The spectrum of kidney biopsies in hospitalized patients with COVID-19, acute kidney injury and/or proteinuria

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ABSTRACT

Background. The coronavirus disease 2019 (COVID-19) may be associated with kidney injury, which may impact patient’s prognosis.

Methods. We report a multicentric retrospective case series of patients with COVID-19 who developed acute kidney injury (AKI) and/or proteinuria and underwent a kidney biopsy in Paris and its metropolitan area.

Results. Forty-seven patients (80.9% men) with COVID-19 who underwent a kidney biopsy between 8 March and 19 May 2020 were included. The median age was 63 years (interquartile range 52–69). Comorbidities included hypertension (66.0%), diabetes mellitus (27.7%), obesity (27.7%), history of chronic kidney disease (25.5%), cardiac diseases (38.6%) and respiratory diseases (27.3%). Initial symptoms were fever (85.1%), cough (63.8%), shortness of breath (55.3%) and diarrhoea (23.4%). Almost all patients developed AKI (97.9%) and 63.8% required renal replacement therapy. Kidney biopsy showed two main histopathological patterns, including acute tubular injury in 20 (42.6%) patients, and glomerular injury consisting of collapsing glomerulopathy (CG) and focal segmental glomerulosclerosis in 17 (36.2%) patients. Two (4.3%) patients had acute vascular nephropathy, while 8 (17%) had an alternative diagnosis most likely unrelated to COVID-19. Acute tubular injury occurred almost invariably in the setting of severe forms of COVID-19, whereas patients with glomerular injury had various profiles of COVID-19 severity and CG was only observed in patients harbouring a combination of APOL1 risk variants. At the last follow-up, 16 of the 30 patients who initially required dialysis were still on dialysis, and 9 had died.

Conclusions. This study describes the spectrum of kidney lesions in patients with COVID-19. While acute tubular injury is correlated with COVID-19 severity, the pattern of glomerular injury is intimately associated with the expression of APOL1 risk variants.

Keywords: acute tubular injury, collapsing glomerulopathy, COVID-19, focal segmental glomerulosclerosis, kidney

INTRODUCTION

In December 2019, a novel coronavirus disease [coronavirus disease 2019 (COVID-19)] caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus occurred in Wuhan, Hubei Province, China, and rapidly spread worldwide [1, 2]. Coronavirus disease 2019 (COVID-19) is transmitted via droplets during the incubation period and throughout the course of illness [3]. Up to 20% of infected patients develop moderate–severe pneumonia and require hospitalization and 5–10% are admitted to an intensive care unit (ICU) for ventilation support [4–8]. According to recent studies, SARS-CoV-2 infection is not limited to the respiratory system and other organs can be affected, leading to a broad spectrum of signs. Recent studies have underscored the high frequency of acute kidney injury (AKI), proteinuria and haematuria during COVID-19 [9, 10]. Moreover, kidney involvement is burdened by a dramatic impact on the patient’s survival [9–11]. Here we report a multicentric case series of patients with COVID-19 who developed AKI and/or proteinuria and underwent a kidney biopsy in Paris and its metropolitan area.

RESULTS

Clinical characteristics and radiologic findings

Forty-seven patients from nine nephrology and ICU departments of Paris and its metropolitan area, including 38 (80.9%) men, were diagnosed with COVID-19 and underwent a kidney biopsy during the recent epidemic from 8 March through 19 May 2020. Of note, during the study period, >14,000 patients with COVID-19 were admitted to the different hospitals of Assistance Publique-Hôpitaux de Paris, including >3000 (21.4%) patients referred to the ICU.

The diagnosis of COVID-19 was confirmed by SARS-CoV-2 reverse-transcriptase polymerase chain reaction (RT-PCR) nasal or pharyngeal swab specimens in 43 (91.5%) patients. In four patients with negative RT-PCR, the diagnosis was established on the results of a chest computed tomography (CT)
scan, showing ground-glass opacities with or without consolida
tive abnormalities highly suggestive of COVID-19 infection.
The median age was 63 years [interquartile range (IQR) 52–69].
Forty-four (93.6%) patients had coexisting medical conditions
and 31 (65.9%) having two or more conditions (Table 1). The
most frequent comorbidities included hypertension (66%),
diabetes mellitus (27.7%), obesity (27.7%) and previous kidney
disease (25.5%), including four patients with heart (n = 1), lung
(n = 1) or kidney (n = 2) transplantation. Of note, all patients
were negative for human immunodeficiency virus (HIV),
except one patient treated for such infection before the onset of
COVID-19 and who had a stable and negative viral load during
the COVID-19 episode. The most common symptoms on ad-
mission included fever and chills (85.1%), cough (63.8%), short-
ness of breath (55.3%) and diarrhoea (23.4%) (Table 2). All
patients required hospital admission, including >50% of
patients who required oxygen therapy on admission [World
Health Organization (WHO) score ≥ 5; Supplementary data,
Table S4]. Of note, 20 (42.6%) patients did not require oxygen
therapy initially (WHO score 2–4) but were hospitalized be-
cause of extrarespiratory features in the setting of COVID-19,
including AKI and proteinuria. Chest CT scan was performed
in 43 patients (91.5%) within the 4 days (IQR 1–9) after initial
symptoms and revealed mild, moderate or severe lesions in 3
(7%), 19 (44.2%) and 21 (48.8%) patients, respectively (Table 2).
During the disease course, most patients developed severe in-
flammatory syndrome characterized by a median blood C-reac-
tive protein level of 199 mg/L (IQR 139–283) and severe
haematological abnormalities including anaemia, lymphopaenia
and thrombopaenia in 38 (80.9%), 21 (45.7%) and 18 (39.1%)
patients, respectively (Supplementary data, Table S1).

Renal laboratory findings

On admission, the serum creatinine level was 158 µmol/L
(IQR 88–370) while the maximum value during the disease
course was 644 µmol/L (IQR 385–768). Overall, only one pa-
tient who presented with nephrotic syndrome had normal renal
function and 3 (6.4%), 2 (4.3%) and 41 (87.2%) patients expe-
rienced AKI Stage I, II and III, respectively. Thirty (63.8%)
patients, including seven (23.3%) with pre-existing chronic
kidney disease (CKD), required acute dialysis with a median delay
of 14 days (IQR 9–19) after initial symptoms. Seven of 12
(58.3%) patients with pre-existing CKD required acute dialysis.
All patients displayed proteinuria >0.3 g/g with a median urine
protein:creatinine ratio (uPCR) of 2.52 g/g (IQR 1.23–6.80).
Eighteen (40%) patients had a uPCR ≥3 g/g, while the median
serum albumin level was 21 g/L (IQR 16–23). Urine
albumin:creatinine ratio was not measured in all patients at
the time of kidney biopsy. Haematuria was observed in 22 (55%)
patients. Other laboratory findings are detailed in
Supplementary data, Table S1.

Kidney biopsy indications

Kidney biopsies, including two renal graft biopsies, were per-
formed with a median delay of 18 days (IQR 10–26) after initial
symptoms. Seventeen patients were biopsied during their ICU
stay because of Stage III AKI or dialysis requirement, including
two anuric patients. Thirteen patients underwent a kidney bi-
opsy after ICU discharge because of persistent AKI and signifi-
cant proteinuria. Finally, the remaining 17 kidney biopsies were
performed in non-critically ill patients because of significant
proteinuria (>1 g/g) in all patients, associated with Stage III
AKI in all patients.

Overall, of the 47 patients, 19 (40.4%) displayed overt ne-
phrotic syndrome with a mean proteinuria level of 12.1 g/g
(IQR 5.96–11.95) and a mean serum albumin level of 18.2 g/L
(IQR 16–22). All 19 patients, except 1, had concomitant AKI
with a mean creatinine level of 692 µmol/L (IQR 370–

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**Table 1. Demographic data and coexisting comorbidities**

| Clinical data                  | Patients (N = 47) |
|-------------------------------|------------------|
| Demographic data              |                  |
| Age (years), median (IQR)     | 63 (52–69)       |
| Male gender, n (%)            | 38 (80.9)        |
| Weight (kg), median (IQR)     | 85.5 (73–96.2)   |
| BMI (kg/m²), median (IQR)     | 26.6 (24.6–30.0) |
| Coexisting conditions, n (%)  |                  |
| ≥2 comorbidities              | 31 (66.0)        |
| Blood hypertension            | 31 (66.0)        |
| ACEi use                      | 11 (23.4)        |
| ARB use                       | 10 (21.3)        |
| Dyslipidaemia                 | 14 (29.8)        |
| Obesity (BMI >30 kg/m²)       | 13 (27.7)        |
| Diabetes mellitus             | 13 (27.7)        |
| Smoking                       | 10 (21.3)        |
| CKD                           | 12 (25.5)        |
| Stage IIIa                    | 5 (14.3)         |
| Stage IIIb                    | 5 (14.3)         |
| Stage IV                      | 2 (6.4)          |
| Chronic cardiac disease       | 10 (21.3)        |
| Chronic respiratory disease   | 1 (2.1)          |
| Cancer                        | 8 (17.0)         |
| Immunosuppressive drugs       | 8 (17.0)         |

| Presenting clinical symptoms, n (%)                  | 40 (85.1) |
| Cough                                               | 30 (63.8) |
| Shortness of breath                                 | 26 (55.3) |
| SPO₂ (%), median (IQR)                              | 91 (89–97) |
| Oxygen therapy (L/min), median (IQR)                 | 1 (0–5)   |
| Initial WHO score 2–4                               | 21 (44.7) |
| Initial WHO score >6                                | 16 (34.0) |
| Diarrhoea                                           | 11 (23.4) |
| SARS-CoV-2 RT-PCR Positive RT-PCR nasal or pharyngeal swab specimens, n (%) | 43 (91.5) |
| Time from initial symptoms (days), median (IQR)     | 3 (1–7)   |
| Chest CT scan, n (%)                                | 43 (91.5) |
| CT scan performed                                   | 43 (91.5) |
| Time from initial symptoms (days), median (IQR)     | 4 (1–9)   |
| Mild                                                | 3 (7)     |
| Moderate                                            | 19 (44.2) |
| Severe                                              | 21 (48.8) |

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**Table 2. Diagnostic features**

| Diagnostic features                  | Patients (N = 47) |
|--------------------------------------|------------------|
| Presenting clinical symptoms, n (%)  |                  |
| Fever                                | 40 (85.1)        |
| Cough                                | 30 (63.8)        |
| Shortness of breath                  | 26 (55.3)        |
| SPO₂ (%), median (IQR)               | 91 (89–97)       |
| Oxygen therapy (L/min), median (IQR) | 1 (0–5)          |
| Initial WHO score 2–4                | 21 (44.7)        |
| Initial WHO score >6                 | 16 (34.0)        |
| Diarrhoea                            | 11 (23.4)        |
| SARS-CoV-2 RT-PCR Positive RT-PCR nasal or pharyngeal swab specimens, n (%) | 43 (91.5) |
| Time from initial symptoms (days), median (IQR) | 3 (1–7) |
| Chest CT scan, n (%)                 | 43 (91.5)        |
| CT scan performed                    | 43 (91.5)        |
| Time from initial symptoms (days), median (IQR) | 4 (1–9) |
| Mild                                 | 3 (7)            |
| Moderate                             | 19 (44.2)        |
| Severe                               | 21 (48.8)        |
880) at kidney biopsy. The remaining 28 patients with no nephrotic syndrome had AKI with a mean serum creatinine level of 569 μmol/L (IQR 388–650) and a mean proteinuria level of 1.6 g/g (IQR 0.97–2.32) (Supplementary data, Table S2).

Pathological analysis

Histopathological examination revealed two main patterns of kidney damage, i.e. tubulointerstitial injury and glomerular injury in 20 (42.6%) and 17 (36.2%), respectively (Table 3). Two patients (4.3%) displayed vascular lesions, including thrombotic microangiopathy and arteritis, consistent with a COVID-19-related vasculopathy. In the remaining eight patients (17.0%), renal findings were consistent with an alternative diagnosis (Table 3), which was most likely unrelated to COVID-19. Thirty-seven kidney biopsies were centrally reviewed by S.F. and detailed scoring of glomerular, tubular, interstitial and vascular lesions is provided in Supplementary data, Table S3.

Acute tubular injury was the dominant injury pattern in 20 (42.6%) patients. Various degrees of tubular damage were

### Table 3. Renal findings on admission and at the time of kidney biopsy

| Renal findings | Patients (N = 47) |
|---------------|------------------|
| **Baseline serum creatinine level (μmol/L), median (IQR)** | 87 (75–118) |
| **Renal parameters on admission** | |
| Serum creatinine level (μmol/L), median (IQR) | 158 (88–370) |
| Serum albumin level (g/L), median (IQR) | 25 (22–31) |
| uPCR (g/g), median (IQR) | 1.86 (0.82–7.79) |
| Haematuria, n (%) | 22 (55.0) |
| Leukocyturia, n (%) | 27 (67.5) |
| **Renal status at the time of kidney biopsy** | |
| Time from initial symptoms (days), median (IQR) | 18 (10–26) |
| uPCR (g/g), median (IQR) | 2.52 (1.23–6.80) |
| uPCR ≥ 3 g/g, n (%) | 18 (40.0) |
| Albuminuria (g/dL), median (IQR) | 21 (16–23) |
| Albuminuria < 30 g/L, n (%) | 40 (95.2) |
| Serum creatinine level (μmol/L), median (IQR) | 644 (385–768) |
| AKI, n (%) | |
| No | 1 (2.1) |
| KDIGO 1 | 3 (6.4) |
| KDIGO 2 | 2 (4.3) |
| KDIGO 3 | 41 (87.2) |
| **Main histopathological findings, n (%)** | |
| Predominant ATN | 20 (42.6) |
| FSGS | 17 (36.2) |
| Collapsing glomerulopathy | 11 (64.7) |
| Not otherwise specified | 5 (29.4) |
| Tip lesion | 1 (5.9) |
| Vascular Nx | 2 (4.3) |
| Thrombotic microangiopathy | 1 |
| Arteritis | 1 |
| Other diagnoses* | 8 (17) |
| AA amyloidosis | 1 |
| PLA2R-positive membranous Nx | 2 |
| Extracapillary glomerulonephritis | 1 |
| IgA Nx | 1 |
| Myeloma cast Nx | 1 |
| Calcineurin inhibitors-related toxicity | 1 |
| IF/TA grade 3b | 1 |

*Please note that no case of anti-glomerular basement membrane disease was observed.

b On kidney graft biopsy.

880) at kidney biopsy. The remaining 28 patients with no nephrotic syndrome had AKI with a mean serum creatinine level of 569 μmol/L (IQR 388–650) and a mean proteinuria level of 1.6 g/g (IQR 0.97–2.32) (Supplementary data, Table S2).

**Figure 1:** Tubulointerstitial and vascular lesions. (A) Acute tubular injury. Dilatation and flattening of the tubular epithelium with some proteinaceous casts (trichrome stain, ×100). (B) Mild interstitial oedema and mononuclear inflammation associated with acute tubular injury and ischaemic glomerulus (trichrome stain, ×200). (C) Various tubular changes observed in case of collapsing glomerulopathy with dilatation of tubules filled with hyaline casts (star) and cytoplasmic protein droplets (arrow) (trichrome stain, ×61). (D) Marked acute tubular injury with cell fragments within the tubular lumen and flattening of the tubular epithelium (trichrome stain, ×400). Scale bars: 50 μm.
noticed, including loss of the brush border, flattening of the tubular epithelium, tubular microvacuolization, blebbing and tubular cell and tubular basement membrane denudation [i.e. acute tubular necrosis (ATN)] (Figure 1A and D). Interstitial infiltration by mononuclear cells was observed in 80% of patients (Figure 1B). Immunophenotyping was performed in four patients and showed the presence of CD3⁺ T lymphocytes and CD68⁺ macrophages. Associated lesions of diabetic nephropathy (Nx) were observed in one patient. Immunofluorescence study was negative for all cases of acute tubulointerstitial injury.

Focal segmental glomerulosclerosis (FSGS) represented the second dominant pattern in 17 patients, including collapsing (Figure 2A and B), not otherwise specified (Figure 2C) and tip lesion variants (Figure 2D) in 11, 5 and 1 patient, respectively. Collapsing glomerulopathy (CG) was associated with tubular microcystic changes in almost half of patients and periodic acid–Schiff–positive protein resorption droplets in proximal tubules in all patients (Figure 1C). Almost all patients harboured mild–severe acute tubular injury. Immunofluorescence study revealed segmental glomerular deposits of immunoglobulin M (IgM) and C3.

Predominant vascular lesions were also observed in two patients, including a patient with thrombotic microangiopathy characterized by the presence of fibrin thrombi in a glomerulus and a patient with necrotizing arteritis. Both patients also harboured moderate lesions of acute tubular injury.

Finally, varying degrees of interstitial fibrosis (IF) and tubular atrophy (TA), as well as chronic vascular lesions, were also present in a vast majority of patients regardless of the main diagnosis. Ultrastructural examination by electron microscopy was performed in nine patients. No electron-dense deposits were observed by electron microscopy in the patients without pre-existing kidney disease. No viral particles were observed. Interestingly, endothelial injury was noted, including mild (62.5%) and moderate (32.5%) swelling of endothelial cells in the glomerular in eight patients and peritubular capillaries in four patients. Tubuloreticular inclusions were observed in seven patients (Figure 3). Of note, diffuse effacement of podocyte foot processes was observed in seven patients, all of which corresponded to glomerular predominant lesions, except one patient with predominant tubular injury. Mild foot process effacement was also observed in a patient with dominant tubular injury.

Anti-SARS-CoV-2 immunohistochemistry staining was performed on 16 kidney biopsies, including 7 patients with predominant acute tubular injury, 4 with CG, 1 with FSGS and 4 with an alternative diagnosis, and yielded negative results in all patients. Of note, appropriate controls were used, including SARS-CoV-2-positive placenta specimen and SARS-CoV-2-negative kidney biopsy tissues (Figure 4).

Clinicopathological correlations

During hospitalization, three profiles of severity could be distinguished based on the worst WHO progression scale. Five patients (10.6%) remained oxygen-free during the whole COVID-19-associated nephropathy

FIGURE 2: Glomerular lesions in the course of COVID-19. (A) Light microscopy examination showing a case of collapsing glomerulopathy characterized by global collapse of glomerular capillaries associated with marked hyperplasia of podocytes, many of which display abundant cytoplasmic protein droplets (trichrome stain, ×200). (B) The same glomerulus with Maritssone methenamine silver stain highlighting the global collapse of capillaries associated with hyperplasia and swelling of overlying podocytes (Maritssone methenamine silver stain, ×200). (C) Not otherwise specified variant of FSGS showing hyalinosis in this advanced sclerotic lesion. There are also adhesions of the sclerotic segments to Bowman’s capsule (trichrome stain, ×400). (D) Tip lesion variant of FSGS and overlying podocytes at the origin of the proximal tubule (trichrome stain, ×200). Scale bars: 50 μm.
disease course (WHO score 2–4). Eleven (23.4%) with a WHO score of 5 required up to 6 L/min of oxygen therapy, whereas 31 (66%) with a WHO score ≥6 required higher amounts (≥9/L) of oxygen therapy and were referred to the ICU in 93.5% of cases.

All biopsies performed in the ICU showed dominant and severe acute tubular injury. None had evidence for glomerular involvement by light microscopy analysis, except one with a pre-existing chronic diabetic Nx. Most (72.7%) patients with dominant acute tubular injury had experienced severe haemodynamic instability compared with only 16% of patients with alternative pathological diagnosis (P < 0.001). Nevertheless, six (27.3%) patients with isolated acute tubular injury and six (35.3%) patients who underwent a biopsy in the ICU did not experience prominent haemodynamic instability. We did not observe a significant association between the need for vasopressor and the severity of acute tubular injury across the different pathological patterns (P = 0.45). Moreover, the range of uPCR was unexpectedly high (>1 g/g) in 70% of patients with acute tubular injury. Nevertheless, the urine albumin level was not available for all patients but was not markedly increased, arguing against glomerular proteinuria in these patients with acute tubular injury and significant proteinuria. The median albumin level was 19 g/L (IQR 16–23), 18 g/L (IQR 16–22), 22 g/L (IQR 20–22) and 21.5 g/L (IQR 20–25.1) for patients with acute tubular injury, CG, FSGS and another alternative diagnosis, respectively (P = 0.75). Overt nephrotic syndrome was observed in 6 (54.5%) and 5 (83.3%) patients with CG and FSGS, respectively.

Kidney biopsies performed after ICU discharge or in non-critically ill patients displayed an admixed type of renal lesions. CG and FSGS coincided with mild, moderate and severe COVID-19 pneumonia in 4 (23.5%), 6 (35.3%) and 7 (41.2%) patients, respectively. Only 5 (29.4%) of the 17 patients with CG and/or FSGS were admitted to the ICU. Notably, apolipoprotein 1 (APOL1) genotyping was available in 11 patients with either CG (n = 7) or FSGS (n = 4). All seven patients with CG were of African ancestry and harboured highly at-risk combinations of APOL1 variants, including either G1/G1 or G1/G2. In contrast, only two of the four patients with other FSGS variants

**FIGURE 3:** Ultrastructural examination by electron microscopy. Electron microscopy (magnification ×10 000) showing numerous tubuloreticular inclusions (arrows) within glomerular endothelial cell and partial foot process effacement (black asterisks). P, podocyte; L, capillary lumen; white asterisk: glomerular basement membrane. Scale bar: 1 μm.

**FIGURE 4:** Anti-SARS-CoV-2 immunohistochemistry staining. Illustration of anti-SARS-CoV-2-negative staining in patients with COVID-19 and collapsing glomerulopathy (A and B) and predominant acute tubular injury (C and D). Background peroxidase activity is illustrated by anti-SARS-CoV-2 immunostaining in kidney tissue specimens from COVID-19-negative patients (E and F), including a patient with HIV-associated Nx. The specificity of anti-SARS-CoV-2 antibody is demonstrated by the staining of placenta specimens from patients with and without COVID-19 (G and H). Scale bars: 50 μm.
displayed a G1/G2 combination, whereas the remaining two had either G0/G2 (not otherwise specified variant) or G0/G0 (tip variant) genotypes.

In order to establish whether the profile of kidney lesions correlated with the severity of COVID-19, we compared the main kidney pathological findings in the 30 patients admitted to the ICU to the 17 remaining patients (Table 4). Interestingly, the predominant pathological patterns differed significantly between the groups, with ICU patients displaying more frequently predominant acute tubular injury (66.7% versus 0%; P < 0.001). Such findings were also observed when comparing the sickest patients (with a worst WHO score ≥6) to those with a WHO score <6.

### Management and outcome

Antibiotic therapy based on penicillin, third-generation cephalosporin combined with macrolides was given in 40 patients (85.1%) during hospitalization (Table 5). Only a minority of patients received hydroxychloroquine or anti-interleukin-6 (IL-6) antibodies. Seventeen patients (36.2%) were administered antiviral therapy, including a combination of lopinavir and ritonavir in 10 (58.8%) patients.

A total of 30 patients (63.8%) were transferred to the ICU with a median delay of 6 days (IQR 3–11) after initial symptoms. Only a minority of patients required mechanical ventilation (MV). A total of 26 patients (86.7%) developed acute respiratory distress syndrome, as well as two (6.7%) who experienced severe haemodynamic instability, and 12 (40%) developed ventilator-associated pneumonia. After a median follow-up of 37 days (IQR 24–54), 16 patients (53.3%) were still on dialysis, including 10 patients (62.5%) with acute tubular injury, 5 (31.3%) with FSGS and 1 with myeloma cast N. Five of the 12 patients who had pre-existing CKD remained dialysis dependent at the last follow-up. Dialysis was discontinued in 14 patients (46.7%), including 9 patients (64.3%) who developed acute tubular injury, 4 (28.6%) with FSGS and 1 with PLA2R-positive membranous N. No clear correlation was observed between chronicity on the kidney biopsy and recovery and dialysis dependence at the last follow-up. The serum creatinine level in dialysis-free patients was 205 µmol/L (IQR 125–261). Nine patients (19.1%) died either from COVID-19 or related adverse events (Table 4), but no autopsy was undertaken.

### DISCUSSION

We report herein a multicentric case series describing the clinical and histopathological spectrum of kidney damage in patients with COVID-19. Two main histopathological patterns were identified: acute tubular (and interstitial) lesions and glomerular injury mainly consisting of CG. A minority of patients display an alteration of both glomerular and tubular injury. Isolated or combined acute tubular injury represents the predominant pattern, seen mostly in patients with serious forms of COVID-19. Although hypoperfusion has been proposed as an underlying mechanism in these patients, almost one-third of patients with acute tubular injury or those admitted to the ICU did not experience COVID-19-associated nephropathy.

| Pattern | ICU patients (n = 30), n (%) | Non-ICU patients (n = 17), n (%) | P-value |
|---------|----------------------------|-------------------------------|---------|
| Predominant ATN | 20 (66.7) | 0 (0) | <0.001 |
| CG/FSGS | 3 + 2 (16.7) | 8 + 4 (70.6) | <0.001 |
| Vascular Nx | 2 (6.7) | 0 (0) | Not significant |
| Other | 3 (10) | 5 (29.4) | Not significant |

n refers to the number of patients per group.

| Factors | Patients (N = 47) |
|---------|-----------------|
| Treatment, n (%) | |
| Antibiotherapy | 40 (85.1) |
| Azithromycin | 22 (46.8) |
| Hydroxychloroquine | 9 (19.1) |
| Anti-IL-6 antibodies | 2 (4.3) |
| Antiviral treatment | 17 (36.2) |
| Respiratory evolution, n (%) | |
| Worst WHO score 2–4 | 5 (10.6) |
| Worst WHO score 5 | 11 (23.4) |
| Worst WHO score ≥6 | 31 (66.0) |
| Acute dialysis, n (%) | 30 (63.8) |
| Transfer to the ICU, n (%) | 30 (63.8) |
| Time from initial symptoms (days), median (IQR) | 6 (3–11) |
| MV | 28 (93.3) |
| ECMO | 3 (10) |
| Vasopressive support | 20 (66.7) |
| Acute respiratory distress syndrome | 26 (86.7) |
| Ventilator-associated pneumonia | 12 (40) |
| Renal status at last follow-up, n (%) | |
| Follow-up (days), median (IQR) | 37 (24–54) |
| Ongoing dialysis | 16 (34.0) |
| Serum creatinine level (µmol/L)*, median (IQR) | 205 (125–261) |
| Other complications, n (%) | |
| Atrial fibrillation | 6 (12.8) |
| Bleeding | 6 (12.8) |
| Pulmonary embolism | 2 (4.3) |
| Other thrombosis | 5 (10.6) |
| Death | 9 (19.1) |
| Delay from initial symptoms (days), median (IQR) | 19 (16–25) |
| Refractory shock | 4 (44.4) |
| Refractory acute respiratory syndrome | 5 (55.6) |
| Status at last follow-up of the surviving patients, n (%) | |
| Discharge from hospital | 26 (68.4) |
| Discharge from ICU but still on hospital | 12 (31.6) |

*After exclusion of patients who required renal replacement therapy at last follow-up.

Table 4. Comparison of the main histopathological pattern of kidney lesions with respect to the severity of COVID-19 (as assessed by ICU admission)

Table 5. Initial management and outcome
prominent haemodynamic instability. These findings suggest that additional factors may likely contribute to tubular damage in the setting of COVID-19 pneumonia, including tissue hypoxia, rhabdomyolysis and the so-called 'cytokine storm', as suggested by the identification by electron microscopy of interferon footprints in glomerular capillary endothelial cells. Hypercoagulability and microangiopathy with complement cascade activation should also be considered [18]. The swelling of endothelial cells, as assessed by electron microscopy, points to endothelial injury as a potential mechanism to explain severe renal damage, as also reported in other organs such as the lungs and heart [19–22]. Alternatively, a direct viral cytopotoxicity on renal cells has been widely debated in the literature, mainly supported by the expression in the kidneys of proteins that facilitate SARS-CoV-2 infection, including angiotensin-converting enzyme (ACE) 2 and transmembrane protease serine 2 [18, 23, 24]. Recent reports have shown positive immunohistochemical staining for SARS-CoV-2 nucleocapsid protein in post-mortem kidneys [12, 13, 25]. Nevertheless, the presence of viral particles within tubular epithelial cells and podocytes remains controversial [14, 26, 27]. Similar to recent reports, we did not observe kidney expression of SARS-CoV-2 nucleoprotein in our study, suggesting the absence of kidney infection by the virus [15, 16, 28].

In addition to tubular damage, COVID-19 may be associated with notable glomerular lesions, particularly in non-critically ill patients, widening the spectrum of COVID-19-associated Nk. In line with recent case reports, CG represents the predominant histopathological pattern of glomerular lesions seen in the course of COVID-19 [14, 29–33]. This peculiar variant of FSGS is characterized by segmental or global glomerular tuft collapse with hypertrophy and hyperplasia of the overlying podocytes [34, 35]. Accompanying acute tubular injury, tubular dilations with microcyst formation and interstitial inflammation, as commonly seen in HIV-associated Nk [36], were less prominent in patients with COVID-19. As in our series, all patients with COVID-19-associated CG previously reported in the literature displayed AKI, heavy proteinuria and hypoalbuminaemia [29–33]. It should be noted that CG and FSGS coincided with varying degrees of severity COVID-19 pulmonary involvement, suggesting that unlike patients with dominant tubulointerstitial lesions, COVID-19-associated glomerular injury is likely multifactorial and somehow unrelated to the severity of respiratory involvement [37]. In this regard, some cases of glomerular involvement may also occur after the recovery of respiratory signs [37]. Because CG and FSGS may be primary or secondary to a wide range of causes, including viral infections and inflammatory diseases [35], many authors suggest a similar causality with SARS-CoV-2 [38, 39]. Nevertheless, several groups failed to detect SARS-CoV-2 RNA by in situ hybridization or RT-PCR on kidney biopsies [29–31, 33, 40]. The term 'COVID-19-associated Nk' should thus be preferred to that of 'SARS-CoV-2 Nk' to stress the point that the demonstration of a direct or indirect role of SARS-CoV-2 in kidney injury remains an unsolved issue to date. Importantly, we and others have identified a crucial role of APOL1 high-risk variants (i.e. G1/G1, G1/G2 or G2/G2 genotypes) in the risk of COVID-19-associated CG [14]. A plausible model is that COVID-19, irrespective of a direct or indirect role of SARS-CoV-2, acts as a second hit that results in podocyte injury and various histopathological patterns depending on the genetic background [14].

In conclusion, the spectrum of COVID-19-associated Nk includes both tubular and glomerular lesions with likely distinctive pathophysiological mechanisms. Kidney biopsy is very helpful to determine the precise nature of renal lesions during COVID-19 and guide subsequent management. Tubular damage is predominantly observed in most severe respiratory cases and may be related to haemodynamic changes and other additional factors. Glomerular lesions, including CG and FSGS, are predominantly observed in non-critically ill patients without an obvious correlation with the severity of respiratory signs. The carriage of APOL1 high-risk variants is crucial to understand the pattern of glomerular lesions. While a direct or indirect effect of SARS-CoV-2 on kidney lesions is a current hot topic in the nephrology field, further investigations using trustworthy tools are necessary to decipher the pathophysiology of COVID-19-associated kidney damage. Finally, and beyond diagnosis, it will also be interesting to correlate kidney biopsy findings to renal recovery and outcome at a distance from the COVID-19 episode.

**CONCISE METHODS**

**Study population**

We included all patients with COVID-19 who underwent a kidney biopsy in nine different nephrology and ICU departments in the Paris region from 8 March to 19 May 2020. A case of COVID-19 was defined by a positive result on an RT-PCR assay based on the WHO standard and targeting the SARS-CoV-2 E gene and RdRp gene of a specimen collected on a nasopharyngeal swab. In case of negative RT-PCR, a second RT-PCR could be performed. Alternatively, the diagnosis could also be established from the results of a chest CT scan, showing ground-glass opacities with or without consolidative abnormalities highly suggestive of COVID-19 infection. The study was approved by the local institutional review board as minimal-risk research using retrospective data collected for routine clinical practice. A declaration on the Commission Nationale de l’Informatique et des Libertés was made according to the French law (Loi Jardé and its subsequent amendments).

**Data collection**

Patients’ data were obtained through a retrospective review of the electronic medical records. Three patients have already been reported as single cases [32, 33]. Demographic data and comorbidities included age, sex, hypertension, diabetes mellitus, body mass index (BMI) and other coexisting comorbidities, including CKD, cardiovascular disease, use of angiotensin receptor blockers (ARBs) or ACE inhibitors and other notable past medical history. The date and nature of presenting signs and oxygen saturation (SpO₂) and oxygen level to reach an oxygen saturation ≥94% were collected. The WHO progression scale (Supplementary data, Table S4) was used to establish three
groups of severity on admission and during follow-up including ambulatory or hospitalized patients who did not require oxygen therapy (WHO score 2–4), hospitalized patients who needed oxygen therapy up to 6 L/min by mask or nasal prongs (WHO score 5) and hospitalized patients who required greater amounts of oxygen therapy by non-invasive ventilation or intubation and MV (WHO score ≥6). The maximum level of oxygen before ICU transfer, use of non-invasive ventilation and MV and severe events during hospitalization, including acute respiratory distress syndrome, thrombosis, bleeding, cardiac arrhythmia, sepsis, and death were also recorded. Dates of admission, transfer to the ICU, initiation of dialysis, MV and date of discharge from the ICU and from the hospital were collected. All laboratory tests and radiologic assessments were performed at the discretion of the physician. Laboratory data included the results of the SARS-CoV-2 RT-PCR nasal or pharyngeal swab specimens and the values of biological parameters on admission and during hospitalization (extreme values), including serum levels of electrolytes, albumin, lactate dehydrogenases, ferritin, C-reactive protein, procalcitonin, D-dimers, fibrinogen and haemoglobin, and lymphocyte, neutrophil and platelet counts. Renal parameters included serum creatinine, urine protein and urine red and white blood cell counts. AKI was scored according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for AKI (https://kdigo.org/guidelines/acute-kidney-injury/). Proteinuria and nephrotic range proteinuria were defined by urine protein >0.3 g/day and ≥3 g/day, respectively. The results of chest CT scan were graded as mild, moderate and severe according to the extent of pulmonary lesions as follows: <10%, 10–25% and 25–50% of the lung parenchyma, respectively. The administration of antibiotics and other notable drugs such as anti-IL-6 antibodies and hydroxychloroquine was also recorded. Patient data were censored at the time of data cut-off, which occurred on 30 May 2020.

**Kidney biopsy processing**

Kidney biopsy specimens were immersed immediately after removal in alcohol–formalin–acetic acid, embedded in paraffin, cut into 3-μm sections and stained with haematoxylin–eosin–saffron, periodic acid–Schiff, Masson’s trichrome and Jones or Marinozzi methenamine silver. Immunofluorescence study was performed in all cases. The presence of immune deposits was determined based on immunostaining for IgG, IgM, IgA, C3, C1q and kappa and lambda light chains. Electron microscopy analysis was performed in nine patients according to the following protocol: samples were fixed in 2.5% glutaraldehyde in 0.1 mmol/L cacodylate buffer (pH 7.4) at 4°C. Fragments were then post-fixed in 1% osmium tetroxide, dehydrated using alcohol series and embedded in epoxy resin. Semithin sections (0.5 μm) were stained using toluidine blue. Ultrastructure sections (80 nm) were contrast enhanced using uranyl acetate and lead citrate and they were examined using a JEOL 1010 electron microscope (JEOL, Tokyo, Japan).

All kidney biopsies were analysed locally by experts in renal pathology (S.F., C.M., D.B., I.B., A.S. and A.M.) from five French departments belonging to the Club Francophone de Pathologie Rénale group. A total of 37 renal biopsy specimens were centrally reviewed by S.F. to establish a scoring of renal lesions by light microscopy. The IF, oedema, inflammatory infiltrate and acute tubular injury lesions were estimated semi-quantitatively and classified as mild if they affected up to 25% of the cortical area, moderate for 26–50% and severe for >50%. Vascular lesions were evaluated according to the severity of the thickness of the intima for arteries and the proportion of vessels showing hyalinosis for arterioles.

Immunohistochemistry staining was performed on 16 renal tissue sections from our series (seven patients with predominant ATN, four with CG, one with FSGS and four with alternative diagnosis) on a semi-automated Bond-III Leica instrument using anti-SARS-CoV-2 primary antibody (Abclonal, rabbit pAB, 2019-nCoV N Protein, citrate pH 6 pre-treatment, 1:200). The sections were treated with a solution of peroxidase-labelled streptavidin and the colour reaction was developed by incubation with 3,3′-diaminobenzidine according to the Bond Polymer Refine detection kit instructions. The nuclei were then counterstained with haematoxylin. Positive controls (SARS-CoV-2-positive placental and broncho-alveolar specimens) and negative (SARS-CoV-2-negative renal biopsy and placenta) controls were done and yielded appropriate results.

**Statistical analysis**

Descriptive statistics were used to summarize the data. Results are reported as medians with IQR for continuous variables and counts and percentages for categorical variables. Univariate analyses were performed using the Kruskal–Wallis test and the chi-squared or Fisher’s exact test, as appropriate. A P-value <0.05 was considered significant.

**Supplementary data**

Supplementary data are available at ndt online.

**Conflict of interest statement**

The authors have no conflicts of interest to declare.

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