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SARS-CoV-2 Causes a Specific Dysfunction of the Kidney Proximal Tubule

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on behalf of the CUSL COVID-19 Research Group

Supplementary material

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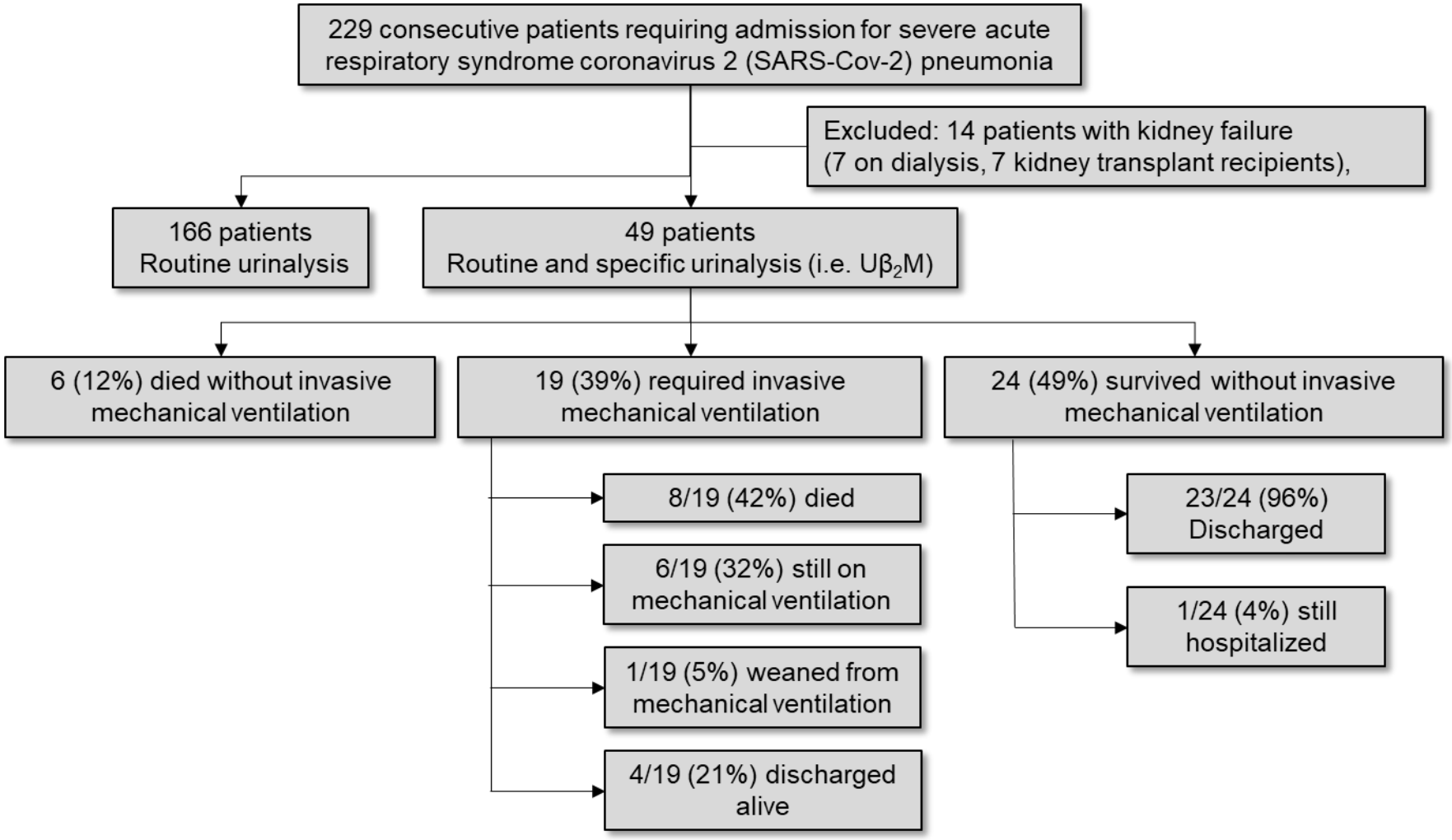
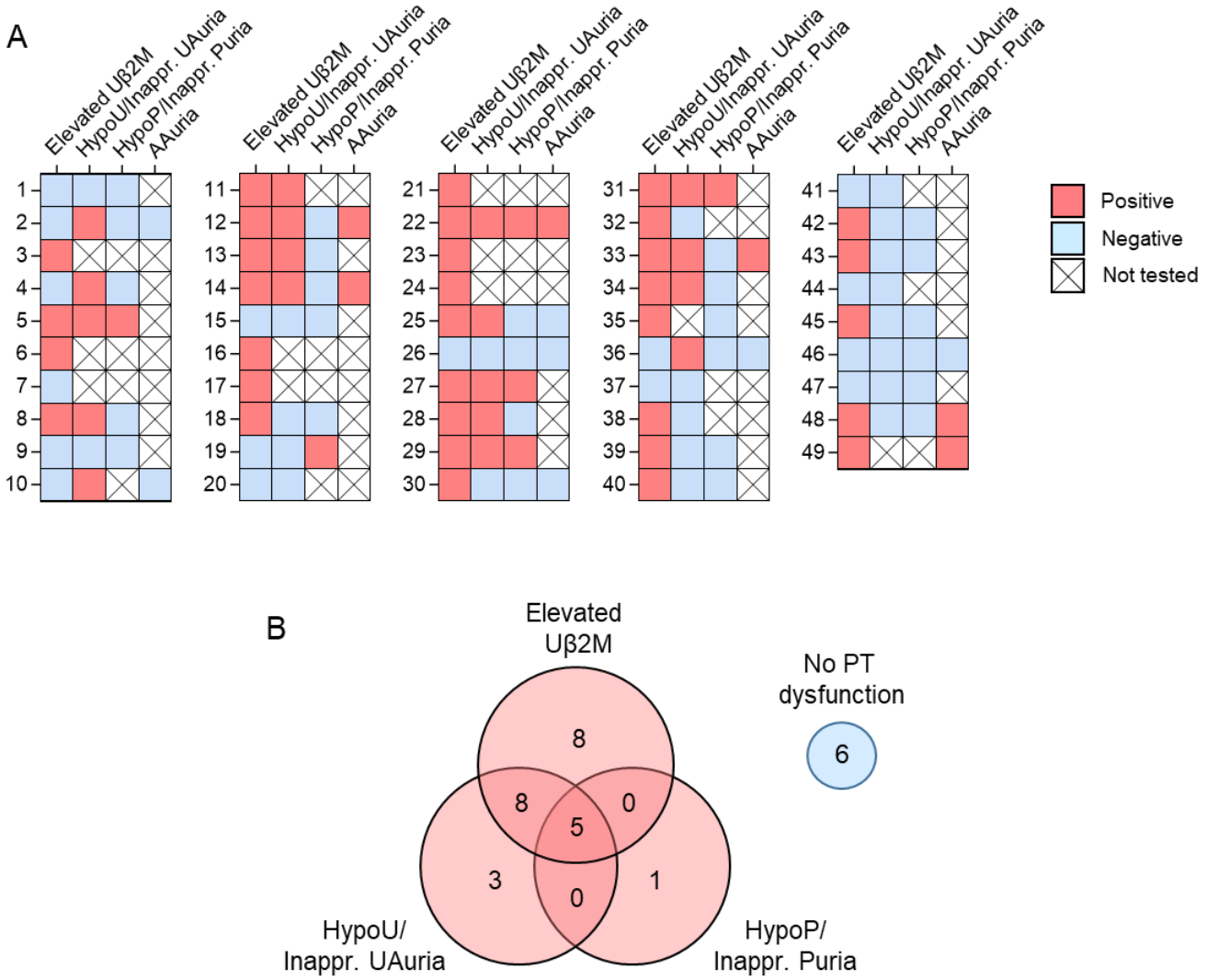
Supplementary Figure 1. Flowchart of the study.



Uβ2M, urinary β2-microglobulin.

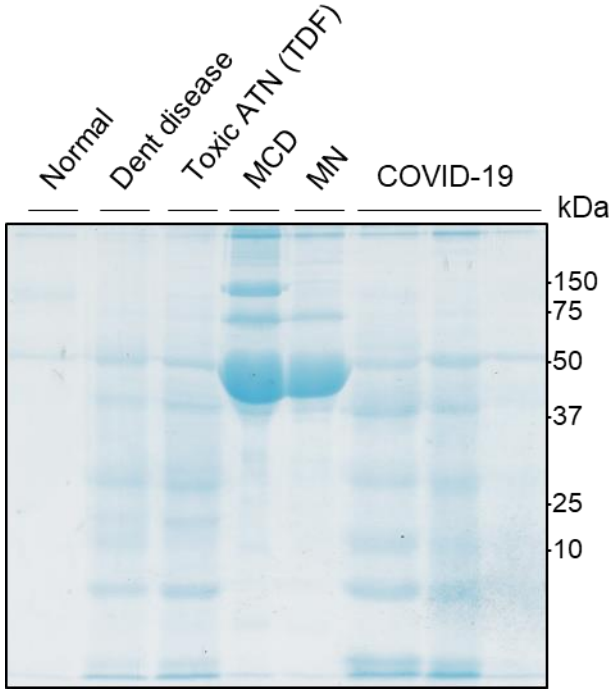
Supplementary Figure 2. Manifestations of proximal tubule dysfunction in individual patients with COVID-19.



A. Presence (red) or absence (blue) of elevated urinary β_2-microglobulin ($U\beta_2M$), hypouricemia with inappropriate uricosuria (HypoU/Inappr. UAuria), hypophosphatemia with inappropriate phosphaturia (HypoP/Inappr. Puria) and aminoaciduria (AAuria) in the 49 patients included in the study (rows labelled from 1 to 49). Patients who were not tested are represented by ticked boxes.

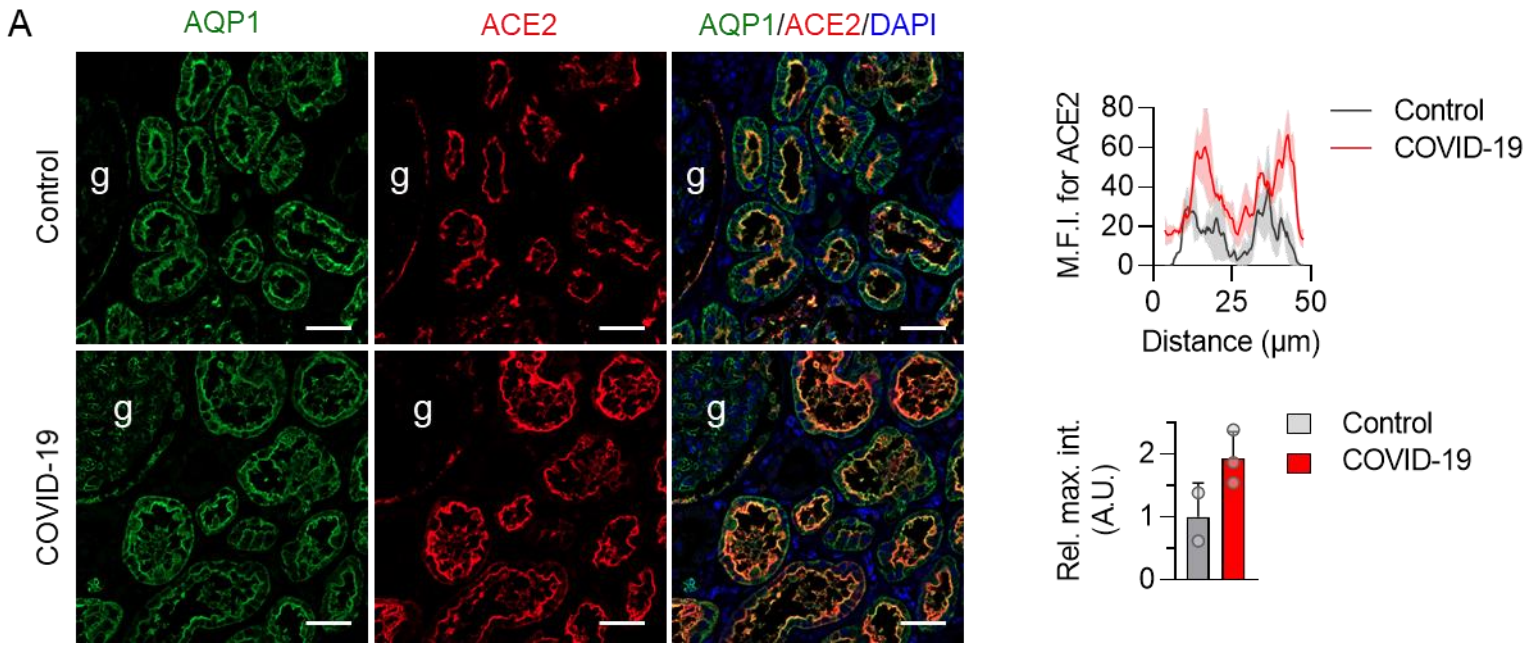
B. Distribution and co-existence of signs of PT dysfunction among the 31 patients with available testing for $U\beta_2M$, HypoU/Inappr. UAuria, and HypoP/Inappr. Puria. The presence of AAuria was not included in the diagram because of the small number of patients tested. Numbers in circles indicate how many patients present the respective PT defects or combinations of them.

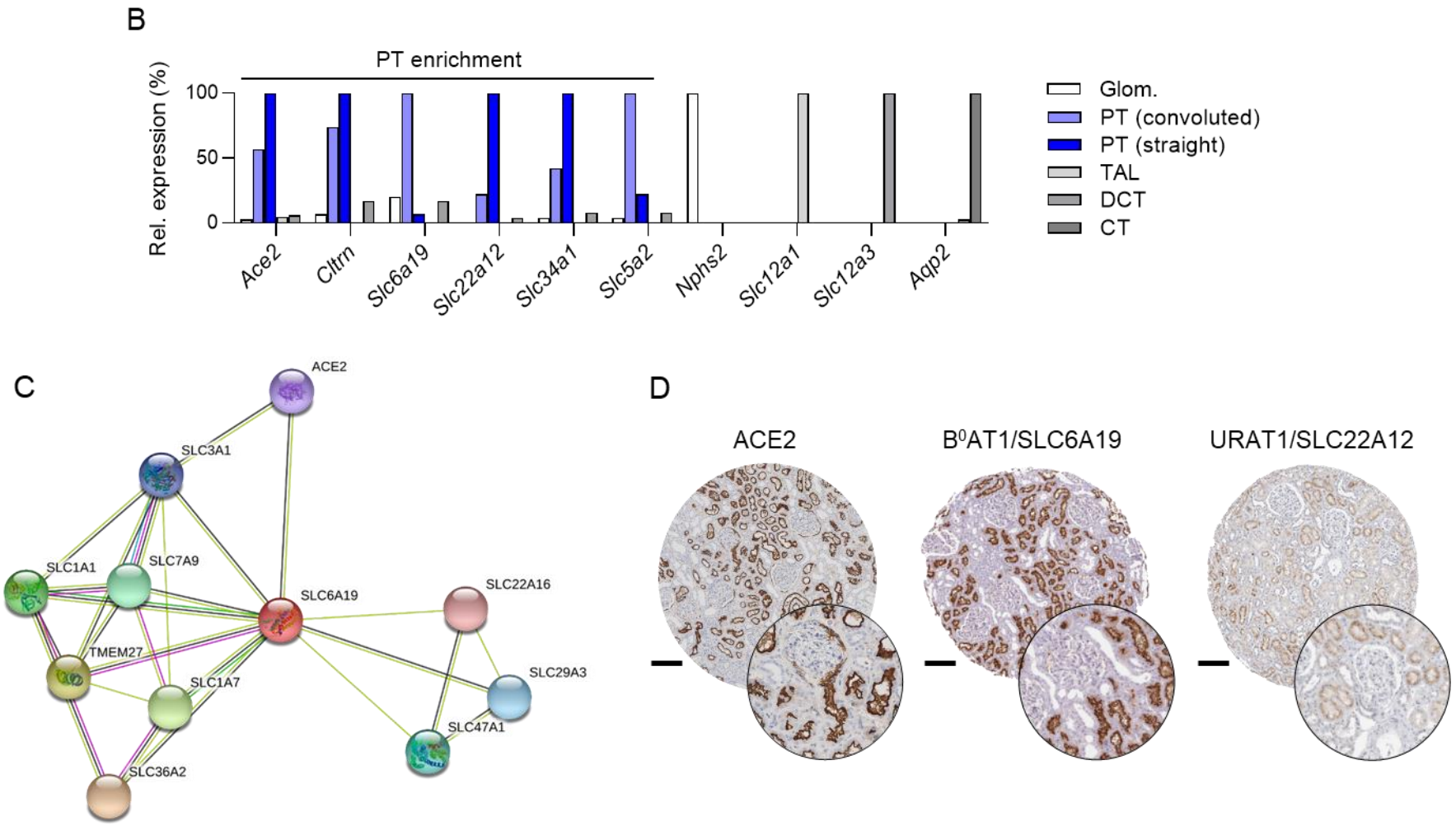
Supplementary Figure 3. Low-molecular weight proteinuria in patients with COVID-19 and controls.



Sodium dodecyl sulfate polyacrylamide gel electrophoresis followed by Coomassie blue staining shows the presence of low-molecular weight proteins in the urine of some patients with COVID-19, compared to patients with Dent disease, toxic acute tubular necrosis (ATN) secondary to tenofovir disoproxil fumarate (TDF), or heavy albuminuria caused by minimal change disease (MCD) or membranous nephropathy (MN). Each lane was loaded with 5-20 µl of urine after normalization for urinary creatinine concentration.

Supplementary Figure 4. Expression of ACE2 in the proximal tubule and interaction with solute transporters.




B
PT enrichment
Rel. expression (%)
100
50
0
Ace2
Cltrn
Slc6a19
Slc22a12
Slc34a1
Slc5a2
Nphs2
Slc12a1
Slc12a3
Aqp2
Glom.
PT (convoluted)
PT (straight)
TAL
DCT
CT
C
ACE2
SLC3A1
SLC1A1
SLC7A9
SLC6A19
SLC22A16
TMEM27
SLC1A7
SLC29A3
SLC47A1
SLC36A2
D
ACE2
B0AT1/SLC6A19
URAT1/SLC22A12

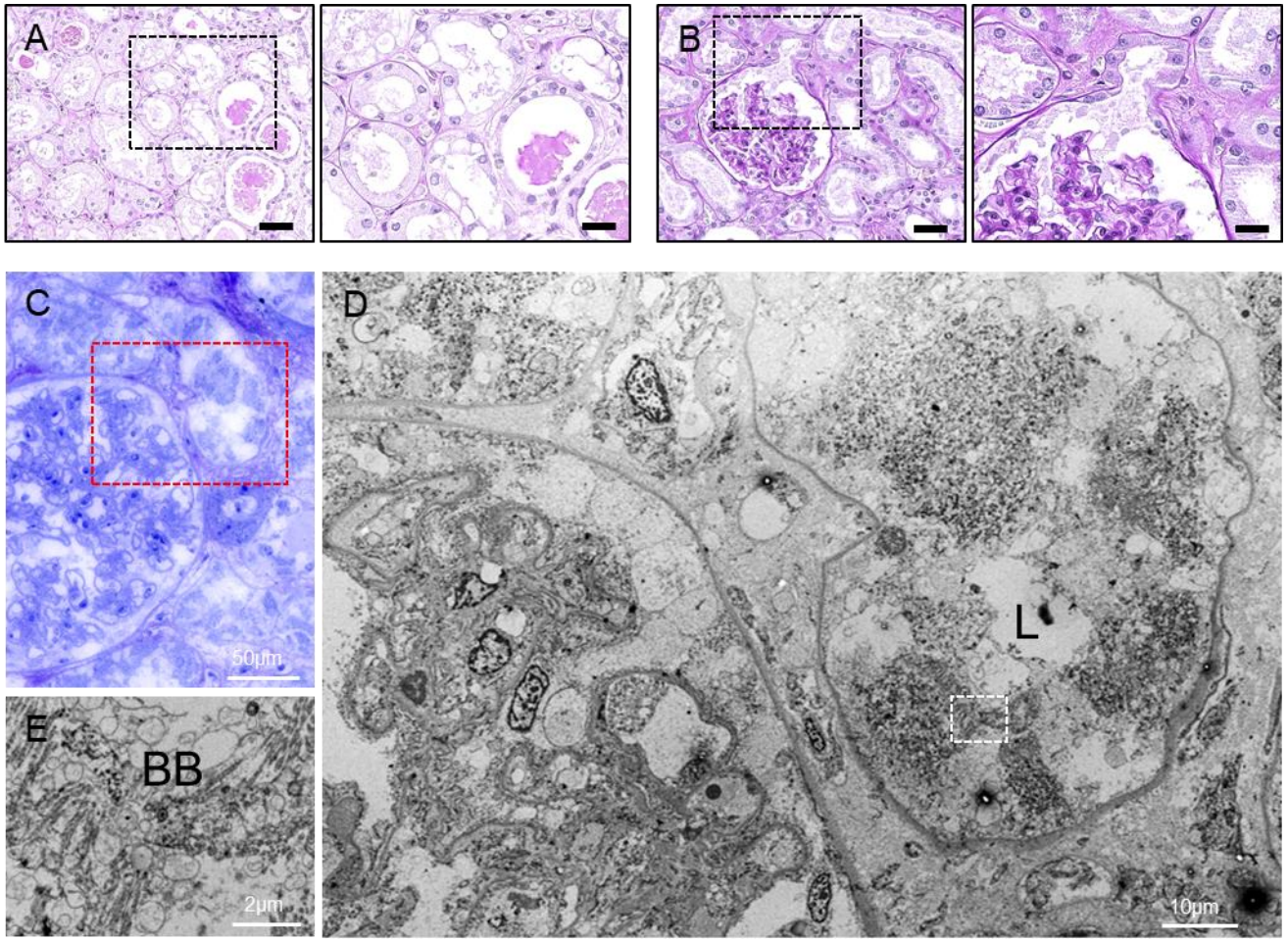
A. Representative pictures of double immunostaining with anti-AQP1 (green channel) and anti-ACE2 (red channel) antibodies viewed under confocal fluorescence microscopy in kidney sections from a control and a patient with COVID-19. Nuclei are stained with DAPI (blue channel). Original magnification, 20x. Bars, 50 µm. Mean fluorescence intensity (M.F.I.) profiles and relative maximal intensity (rel. max. int.) for ACE2 were quantified on cross-sectional sections of PT from 2 controls (grey) and 3 patients who died of COVID-19 (red). Data are mean values and s.e.m.

B. mRNA levels of *Ace2* (encoding for SARS-Cov-2 receptor ACE2), *Cltr* (collectrin or TMEM27), *Slc6a19* (B^0AT1), *Slc22a12* (URAT1), *and Slc34a1* (NaPi-IIa) in specific segments of the mouse nephron analyzed by SYBR green–quantitative PCR. Segment–related genes were used to assess the purity of each fraction: glomerulus (glom.), *Nphs2*, white bars; proximal tubule (PT) (convoluted), *Scl5a2*, light blue; PT (straight), *Slc38a3*, dark blue; thick ascending limb (TAL) of Henle's loop, *Slc12a1*, light grey; distal convoluted tubule (DCT) , *Slc12a3*, intermediate grey; collecting duct (CT), *Aqp2*, dark grey. Quantification of targeted gene was done in comparison with *Gapdh* (n=4).

C. Connectivity network of the interactions between human SLC6A19 (B^0AT1) and other proteins including the SARS-Cov-2 receptor ACE2 and the related protein TMEM27 (collectrin), established using the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database. https://string-db.org/cgi/network.pl?taskId=rsSG9HZgqGNS (accessed on May 31, 2020).

D. Expression of ACE2, URAT1/SLC22A12 and B^0AT1/SLC6A19 in the normal human kidney. URAT1 and B^0AT1 staining were obtained from the Human Protein Atlas, v15.proteinatlas.org, accessed on May 26, 2020.

Supplementary Figure 5. Proximal tubule lesions in the kidneys of patients with COVID-19.



A. Periodic-acid Schiff-stained sections showing tubular injury and vacuolization of proximal tubule cells in a non-diabetic patient who did not receive intravenous iodine-contrast media nor immunoglobulins.
B. Periodic-acid Schiff-stained sections showing alterations of the brush border in the S1 segment of the proximal tubule (B). Original magnification (A and B), 20x and 40x; scale bars, 50 µm and 25 µm.
C. Toluidine blue staining of semi-thin section, showing disorganization of proximal tubule architecture close to a damaged glomerulus and a relatively preserved macula densa. Red square contains image observed by transmission electron microscopy (TEM).
D. Ultrastructure of proximal tubule and glomerulus by TEM, showing the degeneration of proximal tubule epithelial cells and extensive cytoplasmic vacuolization. Vacuolated parietal epithelial cells were also observed at the Bowman's capsule. The basement membrane structures remain relatively well-preserved for both proximal tubule and Bowman's capsule. White square contains image at higher magnification.
E. Disorganized residual brush border among luminal debris in the proximal tubule. L: Lumen, BB: brush border.

Supplementary Table 1. Baseline characteristics and treatment of patients who underwent routine versus specific urinalysis.

Demographics and comorbidities	Whole cohort n=215	Routine urinalysis n=166	Specific urinalysis n=49
Age, median (IQR), years	67 (56-81)	67 (56-84)	64 (54-74)
Male gender – no. (%)	117 (54)	83 (50)	34 (69)
Ethnicity – no. (%)			
Caucasian	180 (84)	138 (83)	42 (86)
Sub-Saharan African	31 (14)	25 (15)	6 (12)
Other	4 (2)	3 (2)	1 (2)
Cardiovascular disease – no. (%)	49 (23)	40 (24)	9 (18)
Chronic kidney disease – no. (%)	43 (20)	36 (22)	7 (14)
Hypertension – no. (%)	105 (49)	82 (49)	23 (47)
Diabetes – no. (%)	51 (24)	41 (25)	10 (20)
Human immunodeficiency virus infection – no. (%)	3 (1)	3 (2)	0 (0)
Chronic liver disease – no. (%)	5 (2)	4 (2)	1 (2)
Chronic pulmonary disease – no. (%)	21 (10)	15 (9)	5 (12)
Medications – no. (%)			
Allopurinol or febuxostat	12 (6)	8 (5)	4 (8)
Angiotensin receptor blocker	31 (14)	21 (13)	10 (20)
ACE inhibitor	43 (20)	33 (20)	10 (20)

Chronic immunosuppressive treatment[a]	16 (7)	12 (7)	4 (8)
Anti-cancer drugs[b]	9 (4)	5 (3)	4 (8)
Symptoms and vitals at admission			
Duration of symptoms, median (IQR), days	6 (2-8)	6 (2-8)	7 (3-9)
Symptoms at admission – no. (%)			
Fever	165/214 (77)	126/165 (76)	39 (80)
Cough	140/213 (66)	111/164 (76)	29 (59)
Dyspnea	148/213 (69)	113/164 (69)	35 (71)
Sore throat	24/213 (11)	22/164 (13)	2 (4)
Confusion	27/213 (13)	21/164 (13)	6 (12)
Anosmia/agueusia	19/213 (9)	13/164 (8)	6 (12)
Rhinitis	38/213 (18)	31/164 (19)	7 (14)
Diarrhea	50/213 (23)	36/164 (22)	14 (29)
Chest pain	14/213 (7)	10/164 (6)	4 (8)
Admission via emergency department – no. (%)	208 (97)	161 (97)	47 (96)
Sa02, median (IQR), %	91 (88-95)	91 (88-95)	92 (87-96)
Systolic BP, median (IQR), mmHg	134 (121-149)	132 (120148)	139 (126-150)
Diastolic BP, median (IQR), mmHg	77 (68-84)	77 (68-85)	75 (69-82)
Heart rate, median (IQR), bpm	90 (82-102)	90 (80-101)	93 (88-103)
Lab tests and dipstick urinalysis at admission			
hsCRP, median (IQR), mg/l	77 (39-130)	71 (35-125)	105 (54-146)

Glycemia, median (IQR), mg/dl	119 (105-139)	117 (105-139)	121 (109-146)
Serum creatinine, median (IQR), mg/dl	1.0 (0.8-1.2)	1.0 (0.8-1.3)	1.0 (0.8-1.2)
eGFR, median (IQR), ml/min/1.73 m2	71 (49-84)	71 (48-84)	72 (54-92)
Serum uric acid, median (IQR), mg/dl	4.8 (3.7-6.2)	4.8 (3.8-6.3)	4.9 (3.3-5.9)
Sodium, median (IQR), mmol/l	137 (134-140)	137 (134-140)	135 (133-138)
Bicarbonate, median (IQR), mmol/l	24 (22-26)	25 (23-27)	23 (22-25)
AST, median (IQR), IU/l	36 (27-59)	36 (27-61)	36 (24-53)
ALT, median (IQR), IU/l	27 (17-44)	27 (17-43)	27 (17-46)
Total bilirubin, median (IQR), mg/dl	0.5 (0.4-0.6)	0.5 (0.3-0.6)	0.5 (0.4-0.7)
CK, median (IQR), IU/l	116 (65-293)	116 (62-293)	119 (74-211)
LDH, median (IQR), IU/l	353 (272-452)	353 (267-448)	356 (279-491)
Lymphocytes, median (IQR), n/µl	840 (600-1160)	870 (650-1180)	650 (500-1060)
Platelets, median (IQR), 10^3/µl	204 (139-254)	204 (146-259)	203 (131-233)
Dipstick proteinuria – no. (%)			
0	36/169 (21)	28/126 (22)	8/43 (19)
1+	55/169 (33)	42/126 (33)	13/43 (30)
2+	68/169 (40)	49/126 (39)	19/43 (44)
3+	10/169 (6)	7/126 (6)	3/43 (7)
Computed tomography scan of the chest upon admission			
Extent of lesions on chest CT scan – no. (%)			
<10%	26/173 (15)	22/128 (17)	4/45 (9)

10-25%	65/173 (38)	47/128 (37)	18/45 (40)
25-50%	54/173 (31)	40/128 (31)	14/45 (31)
>50%	28/173 (16)	19/128 (15)	9/45 (20)
Drugs received for COVID-19			
Hydroxychloroquine – no. (%)	177 (82)	129 (78)	48 (98)
Azithromycin – no. (%)	24 (11)	17 (10)	7 (14)
Anti-viral drugs[c] – no. (%)	2 (1)	2 (1)	0 (0)
Immunomodulatory drugs[d] - no. (%)	30 (14)	14 (8)	16 (33)

[a]Chronic immunosuppressive treatment included (one or more per patient) ciclosporin A (1), corticosteroids (10), methotrexate (2), rituximab (1), etanercept (1), mycophenolate mofetil (1), ocrelizumab (1), tocilizumab (2). [b]Anti-cancer drugs included cyclophosphamide (1), doxorubicine (1), vincristine (1), venetoclax (1), cisplatin (2), cytarabine (1), axitinib (1), bortezomib (2), thalidomide/pomalidomide (2), paclitaxel (1). [c]Antiviral drugs included favipiravir (1) and lopinavir (1). [d]Immunomodulatory drugs for COVID-19 (one or more per patient) included corticosteroids (18), interleukin-7 (11), tocilizumab (1). Continuous variables are expressed as median and interquartile range (IQR), and categorical variables as numbers (no.) and percentages (%). Sa02, oxygen saturation while breathing ambient air; BP, blood pressure; eGFR, CKD-EPI estimated glomerular filtration rate; hsCRP, highly-sensitive C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; CT, computed tomography.

Supplementary Table 2. Characteristics of COVID-19 patients of whom urine was tested for the presence of LMW proteins by immunoblot (Fig. 1D).

Lane	Age (years)	Gender	Hypertension	Diabetes
1	68	Male	-	+
2	63	Male	+	-
3	47	Male	-	-
4	64	Male	-	-
5	46	Male	+	-
6	82	Female	+	-
7	59	Male	+	+

Supplementary Table 3. Urinary concentration of aminoacids in COVID-19 patients.

(mmol/mol creat.)	Normal range	Aminoaciduria (n=6)	No aminoaciduria (n=7)
Neutral			
Threonine	7-29	93±80	15±4
Serine	21-50	133±48	36±11
Asparagine	0-23	70±29	13±4
Glutamine	20-76	138±46	43±15
Tyrosine	2-23	26±7	9±3
Tryptophan	2-10	14±4	5±4
Alanine	16-68	72±34	26±5
Glycine	43-173	173±93	59±27
Isoleucine	0-4	3±1	2±1
Leucine	2-11	5±1	5±3
Valine	3-13	9±1	5±3
Methionine	2-16	8±2	7±2
1/2 cystine	6-34	29±7	17±6
Phenylalanine	2-19	15±4	7±2
Proline	0-9	1±0	1±1
Basic			
Arginine	0-5	4±1	2±2
Histidine	26-153	121±34	48±37
Lysine	7-58	64±37	36±20
Acidic			
Aspartate	2-7	5±2	5±1
Glutamate	0-12	10±3	4±2

Data are means ± SD (mmol/mol creatinine).

Supplementary Table 4. Characteristics of COVID-19 patients with and without elevated urinary β2-microglobulin.

	Normal Uβ2M n=16	Elevated Uβ2M n=33	P
Baseline characteristics			
Age, median (IQR), years	63 (57-71)	64 (54-76)	0.91
Male gender – no. (%)	9 (56)	25 (76)	0.17
Fever – no. (%)	12 (75)	27 (82)	0.58
Dyspnea – no. (%)	11 (69)	24 (73)	0.77
Diarrhea – no. (%)	3 (19)	11 (33)	0.29
Viral load, median (IQR), Ct	33 (28-35)	31 (27-35)	0.66
Disease severity			
Nadir lymphocyte count, median (IQR), per µl	455 (200-905)	390 (250-550)	0.56
Peak hsCRP, median (IQR), mg/l	256 (109-350)	199 (125-333)	0.78
Peak LDH, median (IQR), IU/l	465 (391-604)	494 (357-622)	0.90
Peak D-dimers, median (IQR), ng/ml	1727 (1143-7118)	1979 (1234-5090)	0.98
Proximal tubule dysfunction			
Aminoaciduria – no. (%)	0/5 (0)	6/8 (75)	0.008
Hypouricemia/inappr. uricosuria – no. (%)	4/15 (27)	14/24 (58)	0.05
Hypophosphatemia/inappr. phosphaturia – no. (%)	1/10 (10)	5/22 (23)	0.39
Outcomes			
Follow-up, median (IQR), days	48 (30-57)	44 (31-54)	0.44
Mechanical ventilation – no. (%)	6 (38)	13 (39)	0.90
Death – no. (%)	5 (31)	9 (27)	0.77
Acute kidney injury – no. (%)	3 (19)	8 (24)	0.67
Hospital length of stay, median (IQR), days	17 (13-31)	17 (9-31)	0.96

Uβ2M, urinary β2-microglobulin; hsCRP, highly sensitive C-reactive protein; LDH, lactate dehydrogenase; inappr., inappropriate.

Supplementary Table 5. Characteristics of COVID-19 patients with and without hypouricemia and inappropriate uricosuria.

	Hypouricemia with inappropriate uricosuria		
	Absent n=21	**Present n=18**	**P**
Baseline characteristics			
Age, median (IQR), years	60 (54-75)	67 (61-73)	0.44
Male gender – no. (%)	11 (52)	13 (72)	0.20
Fever – no. (%)	16 (76)	15 (83)	0.58
Dyspnea – no. (%)	16 (76)	12 (67)	0.51
Diarrhea – no. (%)	5 (24)	6 (33)	0.51
Viral load, median (IQR), Ct	33 (30-35)	31 (26-35)	0.30
Disease severity			
Nadir lymphocyte count, median (IQR), per µl	500 (280-910)	250 (100-360)	0.006
Peak hsCRP, median (IQR), mg/l	126 (51-245)	324 (243-349)	0.002
Peak LDH, median (IQR), IU/l	394 (317-466)	584 (524-726)	<0.001
Peak D-dimers, median (IQR), ng/ml	1234 (753-2827)	4461 (2098-13348)	0.001
Proximal tubule dysfunction			
Elevated Uβ2M – no. (%)	10 (48)	14 (78)	0.05
Hypophosphatemia/inappr. phosphaturia – no. (%)	1 (7)	5 (31)	0.008
Aminoaciduria – no. (%)	1/4 (25)	4/8 (50)	0.41
Outcomes			
Follow-up, median (IQR), days	42 (37-52)	38 (17-57)	0.68
Mechanical ventilation – no. (%)	3 (14)	15 (83)	<0.001
Death – no. (%)	3 (14)	9 (50)	0.02
Acute kidney injury – no. (%)	3 (14)	3 (17)	0.84
Hospital length of stay, median (IQR), days	12 (6-17)	27 (17-46)	<0.001

$U\beta_2M$, urinary β_2-microglobulin; hsCRP, highly sensitive C-reactive protein; LDH, lactate dehydrogenase; inappr., inappropriate.

Supplementary Table 6. Characteristics of COVID-19 patients with and without hypophosphatemia and inappropriate phosphaturia.

	Hypophosphatemia with inappropriate phosphaturia		
	Absent n=26	**Present n=6**	**P**
Baseline characteristics			
Age, median (IQR), years	62 (54-73)	72 (64-77)	0.19
Male gender – no. (%)	17 (65)	3 (50)	0.48
Fever – no. (%)	21 (81)	5 (83)	0.89
Dyspnea – no. (%)	21 (81)	3 (50)	0.12
Diarrhea – no. (%)	7 (27)	2 (33)	0.75
Viral load, median (IQR), Ct	32 (28-35)	28 (27-31)	0.13
Disease severity			
Nadir lymphocyte count, median (IQR), per µl	295 (210-500)	565 (280-1000)	0.35
Peak hsCRP, median (IQR), mg/l	244 (107-348)	331 (199-387)	0.19
Peak LDH, median (IQR), IU/l	494 (391-604)	461 (436-524)	0.90
Peak D-dimers, median (IQR), ng/ml	1935 (1208-6973)	14713 (7364-23613)	0.02
Proximal tubule dysfunction			
Elevated Uβ2M – no. (%)	17 (65)	5 (83)	0.39
Hypouricemia/inappr. uricosuria – no. (%)	11/25 (44)	5/6 (83)	0.08
Aminoaciduria – no. (%)	4/10 (40)	1/1 (100)	0.25
Outcomes			
Follow-up, median (IQR), days	44 (36-56)	26 (15-55)	0.28
Mechanical ventilation – no. (%)	14 (54)	4 (67)	0.57
Death – no. (%)	6 (23)	4 (67)	0.04
Acute kidney injury – no. (%)	4 (15)	1 (17)	0.94
Hospital length of stay, median (IQR), days	22 (7-45)	19 (15-29)	0.98

$U\beta_2M$, urinary β_2-microglobulin; hsCRP, highly sensitive C-reactive protein; LDH, lactate dehydrogenase; inappr., inappropriate.

Supplementary Table 7. Characteristics of COVID-19 patients with and without aminoaciduria.

	Aminoaciduria		
	Absent	**Present**	
	n=7	**n=6**	**P**
Baseline characteristics			
Age, median (IQR), years	63 (59-69)	62 (56-76)	0.89
Male gender – no. (%)	5 (71)	6 (100)	0.16
Fever – no. (%)	5 (71)	5 (83)	0.61
Dyspnea – no. (%)	5 (71)	6 (100)	0.16
Diarrhea – no. (%)	1 (14)	2 (33)	0.42
Viral load, median (IQR), Ct	34 (32-35)	34 (33-39)	0.52
Disease severity			
Nadir lymphocyte count, median (IQR), per µl	300 (190-460)	265 (240-470)	0.89
Peak hsCRP, median (IQR), mg/l	284 (245-346)	247 (167-333)	0.67
Peak LDH, median (IQR), IU/l	570 (394-726)	625 (494-769)	0.81
Peak D-dimers, median (IQR), ng/ml	3059 (1143-6973)	3007 (2127-4461)	1.00
Proximal tubule dysfunction			
Elevated Uβ2M – no. (%)	2 (29)	6 (100)	0.008
Hypouricemia/inappr. uricosuria – no. (%)	4 (57)	4/5 (80)	0.41
Hypophosphatemia/inappr. phosphaturia – no. (%)	0 (0)	1/5 (20)	0.25
Outcomes			
Follow-up duration, median (IQR), days	52 (15-57)	41 (34-57)	0.78
Mechanical ventilation – no. (%)	4 (57)	4 (67)	0.73
Death – no. (%)	2 (29)	1 (17)	0.61
Acute kidney injury – no. (%)	2 (29)	0 (0)	0.16
Hospital length of stay, median (IQR), days	23 (14-53)	39 (26-57)	0.67

Uβ2M, urinary β2-microglobulin; hsCRP, highly sensitive C-reactive protein; LDH, lactate dehydrogenase; inappr., inappropriate.

Supplementary Table 8. Cox and competing risks regressions for time to invasive mechanical ventilation according to the presence of proximal tubule dysfunction.

	Unadjusted			Adjusted*		
Cox (mechanical ventilation or death)	**HR**	**95% CI**	**P**	**HR**	**95% CI**	**P**
Elevated urinary β_2-microglobulin	1.03	0.44, 2.39	0.95	-	-	-
Hypophosphatemia with inappropriate phosphaturia	0.86	0.31, 2.41	0.78	-	-	-
Hypouricemia with inappropriate uricosuria	4.60	1.69, 12.51	0.003	6.23	1.93, 20.07	0.002
Aminoaciduria	1.10	0.27, 4.49	0.90	-	-	-
Competing risks (mechanical ventilation)	**sHR**	**95% CI**	**P**	**sHR**	**95% CI**	**P**
Elevated urinary β_2-microglobulin	0.97	0.36, 2.57	0.95	-	-	-
Hypophosphatemia with inappropriate phosphaturia	1.05	0.43, 2.58	0.91	-	-	-
Hypouricemia with inappropriate uricosuria	8.72	2.25, 33.77	0.002	12.14	2.66, 55.37	0.001
Aminoaciduria	0.86	0.22, 3.27	0.82	-	-	-

*Adjusted for prespecified covariates including age, gender, LDH, hsCRP and lymphocyte count at admission.
Competing risk analyses taking into account competing risks of death and discharge.

Supplementary Table 9. Characteristics of COVID-19 patients with post-mortem examination of the kidneys.

Pt	Age (yrs)	Gender	HTN	Diabetes	Hypotension/ vasopressors	UPCR (g/g)	Uβ$_2$M	HypoU Inappr. UAuria	HypoP Inappr. Puria	AAuria	AKI	Dialysis	Pathologic evaluation	EM
1	74	Male	+	+	+	0.7	+	+	-	NA	+	-	+	NA
2	71	Female	+	-	+	1.5	+	+	-	NA	-	-	+	NA
3	64	Male	+	-	-	1.5	+	+	+	NA	-	-	+	NA
4	57	Male	-	-	+	NA	NA	NA	NA	NA	+	+	+	+
5	82	Female	+	-	-	0.6	-	-	-	NA	+	-	+	+
6	60	Male	-	-	+	3.3	-	-	-	NA	+	+	+	+

Pt, patient; yrs, years; HTN, hypertension; UPCR, urinary protein to creatinine ratio; Uβ$_2$M, urinary β$_2$-microglobulin; HypoU Inappr. UAuria, hypouricemia with inappropriate uricosuria; HypoP Inappr. Puria, hypophosphatemia with inappropriate phosphaturia; AAuria, aminoaciduria; AKI, acute kidney injury; EM, electron microscopy; NA, not available.

Supplementary Table 10. Pathologic evaluation of kidneys from patients with COVID-19.

Patient	n scler./total glomeruli	IFTA (%)	Tubular injury	Loss of brush border	Luminal debris	Vacuolization of tubular cells	Erythrocytes aggregates	Glomerular lesions	Interstitial inflammation
1	23/381	1-25	+	+	-	-	+	FSGS[a]	-
2	38/423	1-25	+	-	+	-	+	-	Focal
3	11/184	1-25	+	+	+	-	+	-	Focal
4	6/376	1-25	+	+	+	-	-	-	-
5	45/770	1-25	+	+	-	-	+	-	-
6	11/359	1-25	+	+	+	+[b]	+	-	-

[a]Tip lesion variant. [b]Non-isometric vacuoles. Scler., sclerotic (globally); IFTA, interstitial fibrosis and tubular atrophy; FSGS, focal and segmental sclerosis.

Supplementary Table 11. Mouse primer pairs for gene expression analysis.

Gene name	Forward primer (5'-3')	Reverse primer (5'-3')	PCR products (bps)	Efficiency
Gapdh	TGCACCACCAACTGCTTAGC	GGATGCAGGGATGATGTTCT	176	1.04 ± 0.03
Nphs2	GTCTAGCCCATGTGTCCAAA	CCACTTTGATGCCCCAAATA	162	1.03 ± 0.03
Slc12a3	CATGGTCTCCTTTGCCAACT	TGCCAAAGAAGCTACCATCA	148	1.01 ± 0.03
Slc12a1	CCGTGGCCTACATAGGTGTT	GGCTCGTGTTGACATCTTGA	154	0.99 ± 0.04
Aqp2	TCACTGGGTCTTCTGGATCG	CGTTCCTCCCAGTCAGTGT	147	1.03 ± 0.04
Slc5a2	TTGGGCATCACCATGATTTA	GCTCCCAGGTATTTGTCGAA	164	1.01 ± 0.03
Slc38a3	GTTATCTTCGCCCCCAACAT	TGGGCATGATTCGGAAGTAG	109	0.99 ± 0.02
Ace2	TCCAGACTCCGATCATCAAGC	TGTGGGTTCTTTGGGTTGCA	154	1.01 ± 0.03
Cltrn	GTCGTTCTGGTTTGTGGTCA	GGGGGAGCAAGAGTAGAAG	162	0.98 ± 0.02
Slc6a19	TTGCTGGCTCCATTCCTCTG	GACTGACCACTCTCCACGTG	153	1.02 ± 0.03
Slc22a12	TTACGACCACAGCACCTTCA	TTCTGCGCCCAAACCTATCT	158	1.01 ± 0.02
Slc34a1	CTGGGTCACGGGCTACTTT	ATGTTGGAGTCCAGGGTGAG	153	0.99 ± 0.02