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Effect of gastrointestinal symptoms on patients infected with COVID-19

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Full title: Effect of gastrointestinal symptoms on patients infected with COVID-19

Short title: COVID-19 in China

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Introduction

Because of accumulating evidence pointing to continuous person-to-person transmission of COVID-19 in hospital and family settings[1,2], the World Health Organization (WHO) has recently declared COVID-19 a public health emergency of international concern. Fever and respiratory symptoms tend to be initial and major, whereas gastrointestinal symptoms (GI symptoms) were also observed in a significant portion of patients[3]. RT-PCR positive findings from patients' stool further revealed that COVID-19 may spread by fecal-oral transmission[4]. In addition, recent studies have shown that the receptor of ACE2, which is essential for cells infected by COVID-19, is highly expressed not only in lung AT2 cells but also in absorptive enterocytes in the ileum and colon[5,6]. These results further confirmed that the digestive system may be a potential route for COVID-19 infection. Therefore, a study exploring the correlation between GI symptoms and patients' symptoms, diagnosis, treatment, and outcomes is of great importance to improve the diagnosis and treatment plan of novel coronavirus-infected pneumonia (NCIP).

Materials and Methods

Study design

According to the clinical diagnostic standards in the "Diagnosis and Treatment of NCIP" issued by the National Health Commission of the People's Republic of China, suspected infected patients with clinical features of pneumonia could be regarded as clinically confirmed patients. The central hospital of Wuhan is one of the first major hospitals designated by the government to treat patients with NCIP. We enrolled 254 patients clinically confirmed with NCIP from December 20, 2019, through February 9, 2020. Medical staff and non-medical staff are counted separately. Based on whether they had GI symptoms, patients were divided into GI symptom and non-GI symptom groups. The clinical characteristics, laboratory findings, complications, treatment process, and clinical outcomes were compared between the patients with or without GI symptoms.

Data collection

The epidemiological, clinical, laboratory, radiological characteristics, and treatment outcome data were obtained from medical records. All these data were reviewed by a group of experienced doctors. The recorded information includes medical history, symptoms, signs, potential comorbidities, laboratory findings and treatment measures.

Statistical analysis

Categorical variables are described by frequency and percentages, and continuous variables are described by the mean, median, and interquartile range. Patient characteristics were compared using t tests for continuous variables and X^2 or Fisher exact tests for categorical variables. All statistical analyses were performed using SPSS version 23.0 software. $P \leq 0.05$ was considered statistically significant.

Results

As outlined in Table 1, this study recruited 254 clinically confirmed patients with NCIP [115 males and 139 females; mean age 50.6 years (range 15-87)], including 93 medical staff and 161 nonmedical staff. Among all patients, 211 (83%), 98 (38.6%) and 66 (26%) complained of fever, cough, and GI symptoms, respectively. The most common complication was pneumonia (209, 82.3%), followed by arrhythmia (16, 0.06%) and shock (7, 0.03%). Patients receiving mechanical ventilation, antibiotics, antivirals, immunoglobulins, hormones, and ECMO treatment accounted for 7.09%, 97.6%, 75.6, 59.8%, 88.2%, and 0.008% of the total patients, respectively. At of the end of observation, 46 patients were discharged, 16 died, and 192 patients continued treatment.

Among nonmedical staff, the proportion of GI symptoms in female patients was significantly higher than that in male patients (62.8% vs 37.2%, P = 0.033). Clinical manifestations such as sore throat (P = 0.023), dizziness (P = 0.032), and fatigue (P = 0.012) were also more frequent in patients with GI symptoms. In addition, hemoglobin in the GI symptom group was significantly lower than in the non-GI symptom group [116.7 (106-127) vs 133 (114-141), P=0.028], whereas C-reactive protein [7.3 (2.9-6.6) vs 3.8 (1.8-5.8), P = 0.021] and alanine aminotransferase [64.1 (51.2-64.4) vs 46.6 (31.9-61.2), P = 0.049] were significantly higher than in the GI symptoms group.

However, GI symptoms among medical staff were not significantly correlated with symptoms and laboratory findings. Finally, the GI symptom group appeared to have a similar rate of complications, treatment and clinical prognosis as the non-GI symptom group among medical and non-medical staff.

Discussion

The study suggests that GI symptoms are common clinical symptoms in patients with NCIP. Among nonmedical staff, women are more likely to have GI symptoms, accompanied by higher inflammatory levels and poorer liver function. However, no significant correlation between GI

symptoms and clinical features was observed among medical staff. In addition, the clinical outcome and treatment of patients with NCIP were not associated with GI symptoms in either medical or nonmedical staff.

A possible explanation for non-medical staff with GI symptoms more likely to have more symptoms and poorer liver function is the changes in the intestinal microecology under the dysfunction of the central nervous system. The infection of COVID-19 in intestinal tissues may lead to GI symptoms, such as diarrhea and abdominal pain. Metabolic disorders increase the absorption of harmful metabolites, which will affect the function of the central nervous system through the gut-brain axis and then lead to dizziness and fatigue. Disorders of intestinal metabolism further lead to more harmful metabolites that are harmful to liver tissue.

The reason why medical staff are less susceptible to GI symptoms may be that most of the infected medical staff were younger nurses without comorbidities. In addition, there is less delay from the onset of symptoms to hospital admission. Taking these factors into consideration, we can hypothesize that most of the medical staff infected by COVID-19 were mild on the day of hospital admission.

There are also some deficiencies in this study. First, the standard diagnosis of patients with NCIP is based on nucleic acid testing, but most cases in our study are clinically confirmed patients, which will inevitably lead to several patients without NCIP being included. Second, most patients were still hospitalized at the time of submission. Therefore, it is difficult to further assess the correlation between GI symptoms and clinical outcomes.

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Table1. Clinical features, treatment and prognosis of patients Infected With 2019-nCoV

	Total (254)	Medical staff				Non-medical staff			
		Total (93)	GI symptoms (23,100%)	Non- GI symptoms (70,100%)	P value	Total (161)	GI symptoms (43,100%)	Non- GI symptoms (118,100%)	P value
GI symptoms	66(26.0%)	23	23(100%)	0(0%)	-	43	43(100%)	0(0%)	-
Abdominal pain	3(1.2%)	0	0(0%)	0(0%)	-	3	3(7.0%)	0(0%)	-
Vomiting	15(5.9%)	1	1(4.3%)	0(0%)	-	14	14(32.6%)	0(0%)	-
Diarrhea	46(18.1%)	19	19(82.6%)	0(0%)	-	27	27(62.8%)	0(0%)	-
Nausea	21(8.3%)	5	5(21.7%)	0(0%)	-	16	16(37.2%)	0(0%)	-
Age	50	36	35	36	0.614	62	61	62	0.615
Median (IQR)	(36-65)	(31-41)	(30-40)	(31-42)		(49-69)	(49-67)	(49-70)	
Gender					0.45				0.033
Male	115(45.3%)	32	6(26%)	26(37%)		83	16(37%)	67(57%)	
Female	139(54.7)	61	17(74%)	44(63%)		78	27(63%)	51(43%)	
Symptom									
Fever	213(83.9%)	80	19(83%)	61(87%)	0.729	133	39(91%)	94(80%)	0.157
Sore throat	16(6.3%)	6	0(0%)	6(9%)	0.33	10	6(14%)	4(3%)	0.023
Dry cough	98(38.6%)	41	7(30%)	34(49%)	0.152	57	14(33%)	43(36%)	0.712
Expectoration	107(42.1%)	31	6(26%)	25(36%)	0.454	76	17(40%)	59(50%)	0.286
Chest tightness	67(26.4%)	21	3(13%)	18(26%)	0.261	46	8(19%)	38(32%)	0.115
Dyspnea	10(3.9%)	2	1(4%)	1(1%)	0.435	8	2(5%)	6(5%)	1
Dizziness	18(7.1%)	10	4(17%)	6(9%)	0.256	8	5(12%)	3(3%)	0.032
Headache	28(11.0%)	17	3(13%)	14(20%)	0.549	11	3(7%)	8(7%)	1
Fatigue	133(52.4%)	52	12(52%)	40(57%)	0.809	81	29(67%)	52(44%)	0.012
Myalgia	86(33.9%)	41	10(44%)	31(44%)	1	45	17(40%)	28(24%)	0.073
Sign									
Median (IQR)									
MAP (mmHg)	92 (85-96)	90 (85-96)	88 (83-98)	92 (87-96)	0.252	93 (85-98)	90 (85-98)	93 (86-97)	0.075
HR (bpm)	85 (79-98)	84 (80-100)	82 (76-103)	87 (80-100)	0.302	85 (78-98)	86 (78-98)	85 (78-98)	0.902
Comorbidities									
n (%)									
Hypertension	63(24.8%)	6	0(0%)	6(9%)	0.33	57	14(33%)	43(36%)	0.712
DM	26(10.2%)	3	0(0%)	3(4%)	0.572	23	4(9%)	19(16%)	0.321
CHD	17(6.7%)	2	0(0%)	2(3%)	1	15	6(14%)	9(8%)	0.231
Malignancy	2(0.8%)	1	0(0%)	1(1%)	1	1	0(0%)	1(1%)	1
CKD	0(0%)	0	0(0%)	0(0%)	-	0	0(0%)	0(0%)	-
CVD	13(5.1%)	1	0(0%)	1(1%)	1	12	3(7%)	9(8%)	1
CLD	3(1.2%)	1	0(0%)	1(1%)	1	2	0(0%)	2(2%)	1
COPD	6(2.4%)	1	0(0%)	1(1%)	1	5	2(5%)	3(3%)	0.61
HIV infection	1(0.4%)	0	0(0%)	0(0%)	-	1	1(2%)	0(0%)	0.267
Laboratory									
Findings									
HB	-	-	112 (109.5-111)	120.2 (112.5-127)	0.104	-	116.7 (106-127)	133 (114-141)	0.028
WBC	-	-	5.5(2.6-9.2)	5.6(3.2-6.5)	0.962	-	5.9(3.5-6.3)	5.5(3.3-6.7)	0.708
neutrophil	-	-	5.1(1.3-7.2)	5(1.5-8)	0.968	-	5.9(1.7-9.9)	7.6(2.3-7.7)	0.604

LYM	-	-	1.1(0.7-1.2)	1(0.8-1.1)	0.524	-	1(0.7-1.1)	0.8(0.7-0.9)	0.108
PLT	-	-	223(86-408)	184(88-237)	0.653	-	192(111-248)	176(112-186)	0.842
CRP	-	-	2.2(0.7-2.6)	3(1-2.5)	0.491	-	7.3(2.9-6.6)	3.8(1.8-5.8)	0.021
ALT	-	-	65.9 (23.3-103.3)	75.6 (44.5-114.8)	0.698	-	64.1 (51.2-64.4)	46.6 (31.9-61.2)	0.049
AST	-	-	26.4 (12.7-45.5)	40.4 (12.9-65.3)	0.271	-	47.8 (18.2-50.6)	53.8 (35.7-58.5)	0.44
Albumin	-	-	35.2 (34.5-38.1)	36.7 (34.7-38.7)	0.327	-	35.4 (33.9-36.4)	35 (32.8-37.8)	0.648
Globulin	-	-	39.7 (37.6-42)	38.7 (30.7-43.8)	0.766	-	26.1 (22.7-29.4)	28.9 (25.3-31.6)	0.185
LDH	-	-	156.2 (103-194.8)	289 (229-370.3)	0.069	-	358.9 (256-425)	312.5 (251.5-335)	0.322
CK	-	-	29.8 (15.8-35)	398.5 (28.1-587.3)	0.143	-	316.3 (86-276.5)	201.3 (77.8-294.5)	0.359
Creatinine	-	-	68 (64.2-75.5)	67.6 (73.2-79.3)	0.981	-	56.9 (43.9-72.1)	70.1 (43.8-95.9)	0.217
FBG	-	-	8(6.2-8.7)	7.7(6.5-8.1)	0.787	-	7.3(6.3-8.2)	8.3(6.3-9.5)	0.106
Na^+	-	-	142.6 (139.3-145.8)	134.2 (131-136.4)	0.05	-	138.9 (134.8-141.9)	139.3 (135-145.4)	0.88
K^+	-	-	3.9(3.3-4)	4(3.2-4.5)	0.934	-	3.3(3.1-3.5)	9.1(3.2-4)	0.052
PH	-	-	7.4(7.4-7.5)	7.5(7.4-7.5)	0.485	-	7.4(7.5-7.5)	7.4(7.4-7.5)	0.9
SaO2	-	-	91(97-99)	92(91-99)	0.962	-	93(92-94)	92(91-97)	0.796
PaO2	-	-	74(62-85)	109(52-151)	0.256	-	84(65-105)	86(62-113)	0.809
PaCO2	-	-	42(33-51)	35(31-39)	0.263	-	35(31-36)	35(31-35)	0.777
Complications									
Pneumonia	209(82.3%)	70	18(78.3%)	52(74.3%)	0.787	139	38(88.4%)	101(85.6%)	0.798
Shock	7(2.8%)	2	0(0)	2(2.9%)	1.000	5	1(2.3%)	4(3.4%)	1.000
AHF	6(2.4%)	1	1(4.3%)	0(0)	0.247	5	0(0)	5(4.2%)	0.326
Arrhythmia	16(6.3%)	12	2(8.7%)	10(14.3%)	0.724	4	1(2.3%)	3(2.5%)	1.000
ARDS	5(2%)	2	1(4.3%)	1(1.4%)	0.435	3	1(2.3%)	2(1.7%)	1.000
Treatment									
MV	18(7%)	5	1(4.3%)	4(5.7%)	1.000	13	2(4.7%)	11(9.3%)	0.516
Antibiotics	248(97.6%)	91	23(100%)	68(97.1%)	1.000	157	42(97.7%)	115(97.5%)	1.000
Antivirals	192(75.6%)	63	16(69.6%)	47(67.1%)	1.000	129	31(72.1%)	98(83.1%)	0.179
Immune-globulins	152(59.8%)	62	19(82.6%)	43(61.4%)	0.07	90	28(65.1%)	62(52.5%)	0.209
Hormones	224(88.2%)	77	20(86.9%)	57(81.4%)	0.75	147	37(86%)	110(93.2%)	0.204
ECMO	2(0.8%)	2	1(4.3%)	1(1.4%)	0.435	0	0(0)	0(0)	-
Clinical outcome									
Discharge from hospital	46(18.1%)	32	4(17.4%)	28(40%)	0.075	14	4(9.3%)	10(8.5%)	1.000
Staying in hospital	192(75.6)	59	18(78.3%)	41(58.6%)	0.134	133	36(83.7%)	97(82.2%)	1.000
Death	16(6.3%)	2	1(4.3%)	1(1.43%)	0.435	14	3(7%)	11(9.3%)	0.457

Abbreviations: MAP, mean arterial pressure; HR, heart rate; DM, diabetes mellitus; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; HB, hemoglobin; WBC, blood leukocyte count; LYM, lymphocyte count; PLT, platelet count; CRP, C-reaction protein; ALT, alanine aminotransferase; AST, aspartate

transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; FBG, fasting blood glucose; AHF, acute heart failure; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.