Jikeikai Med J 2023 ; 70 : 19-26

Organ Weights in Autopsy Cases with Severe Acute Respiratory Syndrome Coronavirus 2 Infection and the L452R Mutation

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ABSTRACT

During an autopsy, organ weight is a useful indicator of organ abnormalities. However, no previous study has identified the association between organ weight and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, specifically by viruses with the L452R mutation. Therefore, this study tested for SARS-CoV-2 infection and the L452R mutation during autopsies and compared the organ weights between positive and negative cases. The study included 1,025 deceased persons, of whom 24 were positive for SARS-CoV-2 infection and 12 had the L452R mutation. Both lungs were significantly heavier in SARS-CoV-positive persons than in SARS-CoV-negative persons, but other organ weights did not differ. In SARS-CoV-positive persons, both lungs were significantly heavier if severe diffuse alveolar damage (DAD) was present. Organ weights did not differ on the basis of whether mild DAD or the L452R mutation was present. Overall, the weights of both lungs increased in persons who had been infected with SARS-CoV-2, but even if lung weights had not increased, mild DAD might be present. Additionally, we confirmed that DAD is more likely to develop in deceased persons with the L452R mutation.

(Jikeikai Med J 2023 ; 70 : 19-26)

Key words : SARS-CoV-2 ; autopsy, COVID-19, organ weight

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease 2019 (COVID-19) pandemic, was first detected in 2019 and has since undergone various mutations and caused many deaths worldwide. Variants of SARS-CoV-2 with potential clinical significance, such as increased infectivity and severity and weakened vaccine efficacy, are designated variants of concern. Of these variants, the Delta variant with the L452R mutation is more severe and has a higher mortality rate than the wild type virus[1-3]. Moreover, the Omicron variant BA4/5 has also acquired the L452R mutation and has established a new peak in the number of infections[4]. Therefore, the L452R mutation is the most notable finding when autopsies are performed of persons who have died of SARS-CoV-2 infection.

During an autopsy, organ weight easily indicates organ abnormalities and diseases, such as inflammation, proliferative disease, and functional decline. Among the organ disorders caused by COVID-19 are lung lesions, such as diffuse alveolar damage (DAD)[5-8]. However, to our knowledge, an

Received : December 14, 2022 / Accepted : January 20, 2023
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association between SARS-CoV-2 infection and organ weight has not previously been reported. Therefore, in the present study the reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was used to diagnose SARS-CoV-2 infections and to identify the L452R mutation in deceased persons examined at autopsy, and organ weights were examined to identify relevant patterns.

MATERIALS AND METHODS

This study was approved by The Jikei University School of Medicine Ethics Committee [32-344(10431)].

Selection of deceased persons and autopsy procedures

We reviewed all autopsies performed at our institution from July 14, 2020, to November 30, 2021. Excluded from the study were deceased persons of an unknown identity or date of death and those younger than 20 years. To diagnose a SARS-CoV-2 infection and identify the L452R mutation, immediately before autopsy the nasopharyngeal mucosa was swabbed with a dry swab for the RT-qPCR. Designated as variants of concern by the World Health Organization were the Delta variant in May 2021 and the L452R mutation in June 2021. The ethics committee of our institution has approved the protocols used in this study.

Macroscopic and microscopic findings and alcohol and drug examinations were used to determine the cause of death for each person. Major organs (e.g., the heart, lung, liver, kidney, spleen, pancreas, and brain) were weighed with the same scale (Yamato UDS-1V II-WP ; range of 20-3,000 g at an interval of 1 g [0-1,500 g] or 2 g [1,500-3,000 g]). The organs were then fixed in a 10% formalin solution, dehydrated, paraffin-embedded, and thinly sectioned (3 μm) for hematoxylin and eosin and elastica Masson-Goldner staining. The diagnostic criteria for DAD were classified as severe DAD (Fig. 1a) if hyaline film formation was observed throughout the lung, mild DAD if partially observed, and no DAD (Fig. 1b) if not observed.

RNA extraction, RT-qPCR, and SARS-CoV-2 variant typing

Viral RNA was extracted with a High Pure Viral RNA Kit (cat# 11858882001, Roche Diagnostics, Indianapolis, IN, USA) or a High Pure Viral Nucleic Acid Kit (cat# 11858874001, Roche Diagnostics). The RT-qPCR was performed following the methods of Matsumoto et al[9].

The SARS-CoV-2 typing assay mixtures were prepared with the VirSNiP SARS-CoV-2 Spike L452R Assay kit (cat# 518400781, Roche Diagnostics) and the LightCycler Multiplex RNA Virus Master kit (cat# 518221690, Roche Diagnostics) following the manufacturer's instructions. The assay was performed with a StepOnePlus Real-Time PCR System (Applied Biosystems, Waltham, MA, USA) in the following order : reverse transcription for 5 minutes at 55°C, activation for 5 minutes at 95°C, 45 cycles of 5 seconds at 95°C and 15 seconds at 60°C, and melting curve generation from 40°C to 75°C with fluorescence detection at 0.3°C increments.

Statistical analyses

Continuous variables are expressed as means ± stan-

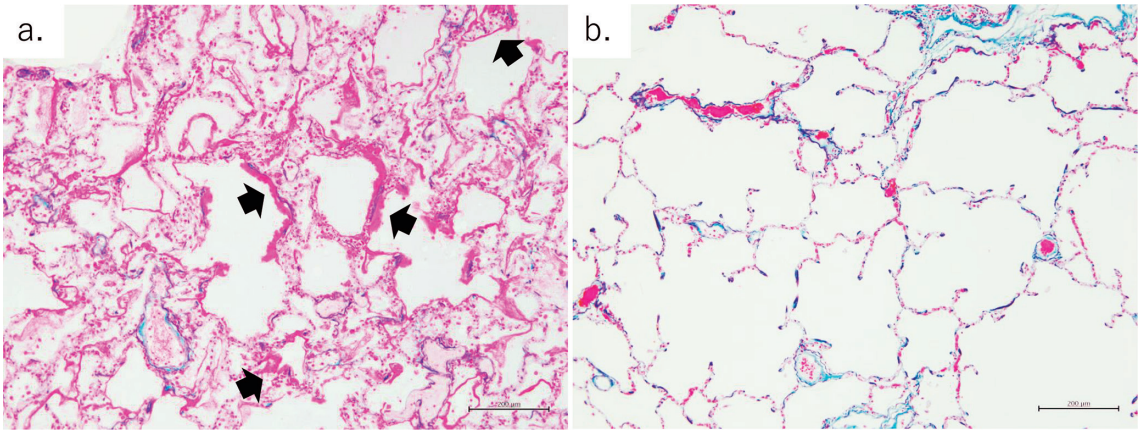

Fig. 1. A representative pathological photograph of diffuse alveolar damage (DAD). Elastica Masson-Goldner staining. a : severe DAD. b : no DAD. Arrow : hyaline film formation)

dard deviations. Student's *t*-test was used to compare 2 groups, and one-way analysis of variance was used to compare 3 groups ; Tukey's multiple comparison test was used for multiple comparisons. Fisher's exact test was used for categorical variables. The software programs Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and GraphPad Prism (version 9, GraphPad Software Inc., San Diego, CA, USA) were used for statistical analysis ; p-values of < 0.05 were considered statistically significant.

Results

RT-qPCR results and organ weight

The study included 1,025 deceased persons (Table 1) ; 24 were positive for SARS-CoV-2 via the RT-qPCR. Age, postmortem time until autopsy, and the male-to-female ratio did not differ significantly between persons who were positive or negative for SARS-CoV-2 (Table 2). Both the right and left lungs were significantly heavier in deceased persons in whom the RT-qPCR was positive for SARS-CoV-2, but other organ weights did not differ regarding RT-qPCR results (Table 3). Similarly, among persons examined at autopsy within 72 hours after death, both the right and left lungs were heavier only when the RT-qPCR was positive for SARS-CoV-2 (Table 4).

Comparison of lung weights of SARS-CoV-2-positive persons, SARS-CoV-2-negative persons with bacterial pneumonia (21 cases), and SARS-CoV-2-negative persons without bacterial pneumonia (982 cases) showed that the right lung was significantly heavier in SARS-CoV-2-positive persons than in SARS-CoV-2-negative persons without bacterial pneumonia ($p = 0.0046$). However, no significant difference was observed between SARS-CoV-2-positive persons and SARS-CoV-2-negative persons with bacterial pneumonia or between SARS-CoV-2-negative

Table 1. Characteristics of deceased persons examined at autopsy ($n = 1,025$)

Variable	Value
Age, years	62.18 ± 16.75
Sex (%), M/F	687 (67.02%)/338 (32.98%)
Postmortem time, hours	94.45 ± 299.42
SARS-CoV-2 RT-qPCR positive cases (%), *n*	24 (2.34%)

Abbreviations : RT-qPCR, reverse transcription-quantitative polymerase chain reaction ; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 2. Characteristics of deceased persons based on the RT-qPCR results

Variable	RT-qPCR results		*p*-value
	Positive ($n = 24$)	Negative ($n = 1001$)	
Age, years	57.17 ± 16.20	62.30 ± 16.75	0.14
Sex (%), M/F	17 (70.83%)/7 (29.17%)	670 (66.93%)/331 (33.07%)	0.83
Postmortem time, hours	73.47 ± 52.38	95.16 ± 303.09	0.73

RT-qPCR : reverse transcription-quantitative polymerase chain reaction

Table 3. Organ weights of deceased persons and reverse transcription-quantitative polymerase chain reaction test results

Organ	Organ weight (g) regarding RT-qPCR result		*p*-value
	Positive	Negative	
Heart	385.71 ± 125.56	384.62 ± 114.11	0.96
Left lung	573.30 ± 254.52	489.80 ± 186.17	0.035
Right lung	723.96 ± 293.77	581.17 ± 215.98	0.0020
Liver	1462.75 ± 600.56	1337.80 ± 516.12	0.24
Left kidney	161.08 ± 62.24	147.06 ± 71.36	0.34
Right kidney	149.75 ± 54.23	139.15 ± 59.59	0.39
Spleen	124.38 ± 76.02	109.13 ± 95.06	0.43
Pancreas	109 ± 37.21	105.39 ± 58.13	0.76
Brain	23.69 ± 6.20	1338.27 ± 195.78	0.98

Abbreviations : RT-qPCR : Reverse transcription-quantitative polymerase chain reaction

Table 4. Organ weights of deceased persons examined at autopsy within 72 hours

Organ	Organ weights (g) regarding RT-qPCR result		*p*-value
	Positive	Negative	
Heart	406.73 ± 120.18	391.08 ± 111.27	0.59
Left lung	616.93 ± 284.67	511.77 ± 188.70	0.041
Right lung	744 ± 300.32	609.59 ± 216.69	0.0053
Liver	1551.27 ± 668.52	1414.79 ± 520.34	0.32
Left kidney	175.07 ± 70.78	152.17 ± 77.87	0.26
Right kidney	162.07 ± 59.59	143.15 ± 62.27	0.24
Spleen	136.8 ± 82.94	119.34 ± 104.05	0.52
Pancreas	110.87 ± 41.20	108.00 ± 63.93	0.68
Brain	1321.29 ± 126.92	1347.92 ± 172.60	0.71

RT-qPCR : Reverse transcription-quantitative polymerase chain reaction

persons with bacterial pneumonia and those without bacterial pneumonia.

Lung weight and DAD findings

Among the 24 SARS-CoV-2-positive deceased persons, the pathological examination identified severe DAD in 10, mild DAD in 6, and no DAD in 8 (Table 5). All persons with severe DAD had COVID-19-related deaths. Among persons with mild DAD, the causes of death were COVID-19-related ($n = 4$), subarachnoid hemorrhage ($n = 1$), or acute epidural hematoma ($n = 1$). Of persons without DAD, 2 were found to have superior sagittal sinus thrombosis and neutrophil-infiltrating pneumonia due to SARS-CoV-2 infection and were considered to have COVID-19-related deaths ; the remaining 6 persons had non-COVID-19-related deaths.

The left lung was significantly heavier in deceased person with severe DAD than in persons without DAD ($p = 0.0028$), but the weights did not differ between persons with severe or mild DAD ($p = 0.12$) or between persons with mild or no DAD ($p = 0.34$; Fig. 2). The right lung was also significantly heavier in persons with severe DAD than in those with mild DAD ($p = 0.042$) or no DAD ($p = 0.0028$), but the weights did not differ between persons with mild DAD and those with no DAD ($p = 0.61$; Fig 2).

Extrapulmonary findings

Extrapulmonary findings in 24 persons found to be SARS-CoV-2-positive showed that 8 had mild to severe lipid droplet deposition in hepatocytes (Table 5). Found in 1 person each were intraglomerular thrombus ; tubular atrophy and interstitial fibrosis (TA/IF) and moderate to severe

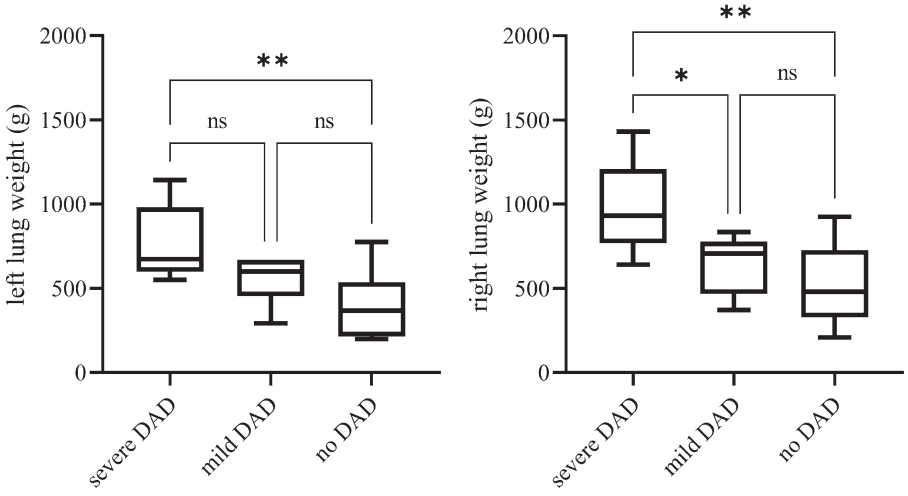

Fig. 2. Associations between the left and right lung weights and diffuse alveolar damage (DAD). ** $P < 0.05$; ns, not significant

glomerulosclerosis ; hemorrhagic infarction accompanied by intra-arterial thrombosis limited to the parietal lobe ; and sinus venous thrombosis (superior sagittal sinus to bilateral transverse sinus).

L452R mutation

Of the 24 SARS-CoV-2-positive deceased persons, 12 were L452R mutation-positive. The weights of no organs had differed between the mutation-positive and mutation-negative persons (Table 6). Furthermore, 11 of the 12 persons with the L452R mutation had DAD (severe in 7 and mild in 4), and 5 of the 12 persons without the L452R mutation had DAD (severe in 3 and mild in 2). Thus, DAD was significantly more common in persons with the L452R mutation than in persons without ($p = 0.027$).

Discussion

The most common autopsy finding in persons who have died of COVID-19 is DAD, but many extrapulmonary lesions have also been reported[5-8]. Therefore, the present study examined organ weights obtained at autopsy to as-

Table 5. Autopsy findings related to cause of death in SARS-CoV-2-positive deceased persons

Deceased person	Age, years/sex	Postmortem time, hours	Cause of death	Lung findings	Other organ findings
1	73/M	40	Hemorrhagic gastric ulcer	Emphysema	Gastric ulcer Atherogenesis in coronary arteries (heart, 324 g)
2	49/M	36	COVID-19 pneumonia	Severe DAD	Cardiac hypertrophy Severe to moderate glomerulosclerosis (heart, 775 g) Tubular atrophy and interstitial fibrosis (left kidney, 356 g ; right kidney, 323 g)
3	47/M	31	Chronic alcoholic liver disease	-	Fatty liver + liver cirrhosis (liver, 2,837 g)
4	82/M	60	Drowning	-	Prostate cancer
5	78/M	210	COVID-19 pneumonia	Severe DAD	Cardiac hypertrophy (heart, 433 g) Fatty liver (liver, 1,201 g)
6	80/M	36	COVID-19 pneumonia	Severe DAD + neutrophil infiltration	Fatty liver (liver, 1,136 g)
7	45/M	81	Subarachnoid hemorrhage	Mild DAD	Subarachnoid hemorrhage (brain, 1,430 g) Cardiac hypertrophy (heart, 636 g) Fatty liver (liver, 1,943 g)
8	66/F	36	Superior sagittal sinus thrombosis	Emphysema	Thrombus in the sinuses of the brain (brain, 1,273 g)
9	54/F	31	COVID-19 pneumonia	Severe DAD	Fatty liver (liver, 2,317 g)
10	38/M	81	COVID-19 pneumonia	Mild DAD	-
11	64/M	28	COVID-19 infection	Severe DAD	-
12	54/M	61	COVID-19 infection	Severe DAD	Fatty liver (liver, 1,139 g)
13	30/M	81	COVID-19 pneumonia	Severe DAD	Fatty liver (liver, 1,955 g)
14	51/M	60	COVID-19 infection	Mild DAD	-
15	51/M	69	COVID-19 pneumonia	Severe DAD	-
16	65/F	81	COVID-19 infection	Mild DAD	-
17	53/M	60	COVID-19 pneumonia	Severe DAD	Parietal lobe hemorrhagic infarction (brain, 1,346 g) Microthrombi in glomeruli (left kidney, 197 g ; right kidney, 163 g)
18	30/M	25	Acute epidural hematoma	Mild DAD	Acute epidural hematoma
19	73/F	50	Suicide (hanging)	-	Atherogenesis in coronary arteries (heart, 262 g)
20	60/M	178	COVID-19 infection	Severe DAD	-
21	76/F	111	COVID-19 infection	Neutrophil infiltration	-
22	70/F	33	COVID-19 pneumonia	Mild DAD	Gastric ulcer Thoracic aortic aneurysm
23	35/F	79	Trauma	-	Multiple fractures Multiple organ injury
24	57/M	201	Acute alcohol intoxication	-	Fatty liver (liver, 1,724 g)

Abbreviations : COVID-19, coronavirus disease 2019 ; DAD, diffuse alveolar damage ; RT-qPCR, reverse transcription-quantitative polymerase chain reaction ; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 6. Organ weights of deceased persons with or without L452R mutations

Organ	Organ weights (g) regarding L452R mutation		*p*-value
	Positive	Negative	
Heart	357.33 ± 64.6	414.08 ± 164.40	0.28
Left lung	601.73 ± 247.11	547.25 ± 269.25	0.62
Right lung	741.45 ± 261.46	707.92 ± 331.47	0.79
Liver	1353.17 ± 498.63	1572.33 ± 692.32	0.38
Left kidney	164 ± 47.27	158.17 ± 76.47	0.82
Right kidney	151.75 ± 40.13	147.75 ± 67.30	0.86
Spleen	138.08 ± 84.05	110.67 ± 67.89	0.39
Pancreas	113.92 ± 41.14	104.08 ± 33.90	0.53
Brain	1337 ± 164.89	1342.5 ± 95.10	0.94

sess COVID-19 organ damage. This study found that 24 of 1,025 deceased persons examined at a forensic autopsy were SARS-CoV-2-positive (2.34%), and both the right and left lungs were significantly heavier in SARS-CoV-2-positive persons. The right lung was significantly heavier in the SARS-CoV-2-positive persons than in SARS-CoV-2-negative persons without bacterial pneumonia. However, lung weight did not differ significantly between SARS-CoV-2-positive persons and SARS-CoV-2-negative persons with bacterial pneumonia, indicating that distinguishing COVID-19 from bacterial pneumonia is difficult on the basis of lung weight alone.

Another finding of this study was the presence of mild to severe DAD in 16 of 24 SARS-CoV-2-positive persons. Conditions caused by DAD include hyaline membrane formation and pneumocyte type 2 hyperplasia[10]. Furthermore, COVID-19-induced DAD does not differ morphologically from DAD caused by other diseases[11]. The DAD occurring in SARS-CoV-2-positive persons in the present study also had similar histology to DAD identified after severe infection or severe invasion. Thus, we suspect that the significantly increased weight of both lungs was due to increased lung exudate and cellular components from DAD. Therefore, during the SARS-CoV-2 pandemic, if autopsy findings exclude cardiogenic or neurogenic pulmonary edema, bacterial pneumonia, or neoplastic lesions, then COVID-19 should be considered if the lungs are abnormally heavy. However, because lung weights did not differ between persons with mild DAD or no DAD, mild DAD can be difficult to estimate on the basis of organ weight. Therefore, during an autopsy, SARS-CoV-2 infection with mild DAD cannot be ruled out if lung weight is as expected.

A well-known complication of COVID-19 is myocarditis[12]. When induced by COVID-19, myocarditis reportedly has a mononuclear or lymphocytic infiltrate associated with myocyte necrosis[7]. In the present study, the heart weight did not differ on the basis of SARS-CoV-2 being positive or negative, and myocarditis was not identified if SARS-CoV-2 was positive. In patients infected with COVID-19, the myocarditis complication rate is reportedly 0.6% to 2.3%[13,14]. In addition, myocarditis might progress to dilated cardiomyopathy and heart failure[15]. The present study included only deceased persons with a short acute phase and was focused on persons in whom SARS-CoV-2 was detectable with RT-qPCR. Thus, if dilated cardiomyopathy had been due to a previous SARS-CoV-2 infection, it was not investigated. However, previous infections might have been present in persons who tested negative for SARS-CoV-2. Long-term follow-up of cases of SARS-CoV-2 infection might show that the weight of the heart had already been increased.

Of patients with COVID-19 infections, liver damage has been reported to occur in 21.5% to 45.7% owing to inflammatory responses, viral-induced cytotoxic T cells, direct cytopathic effects of COVID-19 via the angiotensin-converting enzyme 2 receptor, hypoxia and circulatory changes, and hepatotoxic effects of drugs for treating COVID-19[16-18]. In infected patients the liver has been shown to have a moderate degree of microvesicular steatosis and mild lobular and portal activity[19,20]. In the present study, 8 of the 24 deceased persons who were positive for SARS-CoV-2 had mild to severe lipid droplet deposition in hepatocytes, and 4 of these 8 persons (liver weights and body mass indexes of 1,943 g and 25.4 kg/m^2, 2,317 g and 32.0 kg/m^2, 1,139 g and 36.07 kg/m^2, and 1955 g and 28.05 kg/

m^2) had preobesity or class I obesity based on the World Health Organization cut-off points. Therefore, fatty liver due to overnutrition was considered to be present in these persons. In addition, 2 persons (liver weights of 2,837 g and 1,724 g) had a history of alcoholism and a lifestyle of excessive drinking ; thus, alcoholic fatty liver was diagnosed (1 person with fatty liver only and 1 person with both fatty liver and liver cirrhosis). In 2 other persons (liver weights of 1,136 g and 1,201 g), the cause of fatty liver could not be identified on the basis of the medical history and other autopsy findings, and COVID-19 might have affected lipid droplet deposition in hepatocytes. However, the present study did not observe increased liver weight in SARS-CoV-2-positive persons. Furthermore, fat droplet deposition in hepatocytes due to COVID-19 might be milder than in cases of fatty liver from other causes. Therefore, identifying liver damage due to COVID-19 on the basis of liver weight alone can be difficult.

Related to COVID-19 is a major extrapulmonary lesion : acute kidney injury. Expression of SARS-CoV-2 RNA has been observed from the renal glomeruli, thrombus in glomeruli and arterioles, and tubular atrophy and interstitial fibrosis[21,22]. Of the 24 deceased persons positive for SARS-CoV-2 in the present study, 1 had intraglomerular thrombus (left kidney, 197 g ; right kidney, 163 g) and 1 had tubular atrophy and interstitial fibrosis and moderate to severe glomerulosclerosis (left kidney, 356 g ; right kidney, 323 g). The former person had the complication of intra-arterial thrombosis with hemorrhagic infarction in the parietal lobe, which was considered a renal lesion caused by COVID-19-induced thrombosis. The latter person had had hypertension before the SARS-CoV-2 infection ; thus, the renal disorder was related to hypertension. Our results suggest that the acute COVID-19 phase does not affect kidney weight, but if acute kidney injury progresses to chronic renal failure, the kidney weight might change.

Complications of COVID-19 in the central nervous system (CNS) include encephalopathy, stroke, seizure, meningoencephalitis, and Guillain-Barré syndrome[23]. In the present study, we identified 1 deceased person with hemorrhagic infarction and intra-arterial thrombosis limited to the parietal lobe (brain weight, 1,346 g) and 1 person with sinus venous thrombosis (superior sagittal sinus to bilateral transverse sinus ; brain weight, 1,273 g), both of whom were suspected to have COVID-19-associated thrombus formations. Furthermore, 1 person had subarachnoid hemorrhage with a ruptured aneurysm (diameter, 2 mm) in the anterior communicating artery (brain weight, 1,430 g). However, because it was accompanied by concentric hypertrophy (heart weight, 636 g), it was considered as a hypertensive aneurysm formation and rupture rather than COVID-19-induced vascular disease. Potential COVID-19-related CNS lesions were observed in 2 of the 24 persons (8.33%) of the SARS-CoV-2-positive persons of the present study, but the weights of their brains did not differ from those of SARS-CoV-2-negative persons. Therefore, CNS lesions had little effect on the weight of the brain, perhaps because it is originally a solid organ that fills the skull.

In the present study, the L452R mutation of SARS-CoV-2 was present in significantly more deceased persons who also had DAD, reconfirming that the L452R mutation is more dangerous than other mutations. Furthermore, the lung weight had increased in persons with DAD ; therefore, we expected that lungs would also be heavier in persons with the L452R mutation. However, the weights of organs, including the lungs, did not differ on the basis of the L452R mutation. The small number of persons included in the study might explain this result in the lungs ; thus, further investigations with a greater number of deceased persons are needed.

The longer the postmortem period until an autopsy is performed, the more drying and putrefaction progress ; as a result, the organs are lighter, and using their weights to estimate the presence or absence of lesions is more difficult. Therefore, to exclude the effects of changes in organ weights due to postmortem desiccation or putrefaction, we analyzed persons for whom autopsies had been performed within 72 hours after death. However, we found that regardless of the postmortem time, lung weights had increased similarly in all persons who had been infected with SARS-CoV-2.

In summary, in the present study we performed RT-qPCR to identify who had been infected with SARS-CoV-2 and had L452R mutations among deceased persons examined at autopsy and examined differences in organ weights. We found that lung weight increases in persons who have tested positive for SARS-CoV-2. However, mild DAD can be present, even if lung weight has not been increased. Therefore, care must be taken when diagnosing DAD due

to SARS-CoV-2 infection. In addition, we have confirmed that the L452R mutation is more likely to cause DAD and is more dangerous than other mutations.

ACKNOWLEDGMENTS :

The authors would like to thank Dr. Masayuki Saijo (National Institute of Infectious Diseases, Japan) for the gift of the positive control RNA (SARS-CoV-2 RNA, JPN/AI/I-004). The authors are also grateful to Hiroka Aonuma, Mayumi Kamiura, Yuko Okamoto, and Tomomi Harada for performing RT-qPCR tests for SARS-CoV-2.

The authors would like to thank Editage (www.editage.jp) for the English language review.

Authors have no conflict of interest.

SOURCE OF FUNDING

This work was supported by the Ministry of Health, Labour and Welfare, KAKENHI [Grant Number 20CA2075].

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