Digestive Involvement in SARS-CoV-2 Infection: A Retrospective Multi-center Study

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Research

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Abstract

Background

Coronavirus disease 2019 (COVID-19) is an emerged infection raised wide concerns for the pneumonia and respiratory manifestations. Also, digestive complications are frequently observed in COVID-19 patients but the significance remains undetermined.

Methods

A retrospective analysis of alimentary symptoms, liver dysfunctions and other clinical parameters of 514 hospitalized COVID-19 patients (282 mild, 162 severe and 70 critical cases) admitted to the 3 designated medical units of Wuhan Union Hospital from Jan 20 to Feb 29, 2020 was performed.

Results

1) A series of alimentary symptoms, including poor appetite(50.2%), diarrhea(25.5%), nausea(16.3%), vomit(11.9%) and abdominal pain(3.3%), presented in COVID-19 patients.

2) Diarrhea was common gastrointestinal symptom with higher morbidity in the severe and critical patients (32.1% and 27.1% respectively), and 13.2% patients developed diarrhea in the first 3 days after onset of symptoms. Those with diarrhea were reported more apparent systemic inflammation and liver injury in severe and critical cases compared with patients without diarrhea.

3) Notably, 31 patients (6.03%) presented with diarrhea in the absence of respiratory symptoms. These patients were observed less systemic inflammatory activity relative to diarrhea patients combined with respiratory symptoms.

4) Also, liver injury was high incident in COVID-19 patients with increased alanine aminotransferase (43.3%), aspartate transaminase (36.7%) and decreased albumin (80.9%), but less increased total bilirubin (10.9%) and direct bilirubin(14.2%), which were more serious in the severe to critical patients.

Conclusions

Our data favored in the process of novel SARS-CoV-2 infection. There may be a “gut-type” in the clinical prevention and management that differ from the “lung-type” in COVID-19 sufferers.

Introduction

Coronavirus disease 2019（COVID-19）is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as 2019 novel coronavirus (2019-nCoV), which was firstly identified in Wuhan, China, last December 2019, and has rapidly outbreak worldwide[1-4]. It recently has been declared a public health emergency of international concern by World Health Organization (WHO). As of March 20, 2020, COVID-19 has affected more than 200,000 individuals and caused over 8,500 deaths globally[5].

It is well established that most patients with COVID-19 have fever along with respiratory symptoms, such as dry cough and dyspnea[1, 6]. However, there is increasing evidence that, in addition to typical respiratory symptom, COVID-19 can also present with gastrointestinal symptoms (especially for diarrhea) and liver injury[7, 8]. Moreover, it was also reported that some patients present initially with gastrointestinal symptoms[9]. This may lead to misdiagnosis in the clinic, and the digestive involvement of COVID-19 should be recognized and valued.

SARS-CoV-2 is an accepted respiratory transmitting virus that spread via droplets [10], also through close contact with mucous membranes in the eyes, mouth or nose [11, 12]. Apart from the oropharyngeal swab, nasopharyngeal swab and sputum, the viral nucleic acid could also be detected in saliva and feces[13, 14]. Moreover, in clinical practice, we found stool samples test from COVID-19 were positive while respiratory samples are negative. Importantly, angiotensin converting enzyme 2 (ACE2), identified as the cell entry receptor of SARS-CoV-2[15, 16], were most remarkable expression on the surface of small intestinal epithelial cell[15, 17]. In summary, SARS-CoV-2 may be present in the gut, leading to the alimentary damage and symptoms, and possible fecal-oral transmission.

In this retrospective study, we describe the clinical features of hospitalized COVID-19 patients with variable severity, that is the mild, severe and critical patients. We focused on the alimentary symptoms and liver injury in COVID-19 patients and attempted to find if there is any significant difference in the patients with or without digestive manifestations, to provide evidence for the digestive involvement in the clinical prevention and management of SARS-CoV-2 infection.

Methods

Study Design and Participants

The protocol of this study was seen in Figure 1. The clinical records of 521 consecutive patients fulfilled with the diagnostic criteria of COVID-19 according to World Health Organization interim guidance [18], who admitted to the 3 designated COVID-19 care medical institutions affiliated to Wuhan Union Hospital of Tongji Medical College from Jan 20 to Feb 29, 2020 were enrolled. All patients were given verbal informed consent. Seven cases were excluded for incomplete data, and 514 laboratory-confirmed COVID-19 cases were used for analysis. Patients were divided into mild (282 cases), severe (162 cases) and critical (70 cases) subgroups based on the clinical classification of COVID-19[19]. The clinical outcomes were monitored up to March 8, 2020, the final date of follow-up. This study was approved by the Medical Ethical Review Committee, Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, China ([2020] No.0033).

Study Definitions

The confirmed case of COVID-19 is defined as positive SARS-CoV-2 nucleic acid in oropharyngeal or nasopharyngeal swab specimens via real-time fluorescence reverse transcription-polymerase chain reaction (RT-PCR). Only laboratory-confirmed cases were included in the analysis[18, 19]. The mild cases

refer to mild patient with fever, respiratory and/or other symptoms, and typical imaging findings of viral pneumonia. The severe cases had to meet one or more of the following conditions: 1) with shortness breath and respiratory frequency ≥30 per minute; 2) blood oxygen saturation ≤93% in resting condition; 3) arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ≤300 mmHg. The critical patients should present with 1) respiratory failure that need mechanical ventilation, and/or 2) shock, and/or 3) combined with other organ failure and need intensive care unit (ICU) treatment. All definitions are consistent with the “Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia” (trial version 6) released by Chinese National Health Commission and the World Health Organization interim guidance for COVID-19[19].

Data collection

The demographic data, clinical charts including epidemiological history, past medical history, clinical symptoms and signs, medical and nursing records, laboratory findings, chest CT scans and viral nucleic acid test for all COVID-19 patients were extracted from electronic medical records. Particularly, symptoms of fever, cough, expectoration, fatigue, shortness of breath, chest tightness, muscle soreness, poor appetite, nausea, vomit, diarrhea and abdominal pain were recorded in detail. Main laboratory parameters were extracted, including routine blood tests (white blood cell [WBC], neutrophil and lymphocyte), inflammatory markers (procalcitonin, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], ferritin and fibrinogen), liver injury marker (total and direct bilirubin, alanine aminotransferase [ALT], aspartate transaminase [AST], lactate dehydrogenase [LDH], alkaline phosphatase [ALP], γ-glutamyl transferase [GGT], Pre-albumin and Albumin), kidney injury marker (blood urea nitrogen [BUN], creatinine, urine protein and occult blood), and myocardial injury marker (high sensitive troponin I [hsTNI]). The treatment (ie, antiviral, antibiotic, corticosteroid, immunomodulation and respiratory support) and outcomes data were further obtained. The collected data were reviewed and checked by 4 trained researchers and attending clinicians independently.

Statistical Analysis

Categorical variables were described as number (%) and compared with χ^2 test, or Fisher’s exact test when the data were limited. Continuous data were expressed as median (IQR) and compared via the Kruskal-Wallis test followed by a Dunn’s post-test. A 2- sided α 0.05 was considered statistically significant. All statistical analyses were performed using the R software, version 3.5.1 (R Foundation for Statistical Computing). The statistical graphs were created via the GraphPad Prism package, version 8 (GraphPad Software, LLC).

Results

Baseline Characteristics

The demographic and clinical characteristics were shown in Table 1. A total of 514 hospitalized patients with confirmed SARS-CoV-2 infection including 282 mild, 162 severe and 70 critical cases were included

in the present analysis. The media age was 54 years, ranged from 23 to 96 years, and older in the severe and critical suffers. Totally, 271 (53.1%) patients were male, and the proportion of male was much higher than female in the critical ones (70.0%). The common symptoms were fever (87.6%), cough (70.2%), fatigue (58.4%), chest tightness (52.0%), shortness of breath (44.2%), expectoration (29.8%), muscle soreness (19.8%) and pharyngodynia (2.9%). Compared with mild patients, more serious fever (92.6% and 90.0% respectively) with higher maximal temperature, chest tightness and shortness of breath were observed in the severe and critical patients. Hypertension (43.2%), diabetes (19.3%) and cardiovascular disease (12.7%) were the most common comorbidity. Especially, hypertension was associated with disease severity that higher in severe (60.5%) and critical (55.7%) patients. The severe to critical patients exhibited more serious infection and inflammation with higher white blood cell and neutrophil, declined lymphocyte, enhanced levels of CRP, ESR, procalcitonin and ferritin (all P<0.001).

Table 1 Baseline Characteristics of COVID-19 patients.

	Total (N=514)	Mild (N=282)	Severe (N=162)	Critical (N=70)	P
Age (years)	54 (48-68)	50 (45-64)	65 (56-72)	64 (57-72)	<0.001
Gender (male/female)	271/243	135/147	87/75	49/21	0.004
Fever	450 (87.6%)	237 (84.0%)	150 (92.6%)	63 (90.0%)	0.025
Highest temperature, °C	38.5 (37.9-39.0)	38.5 (37.8-39.0)	38.5 (38.0-39.0)	38.8 (38.2-39.0)	0.020
Cough	361 (70.2%)	195 (69.2%)	122 (75.3%)	44 (62.9%)	0.137
Expectoration	153 (29.8%)	81 (28.7%)	52 (32.1%)	20 (28.6%)	0.735
Fatigue	300 (58.4%)	160 (56.7%)	93 (57.4%)	47 (67.1%)	0.274
Shortness of breath	227 (44.2%)	87 (30.9%)	92 (56.8%)	48 (68.6%)	<0.001
Chest tightness	267 (52.0%)	130 (46.1%)	87 (53.7%)	50 (71.4%)	<0.001
Pharyngodynia	15 (2.9%)	11 (3.9%)	2 (1.2%)	2 (2.9%)	0.275
Muscle soreness	102 (19.8%)	63 (22.3%)	29 (17.9%)	10 (14.3%)	0.241
Presenting Comorbidity					
Hypertension	222 (43.2%)	85 (30.1%)	98 (60.5%)	39 (55.7%)	<0.001
Diabetes	99 (19.3%)	45 (16.0%)	40 (24.7%)	14 (20.0%)	0.079
Cardiovascular disease	65 (12.7%)	32 (11.4%)	21 (13.0%)	12 (17.1%)	0.422
Chronic obstructive pulmonary disease	21 (4.1%)	6 (2.1%)	11 (6.8%)	4 (5.7%)	0.044
Bronchial asthma	10 (2.0%)	7 (2.5%)	2 (1.2%)	1 (1.4%)	0.621
Cerebralvascular disease	9 (1.8%)	9 (3.2%)	7 (4.3%)	5 (7.1%)	0.322
Chronic liver disease	8 (1.6%)	2 (0.7%)	4 (2.5%)	2 (2.9%)	0.226
Chronic kidney disease	21 (4.1%)	2 (0.7%)	5 (3.1%)	2 (2.9%)	0.138
Malignancy	28 (5.5%)	13 (4.6%)	12 (7.4%)	3 (4.3%)	0.412
Infection and Inflammation					
White blood cell ($x10^9$/L)	5.65 (4.38-7.60)	5.08 (4.04-6.64)	6.12 (4.66-8.34)	9.74 (7.19-12.27)	<0.001
Neutrophil ($x10^9$/L)	3.98 (2.97-6.32)	3.46 (2.62-4.38)	4.82 (3.48-6.73)	8.53 (6.30-11.41)	<0.001
Lymphocyte ($x10^9$/L)	0.93 (0.68-1.27)	1.08 (0.82-1.47)	0.77 (0.59-1.04)	0.54 (0.44-0.80)	<0.001
Procalcitonin (ng/mL)	0.09 (0.05-0.16)	0.06 (0.04-0.09)	0.12 (0.07-0.20)	0.33 (0.17-0.89)	<0.001
C-reactive protein (mg/L)	34.82 (11.10-71.97)	16.55 (4.00-38.99)	52.82 (29.27-77.53)	114.60 (74.27-138.80)	<0.001
Erythrocyte sedimentation rate (mm/h)	46 (25-69)	34 (19-53)	61 (44-80)	71 (44-82)	<0.001
Ferritin (ng/mL)	332.1 (127.1-768.9)	160.2 (101.7-300.2)	620.1 (391.0-862.8)	1768.2 (1215.3-2000.0)	<0.001
Fibrinogen (g/L)	4.44 (3.58-5.07)	4.14 (3.35-4.95)	4.73 (4.04-5.19)	4.58 (2.48-5.52)	<0.001

Note: Continuous variables are presented as median (25th-75th percentiles), and categorical variables are presented as count (percentage).

Alimentary symptoms and liver function injury

A series of alimentary symptoms including poor appetite (50.2%), diarrhea (25.5%), nausea (16.3%), vomit (11.9%) and abdominal pain (3.3%) presented in COVID-19 patients (Table 2). Diarrhea was quite common gastrointestinal symptom with higher morbidity in the severe and critical patients (32.1% and 27.1% respectively) than the mild patients (21.3%). The diarrhea was mainly watery in nature without mucus or blood, and abdominal pain was rarely observed. The severity of diarrhea varied among patients, most patients had a few loose or watery stools but some patients had up to 20 bowel movements per day. About 13.2% patients developed diarrhea in the first 3 days after the onset of symptoms, and 63.2% diarrhea was occurred in the previous 10 days (Figure S1). There were 31 patients (6.03%) presented with diarrhea in the absence of respiratory symptoms, including 23 mild cases and 8 severe cases (Figure 2). Moreover, 9 patients (1.75%) had only diarrhea without fever and respiratory symptoms.

Table 2 Digestive system involvements in COVID-19 patients include the alimentary symptoms and liver function injury.

	Total (N=514)	Mild (N=282)	Severe (N=162)	Critical (N=70)	P
Alimentary symptoms					
Poor appetite	258 (50.2%)	124 (44.0%)	92 (56.8%)	42 (60.0%)	0.007
Nausea	84 (16.3%)	50 (17.7%)	27 (16.7%)	7 (10.0%)	0.291
Vomit	61 (11.9%)	33 (11.7%)	23 (14.2%)	5 (7.1%)	0.310
Diarrhea	131 (25.5%)	60 (21.3%)	52 (32.1%)	19 (27.1%)	0.040
Abdominal pain	17 (3.3%)	11 (3.9%)	5 (3.1%)	1 (1.4%)	0.243
Liver function injury					
Total bilirubin (μmol/L)	10.8 (8.1-14.3)	10.2 (7.6-12.4)	11.5 (8.4-15.3)	14.9 (8.7-23.0)	<0.001
≤20.0μmol/L	458 (89.1%)	273 (96.8%)	140 (86.4%)	45 (64.3%)	<0.001
20.0~34.2μmol/L	43 (8.4%)	9 (3.2%)	17 (10.5%)	17 (24.3%)	
>34.2μmol/L	13 (2.5%)	0 (0.0%)	5 (3.1%)	8 (11.4%)	
Direct bilirubin (μmol/L)	3.6 (2.6-4.9)	3.1 (2.4-4.0)	3.9 (3.0-5.2)	6.2 (4.0-10.8)	<0.001
≤6.8μmol/L	441 (85.8%)	269 (95.4%)	134 (82.7%)	38 (54.3%)	<0.001
6.8~13.6μmol/L	61 (11.9%)	13 (4.6%)	23 (14.2%)	25 (35.7%)	
>13.6μmol/L	12 (2.3%)	0 (0.0%)	5 (3.1%)	7 (10.0%)	
Alanine aminotransferase (U/L)	34 (22-55)	28 (19-46)	41 (26-60)	87 (44-111)	<0.001
≤40U/L	290 (56.6%)	185 (65.8%)	81 (50.0%)	24 (34.8%)	<0.001
40~80 U/L	163 (31.8%)	82 (29.2%)	59 (36.4%)	22 (31.9%)	
≥80 U/L	59 (11.5%)	14 (5.0%)	22 (13.6%)	23 (33.3%)	
Aspartate transaminase (U/L)	33 (23-47)	27 (20-39)	38 (26-55)	67 (44-82)	<0.001
≤40U/L	324 (63.3%)	222 (79.0%)	88 (54.3%)	14 (20.3%)	<0.001
40~80 U/L	150 (29.3%)	55 (19.6%)	59 (36.4%)	36 (52.2%)	
≥80 U/L	38 (7.4%)	4 (1.4%)	15 (9.3%)	19 (27.5%)	
Lactate dehydrogenase (U/L)	277 (211-371)	229 (192-295)	314 (251-385)	561 (396-680)	<0.001
≤245U/L	204 (39.7%)	167 (59.4%)	37 (22.7%)	0 (0.0%)	<0.001
>245U/L	310 (60.3%)	115 (40.6%)	125 (77.3%)	70 (100.0%)	
Alkaline phosphatase (U/L)	54 (43-71)	52 (43-66)	53 (43-67)	78 (62-122)	<0.001
≤150U/L	496 (96.5%)	280 (99.3%)	156 (96.3%)	60 (85.7%)	<0.001
>150U/L	18 (3.5%)	2 (0.7%)	6 (3.7%)	10 (14.3%)	
γ-Glutamyl transferase (U/L)	31 (20-56)	27 (17-47)	33 (23-67)	60 (28-116)	<0.001
≤60U/L	396 (77.0%)	246 (87.2%)	115 (71.2%)	35 (50.0%)	<0.001
60~120 U/L	67 (13.0%)	22 (7.8%)	28 (17.2%)	17 (24.3%)	
≥120 U/L	51 (9.9%)	14 (5.0%)	19 (11.7%)	18 (25.7%)	
Pre-albumin (g/L)	129.8 (90.4-186.5)	149.7 (117.5-207.3)	111.6 (80.5-156.2)	84.5 (56.2-109.9)	<0.001
Albumin (g/L)	30.1 (26.8-33.9)	32.1 (28.5-35.3)	28.8 (25.9-31.6)	26.8 (24.1-29.0)	<0.001
≥35 g/L	98 (19.1%)	79 (28.1%)	15 (9.2%)	4 (5.7%)	<0.001
30~35 g/L	164 (31.9%)	111 (39.2%)	46 (27.6%)	9 (12.9%)	
≤30 g/L	252 (49.0%)	92 (32.7%)	103 (63.2%)	57 (81.4%)	
Globulin (g/L)	31.6 (28.6-35.2)	30.9 (27.8-33.6)	32.0 (29.3-36.1)	35.7 (31.2-39.5)	<0.001
≤30 g/L	180 (35.0%)	116 (41.3%)	51 (30.7%)	14 (20.0%)	<0.001
30~35 g/L	203 (39.5%)	127 (44.8%)	59 (36.2%)	18 (25.7%)	
≥35 g/L	131 (25.5%)	39 (13.9%)	54 (33.1%)	38 (54.3%)	
Albumin/Globulin	1.0 (0.8-1.1)	1.0 (0.9-1.2)	0.9 (0.7-1.1)	0.8 (0.6-0.9)	<0.001

Note: Continuous variables are presented as median (25th-75th percentiles), and categorical variables are presented as count (percentage).

Liver injury was also frequently observed in patients with COVID-19 (Table 2), with increased ALT (43.3%), AST (36.7%) and decreased albumin (80.9%), but less increased total bilirubin (10.9%) and direct bilirubin

(14.2%), which were more common in the severe to critical patients. It indicated a major damage of the hepatocytes and synthetic function, but not the function of bile secretion, in COVID-19 associated liver injury. However, most of the cases were mild injury. Those with relatively severe liver damage (ALT≥80 U/L) only accounted for 7.4% of the total patients, and 27.5% of the critical suffers. The liver injury was associated with higher inflammatory activity, such as increased white blood cell and neutrophil counts but declined lymphocyte counts, and elevated levels of CRP, ESR, procalcitonin and ferritin (Table S2).

Clinical characteristics of patients with and without diarrhea

There were 131 patients (25.49%, including 60 mild and 71 severe/critical cases) presented with diarrhea, and 383 patients (74.51%, including 222 mild and 161 severe/critical cases) without diarrhea (Figure 2). In the mild cases, patients with diarrhea had only slightly increased neutrophil (P=0.021) and decreased lymphocyte (P=0.011), but had no significant difference in multiorgan functions, compared with those absent of diarrhea (Table 3). In the severe/critical cases, there was increased WBC (P=0.030) and neutrophil (P=0.010) and trend to decreased lymphocyte (P=0.082), as well as higher level of inflammatory ferritin in patients with diarrhea relative to those without diarrhea. Moreover, diarrhea evidently companied with the more serious liver injury with increased activities of serum ALT, AST and LDH, and raised levels of total and direct bilirubin (Table 3).

Table 3 Comparisons of COVID-19 patients with and without diarrhea, including the systemic inflammation and multiorgan function.

	Mild patients			Severe/ Critical patients		
	With Diarrhea (N=60)	Without Diarrhea (N=222)	P	With Diarrhea (N=71)	Without Diarrhea (N=161)	P
Age (years)	52 (38-63)	54 (46-66)	0.068	65 (57-72)	64 (57-71)	0.798
Gender (m/f)	26/34	109/113	0.428	43/28	93/68	0.690
Fever	45 (75.0%)	192 (86.5%)	0.045	62 (87.3%)	151 (93.8%)	0.098
Highest temperature, °C	38.3 (37.7-38.9)	38.5 (37.8-39.0)	0.140	38.7 (38.0-39.0)	38.5 (38.0-39.0)	0.542
Infection and Inflammation						
White blood cell ($x10^9$/L)	5.08 (4.03-6.27)	5.08 (4.07-6.70)	0.387	7.45 (5.07-10.14)	6.28 (4.50-8.49)	0.030
Neutrophil ($x10^9$/L)	3.51 (2.66-4.76)	3.23 (2.40-3.96)	0.021	6.29 (3.91-8.48)	4.50 (3.04-7.32)	0.010
Lymphocyte ($x10^9$/L)	1.05 (0.81-1.40)	1.17 (0.90-1.88)	0.011	0.61 (0.42-0.89)	0.79 (0.57-1.07)	0.082
Procalcitonin (ng/mL)	0.06 (0.04-0.09)	0.05 (0.04-0.09)	0.119	0.14 (0.09-0.28)	0.14 (0.07-0.40)	0.571
C-reactive protein (mg/L)	17.52 (3.90-36.85)	16.55 (4.25-39.00)	0.956	67.35 (38.70-109.60)	65.92 (26.82-98.94)	0.499
Erythrocyte sedimentation rate (mm/h)	31.0 (18.0-44.0)	34.5 (20.3-53.8)	0.327	62.5 (44.0-80.3)	60.5 (42.5-81.0)	0.689
Ferritin (ng/mL)	173.9 (98.8-300.0)	160.2 (105.4-300.2)	0.896	818.0 (547.8-1562.3)	663.1 (404.8-1298.0)	0.041
Fibrinogen (g/L)	4.03 (3.39-4.88)	4.18 (3.48-5.01)	0.460	4.65 (4.03-5.21)	4.68 (3.85-5.38)	0.786
Multiorgan function injury						
Total bilirubin (μmol/L)	10.5 (7.6-11.7)	10.2 (7.7-12.7)	0.632	12.5 (8.8-16.5)	10.5 (7.1-15.9)	0.024
Direct bilirubin (μmol/L)	3.1 (2.4-3.7)	3.0 (2.4-4.3)	0.339	4.6 (3.2-6.5)	3.8 (2.7-6.4)	0.046
Alanine aminotransferase (U/L)	24.0 (18.8-42.0)	30.0 (19.0-48.0)	0.230	53.0 (33.4-71.4)	43.0 (28.0-70.5)	0.036
Aspartate transaminase (U/L)	27.0 (21.8-34.3)	28.0 (20.0-39.0)	0.803	54.0 (33.8-74.5)	44.0 (31.0-68.3)	0.045
Lactate dehydrogenase (U/L)	225.5 (188.8-297.8)	229.0 (194.0-294.0)	0.634	381.5 (293.5-521.3)	320.0 (241.5-398.0)	<0.001
Pre-albumin (g/L)	155.4 (122.8-241.1)	148.7 (115.8-205.2)	0.198	101.5 (72.4-133.6)	106.1 (73.9-139.9)	0.925
Albumin (g/L)	32.5 (28.4-35.2)	33.5 (30.8-35.4)	0.413	27.2 (25.8-30.2)	28.3 (25.5-30.9)	0.443
Globulin (g/L)	30.9 (27.5-33.6)	30.9 (28.1-33.6)	0.452	33.6 (29.5-36.3)	33.0 (30.0-38.0)	0.663
High sensitive troponin I (ng/L)	3.3 (2.2-8.0)	3.9 (2.2-7.5)	0.590	8.90 (4.90-32.60)	5.90 (3.95-23.20)	0.076
Blood urea nitrogen (mmol/L)	4.03 (3.15-4.91)	4.09 (3.18-5.12)	0.667	5.17 (3.81-7.33)	5.09 (3.73-7.50)	0.905
Creatinine (μmol/L)	65.2 (53.7-82.9)	63.8 (54.7-78.9)	0.714	72.0 (58.6-88.0)	70.0 (58.7-87.9)	0.771
D-dimer (μg/mL)	0.41 (0.16-0.77)	0.37 (0.22-0.69)	0.604	0.93 (0.43-6.77)	0.55 (0.34-2.46)	0.039
Urine Protein (+)	0 (0.0%)	4 (1.9%)	0.299	14 (20.9%)	36 (25.0%)	0.514
Urine occult blood (+)	0 (0.0%)	11 (5.3%)	0.081	11 (16.4%)	26 (18.1%)	0.771
Fecal occult blood (+)	1 (1.8%)	2 (1.0%)	0.603	6 (9.0%)	1 (0.7%)	0.002

Continuous variables are presented as median (25th-75th percentiles), and categorical variables are presented as count (percentage).

Clinical characteristics of diarrhea patients with and without respiratory symptoms

In the patients with diarrhea, 100 subjects (19.45%, including 37 mild and 63 severe/critical cases) presented with respiratory symptoms and 31 subjects (6.03%, including 23 mild and 8 severe cases) absent of respiratory symptoms (Table S1). As it shown, there were higher proportion of mild cases in patients with diarrhea only (74.2%) or with respiratory symptoms only (58.0%) than those with both diarrhea and respiratory symptoms (37.0%) (Figure 2). Notably, the patients with diarrhea in the absence of respiratory symptoms were observed less systemic inflammatory activity, including the lower levels of CRP, ESR and Ferritin, relative to diarrhea combined with respiratory symptoms (Table 4).

Table 4 Comparisons of COVID-19 patients with diarrhea who are present and absent of respiratory symptoms.

	Mild patients with Diarrhea			Severe/ Critical patients with Diarrhea		
	With respiratory symptoms (N=37)	Without respiratory symptoms (N=23)	P	With respiratory symptoms (N=63)	Without respiratory symptoms (N=8)	P
Age (years)	44 (34-63)	60 (55-63)	0.040	66 (58-72)	58 (55-63)	0.057
Gender (m/f)	21/16	5/18	0.008	37/26	6/2	0.375
Fever	28 (75.7%)	17 (73.91%)	0.878	56 (88.89%)	6 (75.00%)	0.266
Highest temperature, °C	38.4 (37.7-38.9)	38.0 (37.5-38.8)	0.385	38.8 (38.0-39.0)	38.3 (38.0-38.7)	0.158
Infection and Inflammation						
White blood cell ($x10^9$/L)	5.14 (4.26-6.08)	4.67 (3.90-6.38)	0.704	6.43 (4.50-8.49)	5.94 (4.88-8.27)	0.964
Neutrophil ($x10^9$/L)	3.29 (2.41-3.82)	3.20 (2.46-4.00)	0.921	4.50 (2.98-7.32)	4.58 (3.76-7.14)	0.750
Lymphocyte ($x10^9$/L)	1.17 (0.75-1.97)	1.08 (0.96-1.71)	0.755	0.77 (0.54-1.04)	0.72 (0.51-0.88)	0.363
Procalcitonin (ng/mL)	0.06 (0.04-0.09)	0.07 (0.06-0.18)	0.087	0.14 (0.07-0.45)	0.15 (0.10-0.22)	0.960
C-reactive protein (mg/L)	21.11 (5.11-52.09)	4.55 (2.13-56.19)	0.041	79.74 (36.82-118.94)	51.87 (34.79-101.75)	0.034
Erythrocyte sedimentation rate (mm/h)	34 (20-61)	18 (18-32)	0.033	61 (45-81)	46 (35-71)	0.046
Ferritin (ng/mL)	240.62 (143.99-344.87)	155.74 (98.80-234.85)	0.042	960.61 (663.69-1439.03)	660.02 (364.72-1258.32)	0.026
Fibrinogen (g/L)	3.92 (3.20-4.68)	3.72 (3.05-4.69)	0.738	4.68 (3.81-5.38)	4.73 (4.42-5.12)	0.709
Multiorgan function injury						
Total bilirubin (μmol/L)	9.60 (7.60-12.40)	10.60 (8.20-10.90)	0.933	10.90 (7.05-16.20)	9.60 (7.25-11.75)	0.757
Direct bilirubin (μmol/L)	3.00 (2.40-3.70)	3.20 (2.30-3.65)	0.709	3.80 (3.05-7.15)	3.15 (2.53-4.15)	0.358
Alanine aminotransferase (U/L)	26 (19-41)	22 (18-44)	0.386	52 (32-75)	38 (25-52)	0.034
Aspartate transaminase (U/L)	25 (21-35)	30 (23-34)	0.749	49 (31-77)	33 (27-54)	0.032
Lactate dehydrogenase (U/L)	218 (189-271)	227 (176-312)	0.808	314 (241-374)	406 (296-440)	0.220
Pre-albumin (g/L)	151.4 (128.5-212.0)	172.3 (114.4-266.7)	0.533	113.6 (73.9-147.7)	86.1 (75.0-106.4)	0.187
Albumin (g/L)	33.4 (30.7-36.9)	34.2 (32.6-35.1)	0.885	27.2 (25.7-30.5)	27.9 (26.4-28.8)	0.913
Globulin (g/L)	30.2 (27.5-34.3)	31.4 (27.8-32.9)	0.796	33.6 (29.5-36.2)	33.0 (28.9-36.5)	0.877
High sensitive troponin I (ng/L)	4.40 (2.60-11.10)	2.80 (1.37-3.32)	0.017	6.30 (4.20-28.20)	4.30 (3.65-14.05)	0.424
Blood urea nitrogen (mmol/L)	3.55 (3.06-4.37)	4.48 (3.51-5.46)	0.023	5.24 (4.04-8.30)	4.68 (3.26-4.91)	0.042
Creatinine (μmol/L)	66.0 (59.0-89.6)	60.8 (50.5-74.8)	0.188	71.2 (58.5-98.4)	63.5 (60.8-68.5)	0.141
D-dimer (μg/mL)	0.38 (0.16-0.71)	0.43 (0.26-0.85)	0.365	0.55 (0.34-2.90)	0.59 (0.48-1.69)	0.891
Urine Protein (+)	0 (0.0%)	0 (0.0%)	-	13 (22.03%)	1 (12.5%)	-
Urine occult blood (+)	0 (0.0%)	0 (0.0%)	-	11 (18.64%)	0 (0.0%)	-
Fecal occult blood (+)	1 (2.7%)	0 (0.0%)	-	6 (10.17%)	0 (0.0%)	-

Note: Continuous variables are presented as median (25th-75th percentiles), and categorical variables are presented as count (percentage).

Discussion

COVID-19 is generally considered a lower respiratory disease via droplet transmission. However, the current study suggested that gut and liver involvement was common in SARS-CoV-2 infection, which may carry significant implications on the pathogenesis and clinical management of COVID-19.

Alimentary symptoms were frequently observed in patients with COVID-19. Diarrhea was the typical gastrointestinal complain that troubled 25.5% of the total COVID-19 patients. This rate was a little higher than early reported 3.8% to 22.2% in 2019-nCoV infection[2-4, 20]. Similarly, SARS-CoV caused 20.3% diarrhea on presentation, and 38.4% patients developed symptoms of diarrhea during the course of illness[21], also middle east respiratory syndrome coronavirus (MERS-CoV) led to 26.0% diarrhea and 21.0% vomiting as for its enteric tropism[22]. About 13.2% patients developed diarrhea in the first 3 days after the onset of symptoms, and 63.2% diarrhea was occurred in the previous 10 days. Thus, diarrhea is more likely to develop in the early phase of infection, and the initial pathophysiology of COVID-19. All supported the gut involvement and diarrhea in the pathogenesis of novel SARS-CoV-2 infection.

Moreover, diarrhea was more common in the severe and critical patients with higher morbidity (32.1% and 27.1% respectively). This was in line with the observation that higher incidence of diarrhea in the severe or ICU cases than non-severe COVID-19 patients[3, 4]. And in the severe/critical subgroup, COVID-19 patients with diarrhea were reported more apparent systemic inflammatory activity and liver injury compared with those without diarrhea. It further indicated that comorbidity of diarrhea may accompany with more serious illness in the severe/critical COVID-19 suffers.

However, the severity of diarrhea, mainly frequency of defecation, was not apparently associated with hypoxemia (oxygen requirement) and the severity based on respiratory dysfunction of these patients. Therefore, the gastrointestinal tract and the lung may react independently and differently to SARS-CoV-2 infection. It may argue that diarrhea is related to the use of drugs in some cases, including mainly antibacterial drugs (moxifloxacin, cephalosporins and azithromycin) and antiviral drugs (abidol, oseltamivir, ribavirin and lopinavir/ritonavir). However, there no significant difference in the prehospital medications between the patients with and without diarrhea. Moreover, the use of antibiotics in the mild cases was rare, but the occurrence of diarrhea also very high (21.3%). In addition, lots of patients presented with diarrhea that had no prior medication history. So, the medication was inadequate to interpret the development of diarrhea, and other potential culprits for diarrhea such as viral load in the gut, intestinal dysbiosis and combined infections are necessary to future determine.

Interestingly, there were 31 patients (6.03%) presented with diarrhea in the absence of respiratory symptoms, and 9 patients (1.75%) of which had only diarrhea without fever and respiratory complaints. It further supported the view of “gut type” in the clinical management of COVID-19. Generally, these patients were mild illness and normal CT findings in the lung, and revealed less systemic inflammatory activity relative to the patients with both diarrhea and respiratory symptoms. It thereby may be easily misdiagnosed, especially for patients with diarrhea and gastrointestinal symptoms as the initial

appearance. Identification of this part of patients with a gut-type may play a critical role in the prevention and management of the epidemic situation.

The mechanism underline intestinal injury and diarrhea in SARS-CoV-2 infection was undiscovered. However, more and more evidences indicated the enteric tropism of SARS-CoV-2. It has been detected the viral nucleic acid in feces[14]. Swallowing sputum and saliva may be an important source of enteric virus[23, 24]. It makes the fecal-oral transmission possible that might be a major transmission route of SARS-CoV-2[14, 23]. Most important, ACE2 is widely expressed on the surface of intestinal epithelial cells[15, 16], which is the known entry target attacked by SARS-CoV-2[16]. All above favored the direct damage of SARS-CoV-2 on the gut mucosa, leading to diarrhea and gastrointestinal symptoms. The intestinal colonization of SARS-CoV-2 and the viral load may be associated with the severity of diarrhea. However, the mechanism of viral colonization and histological changes of the gut on SARS-CoV-2 infection are necessary to revealed.

Apart from alimentary symptoms, the liver injury was also frequently observed in patients with COVID-19[8]. Generally, mild liver dysfunction was common on SARS-CoV-2 infection. Moreover, the major abnormalities were hepatocyte damage with increased activities of ALT and AST, and declined synthetic function with low levels of pre-albumin and albumin, while the function of bile secretion was less involved. However, ACE2 is negative in hepatocytes and sinusoidal endothelium, but high expressed on the bile ducts[15, 25]. Therefore, the liver injury was less likely to be caused by directly attack of SARS-CoV-2. The severity of liver injury and the proportion of serious liver injury were much higher in the severe to critical COVID-19 patients. As we shown, liver injury was associated with higher inflammatory activity, such as increased WBC and neutrophil counts but reduced lymphocyte counts, and elevated levels of CRP, ESR, procalcitonin and ferritin. SARS-CoV-2 activity induced systemic inflammation and immunoreaction may be one cause of the liver dysfunction. Other factors such as drugs and hypoxia injury are likely to participate in the process of hepatic damage under SARS-CoV-2 infection, but it lacks of sufficient evidences.

The present study has several limitations. Firstly, this was a retrospective cohort study, and unrecognized biases cannot be excluded. Secondly, medications may cause diarrhea in some patients although we try to rule out potential drug-induced diarrhea. This should be avoided in the future prospective researches. Finally, only a small part of patients had tested the viral nucleic acid in the stool specimens, and preliminary evidence indicated its correlations with diarrhea. Further research is vital to determine how the dynamic changes and load of fecal virus on the severity and duration of diarrhea, and potential fecal-oral transmission.

Conclusions

In summary, our data favored the digestive involvement in the process of COVID-19. The enteric tropism of SARS-CoV-2 should be the major culprit for diarrhea and other alimentary symptoms, also makes the

fecal-oral transmission possible. There may be a “gut type” of COVID-19 that is significant for the understanding and clinical management of this emerging infection.

Abbreviations

COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; 2019-nCoV, 2019 novel coronavirus; ACE2, angiotensin converting enzyme 2; RT-PCR, reverse transcription-polymerase chain reaction; ICU , intensive care unit; WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; hsTNI, high sensitive troponin I; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; ALB, albumin; MERS-CoV, middle east respiratory syndrome coronavirus.

Declarations

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Competing interests

The authors declare that they have no conflict of interest.

Ethics approval and consent to participate

The study was approved by the institutional review board prior to data collection. All

procedures followed were in accordance with the ethical standards of the responsible

committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was waived due to retrospective study.

Author contributions

Haitao Shang collected medical records data, analyzed the data and drafted the manuscript; Chao Huang and Yuhu Chen helped for data collection; Shengyan Zhang helped for data analysis; Pengcheng Yang and Gaichao Hong supported for data entry and sorting; Lei Zhang and Xiaohua Hou designed and supervised the study and revised the manuscript.

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Availability of data and material

The raw data generated and analyzed in the current study are not publicly available due to appropriate protection of patient personal information but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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Figures

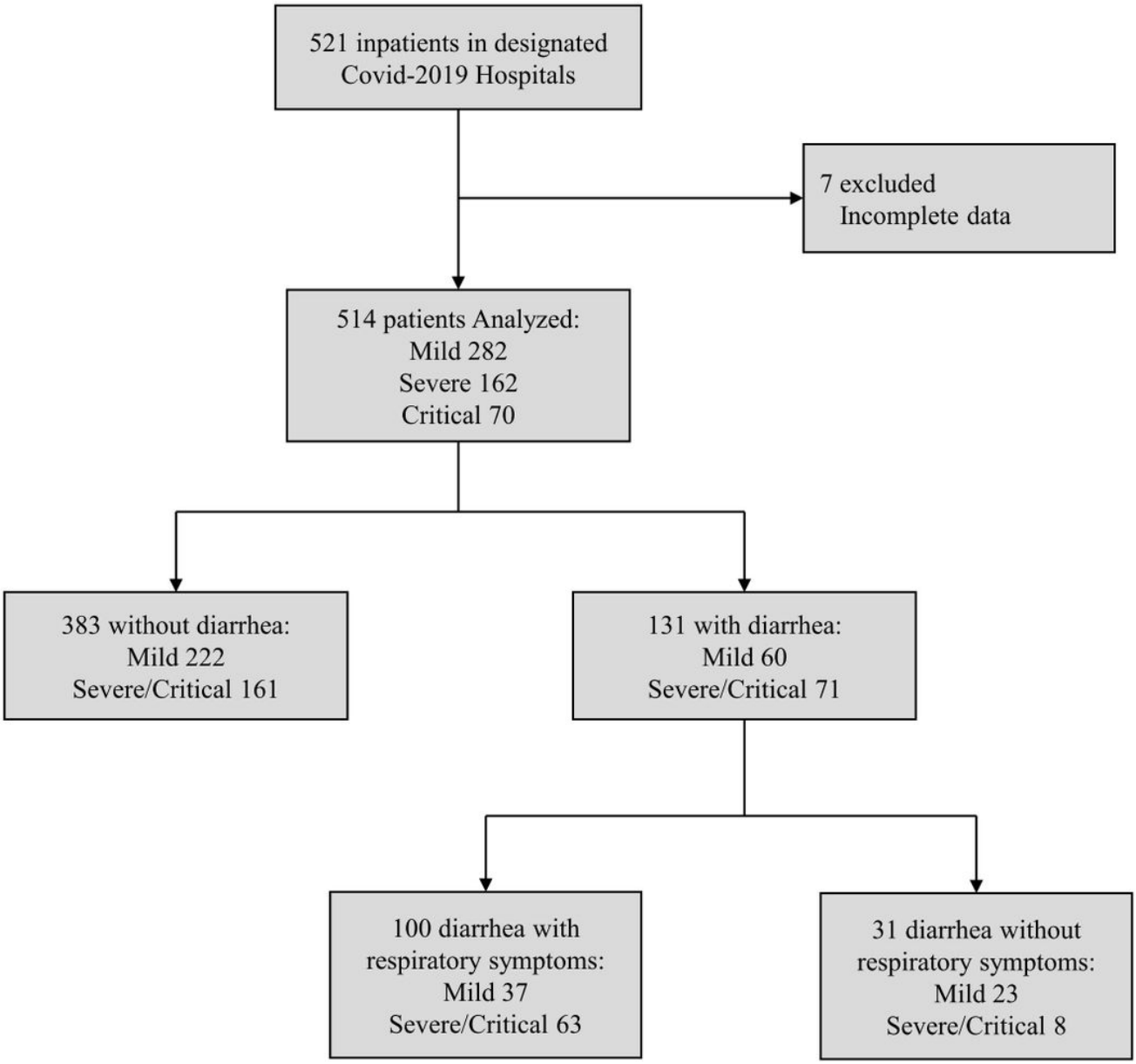

Figure 1

The study protocol.

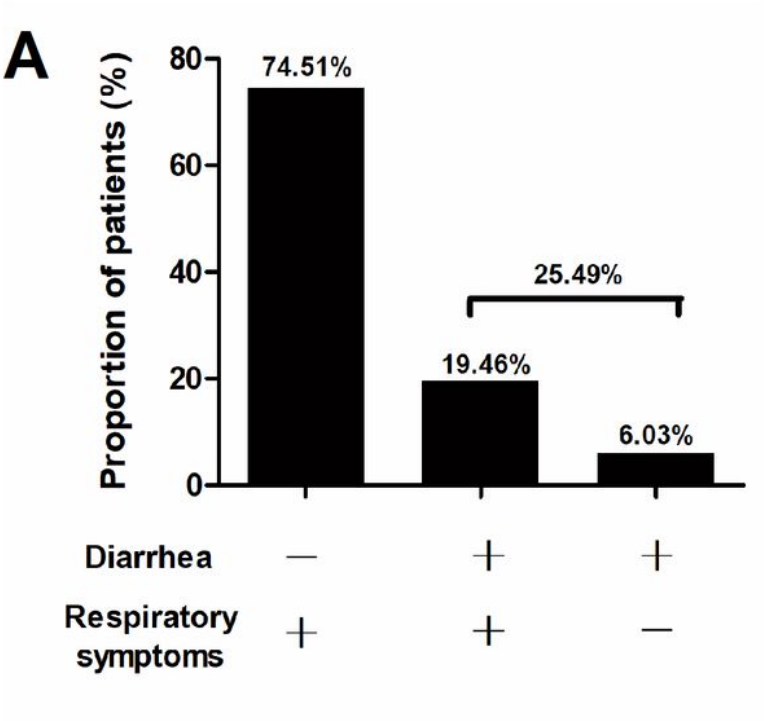

Figure 2

Diarrhea as the common gastrointestinal symptom in COVID-19 patients.

Supplementary Files

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