Supplementary materials

Progressive liver injury and increased mortality risk in COVID-19 patients: a retrospective cohort study in China

Supplementary Table 1 Treatments for 440 patients of COVID-19, by severity of cumulative liver abnormality or injury

	All patients (n=440)	Normal cumulative LB (n=186)	Cumulative LBA (n=185)	Cumulative ALI (n=69)	Cumulative LBAI (n=254)	OR (95%CI)	p value
Medicine							
Antibiotics	353 (80.2%)	133 (37.7%)	158 (44.8%)	62 (17.6%)	220 (62.3%)	2.58 (1.59 to 4.17)	<0.001
Antivirus	390 (88.6%)	155 (39.7%)	173 (44.4%)	62 (15.9%)	235 (60.3%)	2.47 (1.35 to 4.53)	0.003
Oseltamivir	162 (36.8%)	74 (45.7%)	66 (40.7%)	22 (13.6%)	88 (54.3%)	0.80 (0.54 to 1.19)	0.270
Arbidol	302 (68.6%)	122 (40.4%)	130 (43.0%)	50 (16.6%)	180 (59.6%)	1.28 (0.85 to 1.91)	0.239
Lopinavir and ritonavir	62 (14.1%)	21 (33.9%)	32 (51.6%)	9 (14.5%)	41 (66.1%)	1.51 (0.86 to 2.66)	0.150
Other antiviral drugs	70 (15.9%)	19 (27.1%)	35 (50.0%)	16 (22.9%)	51 (72.9%)	2.21 (1.25 to 3.89)	0.006
Traditional Chinese Medicine/Chinese patent drug	368 (83.6%)	160 (43.5%)	157 (42.7%)	51 (13.9%)	208 (56.5%)	0.73 (0.44 to 1.24)	0.005
Intravenous nutrition	106 (24.1%)	12 (11.3%)	59 (55.7%)	35 (33.0%)	94 (88.7%)	8.52 (4.50 to 16.12)	<0.001
Oxygen therapy							
Oxygen inhalation	255 (46.3%)	101 (39.6%)	117 (45.9%)	37 (14.5%)	154 (60.4%)	1.33 (0.91 to 1.96)	0.143
Oxygen mask	89 (20.4%)	9 (10.1%)	58 (65.2%)	22 (24.7%)	80 (89.9%)	9.25 (4.50 to 19.02)	<0.0001
High-flow nasal cannula oxygen therapy	41 (9.4%)	4 (9.8%)	23 (56.1%)	14 (34.1%)	37 (90.2%)	7.83 (2.74 to 22.38)	<0.0001
Non-invasive mechanical ventilation	71 (16.2%)	9 (12.7%)	34 (47.9%)	28 (39.4%)	62 (87.3%)	6.42 (3.10 to 13.30)	<0.0001
Invasive mechanical ventilation	48 (11.0%)	6 (12.5%)	23 (47.9%)	19 (39.6%)	42 (87.5%)	6.00 (2.49 to 14.44)	<0.0001
ECMO	6 (1.4%)	0	3 (50.0%)	3 (50.0%)	6 (100.0%)	—	—
Renal replacement therapy	8 (1.8%)	1 (12.5%)	3 (37.5%)	4 (50.0%)	7 (87.5%)	5.30 (0.65 to 43.46)	0.120

Data are presented as median (IQR) or n (%).

p values comparing normal cumulative LB and cumulative LBAI were calculated by a univariate logistic regression model.

ALI, acute liver injury; OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; LB, liver biochemistry; LBA, liver biochemical abnormality; LBAI, liver biochemical abnormality or injury.

Supplementary Table 2 Cox regression analysis of the association between LBAI and in-hospital mortality in COVID-19 patients: all-in analysis and sensitivity analysis*

	Analyzed population	Crude HR (95% CI) [†]	p value	Adjusted HR (95% CI) [‡]	p value
On-admission ALT	All-in	1.34 (0.88 to 2.03)	0.18	0.88 (0.54 to 1.44)	0.620
	Sensitivity 1	1.31 (0.86 to 2.01)	0.21	0.81 (0.49 to 1.33)	0.400
	Sensitivity 2	1.40 (0.92 to 2.13)	0.12	0.89 (0.54 to 1.47)	0.657
On-admission AST	All-in	2.81 (1.87 to 4.21)	<0.0001	1.62 (1.00 to 2.62)	0.049
	Sensitivity 1	2.74 (1.82 to 4.12)	<0.0001	1.56 (0.96 to 2.53)	0.070
	Sensitivity 2	2.79 (1.86 to 4.19)	<0.0001	1.44 (0.90 to 2.33)	0.130
On-admission TBIL	All-in	3.98 (2.33 to 6.81)	<0.0001	2.14 (1.18 to 3.87)	0.012
	Sensitivity 1	3.74 (2.15 to 6.49)	<0.0001	2.04 (1.10 to 3.77)	0.023
	Sensitivity 2	3.72 (2.18 to 6.37)	<0.0001	1.92 (1.06 to 3.48)	0.031
Peak ALT	All-in	1.41 (0.94 to 2.11)	0.099	0.76 (0.46 to 1.24)	0.273
	Sensitivity 1	1.42 (0.94 to 2.15)	0.092	0.74 (0.45 to 1.22)	0.236
	Sensitivity 2	1.41 (0.94 to 2.12)	0.099	0.78 (0.47 to 1.29)	0.328
Peak AST	All-in	4.70 (2.78 to 7.94)	<0.0001	2.94 (1.47 to 5.88)	0.002
	Sensitivity 1	4.61 (2.73 to 7.79)	<0.0001	2.77 (1.38 to 5.54)	0.004
	Sensitivity 2	4.80 (2.84 to 8.11)	<0.0001	2.72 (1.35 to 5.46)	0.005
Peak TBIL	All-in	4.88 (3.28 to 7.25)	<0.0001	2.79 (1.76 to 4.45)	<0.001
	Sensitivity 1	4.92 (3.29 to 7.34)	<0.0001	2.73 (1.71 to 4.37)	<0.001
	Sensitivity 2	5.52 (3.71 to 8.22)	<0.0001	2.56 (1.60 to 4.09)	<0.001
On-admission LBAI					
Normal LB	All-in or Sensitivity	Ref	—	Ref	
LBA	All-in	2.92 (1.87 to 4.56)	<0.0001	1.78 (1.03 to 3.06)	0.038
	Sensitivity 1	2.89 (1.84 to 4.51)	<0.0001	1.74 (1.01 to 2.99)	0.046

|		Crude HR (95% CI)†	P value	Adjusted HR (95% CI)‡	P value
	Sensitivity 2	1.59 (0.94 to 2.71)	0.084	1.54 (0.89 to 2.65)	0.120
ALI	All-in	4.80 (2.40 to 9.63)	<0.0001	4.00 (1.68 to 9.50)	0.002
	Sensitivity 1	4.32 (2.10 to 8.88)	<0.0001	3.42 (1.38 to 8.45)	0.008
	Sensitivity 2	2.47 (1.16 to 5.24)	0.019	3.61 (1.55 to 8.42)	0.003
Cumulative LBAI					
Normal LB	All-in or Sensitivity	Ref	—	Ref	
LBA	All-in	3.14 (1.62 to 6.07)	0.0010	2.96 (1.18 to 7.44)	0.021
	Sensitivity 1	3.07 (1.59 to 5.96)	0.0010	2.78 (1.11 to 7.00)	0.029
	Sensitivity 2	3.47 (1.79 to 6.71)	<0.0001	2.85 (1.13 to 7.20)	0.027
ALI	All-in	8.41 (4.32 to 16.34)	<0.0001	4.88 (1.88 to 12.64)	0.001
	Sensitivity 1	8.03 (4.12 to 15.64)	<0.0001	4.45 (1.71 to 11.57)	0.002
	Sensitivity 2	8.78 (4.52 to 17.09)	<0.0001	4.47 (1.69 to 11.82)	0.003
Hepatoprotective drugs§	All-in	0.62 (0.41 to 0.96)	0.031	0.67 (0.41 to 1.08)	0.101
	Sensitivity 1	0.65 (0.42 to 1.00)	0.048	0.71 (0.43 to 1.15)	0.159
	Sensitivity 2	0.57 (0.37 to 0.88)	0.012	0.72 (0.44 to 1.17)	0.187

*Sensitivity analysis 1 refers to 428 patients excluding 12 cases with chronic liver disease; and sensitivity analysis 2 refers to 402 patients excluding 38 cases with censored outcomes, i.e. still in hospital at the end of follow-up.

†Crude HR was estimated by univariate Cox proportional hazard regression model.

‡Adjusted HR was estimated by multivariate Cox proportional hazard regression model adjusted for age, sex, comorbidities, in-hospital disease severity status, lymphocyte count, D-dimer, and serum ferritin.

§Subgroup analysis of patients with cumulative LBA.

COVID-19, coronavirus disease 2019; ALI, acute liver injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; CI, confidence interval; LB, liver biochemistry; LBA, liver biochemical abnormality; LBAI, liver biochemical abnormality or injury; TBIL, total bilirubin.
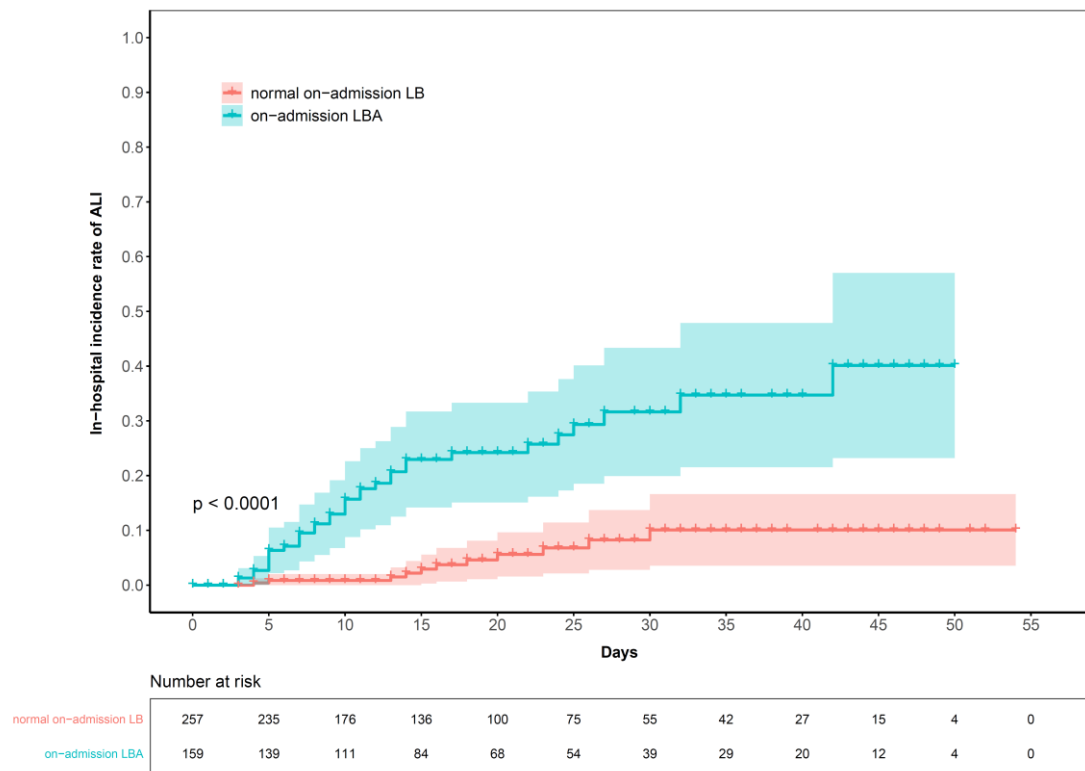
Supplementary Figure 1 In-hospital incidence rate of ALI of 416 COVID-19 patients without ALI on admission, stratified by on-admission LB. ALI, acute liver injury; COVID-19, coronavirus disease; LB, liver biochemistry; LBA, liver biochemical abnormality.
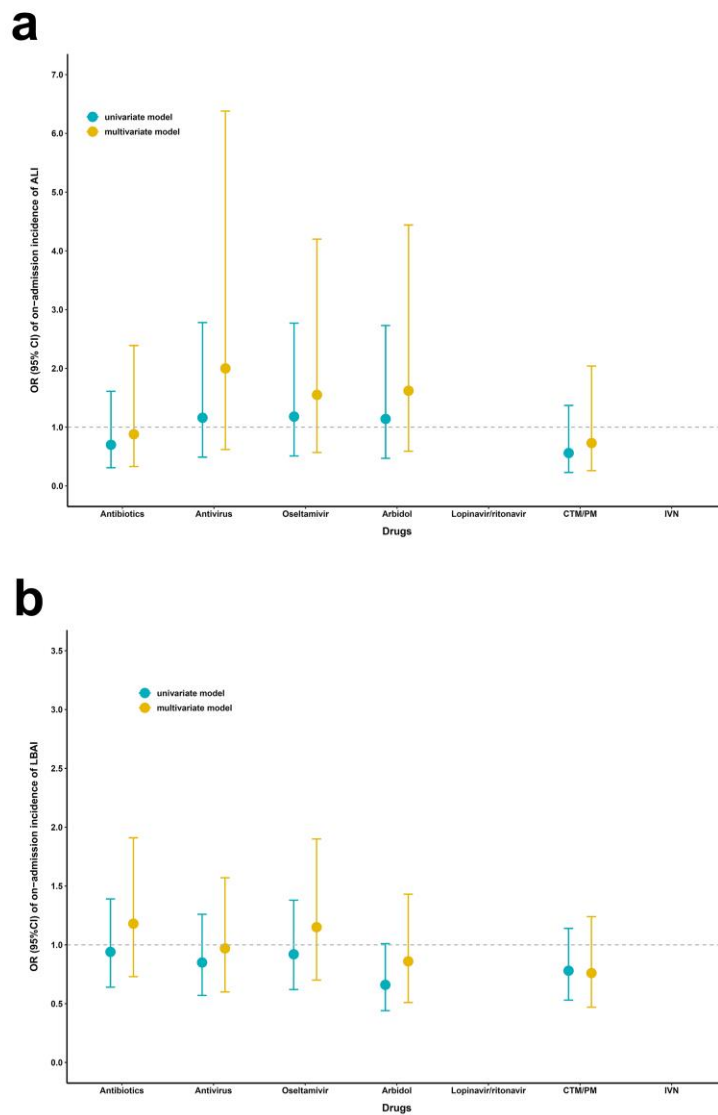
Supplementary Figure 2 Impact of drugs used before on-admission of hospital on the incidence of LBAI. (**a**) association between incidence of on-admission ALI and drugs used before admission; (**b**) association between on-admission incidence of LBAI and drugs used before admission. LB, liver biochemistry; ALI, acute liver injury; LBAI, liver biochemical abnormality or injury; Antivirals include oseltamivir, arbidol, lopinavir/ritonavir, and some other uncommonly used antiviral drugs.
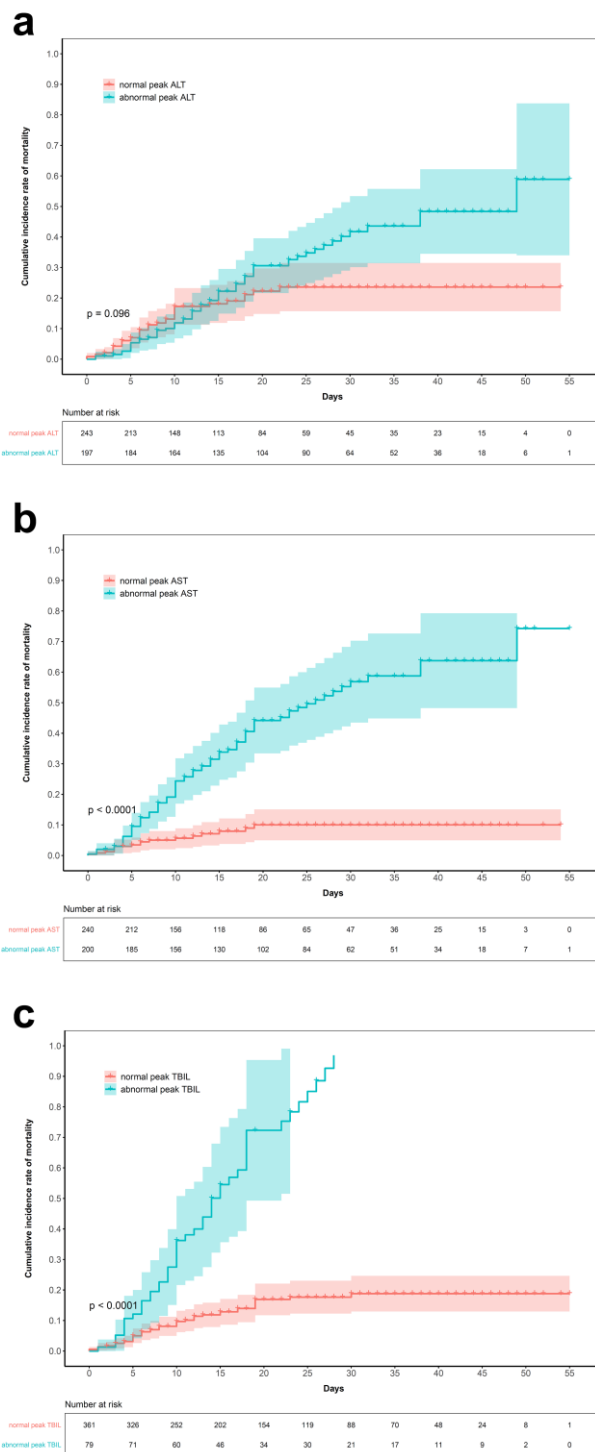
Supplementary Figure 3 Cumulative incidence of in-hospital mortality in COVID-19 patients stratified by peak LB markers. Shadows indicate the 95% confidence intervals of the corresponding estimates: (**a**) peak ALT. (**b**) peak AST. (**c**) peak TBIL. LB, liver biochemistry; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.
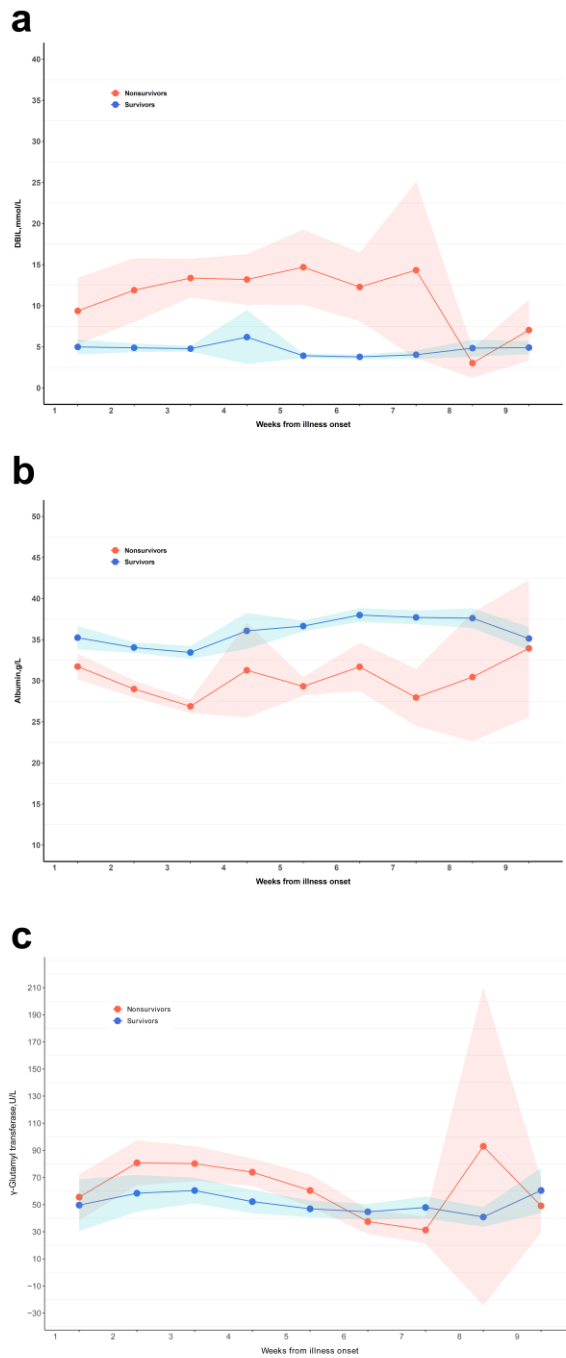
Supplementary Figure 4 Dynamic variations of other LB markers (DBIL, albumin and γ-Glutamyl transferase) with time from illness onset. Shadows indicate the 95% confidence intervals of the corresponding estimates: (**a**) DBIL. (**b**) albumin. (**c**) γ-Glutamyl transferase. LB, liver biochemistry; DBIL, direct bilirubin.