Current and past infections of hepatitis B virus do not increase mortality in patients with COVID-19

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Supplementary Materials

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SUPPLEMENTARY METHODS

Clinical evaluation

All Coronavirus disease 2019 (COVID-19) patients were admitted to medical wards or intensive care units with isolation facilities. Initial investigations included a complete blood count (with a differential count), clotting profile (prothrombin time, activated partial-thromboplastin time, international normalized ratio) and serum biochemical measurements (electrolytes, renal and liver biochemistries, C-reactive protein and lactate dehydrogenase, glucose and procalcitonin). These laboratory assessments and chest radiography were performed regularly as clinically indicated. A real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay was used to detect a conserved region in the E gene of severe acute respiratory syndrome-coronavirus (SARS-CoV) and SARS-CoV-2 as well as other bat-associated SARS-related viruses (*Sarbecovirus*) as screening.(1) All positive samples were sent out to Public Health Laboratory Services Branch Centre For Health Protection, Department Of Health for confirmation by real-time RT-PCR targeting at SAR-CoV-2 specific RNA-dependent-RNA-polymerase gene region. Microbiological workup, including sputum and blood bacterial culture, nasopharyngeal aspirate for respiratory viruses and atypical pathogens, and urine for *Streptococcus pneumoniae* and *Legionella* antigen tests, were performed as appropriate.

Clinical management of COVID-19

Antibacterial therapy, using a beta-lactam-beta-lactamase inhibitor, or third generation cephalosporin with or without a macrolide or doxycycline, was initiated if bacterial infection is suspected or confirmed.(2) Supportive therapy, including supplemental

oxygen, intravenous fluid, vasopressor support, mechanical ventilation, and renal replacement therapy, were given as appropriate. COVID-19 patients were either recruited into clinical trials (NCT04276688, NCT04292730, NCT04292899), or started lopinavir-ritonavir (Kaletra® 200mg/50mg) monotherapy or in combination with ribavirin (400mg twice daily) for up to 14 days, and/or interferon beta-1b, according to local interim guidelines. Systemic corticosteroids were not given routinely, but in selected patients, e.g. those with refractory shock. Patients were discharged when they improved clinically and with two consecutive clinical specimens tested negative for SARS-CoV-2.

REFERENCES

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-733.
[2] Ho PL, Wu TC. Reducing bacterial resistance with IMPACT – Interhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy, 5th Edition 2017. Website: https://www.chp.gov.hk/files/pdf/reducing_bacterial_resistance_with_impact.pdf. Accessed on 4 April 2021.

Supplementary Table 1. List of diagnosis codes and/or virological assays to define coronavirus disease 2019 (COVID-19)/ severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

ICD-9-CM Code	**All Diagnosis Description**
079.89	Infection due to coronavirus (079.89:3)
480.8	Pneumonia due to coronavirus (480.8:1)
519.8	COVID-19 (519.8:8)
519.8	Respiratory infection by 2019 nCoV (519.8:8)
Virological Test Description	
2019 novel Coronavirus (2019-nCoV) PCR	
SARS and SARS related coronaviruses RNA	
RT-PCR for Novel coronavirus (Novel CoV) RNA	
RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA	
Novel coronavirus (Novel-CoV) RNA	

COVID-19 = coronavirus disease 2019; ICD-9-CM = International Classification of Diseases; Ninth Revision, Clinical Modification; nCoV = novel coronavirus; RT-PCR = Reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Supplementary Table 2. Medications used in Hospital Authority internally.

Drug code	Name	Dosage
Antiviral		
KALE02/03	Kaletra (or equiv)	200 MG / 50 MG
OSEL01/04/05/10/14	Oseltamivir (phosphate)	30 MG, 40 MG, 75 MG, 6MG/ML
RIBA06/09	Ribavirin	200 MG, 100MG/ML
Antibiotics		
AUGM01/02/04/05/06/08	Augmentin (or equiv)	375MG, 156MG/5ML, 1.2G 1G, 457MG/5ML, 642.9MG/5ML
AZIT02/03/04	Azithromycin	200MG/5ML, 500MG, 250MG
CEFA08	Cefazolin (sodium)	1G
CEFE04	Cefepime hcl	1G
CEFO04	Cefotaxime (sodium)	1G
CEFP01	Cefpodoxime (proxetil)	100MG
CEFT01/02	Ceftazidime	500MG, 1G
CEFT14	Ceftriaxone disodium	1G
CEFU02/04/07	Cefuroxime (sodium)	750MG, 250MG, 125MG/5ML
LEVO09/10/14/15/18	Levofloxacin	100MG, 0.2G/ML, 330MG, 5MG/ML, 250MG
CIPR01	Ciprofloxacin (hcl)	250MG, 2MG/ML
MERO01/02	Meropenem	500MG, 1G
ERTA01	Ertapenem	1G
ERYT03/05, NOT 01	Erythromycin	200MG/5ML, 250MG
COTR01	Cotrimoxazole	480MG, 240MG/5ML
Antifungal		
NYST02	Nystatin	100000U/ML
FLUC02/03/05/06	Fluconazole	50MG, 150MG 2MG/ML, 50MG/5ML
ITRA01	Itraconazole	100MG
Corticosteroid		
METH30	Methylprednisolone	500MG
PRED01/02/19/29	Prednisolone	1MG, 5MG 25MG, 5MG/ML
HYDR06/07/25/26/30/38	Hydrocortisone	20MG, 100MG 10MG, 25MG 25MG, 2MG/ML
Immunomodulators		
NORM15/20/21	Intravenous immunoglobulin	60G/L, 50MG/ML
INTE20	Interferon beta-1b	8MIU (250MCG)/ML

Supplementary Table 3. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes for comorbidities.

Disease	ICD-9-CM Code	Description
Cardiovascular diseases		
Hypertension and hypertensive diseases	401	Essential hypertension
	402	Hypertensive heart disease
	403	Hypertensive chronic kidney disease
	404	Hypertensive heart and chronic kidney disease
	405	Secondary hypertension
Ischemic heart disease	410	Acute myocardial infarction
	411	Other acute and subacute forms of ischemic heart disease
	412	Old myocardial infarction
	413	Angina pectoris
	414	Other forms of chronic ischemic heart disease
Cardiac dysrhythmias	427	Cardiac dysrhythmias
Heart failure	428	Heart failure
Digestive diseases		
Peptic ulcer	530.2	Ulcer of esophagus
	531	Gastric ulcer
	532	Duodenal ulcer
	533	Peptic ulcer site unspecified
	534	Gastrojejunal ulcer
Chronic liver disease, liver failure, liver cirrhosis and complications	070.2-3	Chronic hepatitis B
	070.41, 44	Hepatitis C with hepatic coma
	070.51, 54	Hepatitis C without mention of hepatic coma
	V02.61	Hepatitis B carrier
	V02.62	Hepatitis C carrier
	070.42, 52	Hepatitis delta without mention of active hepatitis B
	275.0	Hemochromatosis
	275.1	Wilson's disease
	273.4	Alpha-1 antitrypsin disease
	570	Acute and subacute necrosis of liver
	571	Chronic liver disease and cirrhosis
	572	Liver abscess and sequelae of chronic liver disease
	573.0-5	Other disorders of liver
	348.3	Encephalopathy, unspecified
	349.82	Toxic encephalopathy
	456.0, 20	Esophageal varices with bleeding
	456.1, 21	Esophageal varices without bleeding
	456.8:1-2	Bleeding gastric varices
	456.8:4-5	Gastric varices
	567.2:9	Spontaneous bacterial peritonitis
	789.5	Ascites
Biliary disease	574	Cholelithiasis
	575	Disorders of gallbladder
	576	Disorders of biliary tract
Gastrointestinal hemorrhage	578	Gastrointestinal hemorrhage
Diabetes mellitus		
Diabetes mellitus	250	Diabetes mellitus
Malignant tumour		
Malignant neoplasm	140-149	Malignant neoplasm of lip, oral cavity, and pharynx
	150-159	Malignant neoplasm of digestive organs and peritoneum

	160-165	Malignant neoplasm of respiratory and intrathoracic organ
	170-176	Malignant neoplasm of bone, connective tissue, skin, and breas
	179-189	Malignant neoplasm of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites
	200-209	Malignant neoplasm of lymphatic and hematopoietic tissue
	235-238	Neoplasms of uncertain behavior
	239	Neoplasms of unspecified nature
Chemotherapy	V58.1	Encounter for antineoplastic chemotherapy and immunotherapy
	V66.2	Convalescence following chemotherapy
	V67.2	Follow-up examination, following chemotherapy
	99.25	Injection or infusion of cancer chemotherapeutic substance
History of cancer	V10	Personal history of cancer
Nervous system diseases		
Cerebrovascular events	430	Subarachnoid hemorrhage
	431	Intracerebral hemorrhage
	432	Other and unspecified intracranial hemorrhage
	433	Occlusion and stenosis of precerebral arteries
	434	Occlusion of cerebral arteries
	435	Transient cerebral ischemia
	436	Acute, but ill-defined, cerebrovascular disease
	437	Other and ill-defined cerebrovascular disease
	438	Late effects of cerebrovascular disease
Other nervous system disease	320-327	Inflammatory diseases of the central nervous system
	330-337	Hereditary and degenerative diseases of the central nervous system
	340-345	Other disorders of the central nervous system
Respiratory diseases		
Pneumonia	480	Viral pneumonia (other than SARS-CoV and SARS-CoV-2)
	481	Pneumococcal pneumonia [Streptococcus pneumoniae pneumonia]
	482	Other bacterial pneumonia
	483	Pneumonia due to other specified organism
	484	Pneumonia in infectious diseases classified elsewhere
	485	Bronchopneumonia, organism unspecified
	486	Pneumonia, organism unspecified
Influenza with respiratory manifestations	487	Influenza with respiratory manifestations
Chronic obstructive pulmonary disease and allied conditions	490-496	Chronic obstructive pulmonary disease and allied conditions
Pneumoconioses and other lung diseases due to external agents	500-508	Pneumoconioses and other lung diseases due to external agents
Other diseases of respiratory system	510-519	Other diseases of respiratory system
Kidney diseases		
Nephritis, nephrotic syndrome, and nephrosis	581	Nephrotic syndrome
	582	Chronic glomerulonephritis
	583	Nephritis and nephropathy not specified as acute or chronic
	584	Acute kidney failure
	585	Chronic kidney disease
	586	Renal failure, unspecified
	587	Renal sclerosis, unspecified
	588	Disorders resulting from impaired renal function
Renal replacement therapy	V56	Encounter for dialysis and dialysis catheter care
	38.95	Venous catheterization for renal dialysis

	39.27	Arteriovenostomy for renal dialysis
	39.42	Revision of arteriovenous shunt for renal dialysis
	39.43	Removal of arteriovenous shunt for renal dialysis
	39.95	Hemodialysis
	54.98	Peritoneal dialysis
Human immunodeficiency virus (HIV)		
HIV	042	HIV disease.
HIV	079.53	HIV, type 2 [HIV-2]
HIV	V02.9:1	HIV carrier
HIV	V08	Asymptomatic HIV infection status

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Supplementary Table 4. Univariate and multivariable analysis with Cox proportional hazards regression on factors associated with mortality in patients with SARS-CoV-2 infection / COVID-19 after multiple imputation.

Parameters	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	aHR (95% CI)	*P* value
HBV exposure				
- **No HBV**	Referent			
- **Current HBV infection**	1.10 (0.53 – 2.25)	0.802	1.29 (0.61 – 2.70)	0.507
- **Past HBV infection**	1.97 (1.23 – 3.15)	0.005	0.90 (0.56 – 1.46)	0.681
Acute liver injury	6.87 (4.38 – 10.78)	<0.001	2.45 (1.52 – 3.96)	<0.001
Liver cirrhosis	4.35 (2.29 – 8.29)	<0.001	2.08 (1.05 – 4.11)	0.036
Age (per years)	1.11 (1.09 – 1.12)	<0.001	1.09 (1.08 – 1.11)	<0.001
Male sex	1.17 (0.83 – 1.64)	0.362		
Circulatory system disease	11.17 (6.62 – 18.87)	<0.001		
Diabetes mellitus	6.00 (4.13 – 8.72)	<0.001	1.59 (1.06 – 2.39)	0.024
Malignant tumor	5.40 (3.60 – 8.11)	<0.001		
Nervous system disease	4.98 (3.42 – 7.25)	<0.001	2.30 (1.56 – 3.39)	<0.001
Respiratory disease	3.93 (2.62 – 5.89)	<0.001		
Kidney disease	7.42 (4.96 – 11.10)	<0.001	2.00 (1.32 – 3.04)	0.001
Creatinine	1.002 (1.002 – 1.003)	<0.001		
Albumin	0.88 (0.86 – 0.90)	<0.001		
Lactate dehydrogenase	1.003 (1.002 – 1.004)	<0.001	1.002 (1.001 – 1.003)	0.002
C-reactive protein	1.08 (1.06 – 1.10)	<0.001		
Hemoglobin	0.70 (0.65 – 0.75)	<0.001	0.90 (0.83 – 0.98)	0.018
Neutrophil-to-lymphocyte ratio	1.07 (1.06 – 1.08)	<0.001	1.04 (1.03 – 1.06)	<0.001
Platelet	0.998 (0.995 – 1.000)	0.071		

Patients were followed from the date of COVID-19 diagnosis to the date of discharge, the last follow-up date (20 January 2021), or date of death, whichever came first.
Acute liver injury was defined as alanine aminotransferase and/or aspartate aminotransferase ≥2xULN, with total bilirubin ≥2xULN and/or international normalized ratio ≥1.7.
aHR = adjusted hazard ratio; CI = confidence interval; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULN = upper limit of normal.

Supplementary Table 5. Liver-related outcomes during COVID-19/ SARS-CoV-2 infection.

Clinical outcomes	No HBV N = 4,927	Current HBV infection N = 353	Past HBV infection N = 359
Any hepatic events	5 (0.2)	1 (0.3)	4 (1.1)
Median days to hepatic events	14	5	22.5
Liver failure ^	10 (0.2)	1 (0.3)	3 (0.8)
Hepatocellular carcinoma	0 (0)	1 (0.3)	1 (0.3)
Ascites	0 (0)	0 (0)	0 (0)
Nonbleeding varices	0 (0)	0 (0)	0 (0)
Variceal bleeding	0 (0)	0 (0)	0 (0)
Hepatic encephalopathy	0 (0)	0 (0)	0 (0)
Hepatorenal syndrome	0 (0)	0 (0)	0 (0)
Spontaneous bacterial peritonitis	0 (0)	0 (0)	0 (0)
Liver-related death	0 (0)	0 (0)	0 (0)

* Five patients were not included due to history of hepatic events before SARS-CoV infection.

^ Liver failure was defined by diagnosis codes and/or serum total bilirubin ≥2x upper limit of normal and INR ≥1.7. The upper limit of normal of total bilirubin was 19 μmol/L (*i.e.* 1.1 mg/mL).

COVID-19 = coronavirus disease 2019, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Supplementary Table 6. Baseline clinical characteristics of patients with SARS-CoV-2 infection / COVID-19 who had or did not receive HBV antiviral treatment.

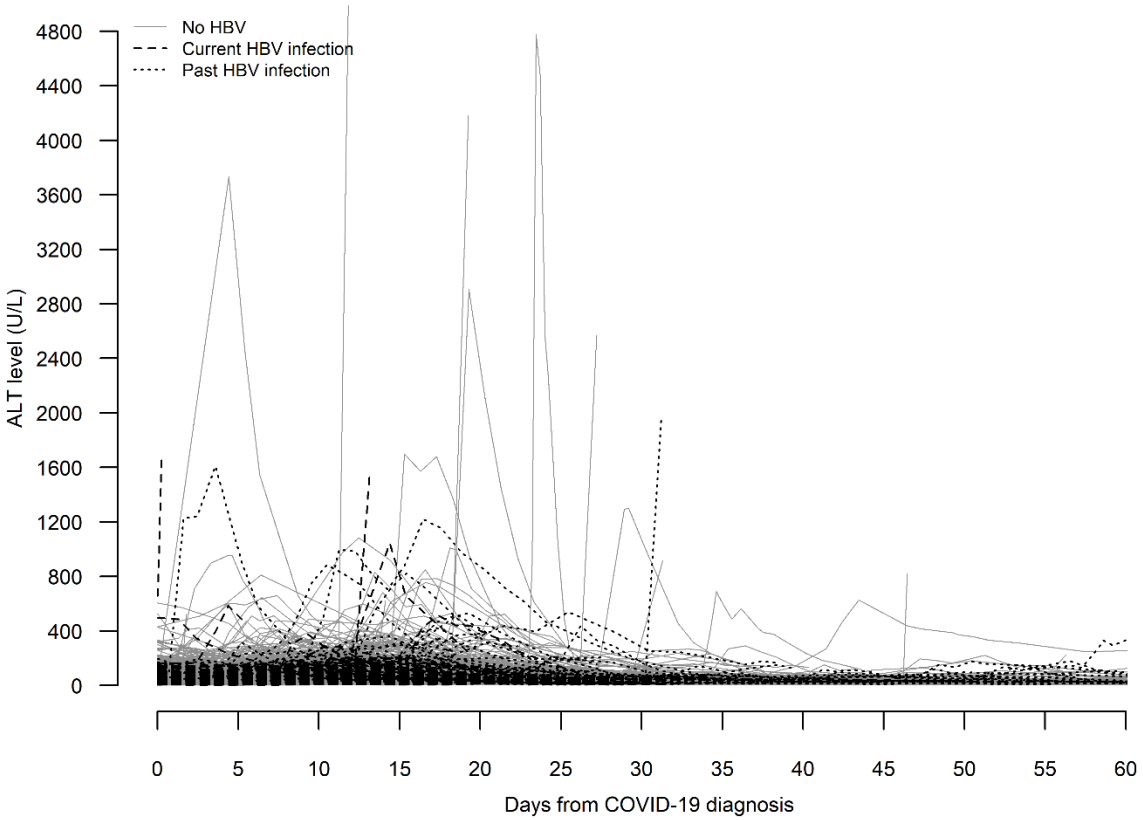
Clinical characteristics	No HBV antiviral treatment N = 5,406	With HBV antiviral treatment N = 233	*P* value
Age (years)	50.2 ± 18.1	63.3 ± 13.4	<0.001
Male gender (n, %)	2590 (47.9)	153 (65.7)	<0.001
HBV exposure			<0.001
- No HBV	4,856 (89.8)	71 (30.5)	
- Current HBV infection	231 (4.3)	122 (52.4)	
- Past HBV infection	319 (5.9)	40 (17.2)	
Liver cirrhosis (n, %)	58 (1.1)	21 (9.0)	<0.001
Albumin (g/L)	40.1 ± 5.2	37.3 ± 5.6	<0.001
Missing (%)	0.1	0	
Total bilirubin (mg/dL)	0.5 ± 0.3	0.6 ± 0.5	0.028
Missing (%)	0.1	0	
Alanine aminotransferase (U/L)	25 (17-39)	29 (19-42)	0.001
Missing (%)	0.1	0	
Aspartate aminotransferase (U/L)	30 (22-47)	42 (27-67)	<0.001
Missing (%)	67.8	37.3	
Alkaline phosphatase (xULN)	0.6 (0.5-0.7)	0.5 (0.4-0.7)	0.052
Missing (%)	0.1	0	
International normalized ratio	1.1 ± 0.2	1.1 ± 0.2	0.095
Missing (%)	33.4	21.0	
Creatinine (μmol/L)	70.0 (59.0-84.0)	79.0 (66.0-95.0)	<0.001
Missing (%)	0.1	0	
C-reactive protein (mg/dL)	1.9 ± 3.6	4.0 ± 5.5	<0.001
Missing (%)	1.0	0.4	
Lactate dehydrogenase (U/L)	220.4 ± 90.1	280.2 ± 132.4	<0.001
Missing (%)	1.2	0.4	
Hemoglobin (g/dL)	13.5 ± 1.7	13.6 ± 1.7	0.632
Missing (%)	0.04	0	
WCC ($x10^9$/L)	5.7 ± 2.2	5.7 ± 2.7	0.861
WCC <3.5$x10^9$/L (n, %)	605 (11.2)	25 (10.7)	0.825
Missing (%)	0.04	0	
Neutrophil ($x10^9$/L)	3.7 ± 1.9	4.0 ± 2.6	0.061
Missing (%)	0.4	0	
Lymphocyte ($x10^9$/L)	1.3 ± 0.8	1.1 ± 0.5	<0.001
Lymphocyte <1$x10^9$/L (n, %)	1730 (32.1)	123 (52.8)	<0.001
Missing (%)	0.4	0	
Neutrophil-to-lymphocyte ratio	3.5 ± 3.1	5.2 ± 7.2	<0.001
Missing (%)	0.4	0	
Platelet ($x10^9$/L)	217.4 ± 74.1	177.4 ± 60.5	<0.001
Platelet <150$x10^9$/L (n, %)	872 (16.1)	85 (36.5)	<0.001
Missing (%)	0.04	0	
Comorbidities (n, %)			
Circulatory system disease	1,692 (31.3)	124 (53.2)	<0.001
Diabetes mellitus	1,077 (19.9)	102 (43.8)	<0.001
Malignant tumor	215 (4.0)	29 (12.4)	<0.001
Nervous system disease	247 (4.6)	17 (7.3)	0.054
Respiratory disease	219 (4.1)	18 (7.7)	0.006
Kidney disease	127 (2.3)	11 (4.7)	0.022
HIV infection	8 (0.1)	1 (0.4)	0.316
Medications during follow-up (n, %)			
Oseltamivir	80 (1.5)	6 (2.6)	0.170

Ribavirin	1,609 (29.8)	94 (40.3)	0.001
Lopinavir-ritonavir	1,687 (31.2)	70 (30.0)	0.707
Interferon beta	2,560 (47.4)	154 (66.1)	<0.001
Remdesivir	438 (8.1)	38 (16.3)	<0.001
Antibiotic treatment	2,329 (43.1)	173 (74.2)	<0.001
Antifungal treatment	38 (0.7)	6 (2.6)	0.009
Corticosteroid	1,109 (20.5)	161 (69.1)	<0.001
Dexamethasone	1,016 (18.8)	157 (67.4)	<0.001
Hydrocortisone	135 (2.5)	17 (7.3)	<0.001
Prednisolone	68 (1.3)	8 (3.4)	0.013
Methylprednisolone	7 (0.1)	1 (0.4)	0.287
Peak daily dose (prednisolone equivalent, mg)	45 (45-45)	45 (45-75)	<0.001
Duration (days)	9 (6-13)	12 (9-19)	<0.001
Intravenous immunoglobulin therapy	6 (0.1)	2 (0.9)	0.040
Clinical outcomes in 60 days (n, %)			
Acute liver injury	64 (1.2)	13 (5.6)	<0.001
Mortality	120 (2.2)	18 (7.7)	<0.001
Follow-up duration (days)	13 (9-20)	19 (13-29)	<0.001

All concomitant medications were represented as binary parameters. Percentages were computed based on non-missing values. Categorical variables were presented as number (percentage). Median age, alanine aminotransferase and follow-up duration were expressed in median (interquartile range), whereas other continuous variables were expressed in mean ± standard deviation. Qualitative and quantitative differences between subgroups were analyzed by Chi-square or Fisher's exact tests for categorical parameters and Student's *t* test or Mann-Whitney *U* test for continuous parameters, as appropriate.

COVID-19 = coronavirus disease 2019; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HIV = human immunodeficiency virus infection, ICU = intensive care unit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULN = upper limit of normal; WCC = white cell count.

Supplementary Figure 1A. Serial alanine aminotransferase (ALT) of patients with SARS-CoV-2 infection / COVID-19 who had had no HBV, current and past HBV infection.
COVID-19 = coronavirus disease 2019, HBV = hepatitis B virus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.



Supplementary Figure 1B. Serial total bilirubin of patients with SARS-CoV-2 infection / COVID-19 who had had no HBV, current and past HBV infection.
COVID-19 = coronavirus disease 2019, HBV = hepatitis B virus, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.