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Original Article

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Changing Features of Liver Injury in COVID-19 Patients: Impact of Infection with the SARS-CoV-2 Delta (B.1.617.2) Variants

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ABSTRACT

Background: There is growing evidence that abnormal liver function tests (LFTs) are common in patients with coronavirus disease 2019 (COVID-19). However, it is not known whether viral involvement in the liver differs according to the strain. We investigated the impact on liver injury in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta (B.1.617.2) variants.
Materials and Methods: We conducted a single-center, retrospective cohort study, including 372 patients admitted during the pre-Delta period (PDP: between February 1 and November 30, 2020) and 137 patients admitted during the Delta period (DP: between August 1 and August 31, 2021). Initial liver injury was defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥3 × the upper limit of normal (ULN) or alkaline phosphatase (ALP) or total bilirubin ≥2 × the ULN within 3 days from admission.
Results: Of 509 patients with COVID-19 included in our study, 38 (7.5%) patients had initial liver injury. The DP group had a significantly higher rate of initial liver injury than the PDP group (PDP: 5.9% *vs.* DP: 11.7%, $P = 0.028$). The DP group (adjusted odds ratio [aOR]: 2.737, 95% confidence interval [CI]: 1.322 – 5.666) was independently associated with initial liver injury. During hospitalization, 160 (31.4%) patients had severe COVID-19. The DP group and initial liver injury had higher odds of progressing to severe COVID-19 (aOR: 2.664, 95% CI: 1.526 - 4.648, and aOR: 4.409, 95% CI: 1.816 - 10.707, respectively). The mediation analysis suggested that initial liver injury mediates the relationship between SARS-CoV-2 Delta variant infection and severe COVID-19 (unstandardized beta coefficient = 0.980, Standard error = 0.284, $P = 0.001$).
Conclusion: Initial liver injury is more common in COVID-19 patients with Delta variants. Also, Delta variants and initial liver injury are associated with poor clinical outcomes.

Keywords: Cohort study; COVID-19, Delta variant; Liver injury; Outcome

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INTRODUCTION

In March 2020, the World Health Organization officially declared a pandemic for coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Similar to severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to invade cells [2]. The virus enters the host's cell and activates the body's immune system, which secretes various cytokines and chemokines [2]. If this worsens, cytokine storm syndrome occurs [2]. This process causes various clinical symptoms and acute lung injury, and in severe cases, acute adult respiratory failure syndrome [2]. On the other hand, it has been demonstrated that the ACE2 receptor is also expressed in hepatocyte, which allows SARS-CoV-2 to invade the liver parenchyma and cause liver damage in patients with COVID-19 [3]. The mechanism of liver damage in COVID-19 is known to include sepsis or drug-induced liver damage, in addition to the direct virus-induced damage to hepatocytes and damage induced by the uncontrolled immune responses mentioned above [4]. It is known that liver damage is an indicator of more serious disease and higher mortality in patients with COVID-19 [5]. Guan W et al. said that the patients with COVID-19 who had aspartate aminotransferase (AST) >40 U/L or alanine aminotransferase (ALT) >40 U/L showed the more frequent admission to intensive care unit (ICU), the use of mechanical ventilation, or death [5]. Determining whether liver damage is present in patients with COVID-19 is an important point in the disease treatment process [6, 7].

The SARS-CoV-2 had many variants, which are likely to amplify human-to-human transmission and reduce vaccine effectiveness. Since the SARS-CoV-2 B.1.617.2 (Delta) variant was first reported in India in October 2020, it had become the dominant variant worldwide [8, 9] and Korea until January, 2022 [10]. The Delta variant has 23 mutations; twelve of these occur within spike proteins, which allow the virus to attach to and enter the host cell [11]. The more mutations in the spike protein, the more difficult it is for the host's immune system to recognize and eliminate the virus [11]. This immune evasion makes the spike protein more able to attach to human cells and the human hosts more susceptible to infection. Although the Delta variant causes symptoms similar to the Alpha variant, the Delta variant is associated with a faster onset of symptoms and a greater viral load in the respiratory system [11]. Also, the Delta variant was associated with increased severity of illness [9]. Several studies have been conducted on the Delta variant so far, but little is known about the difference in liver damage between patients infected with the wild-type SARS-CoV-2 and those with the Delta variant.

Therefore, the purpose of our study was to compare the clinical features of patients infected with the SARS-CoV-2 Delta variant with those of patients infected with other SARS-CoV-2 variants, with a focus on liver damage. Second, we also investigated the association of Delta variant-induced liver damage with disease severity and prognosis.

MATERIALS AND METHODS

1. Study design

We conducted a single-center retrospective cohort study. We reviewed the medical records of patients hospitalized from February 1, 2020, to November 30, 2020, and from August 1, 2021, to August 31, 2021, for COVID-19 at the National Medical Center (NMC) in Korea. All patients were diagnosed when SARS-CoV-2 RNA was detected by real-time polymerase chain reaction

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tests using nasopharyngeal and oropharyngeal swabs. In early 2020, hydroxychloroquine, lopinavir/ritonavir, or abacavir/lamivudine were administered to patients with COVID-19 [12]. After that, remdesivir was administered to patients with severe disease, and in 2021 regdanvimab (CT-P59, Celltrion Inc, Incheon, Korea) was administered to those with mild disease. Steroids were administered not only to those who required oxygen, but also to those with underlying diseases who previously needed steroids. Antibiotics were administered when secondary infection was suspected. Some patients had also been given tocilizumab or baricitinib [13-16].

According to data from the Korea Disease Control and Prevention Agency (KDCA), the detection rate of the Delta variant was only 1.4% in April 2021 but had increased sharply to 53.7% in July 2021 in Korea [17]. Accordingly, a previous study from Korea included patients hospitalized in August 2021 as the Delta dominant group and compared them with minor Delta groups from other periods [18]. With reference to the data of the Korean government on the variant detection rate, the enrolled patients in our study were categorized in 2 groups, according to the following criteria: (1) diagnosed from February 2020 to November 2020 (period of variant detection rate = 0%; pre-Delta period [PDP] group); (2) diagnosed during August 2021 (period of the Delta variant detection rate >90%; Delta period [DP] group) [18]. Patients diagnosed from December 2020 to July 2021 were excluded since the Delta mutation was not the dominant variant during that period, and it coexisted with other variants [17].

We excluded the following patients: (1) patients under 19 years of age; (2) patients who did not measure their body mass index (BMI); (3) patients who were readmitted; (4) patients who had incomplete medical records; (5) patients who had liver cirrhosis or chronic liver disease. We collected the following data through medical records review: age, sex, underlying disease, laboratory data, radiographic evidence of pneumonia, and treatment and outcome for each patient. Laboratory data included complete blood counts, C-reactive protein (CRP), and biochemical tests such as liver and renal function tests.

2. Ethics statement

Our study was approved by the Institutional Review Board of NMC (No.2022-0006-001). The need for informed consent was waived by the board due to the retrospective nature of the study.

3. Definitions

Initial liver injury was defined as ALT or AST levels ≥3 × the upper limit of normal (ULN) or alkaline phosphatase (ALP) or total bilirubin ≥2 × the ULN within 3 days from admission [19]. The ULN values of AST and ALT were defined as 34 U/L in males and 30 U/L in females. The ULN values of ALP and total bilirubin were defined as 130 U/L and 1.2 mg/dL, respectively [20]. Severe COVID-19 was defined as respiration rate ≥30 breaths/min, oxygen saturation ≤93%, or oxygen requirement with pneumonia. Pneumonia was defined as ground-glass opacity, reticular interstitial thickening, reverse halo, or peripheral consolidation in a chest radiograph [21]. Severe pneumonia was defined as infiltration over 50% of lung field. Shock was defined as systolic blood pressure <90 mmHg or need for vasopressors to maintain systolic blood pressure >90 mmHg. Systemic inflammatory response syndrome (SIRS) was defined as two or more of follows: (1) body temperature >38.0°C or <36.0°C, (2) heart rate ≥90 beats/min, (3) respiration rate ≥20 breaths/min, or partial pressure of carbon dioxide (PCO_2) <32 mmHg, and (4) leukocyte >12,000 cells/mm^3 or <4,000 cells/mm^3 or over 10% immature forms or bands [22].

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4. Statistical analysis

Data were analyzed using SPSS (Version 27.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as medians and interquartile ranges (IQR), while categorical variables were presented as frequencies and percentages. The Student's *t*-test or Wilcoxon's rank sum test were used to compare continuous variables, and Pearson's Chi-square test or Fisher's exact test were used for categorical variables.

Univariate logistic regression analysis was performed to assess potential risk factors associated with initial liver injury. We tested the following selected variables considered in a previous study and the study participants' demographic and clinical characteristics: age, sex, obesity (BMI >25 kg/m^2), presence of diabetes mellitus (DM), presence of hypertension, presence of fever (body temperature >38.0°C) at admission, and DP group. Then the potential predictors identified as significant in the univariate analysis were entered into multivariate logistic regression models, excluding highly correlated clinical factors using backward elimination methods with exit criteria of 0.1.

To identify independent risk factors for developing severe COVID-19, we adjusted for the following covariates: age, sex, presence of hypertension, presence of DM, obesity, presence of fever at admission, thrombocytopenia (platelet count <100 × 10^3/mm^3) at admission, hypoalbuminemia (albumin <3.5 g/dL) at admission, and abnormal CRP (>5.0 mg/L) at admission.

We used the mediation analysis proposed by Baron & Kenny to investigate whether initial liver injury is mediated in the relationship between delta variant and the prognosis of COVID-19 [23]. In this analysis, it can be said that mediation exists when the following four conditions are satisfied; (1) The independent variable must significantly affect the dependent variable; (2) The independent variable should significantly affect the mediator; (3) The mediator should significantly affect the dependent variable; (4) After mediator control, the independent variable loses or decreases significant influence. In our study, the independent variable was the Delta group, the mediator was initial liver injury, and the dependent variable was the presence or absence of severe COVID-19. At this time, if the independent variable is still meaningful after the mediator is controlled, the initial liver injury is called a partially-mediated model. When the effect of the independent variable completely disappears after mediator control, the initial liver injury is called complete mediating.

RESULTS

1. Baseline clinical characteristics

A total of 501 patients with COVID-19 were admitted to the NMC during PDP, and a total of 194 patients were admitted for COVID-19 during DP. In each group, 129 and 57 patients were excluded according to the exclusion criteria, respectively. Finally, our study enrolled 372 patients in the PDP group and 137 patients in the DP group. The patient selection flow diagram is presented in **Figure 1**.

Baseline clinical characteristics and treatment regimens of patients in both groups are summarized in **Table 1**. The patients in the PDP group were significantly older than those in the DP group (57 [IQR: 40 - 68] *vs.* 43 [IQR: 32 - 56], *P* <0.001). The proportion of males was higher in the PDP group than in the DP group (65.3% *vs.* 46.7%, *P* <0.001). The patients

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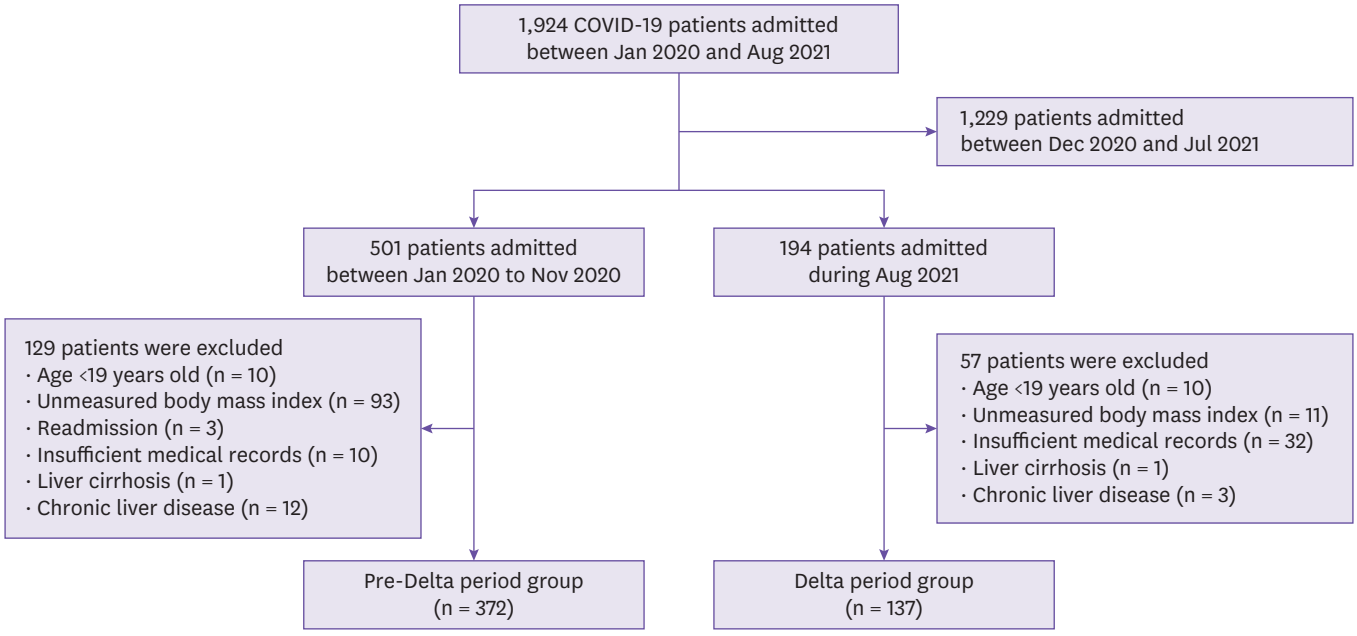

Figure 1. Patient selection flow diagram.
COVID-19, Coronavirus disease 2019.

with DM were higher in the PDP group (22.6% *vs.* 11.0%, $P = 0.003$) and the patients with hypertension were higher in the PDP group (28.0 *vs.* 16.8%, $P = 0.010$) than in the DP group.

In radiologic findings at admission, 252 patients in the PDP group (67.7%) and 92 patients in the DP group (67.2%) had abnormal chest radiograph, and 79 patients in the PDP group (21.2%) and 21 patients in the DP group (15.3%) had severe pneumonia, with no significant differences observed between the groups. The laboratory results of both groups are summarized in **Table 2**. There were no significant differences in the peak value of AST and ALT within 3 days after hospitalization, **Figure 2** shows the change of AST and ALT level over the time by the DP group and the PDP group. CRP levels were higher in the PDP group than the DP group (12.6 mg/L *vs.* 10.6 mg/L, $P = 0.006$).

2. Factors associated with initial liver injury in patients with COVID-19

Of 509 patients with COVID-19, 38 (7.5%) patients had initial liver injury. The DP group had a significantly higher proportion of initial liver injury compared to the PDP group (11.7% *vs.* 5.9%, $P = 0.028$). We examined the clinical factors associated with initial liver injury. In the multivariate logistic regression analyses, the DP group was independently associated with initial liver injury (adjusted odds ratio [aOR]: 2.737, 95% confidence interval [CI]: 1.322 – 5.666; $P = 0.007$; **Table 3**). Also, severe pneumonia on chest radiography at admission was associated with initial liver injury (**Table 3**).

3. Clinical outcomes

Comparisons of clinical outcomes between the PDP and DP groups are summarized in **Table 1**. During hospitalization, 160 patients (31.4%) had severe COVID-19, which occurred more frequently in the DP group than in the PDP group (PDP group: 28.8% *vs.* DP group: 38.7%, $P = 0.030$). However, the difference in mortality rate was not significant between both groups (PDP group: 3.8% *vs.* DP group: 2.2%, $P = 0.579$).

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Table 1. Clinical characteristics of patients with COVID-19 according to the PDP and DP groups

Characteristics	Total (n = 509)	PDP group (n = 372)	DP group (n = 137)	*P*-value
Age (years)	53 (38 - 65)	57 (40 - 68)	43 (32 - 56)	<0.001
Male sex	307 (60.3)	243 (65.3)	64 (46.7)	<0.001
Body mass index, kg/m^2	24.2 (22.1 – 26.5)	24.2 (22.1 – 26.4)	23.9 (22.0 – 26.6)	0.491
Comorbidity				
DM	99 (19.5)	84 (22.6)	15 (11.0)	0.003
Hypertension	127 (25.0)	104 (28.0)	23 (16.8)	0.010
Chronic kidney disease	2 (0.4)	2 (0.5)	0 (0.0)	1.000
Laboratory and radiologic findings				
Initial liver injury[a]	38 (7.5)	22 (5.9)	16 (11.7)	0.028
Duration from symptom onset to LFT examination, days	4 (1.0 - 8.0)	4 (1.0 - 10.0)	2 (1.0 - 5.0)	<0.001
Duration from diagnosis to LFT examination, days	1 (0.0 - 2.0)	1 (0.0 - 2.0)	1 (0.0 - 2.0)	0.050
Abnormal chest radiography at admission	344 (67.6)	252 (67.7)	92 (67.2)	0.900
Severe pneumonia[b] at admission	100 (19.7)	79 (21.2)	21 (15.3)	0.137
Treatment during hospitalization				
Antibiotics	214 (42.0)	155 (41.7)	59 (43.1)	0.777
Lopinavir/ritonavir	59 (11.6)	59 (15.9)	0 (0.0)	<0.001
Abacavir/lamivudine	1 (0.2)	1 (0.3)	0 (0.0)	1.000
Regdanvimab	42 (8.3)	0 (0.0)	42 (30.7)	<0.001
Remdesivir	89 (17.5)	41 (11.0)	48 (35.0)	<0.001
Tocilizumab	2 (0.4)	0 (0.0)	2 (1.5)	0.072
Baricitinib	2 (0.4)	0 (0.0)	2 (1.5)	0.072
Hydroxychloroquine	29 (5.7)	29 (7.8)	0 (0.0)	<0.001
Steroid	131 (25.7)	82 (22.0)	49 (35.8)	0.002
Enoxaparin	69 (13.6)	41 (11.0)	28 (20.4)	0.006
Inotropic agent	28 (5.5)	25 (6.7)	3 (2.2)	0.047
Respiratory support				
Oxygen supplementation	160 (31.4)	107 (28.8)	53 (38.7)	0.032
High flow nasal cannula	38 (7.6)	27 (7.4)	11 (8.2)	0.769
Invasive mechanical ventilation	24 (4.7)	21 (5.7)	3 (2.2)	0.103
Continuous renal replacement therapy	4 (0.8)	3 (0.8)	1 (0.7)	1.000
Extracorporeal membrane oxygenation	5 (1.0)	4 (1.1)	1 (0.7)	1.000
Outcome				
SIRS	282 (55.4)	188 (50.5)	94 (68.6)	<0.001
Shock	101 (19.8)	72 (19.4)	29 (21.2)	0.649
Severe COVID-19	160 (31.4)	107 (28.8)	53 (38.7)	0.030
Death	17 (3.3)	14 (3.8)	3 (2.2)	0.579

Data were presented as either median (interquartile range) or number (%).
[a]Initial liver injury was defined as alanine aminotransferase or aspartate aminotransferase levels ≥3 × upper limit of normal (ULN), or alkaline phosphatase or total bilirubin ≥2 × ULN within 3 days from admission.
[b]Pneumonia involved over 50% of the lung field on the chest image.
COVID-19, Coronavirus disease 2019; PDP, pre-Delta period; DP, Delta period; DM, diabetes mellitus; LFT, liver function test; SIRS, systemic inflammatory response syndrome.

The multivariate logistic regression analyses for severe COVID-19 are presented in **Table 4**. The DP group had higher odds of progressing to severe COVID-19 (aOR: 2.664, 95% CI: 1.526 - 4.648). Moreover, initial liver injury was significant parameter associated with severe COVID-19 (aOR: 4.409, 95% CI: 1.816 - 10.707). In addition, age ≥50 years, obesity, hypoalbuminemia at admission, and abnormal CRP at admission were also significantly associated with severe COVID-19.

4. Mediation analysis

Figure 3 shows the results of the mediation analysis. In the initial regression analysis (regression 1), the DP group was associated with initial liver injury (unstandardized beta coefficient [β] = 0.901, standard error [SE] =0.376, *P* = 0.016). In the second regression analysis (Regression 3), when the initial liver injury was not controlled as a mediator, the relationship between the DP group and severe COVID-19 was significant (β = 1.077, SE =

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Table 2. Laboratory findings at admission of study population according to the PDP and DP groups

Characteristics	Total (n = 509)	PDP group (n = 372)	DP group (n = 137)	*P*-value
Platelet count, × 10^3/mm^3	208 (167 - 260)	212 (169 - 268)	191 (162 - 240)	0.001
<100	8 (1.6)	5 (1.4)	3 (2.2)	0.446
≥100	497 (98.4)	365 (98.6)	132 (97.8)	
C-reactive protein, mg/L	11.9 (2.1 - 54.2)	12.6 (1.8 - 61.0)	10.6 (3.4 - 37.1)	0.006
≤5.0	190 (37.4)	145 (39.1)	45 (32.8)	0.197
>5.0	318 (62.6)	226 (60.9)	92 (67.2)	
Procalcitonin, ng/mL	0.06 (0.04 - 0.09)	0.06 (0.03 - 0.10)	0.06 (0.05 - 0.09)	0.277
Serum albumin, g/dL	4.3 (3.7 - 4.6)	4.2 (3.7 - 4.5)	4.5 (4.1 - 4.8)	
<3.5	61 (12.1)	53 (14.4)	8 (5.8)	0.009
≥3.5	445 (87.9)	316 (85.6)	129 (94.2)	
Blood urea nitrogen, mg/dL	12 (9 - 15)	12 (10 - 16)	11 (8 - 14)	<0.001
Creatinine, mg/dL	0.7 (0.6 - 0.9)	0.7 (0.6 - 0.9)	0.7 (0.6 - 0.9)	0.049
eGFR, mL/min/1.73 m^2	102 (86 - 124)	102 (86 - 123)	105 (87 - 126)	0.130
Sodium, mmol/L	139 (137 - 141)	139 (137 - 141)	138 (137 - 140)	0.315
Potassium, mmol/L	4.0 (3.8 - 4.2)	4.0 (3.8 - 4.3)	3.9 (3.7 - 4.2)	0.058
Liver enzymes[a]				
ALT[b], U/L	23 (16 - 38)	24 (16 - 37)	22 (14 - 45)	0.098
Within normal range	332 (65.2)	248 (66.7)	84 (61.3)	0.137
1 - 3 ULN	149 (29.3)	107 (28.8)	42 (30.7)	
>3 ULN	28 (5.5)	17 (4.6)	11 (8.0)	
AST[b], U/L	29 (21 - 41)	29 (21 - 41)	28 (21 - 47)	0.372
Within normal range	297 (58.2)	218 (58.6)	78 (56.9)	0.473
1 - 3 ULN	189 (37.1)	139 (37.4)	50 (36.5)	
>3 ULN	24 (4.7)	15 (4.0)	9 (6.6)	
ALP, U/L	64 (54 - 79)	65 (54 - 79)	63 (53 - 78)	0.371
≤130	475 (95.0)	346 (95.1)	129 (94.9)	0.927
>130	25 (5.0)	18 (5.0)	7 (5.2)	
Total-bilirubin, mg/dL	0.5 (0.3 - 0.6)	0.5 (0.4 - 0.7)	0.4 (0.3 - 0.5)	<0.001
≤1.2	484 (95.1)	348 (93.6)	136 (99.3)	0.008
>1.2	25 (4.9)	24 (6.5)	1 (0.7)	
GGT, U/L	31 (17 - 61)	31 (19 - 63)	29 (14 - 58)	0.836
≤40	258 (62.6)	178 (62.0)	80 (64.0)	0.703
>40	154 (37.4)	109 (38.0)	45 (36.0)	

Data were presented as either median (interquartile range) or number (%).
[a]Peak values of liver function test results within 3 days after admission.
[b]The ULN values of AST and ALT were defined as 34 U/L in males and 30 U/L in females.
PDP, pre-Delta period; DP, Delta period; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

Table 3. Univariate and multivariate logistic regression models for initial liver injury[a]

Variables	Univariate	Multivariate	*P*-value
	OR (95% CI)	Adjusted OR (95% CI)	
DP group (*vs.* PDP group)	2.104 (1.070 - 4.137)	2.737 (1.322 - 5.666)	0.007
Hypertension (*vs.* No)	1.247 (0.600 - 2.592)		
DM (*vs.* No)	0.608 (0.231 - 1.599)		
Age ≥50 years (*vs.* <50)	1.234 (0.628 - 2.424)		
Male (*vs.* Female)	0.799 (0.411 - 1.555)		
Obesity[b] (*vs.* No)	1.285 (0.661 - 2.502)		
Fever[c] at admission (*vs.* No)	1.694 (0.792 - 3.624)		
Severe COVID-19 at admission (*vs.* No)	5.119 (2.596 - 10.095)		
Severe pneumonia on chest image at admission (*vs.* No)	6.928 (3.481 - 13.788)	7.898 (3.878 - 16.085)	<0.001
Leukocytosis[d] (*vs.* No)	2.151 (0.784 - 5.896)		
Thrombocytopenia[e] at admission (*vs.* No)	1.776 (0.213 - 14.825)		
CRP >5 mg/L at admission (*vs.* ≤5 mg/L)	4.284 (1.643 - 11.174)		

[a]Initial liver injury was defined as alanine aminotransferase or aspartate aminotransferase levels ≥3 × upper limit of normal (ULN), or alkaline phosphatase or total bilirubin ≥2 × ULN within 3 days from admission.
[b]Obesity was defined as body mass index >25 kg/m^2.
[c]Fever was defined as body temperature >38.0°C.
[d]Leukocytosis was defined as white blood count > 10,000/mm^3.
[e]Thrombocytopenia was defined as platelet count < 100 × 10^3/mm^3.
OR, odds ratio; CI, confidence interval; DP, Delta period; PDP, pre-Delta period; DM, diabetes mellitus; COVID-19, coronavirus disease 2019; CRP, C-reactive protein.

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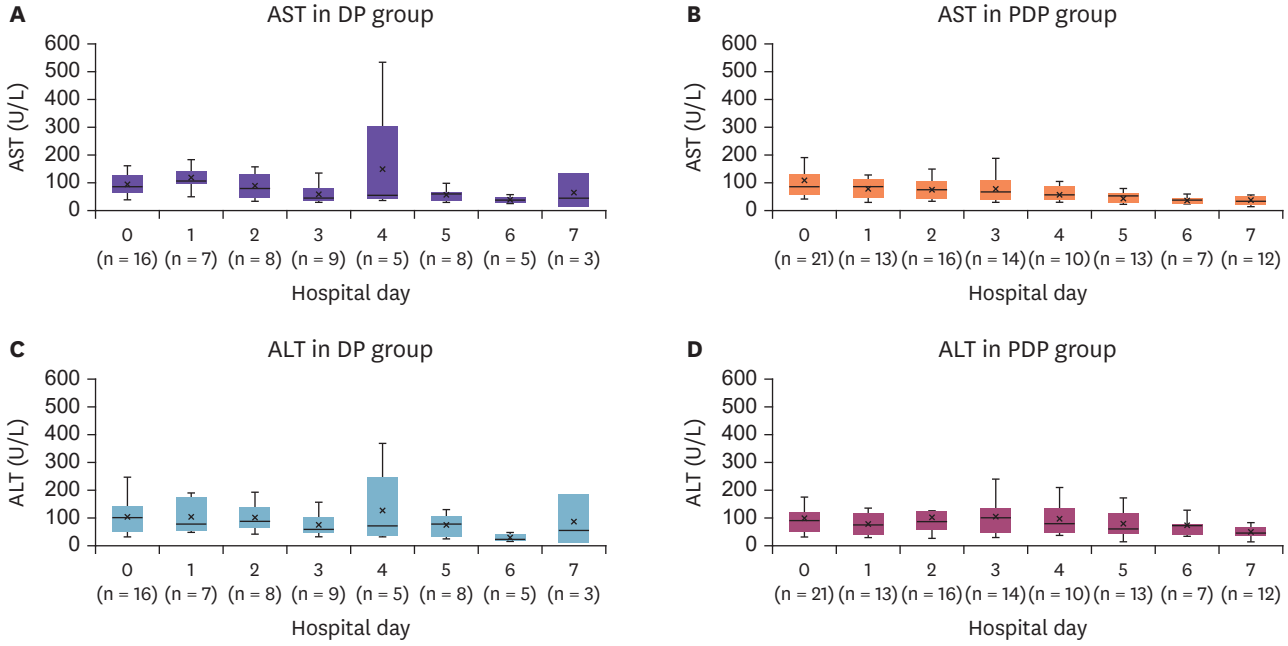

Figure 2. Box and whisker plots showing AST and ALT level in both groups over time. Boxplots show 25th, 50th, 75th quartiles of the estimates, with black whiskers extending 1.5*interquartile range in each direction. (A) AST in DP group, (B) AST in PDP group, (C) ALT in DP group, (D) ALT in PDP group.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; DP, Delta period; PDP, pre-Delta period.

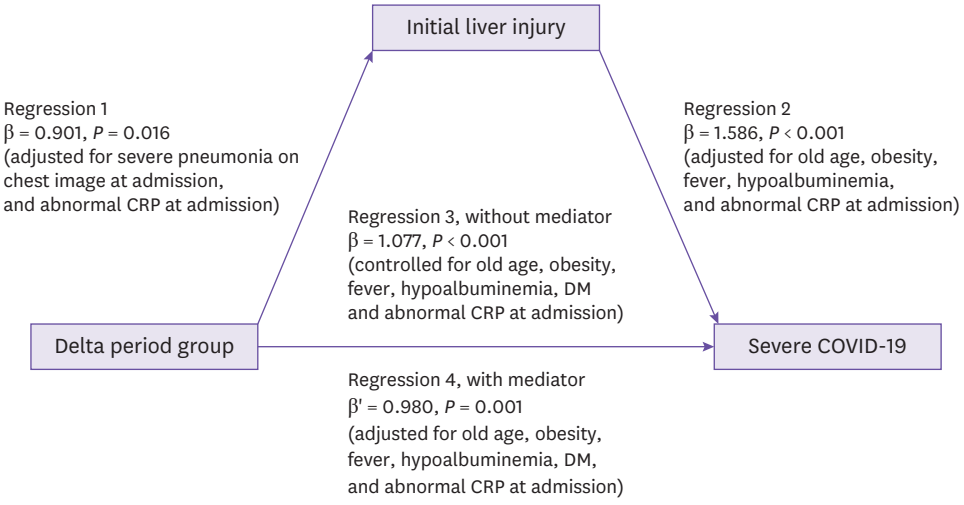

Figure 3. Initial liver injury mediation models of the relationship between the Delta period group and severe COVID-19.
COVID-19, coronavirus disease 2019; *β*, unstandardized beta coefficients; CRP, C-reactive protein; DM, diabetes mellitus.

0.277, P <0.001). Also, in the third regression analysis (regression 2), initial liver injury was associated with severe COVID-19 (β = 1.586, SE = 0.452, P <0.001). Thus, when the initial liver injury was controlled as a mediator (regression 4), the relationship between the DP group and severe COVID-19 was statistically significant (β = 0.980, SE = 0.284, P = 0.001). In addition, since the statistical significance of the relationship between the DP group and severe COVID-19 was decreased in regression 4 compared to regression 3, initial liver injury was confirmed to be a partial mediator.

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Table 4. Univariate and multivariate logistic regression models for severe COVID-19

Variables	Univariate	Multivariate	*P*-value
	OR (95% CI)	Adjusted OR (95% CI)	
DP group (*vs.* PDP group)	1.570 (1.043 - 2.363)	2.664 (1.526 - 4.648)	<0.001
Initial liver injury[a] (*vs.* No)	6.046 (2.917 - 12.532)	4.409 (1.816 - 10.707)	0.001
Hypertension (*vs.* No)	1.938 (1.279 - 2.937)		
DM (*vs.* No)	2.174 (1.387 - 3.407)		
Male (*vs.* Female)	1.026 (0.701 - 1.502)		
Age ≥50 years (*vs.* <50)	4.247 (2.773 - 6.504)	4.163 (2.366 - 7.325)	<0.001
Obesity[b] (*vs.* No)	2.136 (1.461 - 3.123)	2.447 (1.516 - 3.949)	<0.001
Fever[c] at admission (*vs.* No)	2.172 (1.37 - 3.445)	1.612 (0.915 - 2.841)	0.099
Thrombocytopenia[d] at admission (*vs.* No)	3.643 (0.86 - 15.436)		
Hypoalbuminemia[e] at admission (*vs.* No)	7.977 (4.341 - 14.659)	4.202 (2.098 - 8.417)	<0.001
CRP >5 mg/L at admission (*vs.* ≤5 mg/L)	13.244 (7.092 - 24.734)	8.501 (4.162 - 17.366)	<0.001

[a]Initial liver injury was defined as alanine aminotransferase or aspartate aminotransferase levels ≥3 × upper limit of normal (ULN), or alkaline phosphatase or total bilirubin ≥2 × ULN within 3 days from admission.
[b]Obesity was defined as body mass index >25 kg/m^2.
[c]Fever was defined as body temperature >38.0°C.
[d]Thrombocytopenia was defined as platelet count <100 × 10^3/mm^3.
[e]Hypoalbuminemia was defined as serum albumin level <3.5 g/dL.
COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; DP, Delta period; PDP, pre-Delta period; DM, diabetes mellitus; CRP, C-reactive protein.

DISCUSSION

As SARS-CoV-2 evolves by acquiring mutations, clinical phenotypes are also changing. Previous studies have reported that liver enzyme levels are often elevated in patients with COVID-19 and that patients with liver disease are at increased risk of death. In our study, we found that the Delta variant more frequently caused liver injury compared to the wild-type SARS-CoV-2. And, initial liver damage caused by SARS-CoV-2 was associated with severe COVID-19. Furthermore, older age, obesity, hypoalbuminemia and higher CRP were associated with severe COVID-19. This result is consistent with previous studies [24-26].

In terms of clinical outcomes, the DP group required oxygen therapy more frequently, and these results are consistent with a Singapore study that found that patients with the Delta variant had a higher disease severity [9]. In addition, in our study, patients with severe COVID-19 were more in the DP group than in the PDP group (38.7% *vs.* 28.8%, $P = 0.030$). Meanwhile, there was no significant difference in the use of invasive mechanical ventilation or death between both groups. However, Fisman et al. reported that the Delta variant was a risk factor for ICU admission and death [27]. In our study, a rate of 2.2% with mechanical ventilation in the delta variant was observed, whereas Kaiyuan et al. reported that 4.9% of the patients with the Delta variant received tracheal intubation [28]. We think that the reason for this is the following. During pre-Delta variant period, all patients with COVID-19 were admitted in a few referral hospitals for COVID19 patients including our hospital in Korea. Also, most of patients were admitted in that time by transfer from other hospital to our hospital. However, during the Delta variant period, many COVID-19 patients without comorbidity were isolated in home, and residential treatment center was used for the patients with COVID-19 who couldn't be able to be isolated in home because of comorbidity, although they had mild or no symptoms. The patients enrolled in our study included those admitted in residential treatment center belonging to our hospital.

Severe COVID-19 was significantly associated with both the DP group and initial liver injury. The results from mediation analysis showed that initial liver injury is partly a mediator of the association between Delta variant and severe COVID-19. This means that the Delta variant

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partially affected the clinical outcomes through initial liver injury. Mishra et al. reported that liver injury could be a surrogate for inflammation and a predictor of outcomes in COVID-19 [29]. We demonstrated that liver injury within 3 days of admission was related to the prognosis, so it was possible to look at the LFT as an indicator for predicting the prognosis regardless of the mutation. One study reported that liver damage was more common in patients with high viral load [30], and another study reported that the Delta variant had a higher viral load than other variants [31]. Therefore, in patients infected with Delta mutations and relatively large viral loads, the risk of initial liver injury may be increased. The relationship between liver injury and disease severity can also be explained by looking at a study demonstrating that high viral load is related to disease severity [32]. However, in our study, it was not possible to obtain virus load data through medical record reviews, so further studies are required.

In our study, the pattern and prognosis between groups with liver injury within 3 days of admission were compared. This is because, as time passes after hospitalization, the elevation in liver enzymes can be affected by the use of hepatotoxic drugs, shock, or hypoxia. Thus, to evaluate liver damage caused only by the COVID-19 virus, it was considered reasonable to assess liver injury within 3 days of admission. As a result of this analysis, we found that liver injury was more common in the DP group than in the PDP group. The DP group was significantly related with liver injury within 3 days of admission, and the odds ratio was over 2.5 times.

In 2022, the Omicron variant replaced the Delta variant and became the dominant species worldwide [33]. Patients infected with the Omicron variant are known to show relatively mild symptoms compared to those infected with the Delta variant, but deaths still occur in high-risk groups [34]. Deng et al. compared liver function test between 77 Delta and 80 Omicron variant-infected patients. They defined liver injury as at least one of liver function test parameters exceeding the upper limit of normal value. In this study, liver injury, inflammatory markers and peak viral load did not differ between the two groups, and male gender and high peak viral load were independent factors related to liver injury [35]. We believe that further studies for liver injury between Omicrons and other variants are needed.

Our study had several limitations. First, it was a retrospective study involving small number patients in a single center. Therefore, a selection bias was inevitable. Second, we did not identify the actual variant type in the patients included in the study. However, data from KCDA showed that the detection rate of Delta variants in DP was over 90%, so the possibility that the DP group was infected with other variants is very low. Nonetheless, patients with DP group may be infected with different mutations. Third, there may be potential confounders that were not considered in our analysis. For instance, there is no standard way to compensate for the risk associated with liver injury in patients with COVID-19. We have taken the approach addressed in previous studies, but there may still be factors associated with the outcomes. Fourth, we did not include the history of alcohol or non-alcoholic fatty liver disease (NAFLD) of each patient because it was not recorded in the medical record due to insufficient questionnaires in some patient records. However, it is thought that factors corresponding to metabolic syndrome such as hypertension, DM, hyperlipidemia and BMI that can affect NAFLD were included in the study. Finally, as mentioned before, we could not investigate the patients with the Omicron variant. Therefore, our study is difficult to apply directly to the current COVID-19 pandemic in which Omicron is dominant variant.

In summary, we suggested that patients with the Delta variant had more liver injury than those with the Pre-Delta variant and this resulted in more severe COVID-19. The Delta variant

has higher viral loads than other strains with earlier and prolonged shedding. Also, it is associated with poor prognosis such as hospitalization and mortality [31, 36, 37]. Especially, high viral load in COVID-19 was closely related to liver injury [30, 35]. We think that the Delta variant induce more severe viral cytopathic effects and immune system activation than pre-existing variants, and this may result to not only more severe liver injury but poor outcome [36, 37]. In the future, the mutation in SARS-CoV-2 will lead to the emergence of new variants. Therefore, in the COVID-19 era, the initial liver injury may be one of the surrogate markers in predicting the prognosis of COVID-19 regardless of variant.

In conclusion, initial liver injury is more common in patients with COVID-19 infected with the Delta variant than in those infected with the wild-type SARS-CoV-2. Also, the Delta variant is associated with poor clinical outcomes. However, we believe that a large and prospective study is needed to investigate the association between variant-dependent liver injury patterns and their clinical outcomes.

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