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Original Article

Liver Dysfunction in Adult COVID-19 Infection—A Comparison of the Delta Variant and Predecessor Strains

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Abstract

Background and objectives: Multiple factors are responsible for severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2)-associated liver dysfunction. The impact of variants of concern (VoCs) on liver function is less clear. The aims were to determine (1) the prevalence and risk of abnormal liver biochemistry (ALB) and liver injury (LI) and (2) differences in ALB and LI with the Delta variant compared with wild-type and VoCs before Delta variant coronavirus disease of 2019 (COVID-19) infections in Malaysian adults.

Methods: This prospective single-center, observational study enrolled adults hospitalized for COVID-19 infection between 1 February 2020 and 30 October 2021 using a convenience sampling method. Patients with COVID-19 confirmed by real-time reverse-transcriptase polymerase chain reaction of nasal and pharyngeal swabs and having at least one liver function test were recruited and assigned to cohort A (wild-type strain and all VoCs before the Delta variant) or cohort B (Delta variant).

Results: Of 1,246 patients with COVID-19 infection, 58.7% developed ALB and 26.6% developed LI. Multivariate analysis showed that men, moderate and severe disease, and underlying chronic liver disease (CLD) were associated with ALB and LI. Patients with the Delta variant had a significantly higher risk of developing both ALB (71.6% vs. 48.5%, $p < 0.001$) and LI (38.8% vs. 17.1%, $p < 0.001$) compared with previous strains.

Conclusions: ALB was more common than LI, but LI was more frequent in men with underlying CLD, and in those with moderate or severe COVID-19 infections. Patients with Delta variant infections were more likely to have ALB and LI than those with precedent strains.

Keywords: COVID-19 infection; SARS-CoV 2; Delta variant; Liver dysfunction; Liver injury.

Abbreviations: ALB, abnormal liver biochemistry; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; CLD, chronic liver disease; COVID-19, coronavirus disease of 2019; DM, diabetes mellitus; GGT, gamma glutamyl transferase; HCQ, hydroxychloroquine; HTN, hypertension; ICU, intensive care unit; LFT, liver function test; LI, liver injury; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; RT-PCR, real-time polymerase chain reaction; SARS-CoV 2, severe acute respiratory syndrome coronavirus 2; VoC, variant of concern.

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Introduction

In December 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) virus spread globally to the extent of becoming a pandemic. In Malaysia, the first confirmed case of coronavirus disease of 2019 (COVID-19) was detected on 23 February 2020 and until now there have been 3.5 million cases nationwide, with a lower mortality rate of 0.91%.[1] Over 2 years, multiple variants of the original virus have emerged. Variants of concern (VoCs) include Alpha, Beta, Gamma, Delta, and Omicron.[2] The Delta variant is recognized as more infective than the other VoCs and causes more severe infections and more deaths.[3–5] The first case of Delta variant infection was detected in Malaysia on 19 April 2021 and continued to be the predominant strain until January 2022.[1]

SARS-CoV-2 is known to primarily cause upper respiratory tract infections that lead to lower respiratory tract infections in a subset of patients, causing alveolar damage and subsequent respiratory failure.[6–8] Although respiratory tract involvement is the prominent clinical manifestation, liver dysfunction in COVID-19 patients is a recognized entity, and the cause of this phenomenon is multifactorial.[9–15] The incidence of abnormal liver biochemistry (ALB) is common (14–76.3%) and varies widely among populations.[11–14,16–18] These studies also revealed that disease severity, increasing age, and underlying chronic liver disease (CLD) were factors that increased the risk of liver injury (LI). However, data on the extent of liver dysfunction caused by different VoCs are lacking. There is also a paucity of local data regarding factors that increase the risk of liver dysfunction in people with COVID-19 infection. This study aimed to determine (1) the prevalence and risk factors of ALB and LI in adult COVID-19 patients and (2) the differences of ALB and LI in patients with the Delta variant compared with the wild-type and all VoCs that appeared prior to the Delta variant in Malaysia.

Materials and methods

Study design and participants

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of University of Malaya (MECID No. 202146-10036). All subjects gave written informed consent. We performed a prospective observational study and recruited patients who were admitted between 1 February 2020 and 30 October 2021 using a convenience sampling method. Patients 18 years of age and older who were admitted to one hospital in Malaysia with laboratory-confirmed COVID-19 confirmed by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens and had at least a single liver function test (LFT) during hospitalization were recruited into the study. Patients were divided into cohort A (admission between February 2020 and 30 April 2021), which included the COVID-19 wild-type strain and all VoCs before the Delta variant and cohort B (admission between 1 May 2021 and 31 October 2021), which included COVID-19 Delta variant cases. Owing to lack of genomic sequencing, COVID-19 cases detected from May 2021 onwards were presumed to be of the Delta variant, as the first case of Delta variant infection in Malaysia was detected on 12 April 2021 and cases increased rapidly from May 2021 onward.

Data collection

Relevant clinical data, laboratory, and imaging results were obtained by reviewing the electronic medical record of the patients. Information regarding the presence of liver disease diagnosed either before or during admission, pharmacotherapy, disease severity, and outcome were documented. CLD was defined when a patient had a diagnosis of liver cirrhosis, chronic hepatitis B, or C infection, alcoholic liver disease, nonalcoholic steatohepatitis, and/or autoimmune liver disease.

ALB was defined and categorized into hepatocellular type when alanine aminotransaminase (ALT) or aspartate aminotransferase (AST) was more than 40 U/L, cholestatic type when alkaline phosphatase (ALP) was more than 130 U/L or gamma-glutamyl transferase (GGT) was more than 50 U/L, or mixed type if both patterns were present. LI was defined and categorized as hepatocellular if AST or ALT was more than three times the upper limit of normal, cholestatic type if ALP or GGT or total bilirubin was more than two times the upper limit of normal, or mixed if both patterns were present. For patients with more than one LFT result during hospitalization, the most deranged LFT result was documented. COVID-19 disease severity was categorized as mild (category 1–2), moderate (category 3), or severe (category 4–5). Definitions of the categories were: category 1, asymptomatic COVID-19 patients; category 2, symptomatic patients with no evidence of pneumonia and not requiring oxygen support; category 3, patients with clinical or radiological evidence of pneumonia but not requiring oxygen support; category 4, patients with pneumonia and requiring oxygen support; and category 5, patients requiring mechanical ventilation or with organ failure.

Statistical analysis

Categorical variables were reported as numbers and percentages. Chi-square and Fisher's exact tests were used to compare categorical variables. Continuous values were reported as means (standard deviations) and were compared with Student's *t*-test or one-way analysis of variance for parametric data. Continuous values were reported as medians and were compared with Mann-Whitney *U* or Kruskal-Wallis H tests for nonparametric data. Multivariate analysis was performed using multiple linear regression. The statistical analyses were performed with SPSS version 21 (IBM Corp., Armonk, NY, USA). A two-sided significance level of $p \leq 0.05$ was used for all models.

Results

We included 1,246 patients, 697 (58.7%) in cohort A and 549 (44.1%) in cohort B who were admitted to our hospital with COVID-19 infection between 1 February 2020 and 30 October 2021. The median age was 50.0 years with a male:female ratio of 1:1.02. More than half (52.1%) had mild disease and 47.1% were given specific treatment. CLD was present in 11.7% of patients. The baseline and clinical characteristics of these patients are outlined in Table 1.

Prevalence and risk factors for ALB and LI

ALB was seen in 731 (58.7%) patients, but only 26.6% experienced LI and 14 (1.1%) patients had liver failure. Mixed type and cholestasis were the predominant patterns of liver insult seen among patients with ALB and LI, respectively; specifically, 69.3% above 60 years and 72% of male patients had ALB, and incidence increased with disease severity, and 78% of patients who received any disease-modulating pharmacotherapy had ALB. Notably, the majority of patients with comorbidities who required intensive care unit (ICU) admission, or died were found to have ALB as well (Table 2). Multivariate analysis showed a significantly higher risk of developing ALB in men (OR = 2.93, 95% CI: 2.24, 3.83), patients with moderate (OR = 1.66, 95% CI: 1.10, 2.50) or severe (OR = 3.17, 95% CI: 1.53, 6.57) disease, CLD (OR = 19.31, 95% CI: 2.38, 156.53), or hypertension (HTN) (OR = 1.64, 95% CI: 1.16, 2.33). In total, 34.8% of patients older than 60 years of age and 43.8% who received disease-modulating pharmacotherapy were reported to have LI. The frequency of LI also increased with disease severity. The majority of patients who required mechanical ventilation, ICU admission, or died also had LI (Table 3). Multivariate analysis for LI showed significantly higher frequencies in men (OR = 1.79,

Table 1. Demographics and clinical characteristics of COVID-19 patients (*n* = 1,246)

Characteristic	Cohort*			*p*-value
	All, *n* = 1,246	Cohort A, *n* = 697	Cohort B, *n* = 549	
Age in years				
Median [IQR]	50.0 (31)	44.0 (31)	55.0 (27)	<0.001
1–60	846 (67.9)	508 (72.9)	338 (61.6)	<0.001
>60	400 (32.1)	189 (27.1)	211 (38.4)	
Sex				
Male	618 (49.6)	325 (46.6)	256 (53.4)	0.018
Female	628 (50.4)	372 (53.4)	293 (46.6)	
Ethnicity				
Malay	779 (62.5)	427 (61.3)	352 (64.1)	0.123
Chinese	233 (18.7)	126 (18.1)	107 (19.5)	
Indian	189 (15.2)	112 (16.1)	77 (14.0)	
Others	45 (3.6)	32 (4.6)	13 (2.4)	
COVID-19 severity				
Mild	649 (52.1)	450 (64.6)	199 (36.2)	<0.001
Moderate	200 (16.1)	108 (15.5)	92 (16.8)	
Severe	397 (31.9)	139 (19.9)	258 (47.0)	
Disease-modulating pharmacotherapy				
Yes	587 (47.1)	231 (33.1)	356 (64.8)	<0.001
No	659 (52.9)	466 (66.9)	193 (35.2)	
Type of treatment				
NSAID	81 (6.5)	68 (12.4)	13 (1.9)	<0.001
Hydroxychloroquine	25 (2.0)	22 (3.2)	3 (0.5)	0.001
Favipiravir	175 (14.0)	56 (8.0)	119 (21.7)	<0.001
Methylprednisolone	121 (9.7)	40 (5.7)	81 (14.8)	<0.001
Clexane	273 (21.9)	73 (10.5)	200 (36.4)	<0.001
Tocilizumab	110 (8.8)	48 (6.9)	62 (11.3)	0.006
Dexamethasone	455 (36.5)	164 (23.5)	291 (53.0)	<0.001
Baricitinib	5 (0.4)	0 (0.0)	5 (0.9)	0.012
Comorbidities				
CLD	146 (11.7)	75 (10.8)	71 (12.9)	0.237
NAFLD	126 (10.1)	67 (9.6)	59 (10.7)	0.510
DM	388 (31.1)	179 (25.7)	209 (38.1)	<0.001
HTN	441 (35.4)	205 (29.4)	236 (43.0)	<0.001
CKD	91 (7.3)	44 (6.3)	47 (8.6)	0.130
CCF	74 (5.9)	42 (6.0)	32 (5.8)	0.884
Chronic lung disease	86 (6.9)	42 (6.0)	44 (8.0)	0.169
Cancer	51 (4.1)	31 (4.4)	20 (3.6)	0.477
ALB				
Yes	731 (58.7)	338 (48.5)	393 (71.6)	<0.001
No	515 (41.3)	359 (51.5)	156 (28.4)	
Type of ALB				
Hepatocellular	205 (16.5)	116 (16.6)	89 (16.2)	<0.001

(continued)

Table 1. *(continued)*

Characteristic	Cohort*			*p*-value
	All, *n* = 1,246	Cohort A, *n* = 697	Cohort B, *n* = 549	
Cholestasis	80 (6.4)	46 (6.6)	34 (6.2)	
Mixed	446 (35.8)	176 (25.3)	270 (49.2)	
Deranged LFT				
Total bilirubin	153 (21.2)	61 (18.3)	92 (23.6)	0.084
ALP	135 (18.8)	59 (18.0)	76 (19.4)	0.620
ALT	475 (65.1)	192 (57.0)	283 (72.0)	<0.001
AST	583 (82.3)	237 (75.0)	346 (88.3)	<0.001
GGT	391 (54.4)	162 (49.2)	229 (58.7)	0.011
Liver injury				
Yes	332 (26.6)	119 (17.1)	213 (38.8)	<0.001
No	914 (73.4)	578 (82.9)	336 (61.2)	
Type of liver injury				
Hepatocellular	54 (4.3)	27 (3.9)	27 (4.9)	<0.001
Cholestasis	149 (12.0)	54 (7.7)	95 (17.3)	
Mixed	123 (9.9)	37 (5.3)	86 (15.7)	
Abnormal LFT				
Total bilirubin	86 (26.2)	30 (25.4)	56 (26.7)	0.806
ALP	100 (30.3)	39 (33.1)	61 (28.8)	0.418
ALT	267 (80.4)	86 (72.3)	181 (85.0)	0.005
AST	306 (94.4)	102 (91.1)	204 (96.2)	0.054
GGT	291 (88.4)	97 (82.9)	194 (91.5)	0.019
Liver failure				
Yes	14 (1.1)	7 (1.0)	7 (1.3)	0.653
No	1,232 (98.9)	690 (99.0)	542 (98.7)	
ICU admission				
Yes	172 (13.8)	84 (12.1)	88 (16.0)	0.043
No	1,074 (86.2)	613 (87.9)	461 (84.0)	
Ventilator				
Yes	354 (28.4)	123 (17.6)	231 (42.1)	<0.001
No	892 (71.6)	574 (82.4)	318 (57.9)	
Death				
Yes	61 (4.9)	28 (4.0)	33 (6.0)	0.105
No	1,185 (95.1)	669 (96.0)	516 (94.0)	

Data are presented as *n* (%) or median (IQR). *Cohort A: 26 Feb 2020–31 March 2021 and before; Cohort B: 1 April 2021–30 Oct 2021. ALB, abnormal liver biochemistry; CCF, chronic cardiac failure; CLD, chronic liver disease; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; LFT, liver function test; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug.

95% CI: 1.33, 2.41), in patients with moderate (OR = 3.03, 95% CI: 1.87, 4.92) or severe (OR = 4.56, 95% CI: 2.27, 9.18) disease, or CLD (OR = 2.93, 95% CI: 1.04, 8.28). The risk was lower in Indian patients (OR = 0.61, 95% CI: 0.39, 0.95) compared with other ethnic groups.

Differences between cohort A and cohort B

In cohort B, patients were significantly older and more had diabetes mellitus (DM) and HTN compared to cohort A. The majority of patients in cohort A had mild disease (64.6%), whereas cohort B had significantly more patients with severe disease (47%) and required specific treatment, mechanical ventilation, and ICU admission. Notably, both ALB (71.6% vs. 48.5%, $p < 0.001$) and LI (38.8% vs. 17.1%, $p < 0.001$) were more prevalent in cohort B patients. The mean value of ALT and AST is consistently higher in cohort B across all severity of disease for both ALB and LI. Cohort B patients with ALB had significantly higher mean values of ALT, AST, and GGT, whereas ALT and GGT were significantly higher

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Table 2. Multivariate analysis of COVID-19 patients with abnormal liver biochemistry (*n* = 731)

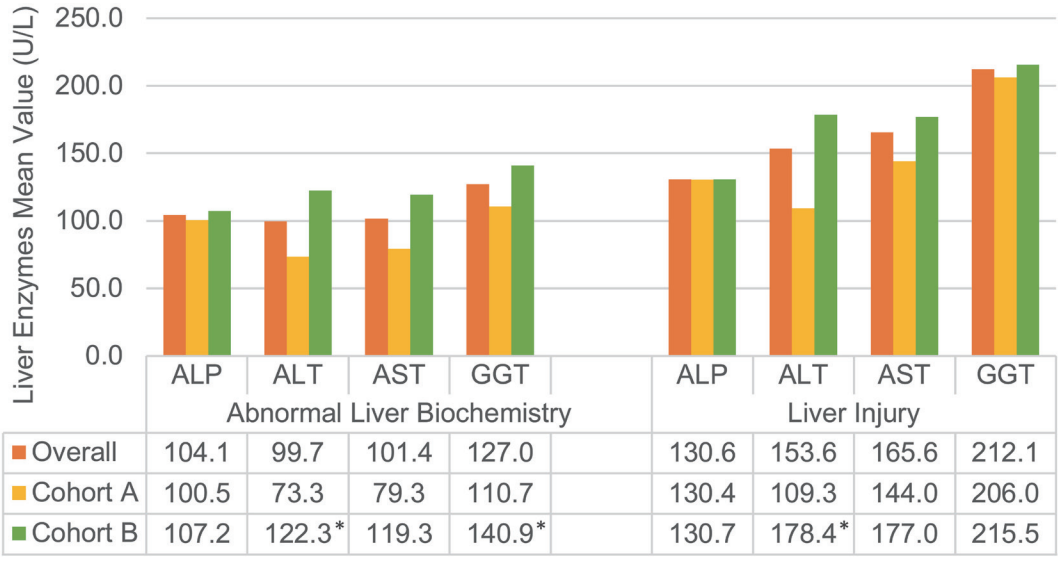
Characteristics	Overall				Cohort A				Cohort B			
	Abnormal Liver Biochemistry		AOR (95% CI)	*p*-value	Abnormal Liver Biochemistry		AOR (95% CI)	*p*-value	Abnormal Liver Biochemistry		AOR (95% CI)	*p*-value
	Yes	No			Yes	No			Yes	No		
Age in years												
≤60	454 (53.7)	392 (46.3)	–	–	219 (43.1)	289 (56.9)	1.08 (0.65, 1.80)	0.770	235 (69.5)	103 (30.5)	1.85 (1.05, 3.28)	0.34
>60	277 (69.3)	123 (30.8)	0.73 (0.51, 1.05)	0.092	119 (63.0)	70 (37.0)	–	–	158 (74.8)	53 (35.1)	–	–
Sex												
Female	286 (45.5)	342 (54.5)	–	–	131 (35.2)	241 (64.8)	–	–	155 (60.5)	101 (39.5)	–	–
Male	445 (72.0)	173 (28.0)	2.93 (2.24, 3.83)	<0.001	207 (63.7)	118 (36.3)	3.28 (2.32, 4.66)	<0.001	238 (81.2)	55 (18.8)	2.79 (1.77, 4.42)	<0.001
Ethnicity												
Malay	440 (56.5)	339 (43.5)	–	–	196 (45.9)	231 (54.1)	–	–	244 (69.3)	108 (30.7)	–	–
Chinese	157 (67.4)	76 (32.6)	0.98 (0.67, 1.43)	0.908	71 (56.3)	55 (43.7)	0.87 (0.53, 1.43)	0.576	86 (80.4)	21 (19.6)	1.13 (0.59, 2.16)	0.674
Indian	105 (55.6)	84 (44.4)	0.71 (0.48, 1.05)	0.085	53 (47.3)	59 (52.7)	0.70 (0.43, 1.14)	0.151	52 (67.5)	25 (32.5)	0.79 (0.41, 1.54)	0.713
Others	29 (64.4)	16 (35.6)	1.52 (0.75, 3.07)	0.241	18 (56.3)	14 (43.8)	1.51 (0.68, 3.35)	0.314	11 (84.6)	2 (15.4)	2.22 (0.38, 12.95)	0.492
COVID-19 severity												
Mild	264 (40.7)	385 (59.3)	–	–	171 (38.0)	279 (62.0)	–	–	93 (46.7)	106 (53.3)	–	–
Moderate	123 (61.5)	77 (38.5)	1.66 (1.10, 2.50)	0.015	61 (56.5)	47 (43.5)	1.29 (0.74, 2.25)	0.363	62 (67.4)	30 (32.6)	1.85 (0.96, 3.57)	0.067
Severe	344 (86.6)	53 (13.4)	3.17 (1.53, 6.57)	0.002	106 (76.3)	33 (23.7)	2.05 (0.68, 6.19)	0.201	238 (92.2)	20 (7.8)	4.54 (1.52, 13.54)	0.007
Treatment												
	458 (78.0)	129 (22.0)	1.07 (0.63, 1.83)	0.796	162 (70.1)	69 (29.9)	2.36 (1.10, 5.03)	0.027	296 (83.1)	60 (16.9)	0.52 (0.21, 1.26)	0.147
Types of treatment												
NSAID	64 (79.0)	17 (21.0)	1.18 (0.60, 2.33)	0.633	176 (37.8)	290 (62.2)	0.55 (0.15, 2.05)	0.374	57 (83.9)	11 (16.2)	1.27 (0.49, 3.27)	0.626
HCQ	16 (64.0)	9 (36.0)	1.22 (0.41, 3.63)	0.722	13 (59.1)	9 (40.9)	0.59 (0.16, 2.18)	0.431	3 (100.00	0	–	–
Favipiravir	140 (80.0)	35 (20.0)	1.51 (0.93, 2.47)	0.099	7 (53.8)	6 (46.2)	1.53 (0.74, 3.17)	0.253	100 (84.0)	19 (16.0)	1.47 (0.71, 3.03)	0.297
Methylpred	110 (90.9)	11 (9.1)	1.40 (0.65, 3.02)	0.395	40 (71.4)	16 (28.6)	1.15 (0.41,3.28)	0.789	77 (95.1)	4 (4.9)	1.38 (0.38, 4.99)	0.620
Clexane	220 (80.6)	53 (19.4)	1.35 (0.86, 2.11)	0.190	33 (82.5)	7 (17.5)	1.02 (0.51, 2.03)	0.958	167 (83.5)	33 (16.5)	1.39 (0.69, 2.78)	0.358
Tocilizumab	97 (88.2)	13 (11.8)	1.25 (0.62, 2.51)	0.528	53 (72.6)	20 (27.4)	1.07 (0.46, 2.51)	0.879	59 (95.2)	3 (4.8)	1.30 (0.32, 5.37)	0.717
Dexamethasone	379 (83.3)	76 (16.7)	1.38 (0.78, 2.44)	0.266	38 (79.2)	10 (20.8)	0.72 (0.32, 1.61)	0.420	260 (89.3)	31 (10.7)	2.07 (0.86, 5.01)	0.106
Comorbidities												
CLD	93 (80.9)	22 (19.1)	19.31 (2.38, 156.53)	0.006	119 (72.6)	45 (27.4)	12.61 (1.33, 119.46)	0.027	65 (91.5)	6 (8.5)	–	0.998
NAFLD	87 (73.1)	21 (19.4)	0.22 (0.03, 1.83)	0.160	58 (77.3)	17 (22.7)	0.41 (0.04, 4.10)	0.445	53 (89.8)	6 (10.2)	–	0.999
DM	285 (73.5)	103 (26.5)	0.94 (0.66, 1.36)	0.751	51 (76.1)	16 (23.9)	0.88 (0.52, 1.44)	0.599	172 (82.3)	37 (17.7)	0.93 (0.53, 1.64)	0.813
HTN	323 (73.2)	118 (26.8)	1.64 (1.16, 2.33)	0.005	113 (63.1)	66 (36.9)	1.42 (0.89, 2.26)	0.143	195 (82.6)	41 (17.4)	2.13 (1.21, 3.75)	0.009
Other Comorbidities*	731(67.6)	84 (32.4)	0.91 (0.64, 1.31)	0.628	128 (62.4)	77 (37.6)	1.03 (0.64, 1.67)	0.901	94 (76.4)	29 (23.6)	0.87 (0.48, 1.56)	0.631
Ventilator												
	426 (47.8)	466 (52.2)	1.13 (0.69, 2.17)	0.710	65 (58.6)	46 (41.4)	0.75 (0.26, 2.15)	0.589	212 (91.8)	19 (8.2)	1.33 (0.54, 3.27)	0.540
ICU admission												
	154 (89.5)	18 (10.5)	1.71 (0.86, 3.38)	0.124	93 (75.6)	30 (24.4)	2.69 (1.01, 6.70)	0.033	85 (96.6)	3 (3.4)	2.85 (0.70, 11.55)	0.143
Death												
	51 (83.6)	10 (16.4)	1.04 (0.44, 2.43)	0.937	69 (82.1)	15 (17.9)	1.02 (0.34, 3.09)	0.966	30 (90.9)	3 (9.1)	0.94 (0.21, 4.16)	0.934

Data are presented as *n* (%). AOR, adjusted odd ratios; CI, confidence interval; CLD, chronic liver disease; DM, diabetes mellitus; HCQ, hydroxychloroquine; HTN, hypertension; ICU, intensive care unit; LFT, liver function test; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug. *Chronic Kidney Disease, Congestive Cardiac Failure, Chronic Lung Disease, Cancers.

Table 3. Multivarite analysis of COVID-19 patients with liver injury (*n* = 332)

Characteristics	Overall				Cohort A				Cohort B			
	Liver injury		AOR (95% CI)	*p*-value	Liver injury		AOR (95% CI)	*p*-value	Liver injury		AOR (95% CI)	*p*-value
	Yes	No			Yes	No			Yes	No		
Age in years												
≤ 60	193 (22.8)	653 (77.2)	1.16 (0.81, 1.66)	0.421	62 (12.2)	446 (87.8)	0.66 (0.37, 1.19)	0.166	131 (38.8)	207 (61.2)	1.51 (0.92, 2.47)	0.102
>60	139 (34.8)	261 (65.3)	–	–	57 (30.2)	132 (69.8)	–	–	82 (38.9)	129 (61.1)	–	–
Sex												
Female	122 (19.4)	506 (80.6)	–	–	39 (10.5)	333 (89.5)	–	–	83 (32.4)	173 (67.6)	–	–
Male	210 (34.0)	408 (66.0)	1.79 (1.33, 2.41)	<0.001	80 (24.6)	245 (75.4)	2.45 (1.52, 3.95)	<0.001	130 (44.4)	163 (55.6)	1.53 (1.01, 2.32)	0.048
Ethnicity												
Malay	197 (25.3)	582 (74.7)	–	–	64 (15.0)	363 (85.0)	–	–	133 (37.8)	219 (62.2)	–	–
Chinese	78 (33.5)	155 (66.5)	0.83 (0.56, 1.21)	0.331	29 (23.0)	97 (77.0)	0.64 (0.34, 1.21)	0.166	49 (45.8)	58 (54.2)	0.93 (0.55, 1.58)	0.792
Indian	43 (22.8)	146 (77.2)	0.61 (0.39, 0.95)	0.029	19 (17.0)	93 (83.0)	0.80 (0.42, 1.52)	0.494	24 (31.2)	53 (68.8)	0.54 (0.29, 1.03)	0.064
Others	14 (31.1)	31 (77.2)	1.50 (0.71, 3.20)	0.292	7 (21.9)	25 (78.1)	1.52 (0.55, 4.21)	0.423	7 (53.8)	6 (46.2)	1.48 (0.41, 5.33)	0.547
COVID-19 severity												
Mild	62 (9.6)	587 (90.4)	–	.–	35 (7.8)	415 (92.2)	–	–	27 (13.6)	172 (86.4)	–	–
Moderate	56 (28.0)	144 (72.0)	3.03 (1.87, 4.92)	0.000	26 (24.1)	82 (75.9)	2.13 (1.04, 4.33)	0.038	30 (32.6)	62 (67.4)	3.26 (1.59, 6.70)	0.001
Severe	214 (53.9)	183 (46.1)	4.56 (2.27, 9.18)	0.000	58 (41.7)	81 (58.3)	3.48 (1.09, 11.09)	0.035	156 (60.5)	102 (39.5)	4.71 (1.82, 12.19)	0.001
Treatment												
	257 (43.8)	330 (56.2)	1.29 (0.72, 2.31)	0.390	80 (34.6)	151 (65.4)	3.74 (1.57, 8.93)	0.003	177 (49.7)	179 (50.3)	0.47 (0.19, 1.19)	0.111
Types of treatment												
NSAID	36 (44.4)	45 (55.6)	0.99 (0.57, 1.72)	0.970	1 (7.7)	12 (92.3)	0.12 (0.01, 1.14)	0.065	35 (51.5)	33 (48.5)	1.03 (0.52, 2.01)	0.939
HCQ	10 (40.0)	60.0 (60.0)	1.57 (0.56–4.40)	0.389	7 (31.8)	15 (68.2)	0.66 (0.17–2.58)	0.562	3 (100.0)	–	0.99 (–)	–
Favipiravir	70 (40.0)	105 (60.0)	0.91 (0.61, 1.35)	0.627	15 (26.8)	41 (73.2)	0.76 (0.36, 1.59)	0.460	55 (46.2)	64 (53.8)	0.89 (0.53, 1.48)	0.649
Methylpred	74 (61.2)	47 (38.8)	1.39 (0.85, 2.28)	0.196	18 (45.0)	22 (55.0)	0.95 (0.41, 2.21)	0.903	56 (69.1)	25 (30.9)	1.64 (0.82, 3.29)	0.163
Clexane	128 (46.9)	145 (53.1)	1.17 (0.80, 1.69)	0.420	24 (32.9)	49 (67.1)	0.88 (0.41, 2.21)	0.716	104 (52.0)	96 (48.0)	1.30 (0.79, 2.15)	0.300
Tocilizumab	59 (53.6)	51 (46.4)	0.93 (0.31, 2.84)	0.767	21 (43.8)	27 (56.3)	1.02 (0.47, 2.21)	0.954	38 (61.3)	24 (38.7)	0.77 (0.37, 1.58)	0.477
Dexamethasone	223 (49.0)	232 (51.0)	1.10 (0.63, 1.92)	0.735	60 (36.6)	104 (63.4)	0.59 (0.25, 1.37)	0.216	163 (56.0)	128 (44.0)	1.60 (0.68, 3.76)	0.286
Comorbidities												
Chronic liver disease	51 (44.3)	64 (55.7)	2.93 (1.04, 8.28)	.043	20 (26.7)	55 (73.3)	7.32 (1.38, 38.84)	.019	46 (64.8)	25 (35.2)	1.59 (0.43, 5.96)	.489
NAFLD	46 (42.6)	62 (57.4)	0.94 (0.31, 2.84)	.917	16 (23.9)	51 (76.1)	0.26 (0.05, 1.56)	.141	40 (67.8)	19 (32.3)	2.44 (0.58, 10.20)	.221
Diabetes mellitus	143 (36.9)	245 (63.1)	0.80 (0.67, 1.14)	.214	40 (22.3)	139 (77.7)	0.44 (0.25, 0.79)	.006	103 (49.3)	106 (50.7)	1.12 (0.70, 1.78)	.645
Hypertension	159 (36.1)	282 (63.9)	1.08 (0.77, 1.52)	.649	152 (74.1)	53 (25.9)	1.31 (0.77, 2.24)	.327	106 (44.9)	130 (44.9)	0.93 (0.57, 1.50)	.754
Other Comorbidities*	76 (34.1)	147 (65.9)	1.01 (0.70, 1.44)	.974	40 (29.4)	96 (70.6)	1.38 (0.788, 2.44)	.269	50 (40.7)	73 (59.3)	0.76 (0.46, 1.26)	.288
Ventilator												
	193 (54.5)	161 (45.5)	1.51 (0.89, 2.56)	.129	50 (40.7)	73 (59.3)	0.73 (0.26, 2.02)	.540	143 (61.9)	88 (38.1)	2.10 (1.10, 4.02)	.025
ICU admission												
	104 (60.5)	68 (39.5)	1.60 (0.99, 2.58)	.054	41 (48.8)	43 (51.2)	2.75 (1.23, 6.19)	.014	63 (71.6)	25 (28.4)	1.72 (0.84, 3.52)	.136
Death												
	34 (55.7)	27 (44.3)	1.25 (0.66, 2.38)	.489	11 (39.3)	17 (60.7)	0.83 (0.29, 2.37)	.727	23 (69.7)	10 (30.3)	1.84 (0.75, 4.55)	.184

Data are presented as *n* (%). AOR, adjusted odds ratio; CI, confidence interval; CLD, chronic liver disease; DM, diabetes mellitus; HCQ, hydroxychloroquine; HTN, hypertension; ICU, intensive care unit; LFT, liver function test; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug. *Chronic Kidney Disease, Congestive Cardiac Failure, Chronic Lung Disease, Ca.



	Abnormal Liver Biochemistry				Liver Injury			
	ALP	ALT	AST	GGT	ALP	ALT	AST	GGT
Overall	104.1	99.7	101.4	127.0	130.6	153.6	165.6	212.1
Cohort A	100.5	73.3	79.3	110.7	130.4	109.3	144.0	206.0
Cohort B	107.2	122.3*	119.3	140.9*	130.7	178.4*	177.0	215.5

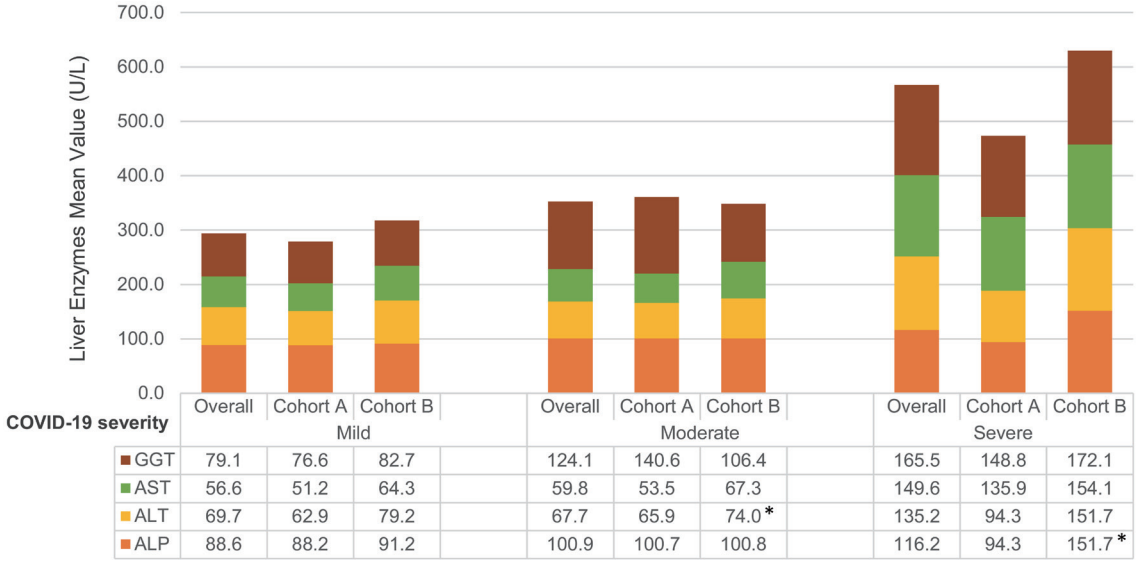
Fig. 1. Liver biochemistry of COVID-19 patients with abnormal liver biochemistry and liver injury. *Significant difference of mean value compared with cohort A ($p < 0.05$). ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.

in those with LI (Fig. 1). The mean values of ALT and AST were consistently higher in cohort B across all severities of disease for both ALB and LI (Figs. 2 and 3).

Multivariate analysis of cohort A found a significantly higher risk of developing both ALB and LI in male patients, those with underlying CLD, who received specific disease-modulating treatment, or who required ICU admission. Additionally, patients in cohort A with moderate or severe disease had a significantly higher risk of developing LI, with a lesser risk in DM patients (Tables 2 and 3). In cohort B, multivariate analysis identified male sex, moderate or severe disease, and HTN as factors that increased the risk of ALB. Male sex, moderate or severe disease, and requiring mechanical ventilation increased the risk of LI (Tables 2 and 3).

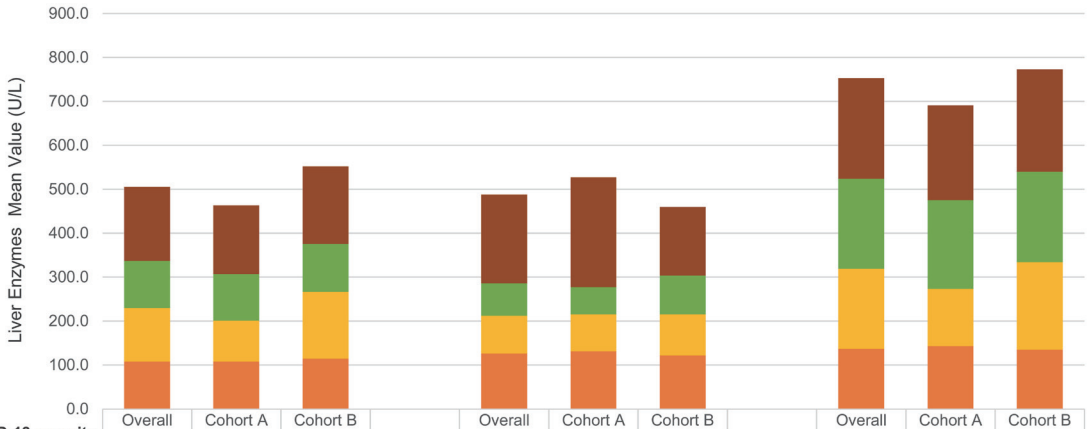
Discussion

From our data, the incidence of mild liver dysfunction in the form of ALB was common (58.7%) among COVID-19 patients. Worldwide, the incidence of mild liver dysfunction ranges from 11.0% to 76.3%.[12,14,16,19–27] Lack of a standard definition of liver dysfunction and heterogeneity of the study population probably contribute to the wide variation. Elevated ALT, AST, and GGT had nearly the same incidence, 36.83%, 34.99%, and 34.91% respectively, which mirrors the findings in other studies that included GGT in the analysis.[25,27] Our data also showed that severe liver dysfunction, represented by LI (26.6%) was less common, and liver failure (1.1%) was very rare in these hospitalized COVID-19 patients. A similar frequency of severe liver dysfunction was reported by Cai *et al*.[16] and Phipps *et al*.[19]



COVID-19 severity	Mild			Moderate			Severe		
	Overall	Cohort A	Cohort B	Overall	Cohort A	Cohort B	Overall	Cohort A	Cohort B
GGT	79.1	76.6	82.7	124.1	140.6	106.4	165.5	148.8	172.1
AST	56.6	51.2	64.3	59.8	53.5	67.3	149.6	135.9	154.1
ALT	69.7	62.9	79.2	67.7	65.9	74.0*	135.2	94.3	151.7
ALP	88.6	88.2	91.2	100.9	100.7	100.8	116.2	94.3	151.7*

Fig. 2. Liver biochemistry of COVID-19 patients with abnormal liver biochemistry and differing disease severity. *Significant difference of mean value compared with cohort A ($p < 0.05$). ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.



COVID-19 severity	Mild			Moderate			Severe		
	Overall	Cohort A	Cohort B	Overall	Cohort A	Cohort B	Overall	Cohort A	Cohort B
GGT	168.1	156.4	177.0	202.1	250.0	156.1	229.0	215.5	233.2
AST	107.5	105.5	108.4	74.0	61.8	87.8 *	205.3	202.1	205.4
ALT	121.5	93.3	152.1 *	85.8	84.5	94.0	181.9	130.0	199.2
ALP	108.1	108.0	114.7	126.3	131.1	121.9	137.0	143.3	135.1

Fig. 3. Liver biochemistry of COVID-19 patients with liver injury and differing disease severity. *Significant difference of mean value compared with cohort A ($p < 0.05$). ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase.

at 21.5% and 27.4%, respectively. Clinical characteristics that were significantly associated with LI were male sex, moderate and severe COVID-19 infection, and underlying CLD.

Several possibilities for liver dysfunction in COVID-19 infection have been suggested. Firstly, SARS-COV-2 virus has been shown to have a direct cytopathic effect on hepatocytes and cholangiocytes.[11,17,28,29] This is supported by presence of SARS-CoV 2-interacting host receptors such as angiotensin-converting enzyme 2, transmembrane serine protease 2, and paired basic amino acid cleaving enzyme, which is expressed at varying levels in hepatocytes, cholangiocytes, and periportal liver sinusoidal endothelial cells.[30,31] Also, as enterocytes are able to bind angiotensin-converting enzyme 2, there is a high possibility of portal vein viremia leading to an increased likelihood of a direct cytopathic effect.[30] Furthermore, analysis of liver samples from two deceased COVID-19 patients with elevated liver enzymes demonstrated the presence of intact viral particles in the cytoplasm of hepatocytes.[32] Secondly, pre-existing CLD may be a contributing factor for liver dysfunction in COVID-19 infection. CLD in COVID-19 patients is a well-established risk factor for developing severe liver dysfunction,[16,33–35] which is also reflected in our study findings (Tables 2 and 3). However, two other studies reported that CLD was not a significant risk factor for developing liver dysfunction.[19,27] This could be attributed to the inclusion of nonalcoholic fatty liver disease which represents the majority of CLD patients and the low prevalence of CLD among the study patients[17] as well as the small number of patients in the study.[27] Thirdly, drug-induced LI has been postulated to cause abnormal liver function in COVID-19 patients. The use of disease-modulating pharmacotherapy such as hydroxychloroquine (HCQ),[17] lopinavir/ritonavir,[16] or even tocilizumab[11,28,29] in moderate and severe COVID-19 infection has been widely reported to cause drug-induced LI. Cohort A patients, who were treated with disease-modulating drugs, were found to have significantly increased occurrences of ALB and LI, but this trend was not observed in cohort B patients. One possible explanation for this would be the use of HCQ in our center during the early wave of COVID-19 infection which fell out of favor thereafter. Hundt *et al*.[20] reported significant liver dysfunction with the use of HCQ, but another center reported no increase in liver dysfunction associated with HCQ.[27]

Additional factors that have been postulated to cause liver dysfunction in COVID-19 infection are cytokine storm, ischemic hepatitis, and liver congestion associated with mechanical ventilation.[17,28,29] In our study, LI was more frequent in Delta-variant patients who required ventilatory support than in those who did not require it. Mechanical ventilation[19,20] and the presence of cytokine storm, in which inflammatory markers such as interleukin-6 and ferritin are elevated have been associated with significant liver dysfunction.[19] The presence of these factors usually implies severe COVID-19 infection. This is in line with our data that showed patients with moderate and severe COVID-19 infection were more likely to develop ALB and LI. Multiple studies have demonstrated that the severity of liver dysfunction was proportionate to the severity of COVID-19 infection.[19,20,26,27]

Apart from the severity of illness and presence of CLD, male sex increased the likelihood of developing ALB and LI. Other studies have reported significantly higher liver dysfunction in men.[20,27] Previous studies have shown that men tended to have a more severe course of illness than women. This was possibly due to several factors such as the difference in sex-related immunological response driven by sex hormones and the X chromosome as well as a high expression of coronavirus receptors (angiotensin-converting enzyme 2) in men.[36,37] Less healthy lifestyle options such as higher levels of smoking and drinking among men than in women may also be a contributing factor.

Only a handful of studies have analyzed the clinical characteristics of the Delta variant. Budhiraja *et al*.,[38] who reviewed nearly 20,000 COVID-19 patients, found that almost 40% of Delta-variant patients had a severe course of disease with significantly increased need of ICU admission, oxygen support, and use of remdesivir, steroids, intravenous immunoglobulin, and enoxaparin. Interestingly, a significant difference in age was not observed, although presence of the Delta variant was notably higher in male patients and in those with DM and HTN.[38] Al Bahrani *et al*.,[39] who analyzed 619 patients, reported those infected with the Delta variant were significantly older but reported a similar need of ICU admission, use of mechanical ventilation, and use of methylprednisolone

for both groups of patients. The mortality rate among Delta-variant patients was lower than the rates in patients with other VoCs.

The frequency of ALB and LI was higher among patients with Delta variant COVID-19 infection (cohort B) compared with predecessor strains (cohort A). In particular, transaminitis was higher in patients infected with Delta variant compared with predecessor strains across all categories of severity for both ALB and LI. Al Bahrani *et al*.[39] reported similar findings, where ALT and AST were significantly higher in patients infected with the Delta variant.[39] Differences in admission criteria that led to differences in the baseline demographics of the cohorts may have contributed to significantly higher ALB and LI rates in patients with mild disease in cohort B than in cohort A, as this would have excluded a proportion of asymptomatic Delta variant patients who most likely would have had no or very slight liver derangement. However, the reason for the higher proportion of ALB and LI among Delta variant patients with moderate and severe disease is not well understood. A possible explanation is that Delta variant has a higher affinity to hepatocytes and cholangiocytes which results in a higher incidence of hepatitis and cholestasis. The Delta variant has a higher cell affinity with better cell fusion and enhanced cell entry.[4,40] Arora *et al*.[40] demonstrated the Delta variant to have enhanced lung and colon cell entry, resulting in more tissue damage and higher virulence than previous variants. This could likely result in a higher burden of portal vein viraemia, further increasing the risk of damage to hepatocytes and cholangiocytes.

This study has some limitations. As the study population is based on convenience sampling, some of the patients with mild disease and relatively short stays with normal LFTs on admission do not have a repeat blood test. Hence, there could be a small proportion of patients who developed liver dysfunction during hospitalization that was not captured in the data. Furthermore, for this same reason, baseline and peak abnormalities of LFT could not be compared. Differences in admission criteria for both cohorts also led to sampling bias among patients with mild disease in this study. As this is a single-center study in an urban area, these data may not be representative of patients in a semi-urban or rural setting. Additionally, vaccination history, which may contribute to liver dysfunction, was not included due to a lack of data.

Conclusions

ALB among COVID-19 patients is common. However, LI is less common among COVID-19 patients. Risk factors that are more likely to be associated with the development of LI were male sex, with moderate and severe COVID-19 infection, underlying CLD, and Delta variant COVID-19 infection.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study design (RBR and SM), data collection (RPS, NP, AK, BMJ, SB, RXN, HCO and PLW), data interpretation (RBR and XHK), manuscript drafting (RBR), and critical revision of manuscript content (SM, SFSO and SP). All authors made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Research Ethics Committee of University of Malaya (MECID No. 202146-10036). All subjects gave written informed consent.

Data sharing statement

The dataset used in this study is not available publicly, but is available from the principle author at drruveena81@gmail.com.

References

[1] Hashim JH, Adman MA, Hashim Z, Mohd Radi MF, Kwan SC. COVID-19 Epidemic in Malaysia: Epidemic Progression, Challenges, and Response. Front Public Health 2021;9:560592. doi:10.3389/fpubh.2021.560592, PMID:34026696.

[2] Aleem A, Akbar Samad AB, Vaqar S. Emerging Variants of SARS-CoV-2 and Novel Therapeutics Against Coronavirus (COVID-19). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. PMID:34033342.

[3] Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, *et al*. Increased transmissibility and global spread of SARS-CoV-2 variants of concern as of June 2021. Euro Surveill 2021;26(24):2100509. doi:10.2807/1560-7917.ES.2021.26.24.2100509, PMID:34142653.

[4] Mlcochova P, Kemp SA, Dhar MS, Papa G, Meng B, Ferreira IATM, *et al*. SARS-CoV-2 B.1.617.2 Delta variant replication and immune evasion. Nature 2021;599(7883):114–119. doi:10.1038/s41586-021-03944-y, PMID:34488225.

[5] Kuzmina A, Wattad S, Khalaila Y, Ottolenghi A, Rosental B, Engel S, *et al*. SARS CoV-2 Delta variant exhibits enhanced infectivity and a minor decrease in neutralization sensitivity to convalescent or post-vaccination sera. iScience 2021;24(12):103467. doi:10.1016/j.isci.2021.103467, PMID:34805783.

[6] Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J 2021;97(1147):312–320. doi:10.1136/postgradmedj-2020-138577, PMID:32978337.

[7] Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol 2020;215:108427. doi:10.1016/j.clim.2020.108427, PMID:32325252.

[8] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020;324(8):782–793. doi:10.1001/jama.2020.12839, PMID:32648899.

[9] Yu D, Du Q, Yan S, Guo XG, He Y, Zhu G, *et al*. Liver injury in COVID-19: clinical features and treatment management. Virol J 2021;18(1):121. doi:10.1186/s12985-021-01593-1, PMID:34108015.

[10] Wu J, Song S, Cao HC, Li LJ. Liver diseases in COVID-19: Etiology, treatment and prognosis. World J Gastroenterol 2020;26(19):2286–2293. doi:10.3748/wjg.v26.i19.2286, PMID:32476793.

[11] Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int 2020;40(6):1278–1281. doi:10.1111/liv.14470, PMID:32251539.

[12] Qi X, Liu C, Jiang Z, Gu Y, Zhang G, Shao C, *et al*. Multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 who develop liver injury. J Hepatol 2020;73(2):455–458. doi:10.1016/j.jhep.2020.04.010, PMID:32305291.

[13] Wang X, Lei J, Li Z, Yan L. Potential Effects of Coronaviruses on the Liv-

er: An Update. Front Med (Lausanne) 2021;8:651658. doi:10.3389/fmed.2021.651658, PMID:34646834.
[14] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5(5):428–430. doi:10.1016/S2468-1253(20)30057-1, PMID:32145190.
[15] Metawea MI, Yousif WI, Moheb I. COVID 19 and liver: An A-Z literature review. Dig Liver Dis 2021;53(2):146–152. doi:10.1016/j.dld.2020.09.010, PMID:32988758.
[16] Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, *et al*. COVID-19: Abnormal liver function tests. J Hepatol 2020;73(3):566–574. doi:10.1016/j.jhep.2020.04.006, PMID:32298767.
[17] Li Y, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. J Med Virol 2020;92(9):1491–1494. doi:10.1002/jmv.25973, PMID:32369204.
[18] Saini RK, Saini N, Ram S, Soni SL, Suri V, Malhotra P, *et al*. COVID-19 associated variations in liver function parameters: a retrospective study. Postgrad Med J 2022;98(1156):91–97. doi:10.1136/postgradmedj-2020-138930, PMID:33184141.
[19] Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, *et al*. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology 2020;72(3):807–817. doi:10.1002/hep.31404, PMID:32473607.
[20] Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal Liver Tests in COVID-19: A Retrospective Observational Cohort Study of 1,827 Patients in a Major U.S. Hospital Network. Hepatology 2020;72(4):1169–1176. doi:10.1002/hep.31487, PMID:32725890.
[21] Voiosu A, Roman A, Pop R, Boeriu A, Popp C, Zurac S, *et al*. Characteristics and outcomes of patients with COVID-19 and liver injury: a retrospective analysis and a multicenter experience. Rom J Intern Med 2022;60(1):49–55. doi:10.2478/rjim-2021-0027, PMID:34253002.
[22] Schattenberg JM, Labenz C, Wörns MA, Menge P, Weinmann A, Galle PR, *et al*. Patterns of liver injury in COVID-19 - a German case series. United European Gastroenterol J 2020;8(7):814–819. doi:10.1177/2050640620931657, PMID:32588791.
[23] Piano S, Dalbeni A, Vettore E, Benfaremo D, Mattioli M, Gambino CG, *et al*. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int 2020;40(10):2394–2406. doi:10.1111/liv.14565, PMID:32526083.
[24] Chaibi S, Boussier J, Hajj WE, Abitbol Y, Taieb S, Horaist C, *et al*. Liver function test abnormalities are associated with a poorer prognosis in Covid-19 patients: Results of a French cohort. Clin Res Hepatol Gastroenterol 2021;45(5):101556. doi:10.1016/j.clinre.2020.10.002, PMID:33139241.
[25] Kalal CR, Joshi H, Kumar V, Gopal D, Rathod D, Shukla A, *et al*. Clinical Significance of Liver Function Abnormality in Patients with COVID-19: A Single-center Experience from Western India. J Clin Transl Hepatol 2021;9(6):878–888. doi:10.14218/JCTH.2020.00099, PMID:34966651.
[26] Saithanyamurthi HV, Munirathinam M, Ananthavadivelu M. Prevalence of liver injury in 445 patients with Corona Virus Disease-19-Single-centre experience from southern India. Indian J Gastroenterol 2021;40(3):303–308. doi:10.1007/s12664-021-01147-x, PMID:33991309.
[27] Guo H, Zhang Z, Zhang Y, Liu Y, Wang J, Qian Z, *et al*. Analysis of liver injury factors in 332 patients with COVID-19 in Shanghai, China. Aging (Albany NY) 2020;12(19):18844–18852. doi:10.18632/aging.103860, PMID:33001040.
[28] Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. Gastrointestinal and Liver Manifestations of COVID-19. J Clin Exp Hepatol 2020;10(3):263–265. doi:10.1016/j.jceh.2020.03.001, PMID:32405183.
[29] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol 2020;5(6):529–530. doi:10.1016/S2468-1253(20)30084-4, PMID:32203680.
[30] Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. Liver Int 2021;41(1):20–32. doi:10.1111/liv.14730, PMID:33190346.
[31] Pirola CJ, Sookoian S. SARS-CoV-2 virus and liver expression of host receptors: Putative mechanisms of liver involvement in COVID-19. Liver Int 2020;40(8):2038–2040. doi:10.1111/liv.14500, PMID:32352224.
[32] Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, *et al*. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. J Hepatol 2020;73(4):807–816. doi:10.1016/j.jhep.2020.05.002, PMID:32437830.
[33] Martinez MA, Franco S. Impact of COVID-19 in Liver Disease Progression. Hepatol Commun 2021;5(7):1138–1150. doi:10.1002/hep4.1745, PMID:34533001.
[34] Nagarajan R, Krishnamoorthy Y, Rajaa S, Hariharan VS. COVID-19 Severity and Mortality Among Chronic Liver Disease Patients: A Systematic Review and Meta-Analysis. Prev Chronic Dis 2022;19:E53. doi:10.5888/pcd19.210228, PMID:36007255.
[35] Qi RB, Wu ZH. Association between COVID-19 and chronic liver disease: Mechanism, diagnosis, damage, and treatment. World J Virol 2023;12(1):22–29. doi:10.5501/wjv.v12.i1.22, PMID:36743657.
[36] Fabião J, Sassi B, Pedrollo EF, Gerchman F, Kramer CK, Leitão CB, *et al*. Why do men have worse COVID-19-related outcomes? A systematic review and meta-analysis with sex adjusted for age. Braz J Med Biol Res 2022;55:e11711. doi:10.1590/1414-431X2021e11711, PMID:35195196.
[37] Bwire GM. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? SN Compr Clin Med 2020;2(7):874–876. doi:10.1007/s42399-020-00341-w, PMID:32838138.
[38] Budhiraja S, Indrayan A, Aggarwal M, Jha V, Jain D, Tarai B. Differentials in the characteristics of COVID-19 cases in Wave-1 and Wave-2 admitted to a network of hospitals in North India. medRxiv 2021. doi:10.1101/2021.06.24.21259438.
[39] AlBahrani S, AlAhmadi N, Hamdan S, Elsheikh N, Osman A, Almuthen S, *et al*. Clinical Presentation and Outcome of Hospitalized Patients With COVID-19 in the First and Second Waves in Saudi Arabia. Int J Infect Dis 2022;118:104–108. doi:10.1016/j.ijid.2022.02.048, PMID:35227868.
[40] Arora P, Sidarovich A, Krüger N, Kempf A, Nehlmeier I, Graichen L, *et al*. B.1.617.2 enters and fuses lung cells with increased efficiency and evades antibodies induced by infection and vaccination. Cell Rep 2021;37(2):109825. doi:10.1016/j.celrep.2021.109825, PMID:34614392.