THE LANCET
Gastroenterology & Hepatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Weng J, Li Y, Li J, et al. Gastrointestinal sequelae 90 days after discharge for COVID-19. *Lancet Gastroenterol Hepatol* 2021; published online March 9. https://doi.org/10.1016/S2468-1253(21)00076-5.

Methods

Study design and patients

Between January 16 to March 7, 2020, 273 patients were admitted to 12 hospitals in Hubei (11 hospitals) and Guangdong (1 hospital) provinces, China, for suspected COVID-19 (Figure 1). These patients were admitted to our hospitals mainly because of respiratory symptoms such as fever, cough and dyspnea. Patients were treated and discharged according to the fifth edition of the Diagnosis and Treatment Guideline for COVID-19, National Health Commission of the People's Republic of China. Patients were discharged when the following criteria were met: no fever for 3 consecutive days, respiratory symptoms and chest imaging being improved, and viral nucleic acid test results were negative in two tests performed 24h apart. The follow-up visits at 14, 28 and 90 days after discharge were recommended. Patient was contacted by phone if the follow-up visit at 90 days after discharge was missed.

Aiming to study the consequences of COVID-19 after discharge, we excluded 56 patients for being negative for SARS-CoV-2 nucleic acid test, and 53 who died during hospitalization. We then excluded 23 patients that cannot be contacted after discharge, 9 who declined to participate in the study, 10 for living in a different city and 5 who are immobile. Thus our study included 117 viral nucleic acid test confirmed COVID-19 patients discharged from our hospitals.

This study was approved by the Institutional Review Boards of Sun Yat-sen University and the participating hospitals. Informed consent was waived for this retrospective chart review.

Data collection

Charts were reviewed for demographic data, clinical, laboratory, and radiological characteristics, treatments and outcomes. Demographic data included age, gender, BMI and co-morbidities including hypertension, diabetes, cardiovascular disease, gastrointestinal diseases, and malignancy. Clinical data recorded included vital signs such as temperature, heart rate, blood pressure and blood oxygen saturation level. In addition to fever, cough and dyspnea, other clinical characteristics recorded included myalgia/muscle fatigue/weakness, hemoptysis, cephalalgia, sputum production, diarrhea (three or more loose or liquid stools per day), bloody stool (stool positive for occult blood test or white blood cell test), and blood oxygen saturation. The hospital course was reviewed for severity of disease. According to the national Diagnosis and Treatment Guideline for COVID-19, severe COVID-19 is defined as COVID-19 patient with any one of the following criteria: (1) dyspnea with respiratory rate >30 breaths/min; (2) resting finger blood oxygen saturation level <=93%; and (3) PaO_2/FiO_2 ratio <=300 mmHg, while critical illness is defined as COVID-19 patient with any one of the following criteria: (1) respiratory failure

requiring mechanical ventilation; (2) presentation of shock; (3) multi-organ failure requiring ICU admission.

Gastrointestinal sequelae were defined as gastrointestinal symptoms that were presented after discharge but were not presented within one month before the onset of COVID-19.

Laboratory data on admission, during hospitalization, before discharge and on return visits (1-month and 3-month) were collected. Laboratory data included complete blood count with differential (lymphocyte, monocyte, neutrophil, platelet, and white blood cell), markers for coagulation function (activated partial thromboplastin time (APTT), d-dimer and fibrinogen), infection-related markers (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR) and procalcitonin), and other blood biochemicals (alanine aminotransferase (ALT), aspartate transaminase (AST), blood urea nitrogen (BUN), creatinine, creatine kinase (CK), lactate dehydrogenase (LDH), SOFA score and total bilirubin).

Use of supplemental oxygen and the intensive care unit (ICU) were recorded. Patients were routinely given antibiotics, usually Moxifloxacin, and antivirus drugs, usually Lopinavir and Ritonavir.

Statistical analysis

For numerical data, significance of the differences between two study groups were tested by Student t test or Mann-Whitney test, when appropriate. Chi-Square test and Fisher's exact tests were performed for comparisons of categorical data. Student t tests, Mann-Whitney U tests, Chi-Square tests and Fisher's exact tests were performed with SPSS (Statistical Package for the Social Sciences) version 24.0 software (SPSS Inc). Univariable and multivariable logistic regressions were performed to calculate odds ratio (OR) for gastrointestinal sequelae and the 95% confidence intervals (CIs) in R (version 3.6.1). Continuous variables, such as laboratory data, were transformed to categorical variables based on reference values. All statistical tests were two sided, with p values of <0.05 considered to be statistically significant.

Weng et al., Figure 1

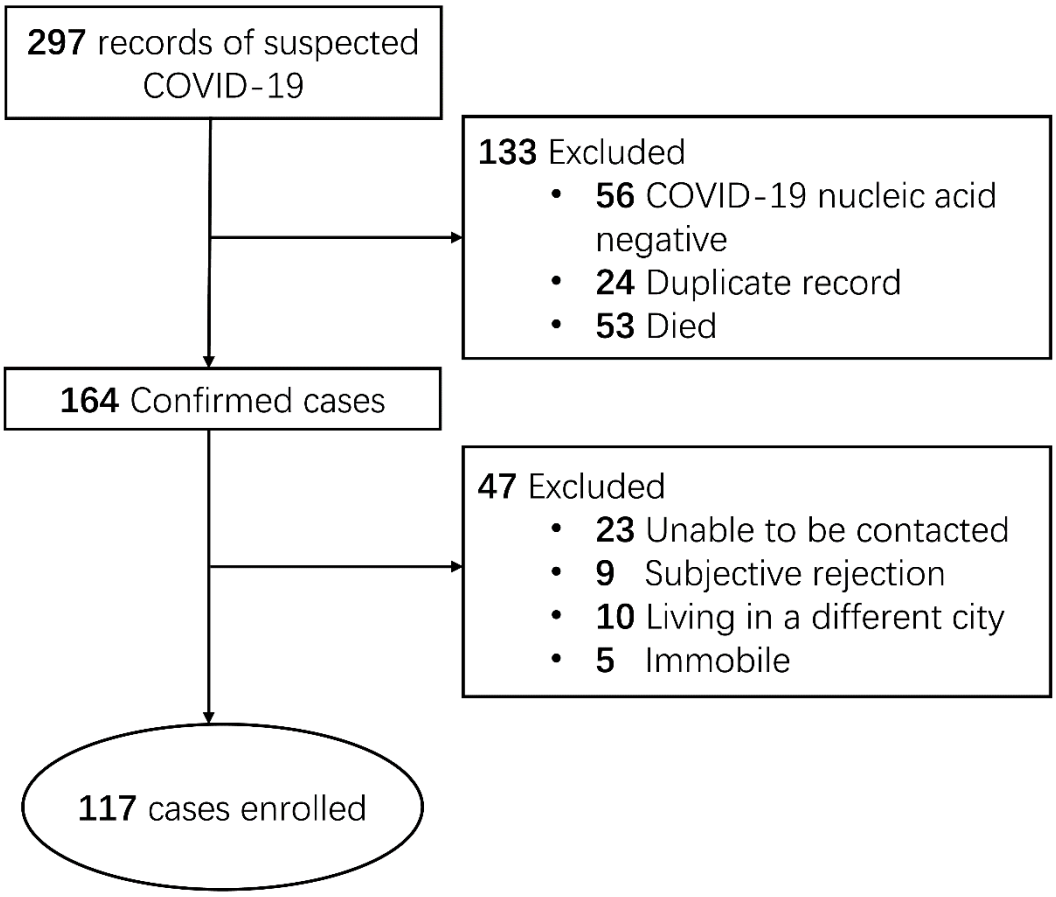

Figure 1, Study flow diagram. Medical records of 117 COVID-19 patients included in the study were accessed from Jingzhou Central Hospital, Jingzhou No.1 People's Hospital, Jingzhou Chest Hospital, Jingzhou Hospital of Traditional Chinese Medicine, Jianli Hospital of Traditional Chinese Medicine, Jianli People's Hospital, Gongan People's Hospital, Shishou Hospital of Traditional Chinese Medicine, Honghu Hospital of Traditional Chinese Medicine, Honghu People's Hospital, Honghu Hospital for the Control of Schistosomiasis, and Dongguan People's Hospital.

Table 1: Demographics and clinical characteristics of COVID-19 patients on admission

Clinical characteristics	Total (N=117)	With gastrointestinal sequelae (N=52)	Without gastrointestinal sequelae (N=65)	P value
Age (⩾60years)	53/117 (45.3%)	23/52 (44.2%)	30/65 (46.2%)	0.492
Sex				0.301
Men	65/117 (55.6%)	27/52 (51.9%)	38/65 (58.5%)	
Women	52/117 (44.4%)	25/52 (48.1%)	27/65 (41.5%)	
BMI	21.78 (20.22-23.48)	21.54 (19.99-23.53)	21.97 (20.35-23.53)	0.422
Comorbidities				
Hypertension	28/117 (23.9%)	8/52 (15.4%)	20/65 (30.8%)	0.053
Diabetes	10/117 (8.5%)	4/52 (7.7%)	6/65 (9.2%)	0.767
Cardiovascular diseases	6/117 (5.1%)	2/52 (3.8%)	4/65 (6.2%)	0.574
Gastrointestinal diseases	2/117 (1.7%)	1/52 (1.9%)	1/65 (1.5%)	0.873
Malignant tumour	2/117 (1.7%)	0/52 (0%)	2/65 (3.1%)	0.202
Length of hospital stay, days	19.00 (16.00-23.00)	19.00 (15.25-21.00)	18.00 (16.00-24.50)	0.664
Symptom				
Any symptom	107/117 (91.5%)	47/52 (90.4%)	60/65 (92.3%)	0.481
Fever (≥37.3℃)	79/114 (69.3%)	37/50 (74.0%)	42/64 (65.6%)	0.225
Cough	77/117 (65.8%)	30/52 (57.7%)	47/65 (72.3%)	0.072
Dyspnea	20/117 (17.1%)	12/52 (23.1%)	8/65 (12.3%)	0.099
Myalgia	16/117 (13.7%)	9/52 (17.3%)	7/65 (10.8%)	0.200
Cephalalgia	14/117 (12.0%)	6/52 (11.5%)	8/65 (12.3%)	0.566
Sputum production	41/117 (35.0%)	16/52 (30.8%)	25/65 (38.5%)	0.251
Severely ill	33/117 (28.2%)	9/52 (17.3%)	24/65 (36.9%)	0.021
Decreased blood oxygen saturation*	24/111 (21.6%)	15/51 (29.4%)	9/60 (15.0%)	0.054
Treatment received during hospital stay				
ICU admission	28/117 (23.9%)	9/52 (17.3%)	19/65 (29.2%)	0.120
Admitted to hospital, not requiring supplemental oxygen	15/117 (12.8%)	11/52 (21.2%)	4/65 (6.2%)	**0.016**
Admitted to hospital, requiring supplemental oxygen	102/117 (87.2%)	41/52 (78.8%)	61/65 (93.8%)	**0.016**
Admitted to hospital, requiring HFNC or non-IMV or both	20/117 (17.1%)	9/52 (17.3%)	11/65 (16.9%)	0.574
PPI	40/117 (34.2%)	31/52 (59.6%)	9/65 (13.8%)	**0.000**
Corticosteroids	29/117 (24.8%)	18/52 (34.6%)	11/65 (16.9%)	**0.024**
Thymosin alpha	2/117 (1.7%)	2/52 (3.8%)	0/65 (0%)	0.195
Arbidol	55/117 (47.0%)	20/52 (38.5%)	35/65 (53.8%)	0.070
Lopinavir–ritonavir	35/117 (29.9%)	17/52 (32.7%)	18/65 (27.7%)	0.350
Interferon	31/117 (26.5%)	11/52 (21.2%)	20/65 (30.8%)	0.169

Antibiotics	88/117 (75.2%)	43/52 (82.7%)	45/65 (69.2%)	0.071
Length of antibiotics, days	7.00 (5.00-9.00)	7.00 (5.00-8.00)	7.00 (5.00-9.00)	0.513
Enteral nutrition	24/117 (20.5%)	5/52 (9.6%)	19/65 (29.2%)	**0.007**
Parenteral nutrition	62/116 (53.4%)	24/51 (47.1%)	38/65 (58.5%)	0.150
Time from discharge to follow-up, days	89.51 ± 8.52	91.00 ± 7.90	88.21 ± 8.89	0.095

Data are mean ± standard deviation, median (interquartile range, IQR), or n/N (%). P values comparing groups with and without gastrointestinal sequelae are from Student t test, Mann-Whitney U test, Chi-Square test or Fisher's exact test, as appropriate. The differing denominators used indicate missing data. HFNC=high-flow nasal cannula for oxygen therapy. NIV=non-invasive ventilation. IMV=invasive mechanical ventilation. NA=not applicable. ECMO=extracorporeal membrane oxygenation. ICU=intensive care unit. WBC=White blood cell count. ESR=Erythrocyte sedimentation rate. CRP=C-reactive protein. COVID-19=Coronavirus Disease 2019. *Defined as finger blood oxygen saturation <95%.

Table 2: Logistic univariate and multivariate regression analyses on the associations between gastrointestinal sequelae and the potential risk factors

	Univariable OR (95%CI)	p value	Multivariable OR (95%CI)	p value
Age⩾60 years	0.925 (0.445-1.926)	0.836	1.125 (0.434-2.913)	0.809
Male sex	0.817 (0.393-1.701)	0.589	0.538 (0.205-1.411)	0.208
Decreased blood oxygen saturation	2.361 (0.932-5.984)	0.070	**5.429 (1.222-24.116)**	**0.026**
PPI	9.185 (3.751-22.495)	**0.000**	**5.623 (2.054-15.398)**	**0.001**
Corticosteroids	2.599 (1.095-6.167)	**0.030**	2.031 (0.621-6.636)	0.241
Enteral nutrition	0.258 (0.089-0.748)	**0.013**	**0.272 (0.076-0.968)**	**0.044**
Requiring supplemental oxygen	1.108 (0.374-3.287)	0.853		
Severely ill	0.358 (0.149-0.860)	**0.022**	0.274 (0.075-1.003)	0.051

OR=odds ratio. CI=confidence interval. Multivariable logistic regression were adjusted for age, sex, decreased blood oxygen saturation, treatments with PPI, corticosteroids, and enteral nutrition, and severe illness.

Table 3: Laboratory findings of COVID-19 patients with and without gastrointestinal sequelae on admission

	Reference values	Total (n=117)	With gastrointestinal sequelae (n=52)	Without gastrointestinal sequelae (n=65)	p value
White blood cell count ($X10^9$/L)	4.00-10.00	5.12 (4.16-7.17)	6.02 (4.62-8.77)	4.56 (3.81-6.47)	**0.001**
Lymphocyte count ($X10^9$/L)	1.50-4.00	1.35 (0.98-1.94)	1.67 (0.96-2.53)	1.33 (0.99-1.68)	0.060
Neutrophil count ($X10^9$/L)	2.00-7.00	3.20 (2.50-4.44)	3.50 (2.70-6.34)	2.20 (2.27-3.90)	**0.002**
NLR	1.33-4.67	2.10 (1.51-3.46)	2.33 (1.45-4.11)	1.96 (1.51-3.34)	0.291
Monocyte count ($X10^9$/L)	0.12-1.00	0.33 (0.19-0.51)	0.32 (0.17-0.61)	0.34 (0.24-0.50)	0.763
Platelet count ($X10^9$/L)	99.00-303.00	188.00 (157.00-243.00)	197.00 (156.50-243.50)	187.00 (154.50-243.00)	0.532
APTT(s)	21.00-37.00	29.32 ± 5.72	28.95 ± 5.61	29.62 ± 5.84	0.836
fibrinogen (g/L)	2.00-4.00	3.34 (2.60-4.16)	3.32（ 2.60-3.89)	3.34 (2.64-3.93)	0.717
D-dimer (μg/mL)	0.00-0.55	0.37 (0.29-0.57)	0.37 (0.26-0.57)	0.38 (0.31-0.61)	0.533
Procalcitonin (ng/mL)	0.00-0.50	0.14 (0.06-0.33)	0.23 (0.09-0.37)	0.12 (0.05-0.31)	**0.035**
CRP(mg/L)	0.00-10.00	16.23 (7.54-45.70)	29.61 (8.55-69.85)	12.43 (6.80-38.22)	**0.018**
ESR (mm/1h)	0.00-30.00	25.00 (12.25-45.00)	36.00 (14.00-49.25)	22.50 (12.00-30.25)	0.056
Creatine kinase (U/L)	25.00-200.00	92.5 (62.30-168.75)	107.05 (66.25-173.00)	80.50 (56.50-168.75)	0.293
Lactate dehydrogenase (U/L)	91.00-230.00	200.00 (167.00-257.00)	199.00 (161.00-263.50)	206.00 (169.50-250.80)	1.000
Creatinine (μmol/L)	44.00-112.00	74.63 ± 20.92	71.71 ± 20.51	76.94 ± 21.10	0.790
BUN (mmol/L)	2.50-7.10	4.99 (3.48-6.13)	4.98 (3.47-6.40)	5.00 (3.48-5.95)	0.958
AST (U/L)	0.00-40.00	34.00 (23.00-45.00)	36.00 (25.15-45.00)	31.00 (21.25-44.50)	0.176
ALT (U/L)	0.00-50.00	34.00 (23.00-55.00)	35.95 (26.00-56.93)	34.95 (19.88-50.50)	0.224
Total bilirubin (μmol/L)	3.00-21.00	12.40 (8.55-18.30)	9.99 (7.65-17.78)	14.75 (8.8-18.85)	0.191

Data are median (IQR) or mean ± standard deviation. p values comparing groups with gastrointestinal sequelae and without gastrointestinal sequelae are from Mann-Whitney *U* test or Student's *t* test, as appropriate. NLR=neutrophil-to-lymphocyte ratio. APTT=activated partial thromboplastin time. ESR=Erythrocyte sedimentation rate. CRP=C-reactive protein. BUN= blood urea nitrogen. AST=aspartate transaminase. ALT=alanine aminotransferase.

Table 4: Laboratory findings of COVID-19 patients with and without gastrointestinal sequelae at 90 days after discharge

	Reference values	Total (n=106)	With gastrointestinal sequelae (n=50)	Without gastrointestinal sequelae (n=56)	p value
White blood cell count ($X10^9$/L)	4.00-10.00	5.78 (4.62-7.06)	5.65 (4.62-6.82)	5.83 (4.61-7.67)	0.653
Lymphocyte count ($X10^9$/L)	1.50-4.00	1.61 (1.19-2.25)	1.54 (1.12-2.23)	1.80 (1.29-2.28)	0.281
Neutrophil count ($X10^9$/L)	2.00-7.00	3.39 (2.72-4.64)	3.28 (2.62-4.64)	3.51 (2.89-4.71)	0.617
NLR	1.33-4.67	1.90 (1.45-3.28)	2.03 (1.33-3.59)	1.80 (1.47-2.72)	0.690
Monocyte count ($X10^9$/L)	0.12-1.00	0.45 (0.32-0.68)	0.47 (0.29-0.66)	0.44 (0.32-0.69)	0.839
Platelet count ($X10^9$/L)	99.00-303.00	184.00 (158.50-236.50)	195.00 (161.00-248.50)	184.00 (157.50-220.00)	0.343
Creatinine (µmol/L)	44.00-112.00	70.27 ± 20.65	71.50 ± 21.75	69.03 ± 19.89	0.705
AST (U/L)	0.00-40.00	28.00 (21.00-37.00)	30.60 (24.50-37.50)	27.00 (21.00-37.00)	0.201
ALT (U/L)	0.00-50.00	29.00 (22.75-39.00)	32.00 (26.00-41.00)	26.50 (18.25-37.00)	0.020
Total bilirubin (µmol/L)	3.00-21.00	12.51 ± 4.92	13.44 ± 4.58	11.68 ± 5.10	0.065

Data are median (IQR) or mean ± standard deviation. p values comparing groups with gastrointestinal sequelae and without gastrointestinal sequelae are from Mann-Whitney *U* test or Student's *t* test, as appropriate. NLR=neutrophil-to-lymphocyte ratio. APTT=activated partial thromboplastin time. ESR=Erythrocyte sedimentation rate. CRP=C-reactive protein. BUN= blood urea nitrogen. AST=aspartate transaminase. ALT=alanine aminotransferase.