Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Urine sediment findings were milder in patients with COVID-19-associated renal injuries than in those with non-COVID-19-associated renal injuries

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ABSTRACT

Background: Acute renal injury is an important complication of coronavirus disease 2019 (COVID-19). Both COVID-19-specific mechanisms, such as damage to the renal parenchyma by direct infection, and non-specific mechanisms, such as the pre-renal injury factors, have been proposed to be involved in COVID-19-associated renal injuries. In this study, we aimed to elucidate the characteristics of COVID-19-associated renal injuries, focusing mainly on urine sediment findings.

Methods: We compared the urine sediment findings and their associations with renal functions or urinary clinical parameters between subjects with COVID-19 and subjects without COVID-19 with acute renal injuries.

Results: We found that the number of urine sediment particles and the levels of N-acetyl-β-D-glucosaminidase, α1-microglobulin, liver type fatty acid-binding protein, and neutrophil gelatinase-associated lipocalin were associated with the severity of COVID-19. In addition, we observed that the number of granular casts, epithelial casts, waxy casts, and urinary chemical marker levels were lower in the subjects with COVID-19 than subjects without COVID-19 with acute renal injuries when the subjects were classified according to their renal function.

Conclusions: These results suggest that pre-renal injury factors might be largely involved in the pathogenesis of COVID-19-associated renal injuries compared with non-COVID-19-associated renal injuries arising from surgery or sepsis.

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly progressed into a global pandemic. Subjects with COVID-19 frequently develop pneumonia, which can lead to hypoxemic respiratory failure. Various additional complications can also occur. Among them, patients with COVID-19 can suffer from renal complications, especially acute kidney injury (AKI). AKI is a frequent complication in patients with critically severe COVID-19, and a meta-analysis report has shown that the average incidence of AKI was 11% among all subjects with COVID-19 and 23% among critically ill patients (Gabarre et al., 2020). As patients with COVID-19 with kidney disease reportedly have a higher risk of in-hospital death (Cheng et al., 2020), the early diagnosis of kidney injuries might improve the prognosis.

Abbreviations: AKI, acute kidney injury; ACE2, angiotensin-converting enzyme 2; α1-MG, α1-microglobulin; COVID-19, coronavirus disease 2019; L-FABP, liver type fatty acid-binding protein; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; RTEs, renal tubular epithelial cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2.

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At present, the detailed mechanisms of COVID-19-associated renal injuries have not been elucidated; although, several mechanisms have been proposed. Angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), which are key proteins in the entry of SARS-CoV-2 into human cells (Hoffmann et al., 2020), are well expressed in podocytes and the proximal tubules in the kidney (Pan et al., 2020), and SARS-CoV-2 can directly infect and damage the kidney (Yeung et al., 2016). A recent study has shown that a high SARS-CoV-2 viral load is associated with renal complications and the severity of COVID-19 (Caceres et al., 2021). Complications such as thrombosis and endotheliitis are also frequently observed in subjects with COVID-19 (Li et al., 2020 Shimura et al. 2021; Xiong et al., 2020;); theoretically, such complications could lead to renal impairment. In addition, other mechanisms not specific to COVID-19 have also been proposed. Mechanical ventilation due to acute lung failure (Vieillard-Baron et al., 2007), right heart failure due to myocardial infarction (Bradley et al., 2020, Edler et al., 2020) or myocarditis (Bradley et al., 2020), or rhabdomyolysis (Gamboa et al., 1979), which can result in AKI (Legrand et al., 2013), might also be involved in COVID-19-associated renal injuries. As both COVID-19-specific and nonspecific mechanisms are possible, comparing urine parameters between patients with renal injuries caused by COVID-19 and those with renal injuries caused by other diseases will be important for understanding the pathophysiological conditions characteristic for COVID-19-associated renal injuries. Until now, postmortem kidney pathologic examinations have revealed that the histologic degree of acute tubular injury is less severe than that predicted based on the degree of creatinine elevation (Santoriello et al., 2020), suggesting that COVID-19-associated renal injuries might possess unique characteristics compared with non-COVID-19-associated renal injuries.

Urinalysis and urine sediment examinations are the oldest and most commonly performed tests for assessing the pathophysiological condition of the kidney/urethral system. Urinalysis findings such as proteinuria, hematuria, and leukocyturia are reportedly associated with COVID-19-associated renal injuries and the severity of COVID-19 (Allemailem et al., 2021 Chan et al., 2020; Liu et al., 2020; Ouahmi et al., 2021; Pei et al., 2020; Yang et al., 2020;), and several urinary chemical biomarkers such as N-acetyl-β-D-glucosaminidase (NAG), α1-microglobulin (α1-MG), and neutrophil gelatinase-associated lipocalin (NGAL) have been proposed to be associated with AKI in hospitalized patients with COVID-19 (Fukao et al., 2021 Huart et al., 2021; Husain-Syed et al., 2020; Luther et al., 2021;). However, the characteristics of the urine sediment findings related to COVID-19 have not yet been studied adequately. Until now, only one case report and one study have reported urine sediment findings in patients with COVID-19 and have suggested the possible association between granular casts and the severity of COVID-19 (Allemailem et al., 2021, Fujimaru et al., 2020). In general, urine sediment findings can enable non-invasive estimates of the severity and/or cause of kidney injury. For example, the presence of renal tubular epithelial cells (RTEs) and granular casts is useful for differentiating between renal injury and prerenal injury (Perazella et al., 2008), and waxy casts are reportedly associated with renal failure (Spinelli et al., 2013).

Considering these backgrounds, urine sediment findings are expected to be useful for the indirect evaluation of kidney injury levels in subjects with COVID-19. Therefore, in the present study, we investigated the association between serum or urinary clinical parameters and urine sediment findings among subjects with COVID-19 and subjects without COVID-19 to elucidate the characteristics of urine sediment tests and to estimate the underlying mechanisms for COVID-19-associated renal injuries.

Materials and Methods

Subjects

Residual urine samples were collected from 88 subjects with COVID-19 (total: 279 samples; average: 3 samples per patient; range: 1–16 samples) diagnosed using RT-PCR. The severity of COVID-19 was defined as follows: mild, did not require oxygen therapy; moderate, required oxygen therapy but not mechanical ventilatory support; and severe, required mechanical ventilatory support. We also collected urine samples from 78 subjects (total: 147 samples; average: 2 samples per patient; range: 1–9 samples) with acute renal injuries caused by non-COVID-19 factors, who were admitted to an emergency or intensive care unit (ICU). Residual urine specimens were collected after routine laboratory testing, and the supernatant was stored at -80°C. The characteristics of the subjects are described in Table 1.

The present study was performed in accordance with the ethical guidelines laid down in the Declaration of Helsinki. Written informed consent for sample analysis was obtained from some of the patients. For the remaining participants from whom written informed consent could not be obtained because they had been discharged or transferred from the hospital, informed consent was obtained in the form of an opt-out on a website, as follows. Patients were informed about the study on the website, and those who did not wish to be enrolled in the study were excluded. The study design was approved by the University of Tokyo Medical Research Center Ethics Committee, which waived the need for written informed consent when written informed consent could not be obtained because archived specimens were used and all the data that were used in this retrospective study had been retrieved from medical records (3683, 3333-101, 3333-140, and 2020206NI).

Urinalysis

The urine sediment examination was performed using manual microscopy and complied with the Japanese Committee for Clinical Laboratory Standards (JCCLS). RTEs were counted per high-power field of view (/HPF), and urinary casts were classified into hyaline casts (HyaC), granular casts (GraC), epithelial casts (RTEC), and waxy casts (WaxC) and their numbers were counted per whole field (/WF). For the measurement of urinary clinical markers, we used the following reagents: urinary creatinine (uCr) was measured using an enzyme assay (L-type Wako CRE•M; FUJIFILM Wako Pure Chemical, Osaka, Japan); total protein (TP) (Micro TP-test Wako; FUJIFILM Wako) was measured using the pyrogallol red method; microalbumin (μAlb) (Auto Wako microalbumin; FUJIFILM Wako) was measured using a turbidimetric immunoassay (TIA); NAG (Ltype Wako NAG; Wako, Japan) was measured using an enzyme assay; α1-MG (LZtest 'Eiken' α1-M; Eiken Chemical, Japan) was measured using latex agglutination turbidimetry; liver type fatty acid-binding protein (L-FABP) (NORUDIA L-FABP; SEKISUI MEDICAL, Japan) was measured using latex agglutination turbidimetry; and NGAL (U-NGAL Abbott; Abbott, Japan) was measured using a chemiluminescence immunoassay (CLIA). Urinary specific gravity (SG) was measured using automated urine chemical analyzer US-3500 (Eiken Chemical, Japan) and urinary sodium was measured using electrode method. The involvement of the pre-renal injury was confirmed when the SG was 1.020 or higher or urine sodium was 20 mmol/L or lower, whereas the involvement of renal injury was estimated when the SG was 1.010 or lower or urine Na was 40 mmol/L or higher.

Table 1
Clinical characteristics of subjects

	non-COVID-19	COVID-19	*P* value
n (case)	147 (78)	279 (88)	
Age, in years	60.6±17.3	63.8±15.6	0.404
Sex (M/F)	51/27	60/27	
serum creatinine, mg/dL (n)	1.69±1.71 (147)	0.95±0.49 (279)	<0.001
eGFR, mL/min/1.73 m^2 (n)	55.2±37.2 (147)	70.4±25.8 (279)	<0.001
urine specific gravity			
>1.020	15	24	0.860
<1.010	5	6	
1.010 - 1.020	41	56	
N/A	17	2	
urine sodium, mmol/L			
<20	8	12	0.816
>40	43	62	
20-40	12	13	
N/A	15	1	
The severity of COVID-19 (Maximum stage during admission)			
Mild	-	23 (26.1%)	
Moderate	-	45 (51.1%)	
Severe	-	20 (22.7%)	
Comorbidities			
Diabetes	13 (19.1%)	37 (43.5%)	
Hypertension	10 (14.7%)	52 (59.8%)	
Post-Surgery	24 (30.8%)	-	
Cardiac surgery	7 (9.0%)	-	
Others	17 (21.8%)	-	
Sepsis	8 (10.3%)	-	
Other comorbidities			
Infectious diseases	17 (21.8%)		
Bleeding	13 (19.1%)		
Drug-induced kidney injury	3 (3.8%)		

The severity of COVID-19 was defined as follows: mild, did not require oxygen therapy; moderate, required oxygen therapy but not mechanical ventilatory support; and severe, required mechanical ventilatory support.

Statistical analysis

The data analysis was performed using SPSS (Chicago, IL). The Kruskal-Wallis test was used to compare the number of urine sediment particles and urinary markers according to the severity of the subjects with COVID-19. The chi-square test and the Mann-Whitney *U* test was used to compare the urinary markers and the numbers of urine sediment particles between subjects with and those without COVID-19, and the Spearman correlation test was used to analyze the association between the urinary markers and the urine sediment particles among the subjects. Statistical significance was deemed as a P value < 0.05.

Results

The number of urine sediment particles and NAG, α1-MG, L-FABP, and NGAL levels were associated with the severity of COVID-19

First, we investigated the numbers of urine sediment particles and the levels of urinary chemical markers according to the severity of COVID-19 (Figure 1 and 2). The RBC count was significantly higher in the moderate and severe COVID-19 groups than in the mild group (Figure 1A). The numbers of HyaC and GraC were significantly higher in the severe group than in the mild and moderate groups (Figure 1D and E), and the RTEC was also significantly higher in the severe group than in the moderate group (Figure 1F). No significant association with COVID-19 severity was observed for the WBC and RTE counts (Figure 1B and C). Representative pictures of the urinary sediments in COVID-19 patients are shown in Figure 1H-J. Regarding the urinary chemical markers, the NAG, α1-MG, and L-FABP levels were significantly higher in the severe group than in the mild and moderate groups, and they were also higher in the moderate group than in the mild group (Figure 2C-E). NGAL was significantly higher in the moderate and severe groups than in the mild group (Figure 2F). No significant association with COVID-19 severity was observed for the urinary levels of total protein and albumin (Figure 2A and B). The representative time course of the urinary sediment findings and chemical biomarkers in some subjects with COVID-19, of whom the serial urine samples were available for analyses are shown in Figure S1.

The number of granular casts was lower in subjects with COVID-19 than in subjects without COVID-19 with impaired renal function

Next, we compared the number of urine sediment particles between the subjects with COVID-19 and subjects without COVID-19 with the specific levels of renal function because the renal function differed significantly between the two groups (Table 1) and should be considered as a potential confounding factor. We classified the subjects according to the eGFR quartile (Q1, >85.0; Q2, 60.0-85.0; Q3, 30.0-59.9; Q4, <30.0 mL/min/1.73 m^2) (Figure 3), the sCr quartile (Q1, <0.70; Q2, 0.70-0.85; Q3, 0.86-1.33; Q4, >1.33 mg/dL) (Figure S2), the urinary TP quartile (Q1, <0.15; Q2, 0.15-0.30; Q3, 0.31-1.00; Q4, >1.00 g/gCr) (Figure S3), or the urinary NGAL quartile (Q1, <21.7; Q2, 21.7-47.0; Q3, 47.1-170.0; Q4, >170.0 μg/gCr) (Figure S4).

When we classified the subjects according to the eGFR quartile, the numbers of GraC in all the groups (Figure 3C) and the RTEC and WaxC in the Q2-Q4 groups (Figure 3D and E) were significantly lower in the subjects with COVID-19 than in those without COVID-19. Concordantly, when we classified the subjects according to the sCr quartile, the numbers of GraC in all the groups (Figure S2C), the HyaC in the Q3 group (Figure S2B), and the RTEC and WaxC in the Q3 and Q4 groups (Figure S2D and E) were significantly lower in the subjects with COVID-19 than in those without COVID-19.

When we classified the subjects according to the urinary TP quartile, the HyaC in the Q2 and Q4 groups (Figure S3B), the GraC

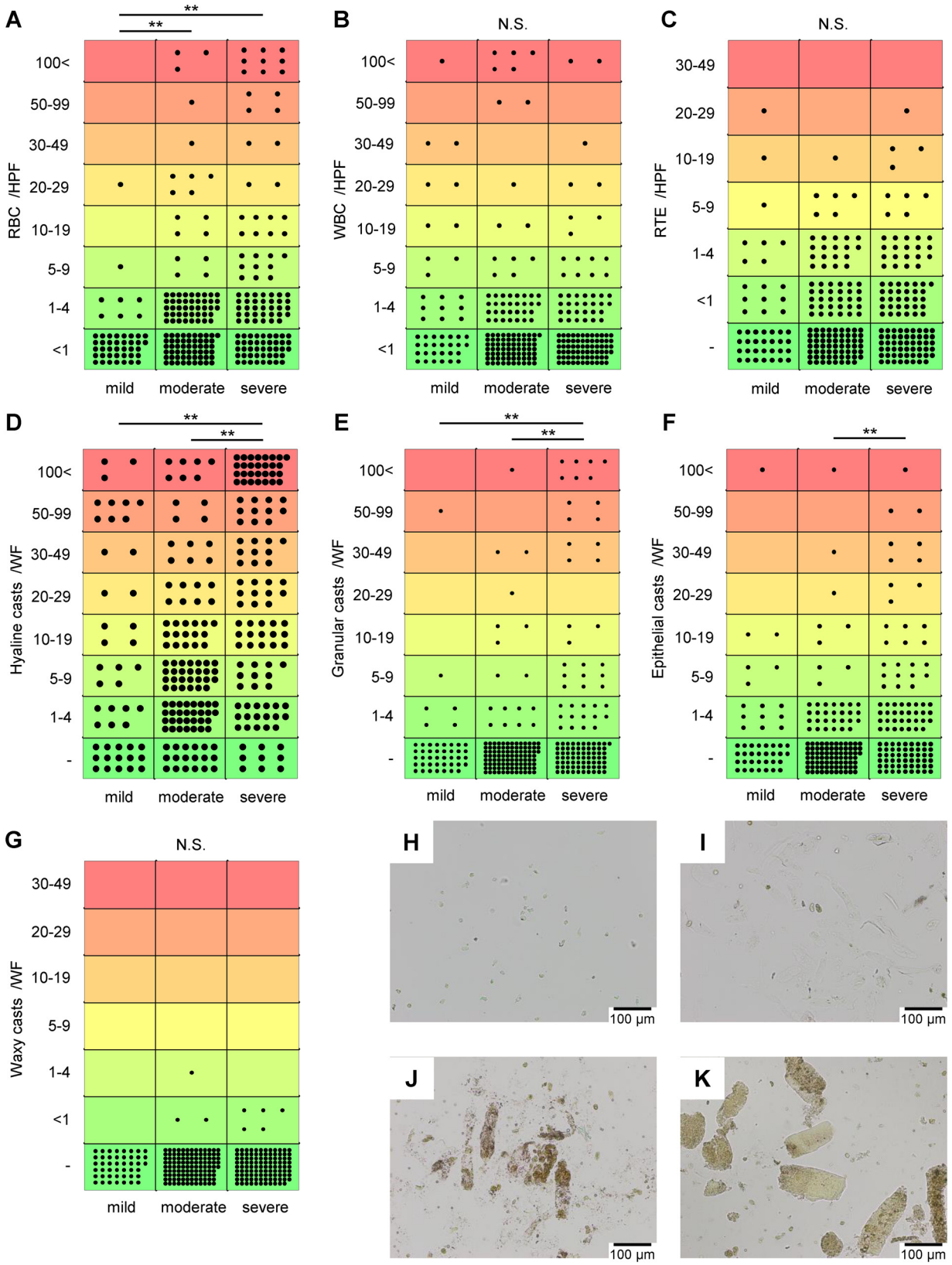

Figure 1. Comparison of the number of urine sediment particles according to the severity of subjects with COVID-19. We compared the numbers of urine sediment particles according to the severity of subjects with COVID-19. (A) Red blood cells (RBCs), (B) white blood cells (WBCs), (C) renal tubular epithelial cells (RTE), (D) hyaline casts (HyaC), (E) granular casts (GraC), (F) epithelial casts (RTEC), and (G) waxy casts (WaxC) are shown. Images of a urine sediment examination are shown in H-K: renal tubular epithelial cells (H), hyaline casts (I), epithelial casts and granular casts (J), and granular casts and waxy casts (K). Image H, I, and J were obtained from subjects with COVID-19 and image K was obtained from a subject without COVID-19.

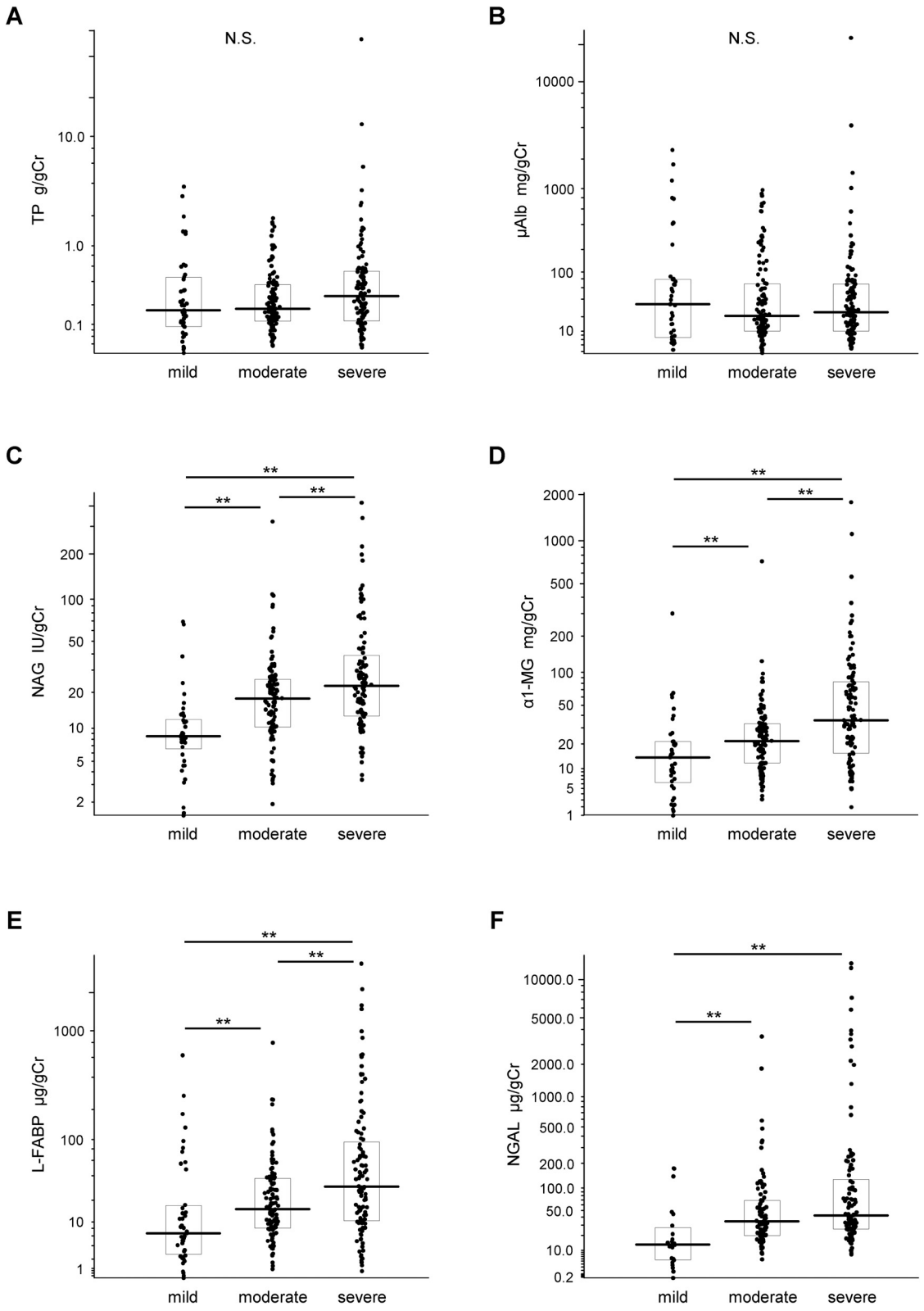

Figure 2. Comparison of urinary chemical markers according to the severity of subjects with COVID-19. We compared the levels of urinary markers according to the severity of subjects with COVID-19. (A) Total protein (TP), (B) microalbumin (μAlb), (C) N-acetyl-β-D-glucosaminidase (NAG), (D) α1-microglobulin (α1-MG), (E) liver type fatty acid-binding protein (L-FABP), and (F) neutrophil gelatinase-associated lipocalin (NGAL) are shown.

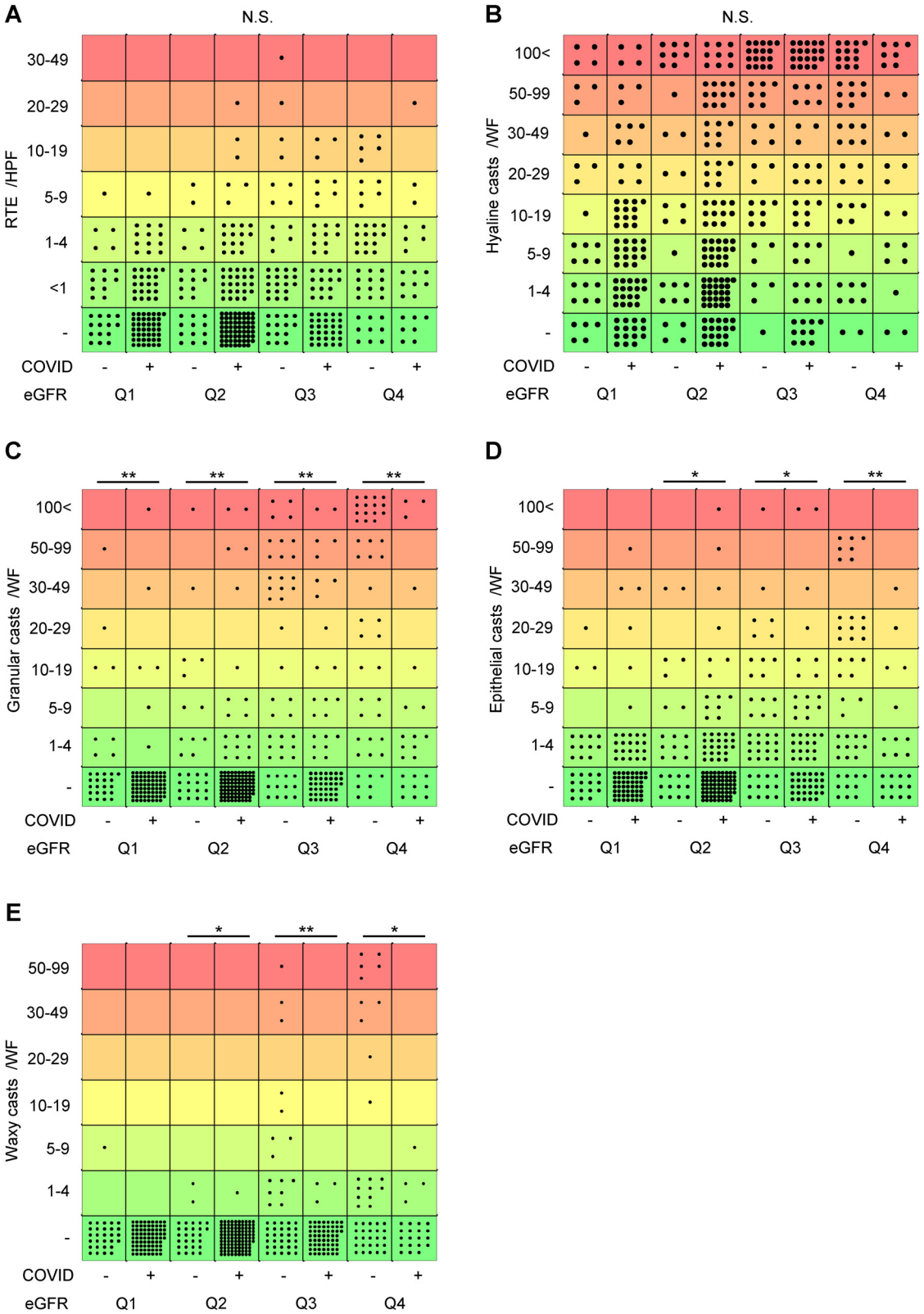

Figure 3. Comparison of urinary RTEs and casts between subjects with COVID-19 and those without COVID-19 according to the eGFR quartile. We compared the numbers of urine sediment particles between the subjects with COVID-19 and those without COVID-19 according to the eGFR quartile: Q1, >85.0; Q2, 60.0-85.0; Q3, 30.0-59.9; Q4, <30.0 mL/min/1.73 m^2. (A) Renal tubular epithelial cells (RTE), (B) hyaline casts (HyaC), (C) granular casts (GraC), (D) epithelial casts (RTEC), and (E) waxy casts (WaxC) are shown.

in all the groups (Figure S3C), the RTEC in the Q2 and Q3 groups (Figure S3D), and WaxC in the Q1, Q3, and Q4 groups (Figure S3E) showed lower numbers of particles in the subjects with COVID-19 than in those without COVID-19.

When we classified the subjects according to the urinary NGAL quartile, the numbers of RTE in the Q2 group (Figure S4A), the HyaC in the Q3 group (Figure S4B), the GraC in all the groups (Figure S4C), the RTEC in the Q2 and Q3 groups (Figure S4D), and the WaxC in the Q2-Q4 groups (Figure S4E) were lower in the subjects with COVID-19 than in those without COVID-19. These results suggested that the urinary sediment findings might be milder in patients with COVID-19-associated renal injuries than in those with non-COVID-19-associated renal injuries when adjusted according to renal function or urinary markers associated with renal injuries.

Urinary chemical markers were lower in subjects with COVID-19 than in subjects with COVID-19 with impaired renal function

Next, we compared the levels of urinary chemical markers between the subjects with COVID-19 and those without COVID-19 according to their renal function. When we classified the subjects according to the eGFR quartile, the urinary TP in the Q3 group (Figure 4A), the μAlb in all the groups (Figure 4B), the NAG in the Q1 and Q3 groups (Figure 4C), the L-FABP in the Q3 group (Figure 4E), and the NGAL in the Q3 group (Figure 4F) were significantly lower in the subjects with COVID-19 than in the subjects without COVID-19. When we classified the subjects according to the sCr quartile, we found that the urinary TP was significantly lower in the subjects with COVID-19 than in the subjects without COVID-19 among the Q3 and Q4 groups (Figure S5A), the μAlb was significantly lower in all the groups (Figure S5B), the NAG was significantly lower in the Q1 and Q3 groups (Figure S5C), the L-FABP was significantly lower in the Q3 group (Figure S5E), and the NGAL was significantly lower in the Q1 group (Figure S5F). These results suggested that although the urinary proteins and urinary markers associated with renal tubular damages were also milder in patients with COVID-19-associated renal injuries than in those with non-COVID-19-associated renal injuries, the difference seemed smaller than that for the urinary sediment findings.

Stratified analysis for the urine sediment particles and chemical markers by diabetes or hypertension

So far, we showed milder urine sediment findings and the lower chemical markers in the subjects with COVID-19 than subjects without COVID-19. As some comorbidities including diabetes and hypertension should influence the degree of renal injuries, we further performed the stratified analyses for the urine sediment particles and the chemical biomarkers by the presence or absence of diabetes or hypertension between the subjects with and without COVID-19. After the stratified analyses by diabetes, the number of granular casts, epithelial casts, waxy casts, and urinary levels of TP, μAlb, NAG, α1-MG, L-FABP, and NGAL in the COVID-19 group were still significantly lower than the non-COVID-19 group regardless of the presence of diabetes (Table S1). After the stratified analyses by hypertension, the number of hyaline casts was lower in the subjects with hypertension and the number of granular casts, epithelial casts, waxy casts, and urinary levels of TP, μAlb, NAG, α1-MG, L-FABP, and NGAL in COVID-19 group were still significantly lower than non-COVID-19 group regardless of the presence of hypertension (Table S2). These results suggested that milder urine sediment findings and lower urinary chemical biomarkers might be observed at least to some degree regardless of the presence of diabetes and hypertension.

Discussion

In the present study, we investigated the association between urine sediment findings and clinical biomarkers that were indicators of kidney injury among the COVID-19 subjects to elucidate the characteristics of COVID-19-associated AKI. Our results demonstrated that the urine sediment particles as well as the urinary NAG, α1-MG, L-FABP, and NGAL levels were associated with the severity of COVID-19 (Figure 1 and 2). Until now, only a limited paper and a case report have proposed a potential association between granular casts and the severity of COVID-19 (Allemailem et al., 2021 Fujimaru et al., 2020;). In the present study, we demonstrated in detail an association between the severity of COVID-19 and urinary sediment findings, including HyaC and RTEC as well as GraC for the first time.

Regarding the association between urinary chemical markers and the severity of COVID-19, the results of the present study were partially concordant with those of previous papers (Fukao et al.; 2021, Huart et al.; 2021, Katagiri et al.; 2020, Luther et al., 2021 Tantry et al., 2021;) except for the association between the urinary NAG levels and the severity of COVID-19, which was denied in a previous article (Vogel et al., 2021). In contrast, we did not observe a significant association between the urinary protein levels and the severity of COVID-19, which has been shown in previous studies (Allemailem et al., 2021 Ouahmi et al., 2021;). Although the reasons for these discrepancies remain unknown, the present results suggested that urinary chemical markers might reflect the severity of COVID-19 in a manner that is independent of the state of proteinuria.

Considering that the numbers of urine sediment particles were lower in the COVID-19 subjects than in the non-COVID-19 subjects when we classified the subjects according to renal function or urinary biomarkers (Figure 3 and S2-S4) and that the difference seemed smaller when we compared the urinary chemical markers between the subjects with COVID-19 and the subjects without COVID-19 when we classified the subjects according to renal function (Figure 4 and S5), the urinary sediment findings might be associated with COVID-19 to a greater degree than the urinary chemical markers. Considering the time course of some subjects with severe COVID-19 as shown in Figure S1, although the urinary sediment findings were surely aggravated in the acute phase of COVID-19, the dynamics of urinary sediment findings in some subjects even with severe COVID-19 seemed rather mild.

These results led us to two possible hypotheses: first, the degree of damage to the renal parenchyma caused by COVID-19 might be milder than that seen in subjects without COVID-19 with renal injuries; and second, subjects with COVID-19 may exhibit impaired kidney function even when the damage to the renal parenchyma is relatively mild. Anyway, the involvement of pre-renal injury factors seemed to be larger in the COVID-19-associated renal injuries, as the urinary sediment findings, as well as the urinary chemical markers, should reflect the damage to the renal parenchyma. In addition, as described in Table 1, we observed no difference in urine SG (1.015 [1.005-1.035] versus 1.017 [1.005-1.035]) or sodium (61.7 [7.4-202.0] mmol/L versus 71.0 [10.0-203.1] mmol/L) between both groups (median [range], COVID-19 group versus non-COVID-19 group). The causes of kidney injury among the subjects without COVID-19 in the present study were post-operation (cardiac surgery, transplantation) and sepsis. Other subjects without COVID-19 also had pre-renal causes, such as infection (e.g., acute hepatitis and myocarditis) and bleeding (acute aortic dissection, cerebral hemorrhage, or trauma) (Table 1). Therefore, the results that no difference was observed in urine SG or sodium between the COVID-19 group and non-COVID-19 group in the present study might also support our hypothesis that the main mechanism for COVID-19-associated renal injuries might be pre-

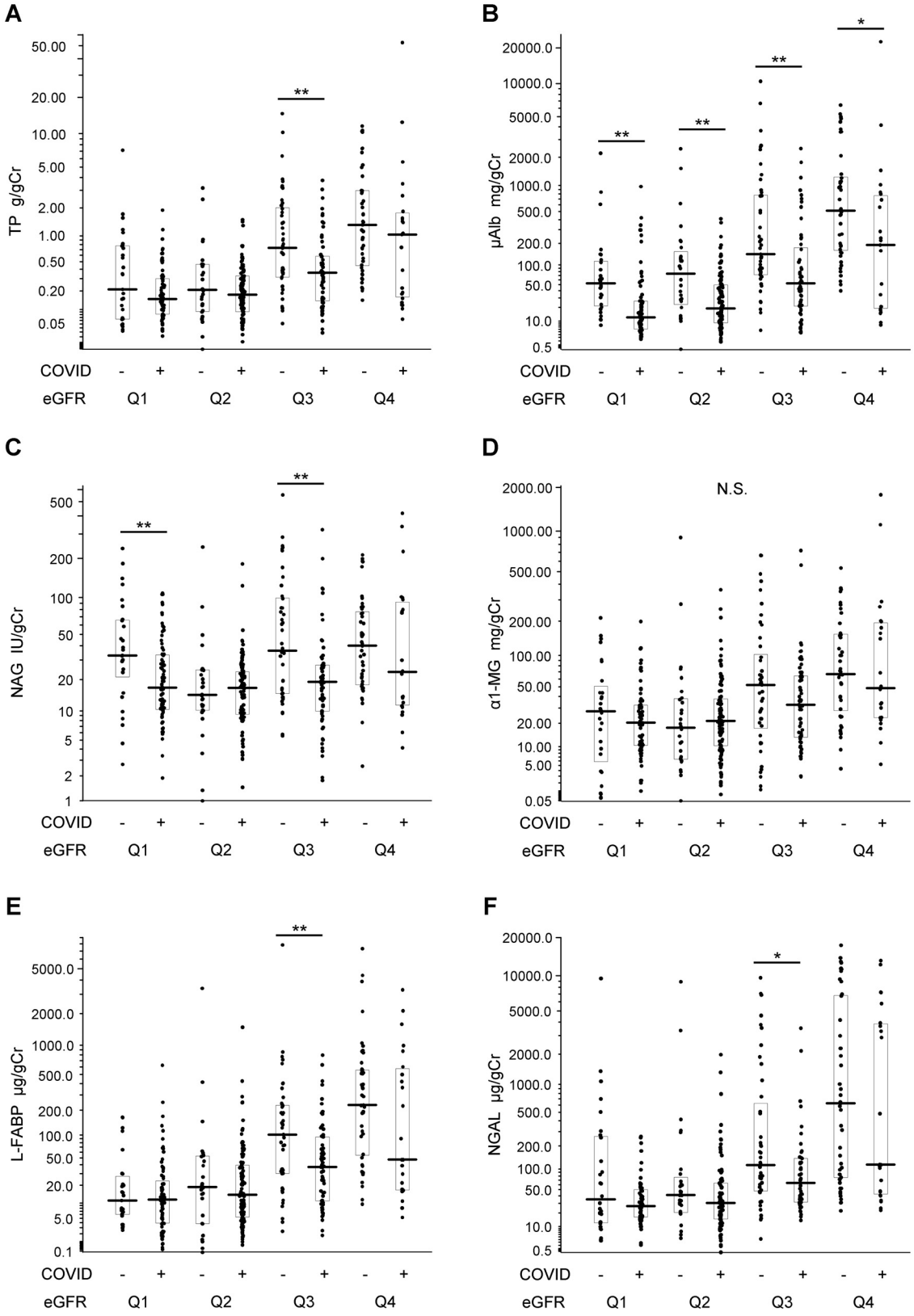

Figure 4. Comparison of urinary markers between subjects with COVID-19 and those without COVID-19 according to the eGFR quartile. We compared the levels of urinary markers between the subjects with COVID-19 and those without COVID-19 according to the eGFR quartile: Q1, >85.0; Q2, 60.0-85.0; Q3, 30.0-59.9; Q4, <30.0 mL/min/1.73 m^2. (A) Total protein (TP), (B) microalbumin (μAlb), (C) N-acetyl-β-D-glucosaminidase (NAG), (D) α1-microglobulin (α1-MG), (E) liver type fatty acid-binding protein (L-FABP), and (F) neutrophil gelatinase-associated lipocalin (NGAL) are shown.

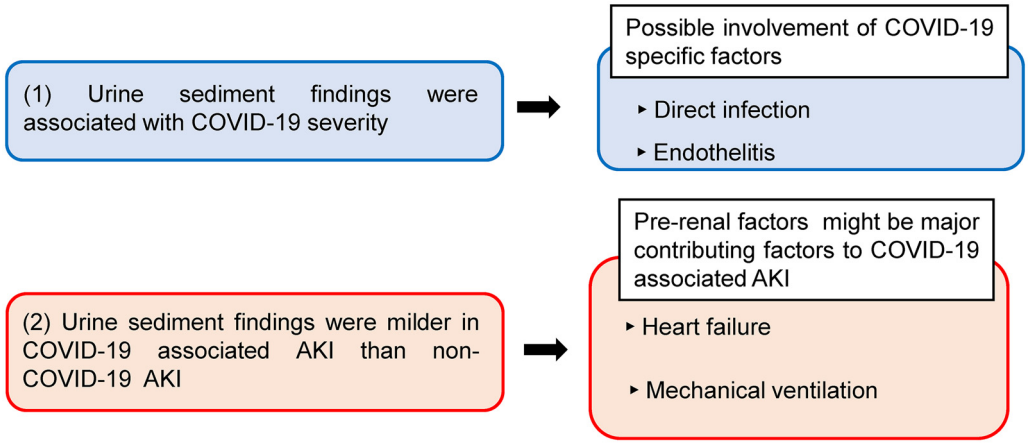

Figure 5. Scheme of the results of the present study and their interpretation.

renal. Our results are consistent with histological findings reported by Santoriello et al. (Santoriello et al., 2020).

Although the main underlying mechanisms for COVID-19-associated renal injuries might be pre-renal injury factors, the direct viral invasion has also been proposed to be involved in acute tubular necrosis, as described in the Introduction section. In the present study, 12 of the 88 cases with COVID-19-associated renal injury had a large number of RTEs (more than 10 particles/HPF) observed in urine sediment (Figure 1H). Whether these sediment findings indicated direct viral invasion into RTEs, such as the "decoy cells" found in BK virus infection (Poloni et al., 2016), remains unclear. In the present study, no decoy cells were observed, and the morphology of the RTEs suggested that they appeared in the urine as a result of secondary or direct tubular damage.

A limitation of this study is that the renal function and comorbidities might have differed between the two groups, and accurate estimations of the contributions of various factors, such as surgery, sepsis, and COVID-19, to the renal injuries are difficult. However, the stratified analyses by the renal function or the presence of diabetes or hypertension suggested that the milder urinary urine sediment findings and lower urinary chemical biomarkers might be observed, at least to some degree, regardless of the renal function or the presence of diabetes and hypertension (Figure 3, 4, Figure S2, Table S1 and S2). Another limitation is that we were unable to predict the renal prognosis because this was a retrospective study. However, theoretically, if pre-renal injury factors are mainly involved in COVID-19-associated renal injuries, these factors could be expected to be reversible, resulting in a better renal prognosis than if the renal injuries were caused by non-COVID-19 factors. Further studies examining larger numbers and serial and independent samples are also necessary.

In conclusion, the urinary sediment findings were milder in subjects with COVID-19 when compared according to their renal functions, suggesting that pre-renal injury factors might be largely involved in the pathogenesis of COVID-19-associated renal injuries than non-COVID-19-associated renal injuries in patients with AKI arising from surgery or sepsis (Figure 5).

Competing interests

The present study was performed under a collaborative research project at the University of Tokyo, Abbott Japan, and Sekisui Medical.

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None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.024.

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