Supplementary methods

Clinical evaluation

The clinical evaluation and management of severe acute respiratory syndrome (SARS) patients back in 2003 were described in details in our previous publications.[1, 2] 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 normalised ratio [INR]) 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 SARS-coronavirus (CoV) and SARS-CoV-2 as well as other bat-associated SARS-related viruses (*Sarbecovirus*) as screening.[3] 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, nasophayngeal 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.[4] Supportive therapy, including supplemental oxygen, intravenous

fluid, vasopressor support, mechanical ventilation, and renal replacement therapy, were given as appropriate. For 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 Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM*, et al.* A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;**348**:1986-94.
2 Sung JJ, Wu A, Joynt GM, Yuen KY, Lee N, Chan PK*, et al.* Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. Thorax 2004;**59**:414-20.
3 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**:727-33.
4 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 29 April 2020.

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

Disease	ICD-9-CM Code	All Diagnosis Description
SARS	465.9	SARS - upper respiratory (465.9:2)
	466.0	SARS - acute bronchitis (466.0:1)
	480.8	SARS with atypical pneumonia (480.8:2)
	480.8	Pneumonia due to coronavirus (480.8:1)
	486	Atypical pneumonia (486:1)
	V67.59	SARS follow up (V67.59:1)
COVID-19	079.89	Infection due to coronavirus (079.89:3)
	480.8	Pneumonia due to coronavirus (480.8:1)
	Virological Test Description	
SARS	Test for Severe Respiratory Syndrome (SRS) agent by RT-PCR	
COVID-19	2019 novel Coronavirus (2019-nCoV) PCR	
	RT-PCR for Novel coronavirus (Novel CoV) RNA	
	Novel coronavirus (Novel-CoV) RNA	
	Xpert RT-PCR for SARS-CoV-2 RNA	

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

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. ICD-9-CM diagnosis and procedure codes for hypertension, hepatic complications, liver cirrhosis, hepatocellular carcinoma, and liver failure.

Disease	ICD-9-CM Code	Description
Hypertension		
Hypertension	401	Essential hypertension
Hypertension	402	Hypertensive heart disease
Hypertension	403	Hypertensive chronic kidney disease
Hypertension	404	Hypertensive heart and chronic kidney disease
Hepatic complications/ Liver-related outcomes		
Ascites	789.5	Ascites
SBP	567.2:9	Spontaneous bacterial peritonitis
EVB *	456.0	Esophageal varices with bleeding
EVB	456.20	Esophageal varices classified elsewhere with bleeding
GVB *	456.8:1	Fundal varices, bleeding
GVB	456.8:2	Bleeding gastric varices
HE	348.3	Encephalopathy, unspecified
HE	349.82	Toxic encephalopathy
HE	572.2	Hepatic coma
HRS	572.4	Hepatorenal syndrome
Portal hypertension	572.3	Portal hypertension
Varices	456.1	Esophageal varices without bleeding
Varices	456.21	Esophageal varices in diseases classified elsewhere without bleeding
Varices	456.8:4	Fundal varices
Varices	456.8:5	Gastric varices
Liver cirrhosis		
Liver cirrhosis	571.2	Alcoholic cirrhosis of liver
Liver cirrhosis	571.5	Cirrhosis of liver without mention of alcohol
Hepatocellular carcinoma (HCC)		
HCC	155.0	Malignant neoplasm of liver, primary
HCC	155.2	Malignant neoplasm of liver, not specified
Liver failure		
Liver failure	570	Acute and subacute necrosis of liver
Hepatitis		
Chronic hepatitis B	070.22	Chronic viral hepatitis B with hepatic coma without hepatitis delta
Chronic hepatitis B	070.23	Chronic viral hepatitis B with hepatic coma with hepatitis delta
Chronic hepatitis B	070.32	Chronic viral hepatitis B without mention of hepatic coma without mention of hepatitis delta
Chronic hepatitis B	070.33	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
Chronic hepatitis B	V02.61	Hepatitis B carrier
Acute hepatitis B	070.20	Viral hepatitis B with hepatic coma, acute or unspecified, without mention of hepatitis delta
Acute hepatitis B	070.21	Viral hepatitis B with hepatic coma, acute or unspecified, with hepatitis delta
Acute hepatitis B	070.30	Viral hepatitis B without mention of hepatic coma, acute or unspecified, without mention of hepatitis delta
Acute hepatitis B	070.31	Viral hepatitis B without mention of hepatic coma, acute or unspecified, with hepatitis delta
Hepatitis C	070.41	Acute hepatitis C with hepatic coma

Hepatitis C	070.44	Chronic hepatitis C with hepatic coma
Hepatitis C	070.51	Acute hepatitis C without mention of hepatic coma
Hepatitis C	070.54	Chronic hepatitis C without mention of hepatic coma
Hepatitis C	V02.62	Hepatitis C carrier
Hepatitis D	070.23	Chronic viral hepatitis B with hepatic coma with hepatitis delta
Hepatitis D	070.33	Chronic viral hepatitis B without mention of hepatic coma with hepatitis delta
Hepatitis D	070.42	Hepatitis delta without mention of active hepatitis B disease with hepatic coma
Hepatitis D	070.52	Hepatitis delta without mention of active hepatitis B disease or hepatic coma

* Esophageal or gastric variceal bleeding was also defined by the ICD-9-CM procedure codes of 42.33:3, 42.33:6, 42.33:13, and 43.41:1.

Abbreviations: EVB = esophageal variceal bleeding; GVB = gastric variceal bleeding, HCC = hepatocellular carcinoma, HE = hepatic encephalopathy, HRS = hepatorenal syndrome, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, SBP = spontaneous bacterial peritonitis.

Supplementary Table 4. Liver-related outcomes during coronavirus infection.

Clinical outcomes	**SARS-CoV * N = 1,665**	**SARS-CoV-2 N = 489**	**HCoV-229E N = 127**	**HCoV-HKU1 N = 117**	**HCoV-NL63 N = 56**	**HCoV-OC43 N = 385**
Any hepatic events	19 (1.1)	0 (0)	2 (0.8)	1 (0.9)	1 (1.8)	1 (0.3)
Time to hepatic events (days) #	16 (8-20)	-	0	3.5 (1-6)	0	0
Liver failure ^	16 (1.0)	0 (0)	2 (1.6)	2 (1.7)	1 (1.8)	1 (0.3)
Hepatocellular carcinoma	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ascites	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nonbleeding varices	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Variceal bleeding	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatic encephalopathy	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatorenal syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Spontaneous bacterial peritonitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver-related death	2 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

Presented in median (range), or the exact time if there was only one event.

^ Liver failure was defined by diagnosis codes and/or serum total bilirubin ≥2x upper limit of normal and INR ≥2. The upper limit of normal of total bilirubin was 19 μmol/L.

HCoV = human coronavirus; SARS = severe acute respiratory syndrome.

Supplementary Table 5. Comparison of peak alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) of 816 COVID-19 patients who had serial measurement of liver biochemistries with and with invasive mechanical ventilation.

Age <50 years	**Without invasive mechanical ventilation N=544**	**With invasive mechanical ventilation N=7**	***P* value**
Peak ALT/AST (U/L)	33 (22-61)	209 (72-299)	<0.001
Peak total bilirubin (μmol/L)	18 (12-27)	43 (27-44)	0.001
Age ≥50 years	**Without invasive mechanical ventilation N=250**	**With invasive mechanical ventilation N=15**	***P* value**
Peak ALT/AST (U/L)	48 (31-87)	137 (76-252)	<0.001
Peak total bilirubin (μmol/L)	21 (14-29)	28 (14-71)	0.020
With diabetes mellitus	**Without invasive mechanical ventilation N=61**	**With invasive mechanical ventilation N=15**	***P* value**
Peak ALT/AST (U/L)	52 (37-115)	100 (72-252)	0.042
Peak total bilirubin (μmol/L)	22 (17-33)	35 (27-71)	0.007
Without diabetes mellitus	**Without invasive mechanical ventilation N=733**	**With invasive mechanical ventilation N=7**	***P* value**
Peak ALT/AST (U/L)	35 (23-67)	209 (117-299)	<0.001
Peak total bilirubin (μmol/L)	19 (13-27)	26 (22-44)	0.049
With hypertension	**Without invasive mechanical ventilation N=116**	**With invasive mechanical ventilation N=14**	***P* value**
Peak ALT/AST (U/L)	52 (33-109)	185 (105-264)	<0.001
Peak total bilirubin (μmol/L)	20 (13-29)	31 (14-76)	0.018
Without hypertension	**Without invasive mechanical ventilation N=678**	**With invasive mechanical ventilation N=8**	***P* value**
Peak ALT/AST (U/L)	35 (23-66)	85 (72-314)	0.001
Peak total bilirubin (μmol/L)	19 (13-27)	34 (27-43)	0.001
Duration of COVID-19 <7 days at peak ALT/AST or at the start of invasive mechanical ventilation	**Without invasive mechanical ventilation N=406**	**With invasive mechanical ventilation N=17**	***P* value**
Peak ALT/AST (U/L)	31 (22-51)	171 (72-276)	<0.001
Duration of COVID-19 ≥7 days at peak ALT/AST or at the start of invasive mechanical ventilation	**Without invasive mechanical ventilation N=388**	**With invasive mechanical ventilation N=5**	***P* value**
Peak ALT/AST (U/L)	49 (29-97)	137 (88-530)	0.008
Duration of COVID-19 <7 days at peak total bilirubin or at the start of invasive mechanical ventilation	**Without invasive mechanical ventilation N=518**	**With invasive mechanical ventilation N=17**	***P* value**
Peak ALT/AST (U/L)	20 (13-29)	34 (25-81)	<0.001
Duration of COVID-19 ≥7 days at peak total bilirubin or at the start of invasive mechanical ventilation	**Without invasive mechanical ventilation N=276**	**With invasive mechanical ventilation N=5**	***P* value**
Peak ALT/AST (U/L)	18 (12-24)	33 (13-37)	0.232

Peak ALT/AST and total bilirubin between COVID-19 patients with and with invasive mechanical ventilation were compared by Mann-Whitney *U* test.
COVID-19 = Coronavirus disease 2019.

Supplementary Table 6. Univariate and multivariable analysis with logistic regression on factors associated with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation with total bilirubin elevation and/or raised international normalised ratio (INR) in patients infected by SARS-CoV-2.

Parameters	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Use of antiviral agents - No use of antiviral agents - Lopinavir-ritonavir ± ribavirin - Lopinavir-ritonavir ± ribavirin + interferon beta	Not available*		Not available	
Use of corticosteroid	6.98 (4.00-12.19)	<0.001	4.76 (1.56-14.50)	0.006
Age	1.07 (1.04-1.11)	<0.001	1.04 (1.00-1.09)	0.039
Male gender	3.63 (1.02-12.96)	0.047		
Diabetes mellitus	9.28 (3.27-26.37)	<0.001		
Hypertension	15.76 (4.94-50.32)	<0.001	5.21 (1.41-19.16)	0.013

ALT and/or AST elevation with total bilirubin elevation and/or raised INR was defined by ALT and/or AST ≥2x upper limit of normal (ULN) with total bilirubin ≥2xULN and/or INR ≥1.7 at baseline or during follow-up. The upper limit of normal of ALT and AST were 40 U/L. The ULN of total bilirubin was 19 μmol/L.

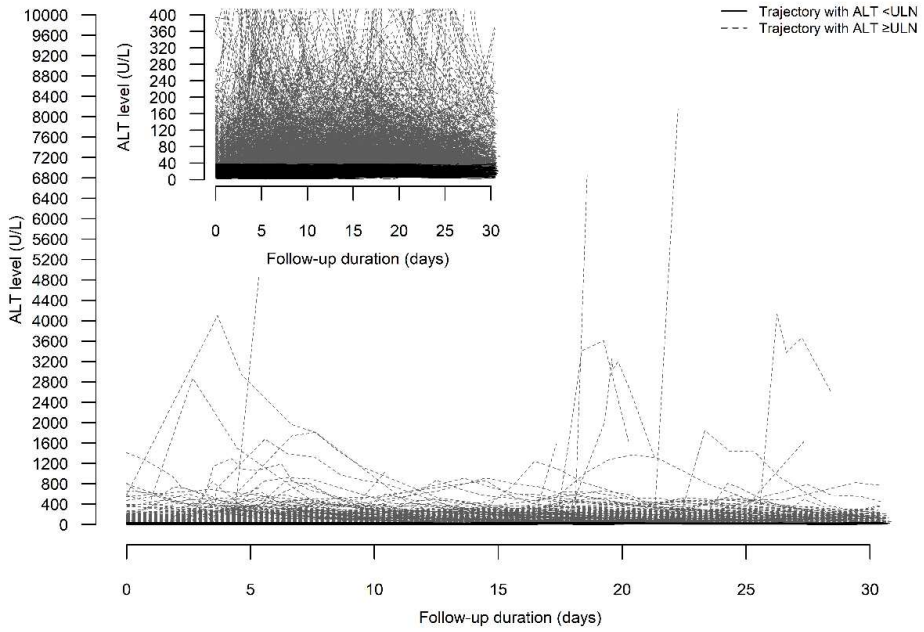
***** Odds ratio was no available as acute liver injury occurred in 9 (2.8%), 6 (2.1%), and 0 (0%) of patients who used lopinavir-ritonavir ± ribavirin + interferon beta, lopinavir-ritonavir ± ribavirin, and those who did not used these antiviral agents (Chi-square test for linear trend, *P*=0.027).

P value = 0.418 for Hosmer-Lemeshow goodness-of-fit test, which did not indicate significant poor fit.

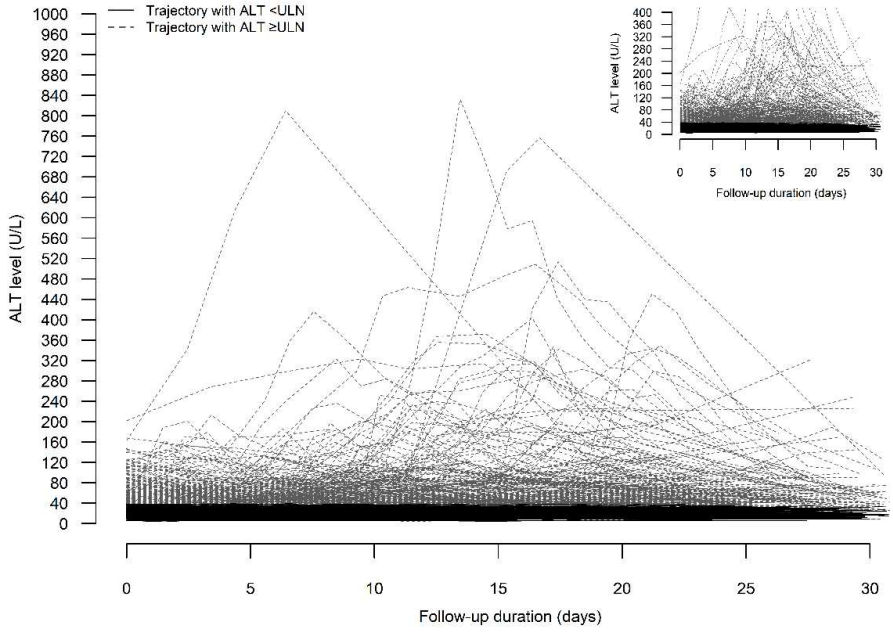
aOR = adjusted odds ratio; CI = confidence interval; CoV = coronavirus; SARS = severe acute respiratory syndrome.

Supplementary Figure 1. Serial serum alanine aminotransferase (ALT) of patients infected with A. SARS-CoV; B. SARS-CoV-2; and C. other HCoVs. ALT=alanine aminotransferase, HCoV = human coronavirus, SARS = severe acute respiratory syndrome, ULN = upper limit of normal.

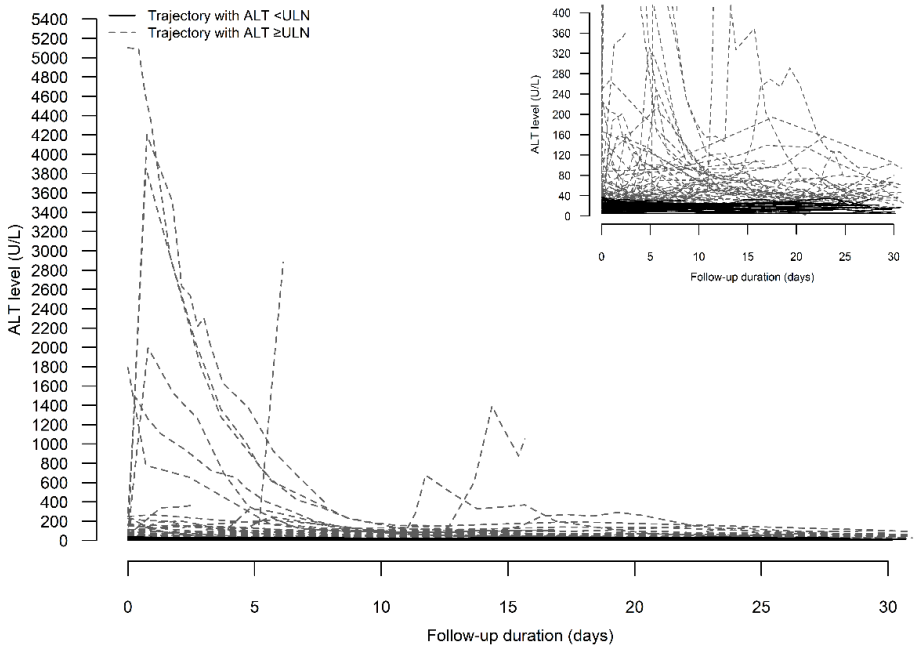
A.



B.

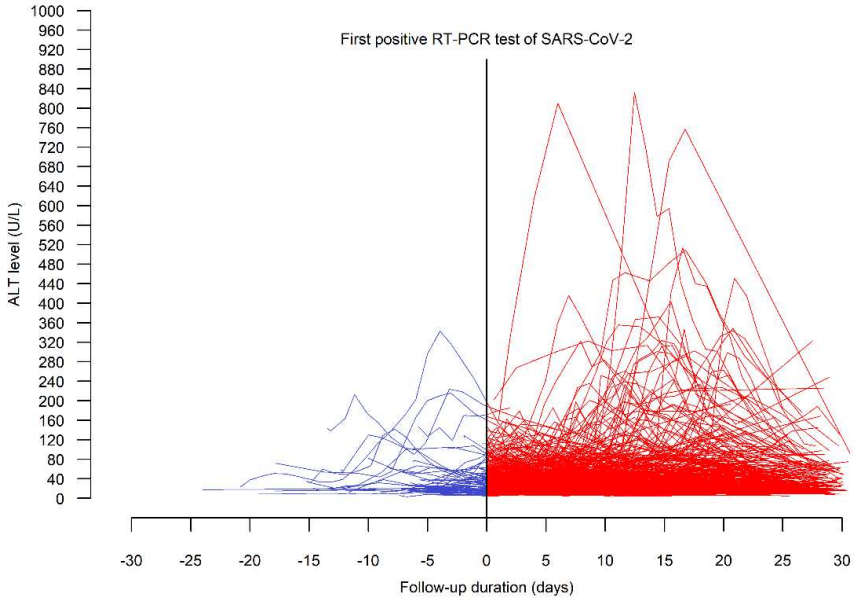


C.

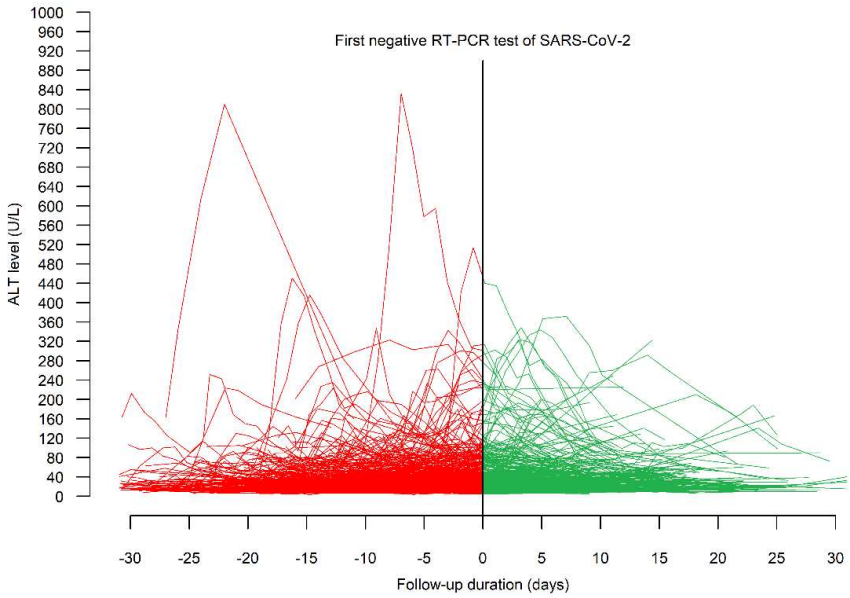

Trajectory with ALT <ULN
Trajectory with ALT ≥ULN
ALT level (U/L)
Follow-up duration (days)

Supplementary Figure 2. Serial serum alanine aminotransferase (ALT) of patients infected with SARS-CoV-2 with reference to the time of A. first positive RT-PCR test of SARS-CoV-2; and B. first negative RT-PCR test of SARS-CoV-2.
CoV = coronavirus, RT-PCR = reverse transcription polymerase chain reaction, SARS = severe acute respiratory syndrome.

A.

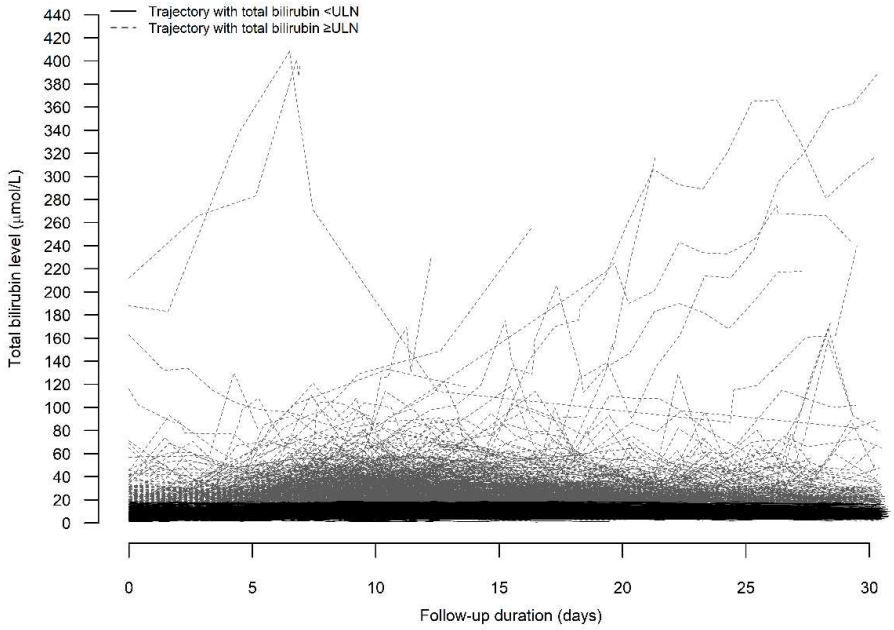


B.

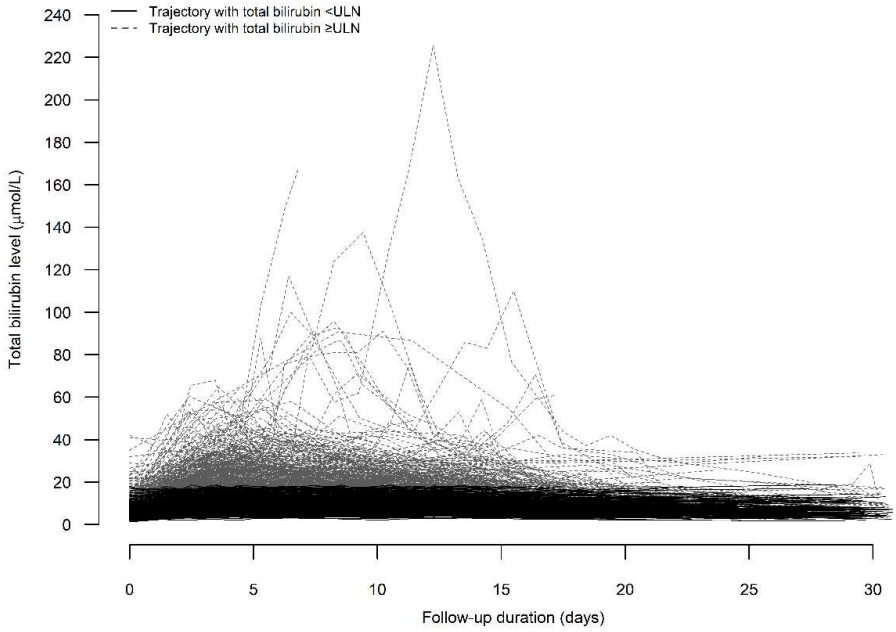


Supplementary Figure 3. Serial serum total bilirubin of patients infected with A. SARS-CoV; B. SARS-CoV-2; and C. other HCoVs. HCoV = human coronavirus, SARS = severe acute respiratory syndrome, ULN = upper limit of normal.

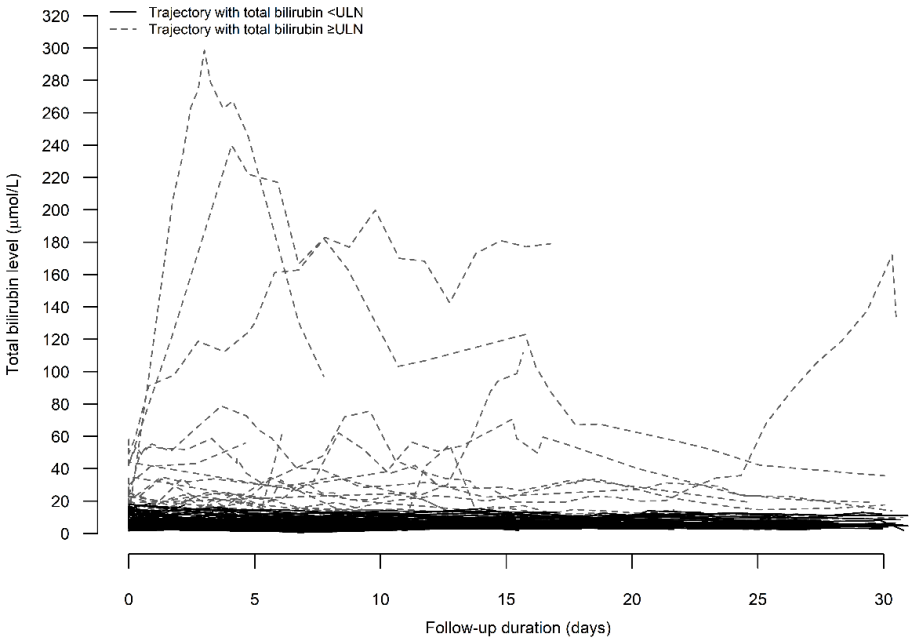
A.



B.

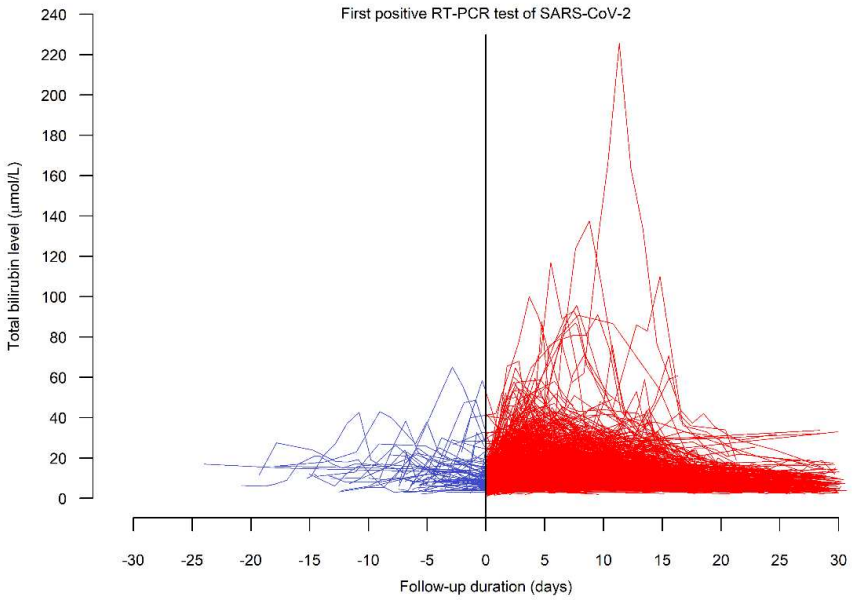


C.

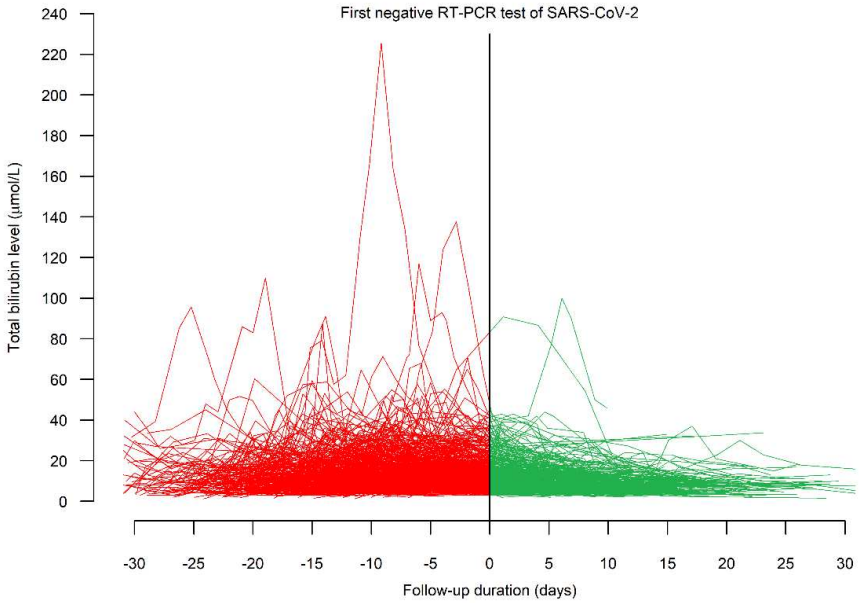

Trajectory with total bilirubin <ULN
Trajectory with total bilirubin ≥ULN
Total bilirubin level (µmol/L)
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Follow-up duration (days)

Supplementary Figure 4. Serial serum total bilirubin of patients infected with SARS-CoV-2 with reference to the time of A. first positive RT-PCR test of SARS-CoV-2; and B. first negative RT-PCR test of SARS-CoV-2.
CoV = coronavirus, RT-PCR = reverse transcription polymerase chain reaction, SARS = severe acute respiratory syndrome.

A.

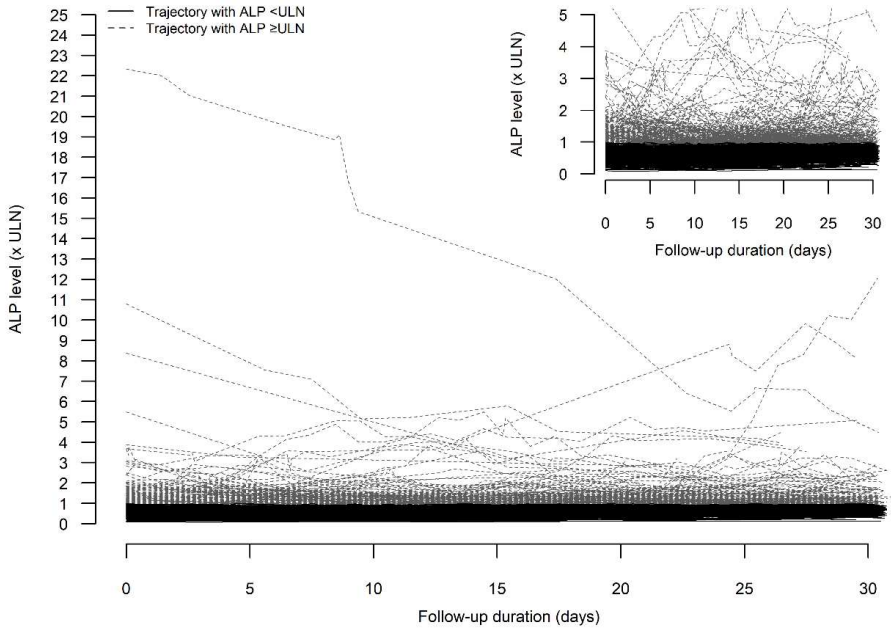


B.



Supplementary Figure 5. Serial serum alkaline phosphatase (ALP) of patients infected with A. SARS-CoV; B. SARS-CoV-2; and C. Other HCoVs. HCoV=human coronavirus, ULN=upper limit of normal, SARS=severe acute respiratory syndrome.

A.



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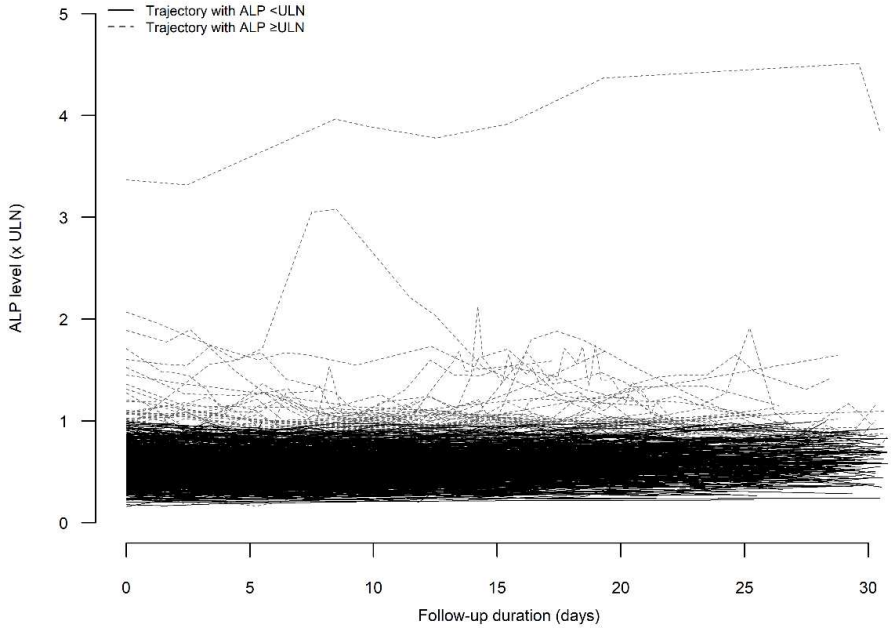
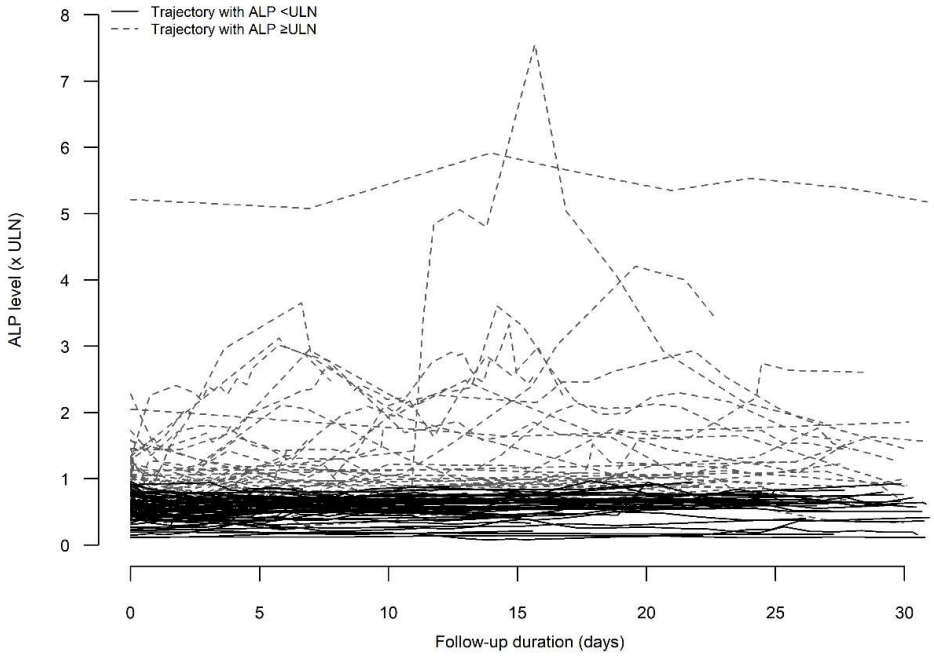
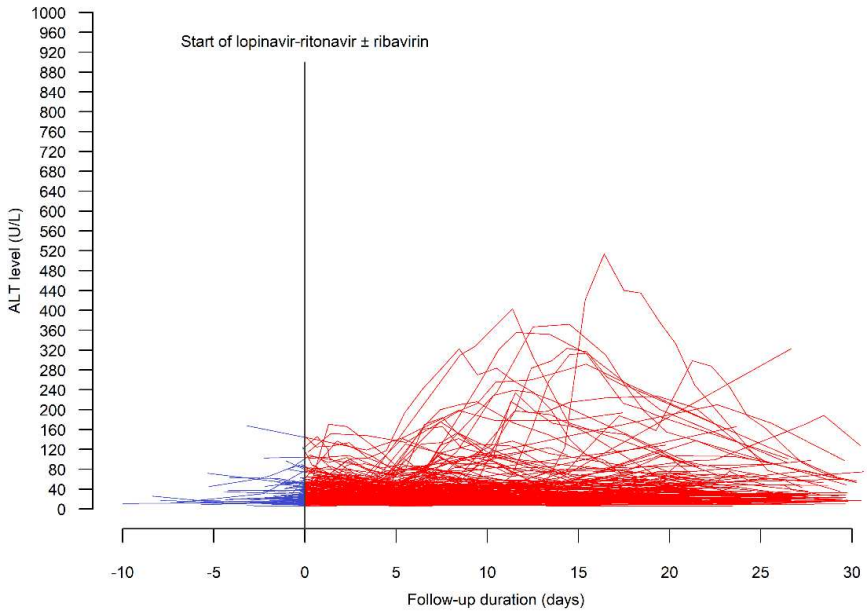


C.

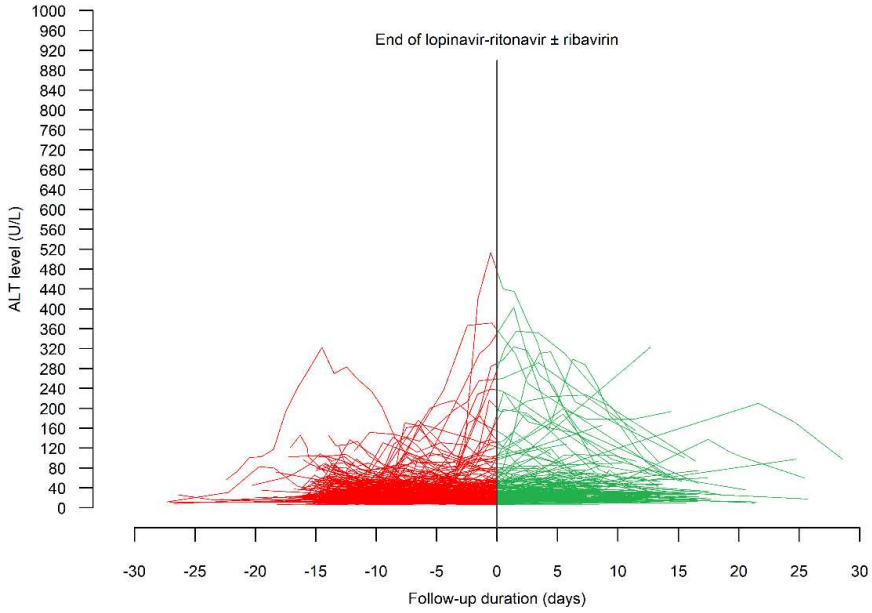

Trajectory with ALP <ULN
Trajectory with ALP ≥ULN
ALP level (x ULN)
0
1
2
3
4
5
6
7
8
0
5
10
15
20
25
30
Follow-up duration (days)

Supplementary Figure 6. Serial serum alanine aminotransferase (ALT) of patients infected with SARS-CoV-2 with reference to the time of A. start and B. end of lopinavir-ritonavir ± ribavirin; and C. start and D. end of lopinavir-ritonavir ± ribavirin + interferon beta.
CoV = coronavirus, SARS = severe acute respiratory syndrome.

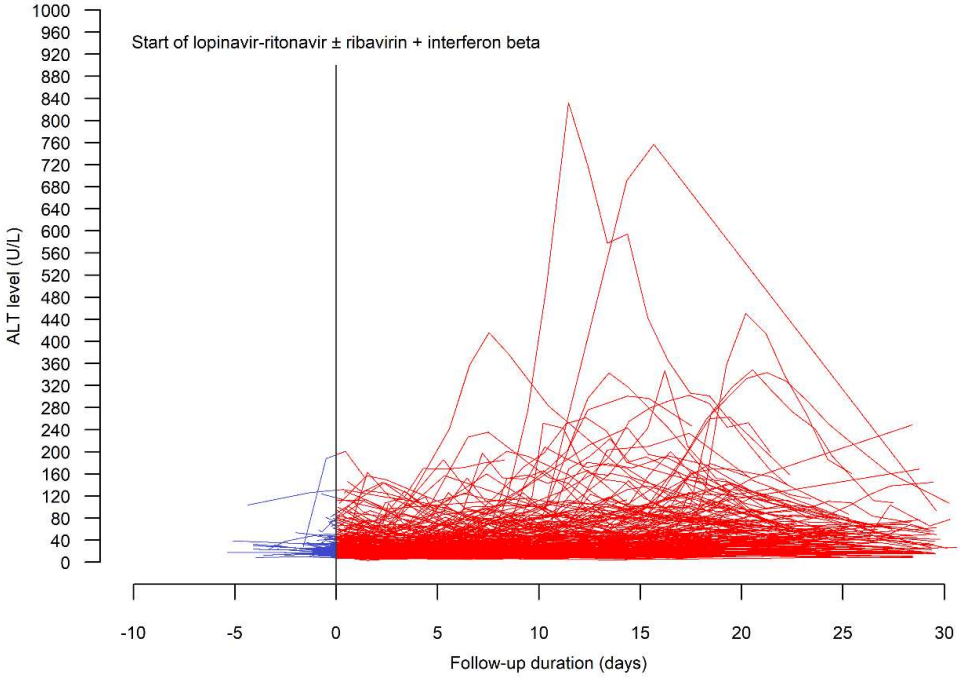
A.



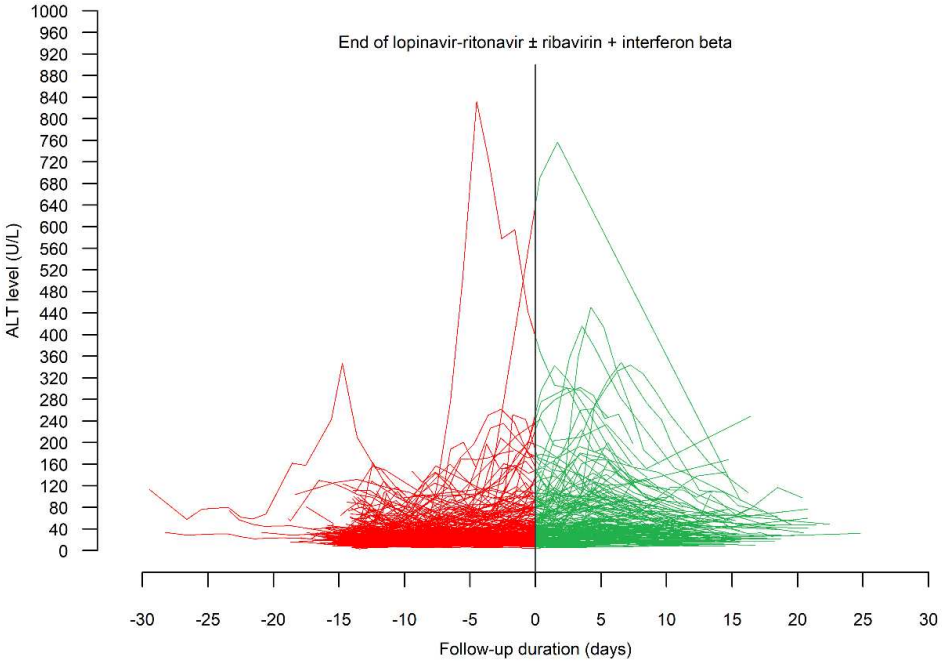
B.



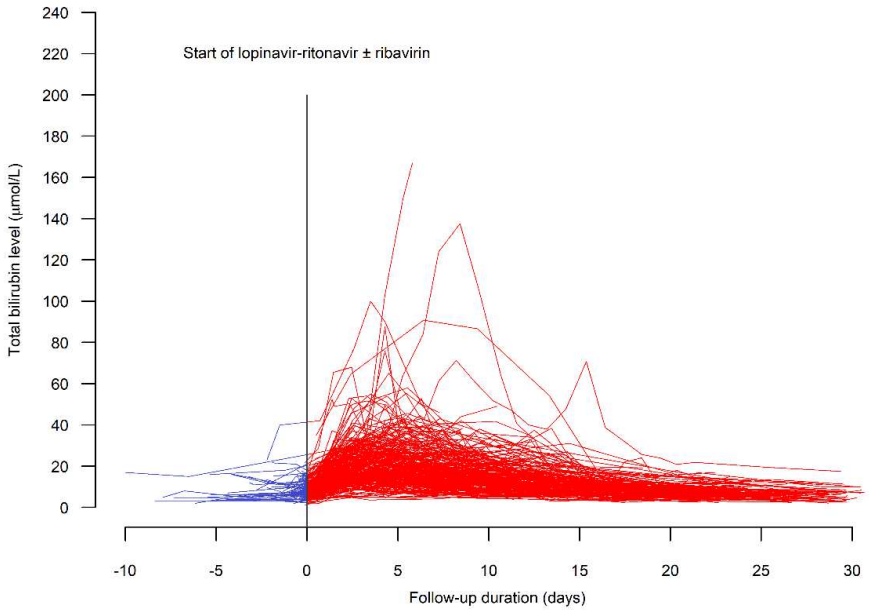
C.


Start of lopinavir-ritonavir ± ribavirin + interferon beta
ALT level (U/L)
1000
960
920
880
840
800
760
720
680
640
600
560
520
480
440
400
360
320
280
240
200
160
120
80
40
0
-10
-5
0
5
10
15
20
25
30
Follow-up duration (days)

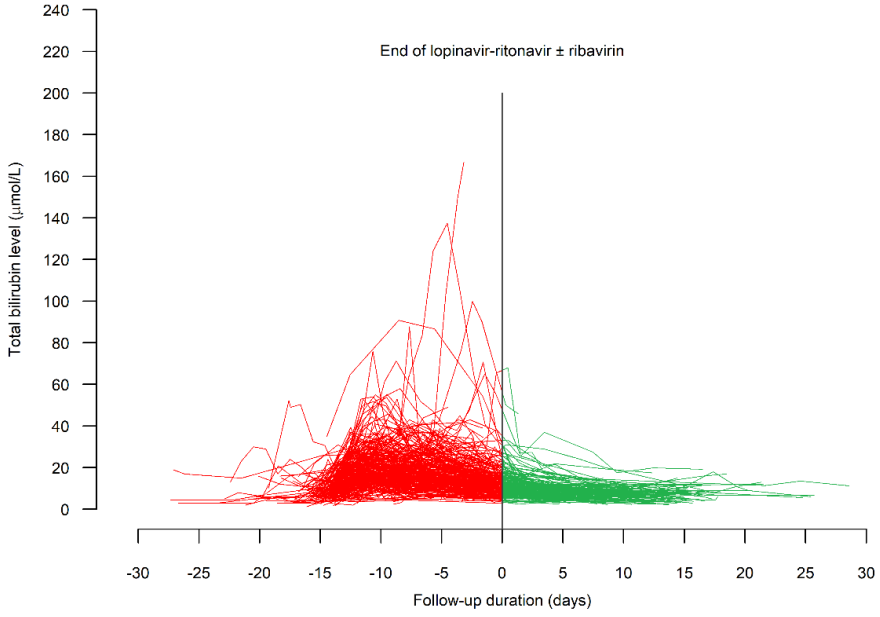
D.


End of lopinavir-ritonavir ± ribavirin + interferon beta
ALT level (U/L)
1000
960
920
880
840
800
760
720
680
640
600
560
520
480
440
400
360
320
280
240
200
160
120
80
40
0
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Follow-up duration (days)

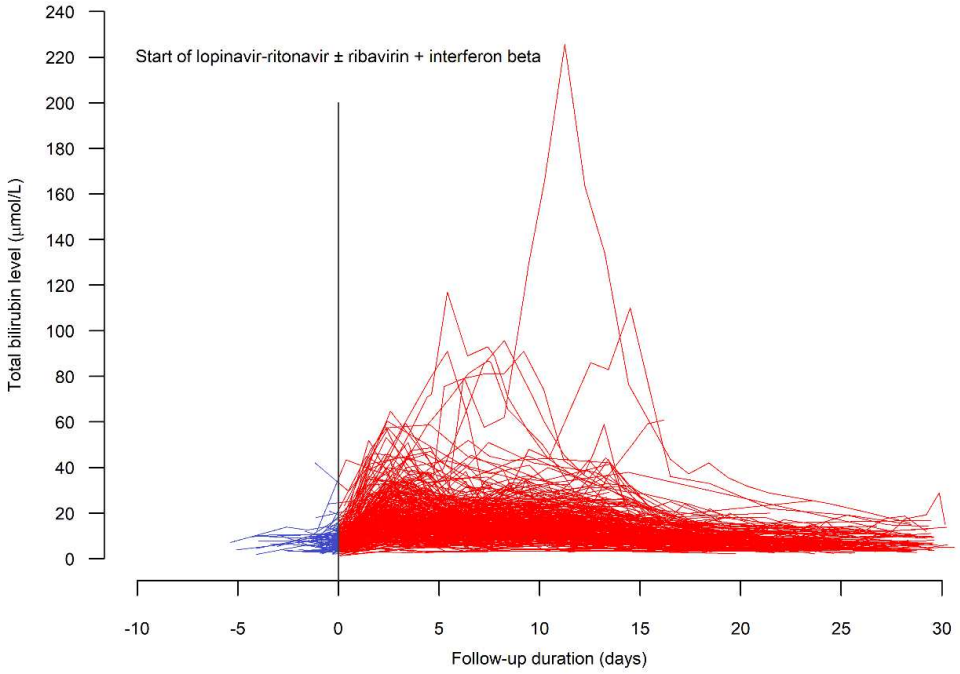
Supplementary Figure 7. Serial serum total bilirubin of patients infected with SARS-CoV-2 with reference to the time of A. start and B. end of lopinavir-ritonavir ± ribavirin; and C. start and D. end of lopinavir-ritonavir ± ribavirin + interferon beta.
CoV = coronavirus, SARS = severe acute respiratory syndrome.
A.



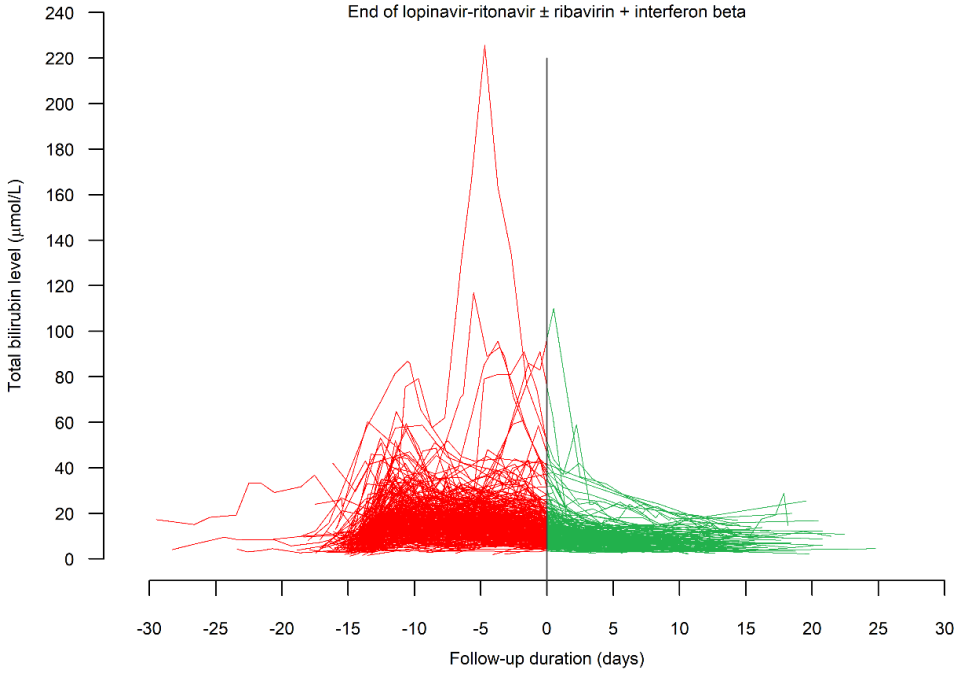
B.



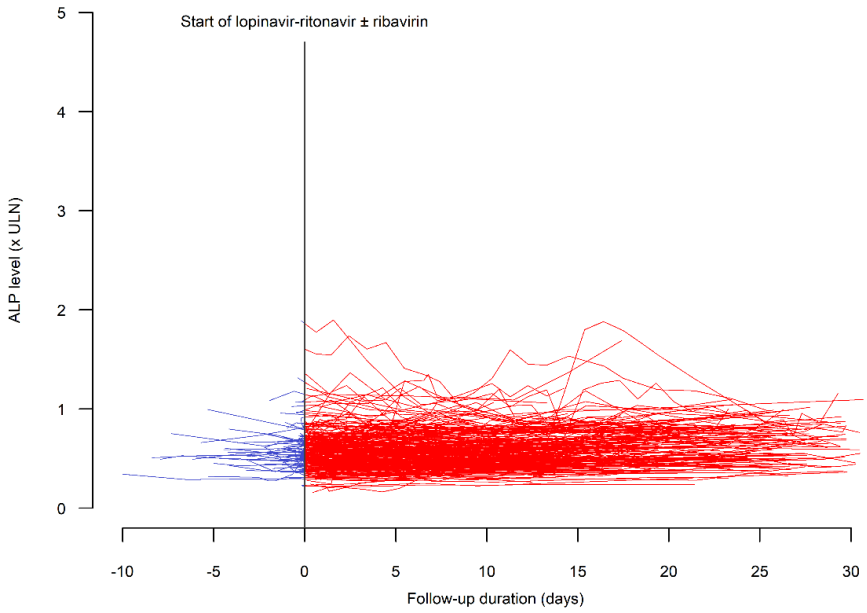
C.


Start of lopinavir-ritonavir ± ribavirin + interferon beta
Total bilirubin level (μmol/L)
240
220
200
180
160
140
120
100
80
60
40
20
0
-10
-5
0
5
10
15
20
25
30
Follow-up duration (days)

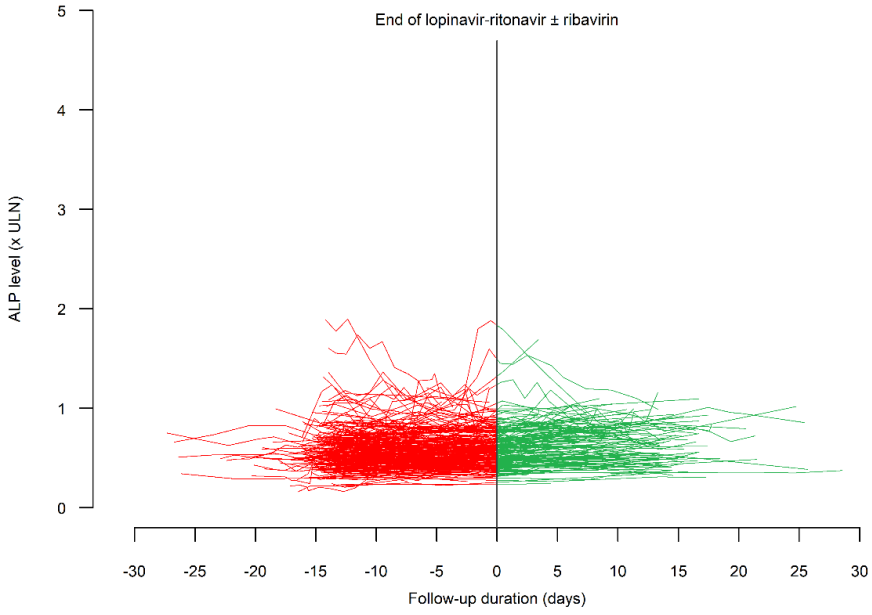
D.


End of lopinavir-ritonavir ± ribavirin + interferon beta
Total bilirubin level (μmol/L)
240
220
200
180
160
140
120
100
80
60
40
20
0
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Follow-up duration (days)

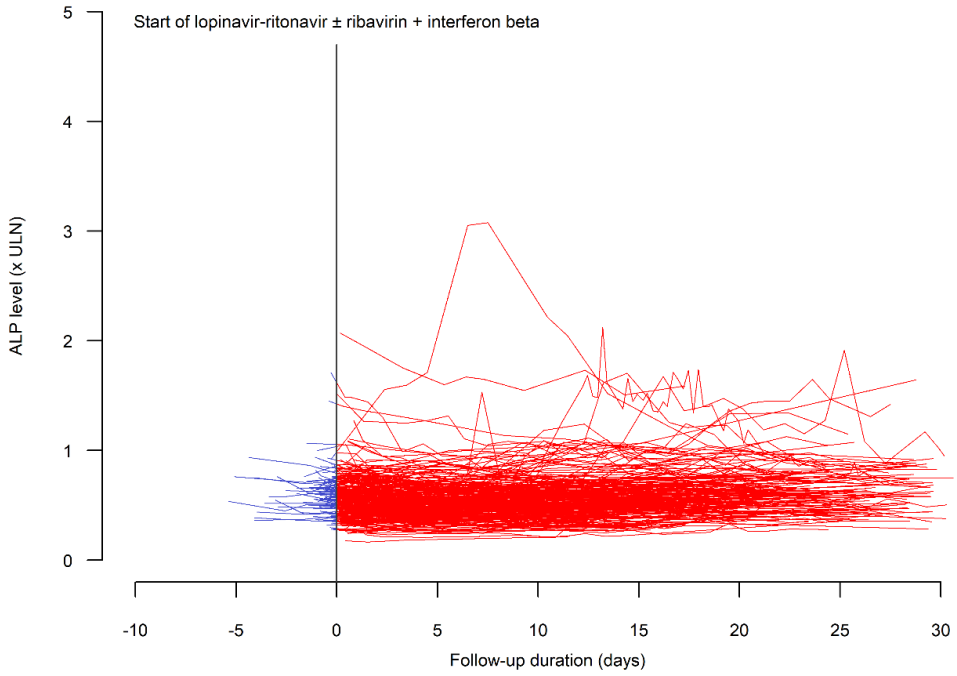
Supplementary Figure 8. Serial serum alkaline phosphatase (ALP) of patients infected with SARS-CoV-2 with reference to the time of A. start and B. end of lopinavir-ritonavir ± ribavirin; and C. start and D. end of lopinavir-ritonavir ± ribavirin + interferon beta.
CoV = coronavirus, SARS = severe acute respiratory syndrome.
A.



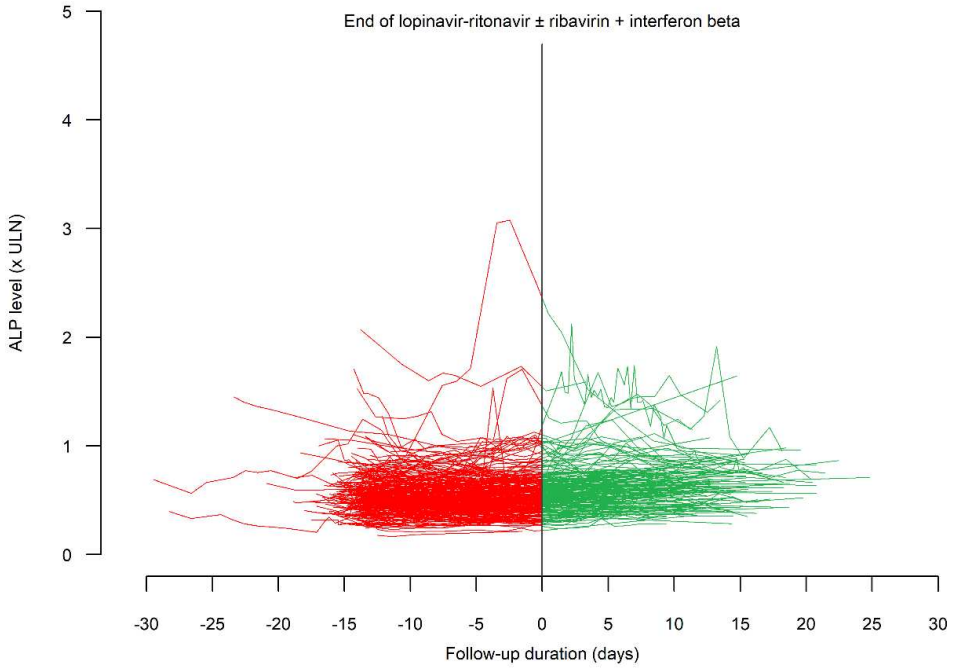
B.



C.


Start of lopinavir-ritonavir ± ribavirin + interferon beta
ALP level (x ULN)
0
1
2
3
4
5
-10
-5
0
5
10
15
20
25
30
Follow-up duration (days)

D.


End of lopinavir-ritonavir ± ribavirin + interferon beta
ALP level (x ULN)
0
1
2
3
4
5
-30
-25
-20
-15
-10
-5
0
5
10
15
20
25
30
Follow-up duration (days)