC, JF, VB, RL, and ED collected clinical and biological data. HO, LM, and SB-S analyzed and interpreted the data. HO, JC, JF, VB, RL, VE, BS-P, ED, JD, and SB-S provided medical oversight. All authors approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.611772/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.