İstanbul Med J 2024; 25(2): 110-5
DOI: 10.4274/imj.galenos.2024.61889

Comparison of COVID-19 RT-PCR-Positive Patients in Oro-Nasopharynx Samples with RT-PCR Results in Simultaneous Stool Samples, Prospective Study

Burak Sarıkaya[1], Rıza Aytaç Çetinkaya[2], Betül Doğantekin[3], Soner Yılmaz[4], Yüksel Akkaya[5], Başak Çakır Güney[3], Eriş Özkan[3], Merve Tanır Kırsoy[3], Vahibe Aydın Sarıkaya[6], Mustafa Kaplan[7]

[1]University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[2]Reyap Health Group, Department of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[3]University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Turkey
[4]University of Health Sciences Turkey, Gülhane Training and Research Hospital, Regional Blood Center, Ankara, Turkey
[5]University of Health Sciences Turkey, Ümraniye Training and Research Hospital, Clinic of Medical Microbiology, İstanbul, Turkey
[6]University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
[7]University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Turkey

ABSTRACT

Introduction: The definitive diagnosis of coronavirus disease-2019 (COVID-19) infection is made by polymerase chain reaction (PCR) tests on nasopharyngeal and oropharyngeal swab samples. However, the presence of viral RNA has also been identified in stool samples. In this study, we aimed to investigate the relationship between severe acute respiratory syndrome-coronavirus-2 positivity in stool and the outcomes of COVID-19 disease.

Methods: Fifty-four patients who were hospitalized between April-June 2020 and had positive COVID-19 PCR tests in nasopharyngeal and oropharyngeal swab samples were included in the study. PCR was performed on the stool samples of all patients. In addition, laboratory findings, clinical data, and computed tomography (CT) results of these patients were recorded and analyzed.

Results: Among the patients, 13 out of 28 (46.4%) with positive fecal PCR test results were female, whereas 11 out of 26 (46.4%) with negative fecal PCR test results were female. Furthermore, 19 out of 28 patients (67.9%) with positive fecal PCR test results recovered, whereas 23 out of 26 patients (88.5%) with negative fecal PCR test results recovered. Notably, patients with fecal PCR-positive results exhibited more severe dyspnea, higher blood pressure, abnormal CT findings, and elevated D-dimer levels. Moreover, compared with patients with negative PCR results, those with positive fecal PCR results had lower levels of procalcitonin, hemoglobin, hematocrit, and lymphocytes.

Conclusion: Considering the relationship between stool PCR positivity and the prognosis of the disease and laboratory test results, routine stool PCR tests may be useful, especially in COVID-19 patients presenting with gastrointestinal symptoms.

Keywords: COVID-19, fecal PCR, enteric pathogen, SARS-CoV-2

Introduction

The new coronavirus infection, which began in Wuhan in 2019, was officially named coronavirus disease-2019 (COVID-19) by the World Health Organization. On February 20th, 2020, due to the escalating numbers of cases with over 75,000 patients and 2,130 deaths in five continents, COVID-19 was declared a pandemic. It is generally regarded as a respiratory disease, with its main clinical manifestations being fever, cough, shortness of breath, weakness, and joint pain. To diagnose the infection, nasopharyngeal swab samples are taken from patients exhibiting these symptoms, and polymerase chain reaction (PCR) tests are employed to detect viral RNA. PCR tests are also used during the treatment and follow-up processes.

Address for Correspondence: Burak Sarıkaya MD, University of Health Sciences Turkey, Sultan 2. Abdulhamid Han Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey
Phone: +90 533 326 15 53 **E-mail:** burak_tibbiyeli@hotmail.com **ORCID ID:** orcid.org/0000-0002-0026-1927

Cite this article as: Sarıkaya B, Çetinkaya RA, Doğantekin B, Yılmaz S, Akkaya Y, Çakır Güney B, Özkan E, Tanır Kırsoy M, Aydın Sarıkaya V, Kaplan M. Comparison of COVID-19 RT-PCR-Positive Patients in Oro-Nasopharynx Samples with RT-PCR Results in Simultaneous Stool Samples, Prospective Study. İstanbul Med J 2024; 25(2): 110-5

Received: 06.02.2024
Accepted: 01.04.2024

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) causes this emerging pandemic (1). Outbreaks of emerging infectious diseases pose a significant challenge and threat to healthcare providers because of the limited information available about these diseases.

COVID-19 primarily spreads through contact with respiratory droplets or contaminated surfaces and primarily affects the respiratory system (2). Previous studies have detected coronaviruses in various bodily samples, such as nasal or nasopharyngeal swabs, sputum, conjunctival scraps, urine, feces, tears, endotracheal aspirate, bronchoalveolar lavage, blood, and lung tissues (3,4). Although the infection is commonly detected in nasopharyngeal swab samples, it has been observed that the RNA of the virus can also be found in stool samples. Furthermore, this positivity in stool samples may persist even after nasopharyngeal swab samples show negative results.

The aim of our study was to evaluate and interpret the relationship between clinical findings, laboratory test results used in the follow-up and treatment of COVID-19 patients, and stool PCR test results.

Methods

Study Population

The study was approved by the University of Health Sciences Turkey, Hamidiye Faculty of Medicine Clinical Research Ethics Committee (approval number: 2021.02.11-84, date: 11.02.2021).

Our study was conducted on 54 patients clinically diagnosed with COVID-19 hospitalized in the intensive care unit and COVID-19 clinics between April and June 2020 at University of Health Sciences Turkey, Sultan 2. Abdulhamid Khan Training and Research Hospital in İstanbul, Turkey. Patients were included in this study according to the inclusion and exclusion criteria stated below: (a) clinically confirmed COVID-19 patients (b) serum C-reactive protein, D-dimer, ferritin, complete blood count, and the patients whose nasopharynx samples were PCR positive at diagnosis (c) patients who have been appropriately clinically monitored and can be reached; (d) without other inflammatory diseases and (e) non-malignant.

Swab Samples of Patients

In the University of Health Sciences Turkey, Sultan 2. Abdulhamid Khan Training and Research Hospital's accredited laboratory, patient naso-oropharyngeal swab samples were examined. Using a Rotor-Gene® Q MDx device (Self-screen B.V., Biothof 15-1, 1098 RX Amsterdam, The Netherlands), viral RNA was extracted using Bio-speedy® viral nucleic acid buffer (Bioexen LTD, Turkey), and real-time polymerase chain reaction (RT-PCR) was performed using the Bio-speedy® COVID-19 RT-qPCR kit with primers and probes targeting the SARS-CoV-2 nucleocapsid (N) gene fragment. A positive outcome was defined as a computed tomography (CT) value of ≤38. The kit's specificity was 100% and its analytical sensitivity was 98.7%. Patients who tested positive for PCR had their nasopharynx and stool samples taken every week.

Using the spin clone method and Anatolia's Bosphore viral DNA-RNA extraction kit, stool viral RNA was extracted. The Bosphore Novel Coronavirus (2019-nCov) Detection Kit from Anatolia (Anatolia Geneworks, Anatolia Diagnostics and Biotechnology Products Inc., İstanbul, Turkey) was used for RT-PCR. In accordance with the manufacturer's instructions, automated RT-PCR amplification and detection of PCR products were performed using an Abbot m2000 RT-PCR device (Abbott Molecular 33 Inc., Des Plaines, IL). A CT value below 32 was considered a positive result.

Outcomes

The demographics, baseline characteristics, and laboratory and radiological findings of patients with COVID-19 were recorded from the hospital database. The symptoms of the patients on admission, comorbidities, physical and laboratory findings, chest CT imaging findings, intubation/intensive care requirement, and survival outcomes were recorded and analyzed.

Statistical Analysis

The analyses in the study were performed using SPSS 15.0 software. In the statistical analysis, numerical data for continuous variables were presented as medians and quartile ranges (P 25-75). Categorical variables are expressed as numerical percentages. Student's t-test was applied for normally distributed variables, and Mann-Whitney U test was applied for non-normally distributed variables. The chi-square (χ^2) test or Fisher's exact test was used to examine classified variables, with statistical significance set at p-values <0.05.

Results

A total of 54 patients, 24 (44.4%) women and 30 (55.6%) men, were included in the study. Thirteen of 28 patients (46.4%) with positive fecal PCR test results were female, whereas 11 of 26 patients (46.4%) with negative fecal PCR test results were female (p=0.76). The age of patients ranged between 20 and 90 years. The median age of patients with a fecal PCR test positive was 63.68±17.67 while 54.65±21.8 in fecal PCR test-negative patients (p=0.119). Nineteen of 28 patients (67.9%) with positive fecal PCR test results recovered, whereas 23 of 26 patients (88.5%) with negative fecal PCR test results recovered (p=0.069).

Dyspnea (p=0.014), hypertension (p=0.045), and CT grade (p=0.02) were statistically significantly higher in patients with fecal PCR-positive compared with PCR-negative patients. Clinical signs and symptoms, comorbidities, mechanical ventilation needs, and CT findings are summarized in Table 1.

Procalcitonin (p=0.027), hemoglobin (p<0.001), hematocrit (p<0.001), and lymphocyte (p=0.04) values were statistically significantly lower in patients with fecal PCR-positive compared with those with fecal PCR-negatives. Only the D-dimer levels (p=0.025) among the laboratory findings were statistically significantly higher in patients with fecal PCR positivity. Laboratory and physical findings of patients with COVID-19 at admission are shown in Table 2.

Discussion

Fecal PCR test results were positive in 28 of 54 patients. According to the study data, dyspnea and concomitant hypertension were significantly more common in fecal PCR-positive patients, and it was shown that CT

Table 1. Clinical characteristics of patients with COVID-19

		SARS-CoV-2 RNA in feces						p
		Positive (n=28)		Negative (n=26)		Total		
		n	%	n	%	n	%	
Clinical signs and symptoms								
Dry cough	a	15	53.6%	15	57.7%	30	55.6%	0.761
	p	13	46.4%	11	42.3%	24	44.4%	
Dyspnea	a	10	35.7%	18	69.2%	28	51.9%	**0.014***
	p	18	64.3%	8	30.8%	26	48.1%	
Nausea/vomiting	a	23	82.1%	24	92.3%	47	87.0%	0.267
	p	5	17.9%	2	7.7%	7	13.0%	
Diarrhea	a	23	82.1%	24	92.3%	47	87.0%	0.267
	p	5	17.9%	2	7.7%	7	13.0%	
Fatigue	a	8	28.6%	12	46.2%	20	37.0%	0.181
	p	20	71.4%	14	53.8%	34	63.0%	
Comorbidities								
Diabetes mellitus	p	3	10.7%	4	15.4%	7	13.0%	0.61
	a	25	89.3%	22	84.6%	47	87.0%	
Hypertension	a	11	39.3%	4	15.4%	15	27.8%	**0.045***
	p	17	60.7%	22	84.6%	39	72.2%	
COPD	p	5	17.9%	4	15.4%	9	16.7%	0.81
	a	23	82.1%	22	84.6%	45	83.3%	
Chronic kidney disease	p	3	10.7%	2	7.7%	5	9.3%	0.7
	a	25	89.3%	24	92.3%	49	90.7%	
Cardiovascular disease	n	10	35.7%	7	26.9%	17	31.5%	0.48
	p	18	64.3%	19	73.1%	37	68.5%	
	a	26	96.3%	26	100.0%	52	98.1%	
Mechanical ventilation need and CT scan findings								
Mechanical ventilation (None: 0 NIMV: 1 IMV: 2)	0	12	42.9%	18	69.2%	30	55.6%	0.13
	1	8	28.6%	3	11.5%	11	20.4%	
	2	8	28.6%	5	19.2%	13	24.1%	
CT findings (grade) Grade 0: None Grade 1: Partially Grade 2: Moderate Grade 3: Advance	0	4	14.3%	13	50.0%	17	31.5%	**0.02***
	1	11	39.3%	9	34.6%	20	37.0%	
	2	8	28.6%	2	7.7%	10	18.5%	
	3	5	17.9%	2	7.7%	7	13.0%	

COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COPD: Chronic obstructive pulmonary disease, CT: Computed tomography, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, a: Absent, p: Present, n: Not known

grade and D-dimer levels were significantly higher in patients with a positive test. However, the procalcitonin, hemoglobin, hematocrit, and lymphocyte values were found to be significantly lower.

Bioinformatic studies have revealed the presence of cells in the human lung and gastrointestinal system that contain angiotensin-converting enzyme 2 (ACE2) receptors. These ACE2 receptors are involved in epithelial cells in the esophagus and nutrient-absorbing enterocyte in the small and large intestines. When the virus infects these cells in the gastrointestinal system, it results in increased permeability in the gastrointestinal mucosal wall, manifesting as diarrhea or watery stool in the patient. Previous studies have reported that viral RNA was detected in stool samples of patients diagnosed with COVID-19, even if their nasal/pharyngeal swabs were negative (5). Our study, which included 54 patients diagnosed with COVID-19 through nasopharyngeal and oropharyngeal sampling, revealed fecal PCR positivity in 28 (58.4%) of these patients, indicating fecal sampling as a potentially valuable alternative or additional method.

Continuous PCR-RNA test positivity in feces suggests that viruses are released from infected gastrointestinal cells. Wong et al. (6), in a meta-analysis examining 17 studies, reported that the pooled detection rate of SARS-CoV-2 PCR positivity in stool was 43.7% based on the number of patients and 33.7% based on the number of samples. Stool PCR positivity was observed to be higher in patients with more severe disease, gastrointestinal symptoms, and female gender. Parasa et al. (7) also

Table 2. Laboratory and physical findings of patients with COVID-19 at admission

	SARS-CoV-2 RNA in feces			p
	Positive (n=28)	Negative (n=26)	Total	
Temperature, °C	37.68±0.84	37.79±1.06	37.73±0.94	0.788
Heart rate, bpm	87.11±22.35	81.54±9.83	84.43±17.55	0.931
O_2 saturation	92.75±2.79	93.58±2.8	93.17±2.79	0.375
Respiratory rate (rpm)	17±2.8	16.08±3.89	16.54±3.38	0.169
Urea (mg/dL)	133.67±80.94	141.5±102.7	137.09±89.62	0.970
Creatinine (mg/dL)	2.18±1.9	17.23±79.54	9.28±54.58	0.544
AST (U/L)	131.46±212.27	56.76±44.28	96.23±160.37	0.412
ALT (U/L)	123.46±191.91	64.12±64.22	95.47±148.06	0.123
D. bil. (mg/dL)	1.4±2.09	0.35±0.32	0.92±1.63	0.164
LDH (U/L)	896.71±529.07	723.17±464.01	818.45±503.48	0.237
CRP (mg/L)	126.32±83.82	86.17±78.58	108.21±83.17	0.078
Sedimentation	96.2±29.47	69±49.65	83.47±42.03	0.082
Ferritin (ng/mL)	1457.63±3431.44	633.6±940.6	1097.12±2657.22	0.339
Procalcitonin	3.31±3.22	4.68±13.19	3.95±9.18	**0.027***
CK (U/L)	103.62±101.34	174.1±386.61	138±278.22	0.958
CKMB (ng/mL)	4.38±6.49	5.48±9.5	4.99±7.68	0.623
D-dimer (ng/mL)	6033.54±7044.56	2056.83±2434.93	4166.92±5708.33	**0.025***
Fibrinogen (mg/dL)	618.13±208.74	529.75±192.01	577.02±203.7	0.113
WBC (10^3x mm^3)	8.65±4.68	7.6±3.76	8.17±4.27	0.321
HGB (g/dL)	10.1±2.1	13.45±5.37	11.68±4.3	**0.001***
HTC (%)	31.28±5.91	39.14±12.31	34.98±10.18	**0.001***
MCV (fL)	88.42±7.56	87.42±10.28	87.95±8.87	0.086
PLT (10^3x mm^3)	173.79±97.45	207.35±71.58	189.62±87.07	0.051
MPV (fL)	10.65±1.21	10.19±1.06	10.44±1.16	0.134
NEUT (10^3x mm^3)	7.38±4.88	5.28±3.48	6.39±4.36	0.121
LYM (10^3x mm^3)	0.82±0.6	1.25±0.79	1.02±0.72	**0.040***
EOS (10^3x mm^3)	0.06±0.12	0.05±0.08	0.05±0.1	0.455
pH	7.39±0.12	7.38±0.12	7.39±0.12	0.943
PCO_2 (mmHg)	41.78±15.75	43.27±10.24	42.35±13.75	0.385
PO_2 (mmHg)	53.8±17.54	55±20.16	54.26±18.29	0.790
SaO_2 (%)	78.93±15.13	77.62±21.91	78.43±17.71	0.804
HCO_3 (mmol/L)	24.34±5.23	24.35±4.63	24.34±4.94	0.901
Lactate (mmol/L)	2.51±1.23	2.02±1.02	2.32±1.16	0.202

COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, D. bil.: Direct bilirubin, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CK: Creatine kinase, CKMB: Creatine kinase MB isoenzyme, WBC: White blood cells, HGB: Hemoglobin, HTC: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet, MPV: Mean platelet volume, NEUT: Neutrophil, LYM: Lymphocyte, EOS: Eosinophil, PCO_2: Partial pressure of carbon dioxide, PO_2: Partial pressure of oxygen, SaO_2: Oxygen saturation, HCO_3: Bicarbonate

reported viral RNA shedding in feces in 40.5% of COVID-19 patients, with 12% manifesting gastrointestinal symptoms. In our study, only seven patients (12.9%; 7/54) had gastrointestinal symptoms (nausea/vomiting and diarrhea). However, the fecal PCR test was positive in five of these seven patients. Considering the detection of viruses in feces and positive rectal swabs in a substantial number of patients and the correlation between diarrhea and stool positivity, we recommend routine PCR testing of feces in COVID-19 patients, particularly those presenting with gastrointestinal symptoms. We also suggest that transmission-based precautions for hospitalized patients should be continued if a fecal PCR test for COVID-19 is positive (8-10).

Our study also revealed that patients with SARS-CoV-2 RNA-positive fecal results had different laboratory findings than those with negative results. These findings generally correlated with the recent meta-analysis of Ghahramani et al. (11), which compared patients with severe and mild disease. Interestingly, in our study, procalcitonin levels were lower in patients with positive fecal PCR tests. In contrast, Xu et al. (12) indicated

that higher procalcitonin levels were more prevalent in patients with severe disease.

In addition, our study emphasizes the importance of evaluating patients who describe gastrointestinal complaints in the patient group diagnosed with COVID-19. Liu et al. (13) reported that there were not enough data to show an association between gastrointestinal symptoms and severe COVID-19 disease, but we observed that those with gastrointestinal symptoms had symptoms for a longer duration. Tariq et al. (14) reported that gastrointestinal symptoms were observed in 20% of COVID-19 patients and that more high-quality evidence is needed to explore factors causing mortality in these patients. Therefore, testing for COVID-19 should be performed using both respiratory and stool samples, if available (15).

In our study, diarrhea, nausea, and/or vomiting (13%) were the most common gastrointestinal symptoms. In a recent meta-analysis by Suresh Kumar et al. (16), it was emphasized that nausea and/or vomiting are very common gastrointestinal symptoms in patients diagnosed with COVID-19. Interestingly, we found that hypertension was more common in patients with PCR-positive stool. Zhang et al. (17) reported that hypertension significantly increased the risk of severe COVID-19. One can speculate that there may be a relationship between hypertension and SARS-CoV-2 PCR positivity in feces in terms of disease severity, but larger, prospective, and randomized studies are needed to confirm this.

Patients with fecal PCR-positive and -negative results exhibited differences in clinical and laboratory findings. PCR results in stool sampling may be crucial for the detection and follow-up of this disease, especially considering the low rate of PCR positivity and high rate of false-negative results in nasopharyngeal and oropharyngeal swab samples.

Study Limitations

Our study has some limitations. If we count the reasons for our small number of cases; 1. The limited number of PCR test kits that are examined by fecal method and the necessity to be performed very carefully. 2. Fecal PCR test kits are difficult to access and finance because of their high cost. For these reasons, we could not include more cases in our study.

Conclusion

Fecal PCR testing presents a promising alternative or supplementary diagnostic method for COVID-19, particularly in cases where respiratory swabs may yield false-negative results. It could aid in more accurate and timely diagnosis, contributing to better disease management and control. Our findings shed light on the potential benefits of incorporating fecal sampling in COVID-19 testing protocols, and we recommend further research to better understand its implications on disease severity and transmission.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Hamidiye Faculty of Medicine Clinical Research Ethics Committee (approval number: 2021.02.11-84, date: 11.02.2021).

Informed Consent: It was obtained.

Authorship Contributions: Surgical and Medical Practices - B.S., R.A.Ç., B.D., Y.A., E.Ö., V.A.S., M.K.; Concept - B.S., R.A.Ç., B.D., S.Y., Y.A., B.Ç.G., E.Ö., M.T.K., V.A.S., M.K.; Design - B.S., R.A.Ç., S.Y., Y.A., E.Ö., V.A.S., M.K.; Data Collection or Processing - B.S., R.A.Ç., B.D., S.Y., Y.A., E.Ö., V.A.S., Analysis or Interpretation - B.S., B.D., Y.A., E.Ö., V.A.S., M.K.; Literature Search - B.S., B.D., S.Y., B.Ç.G., M.T.K., V.A.S., M.K.; Writing - B.S., R.A.Ç., B.D., S.Y., Y.A., B.Ç.G., E.Ö., M.T.K., V.A.S., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323: 1061-9.
2. Seto WH, Tsang D, Yung RW, Ching TY, Ng TK, Ho M, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). Lancet 2003; 361: 1519-20.
3. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev 2007; 20: 660-94.
4. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. Lancet 2020; 395: 1063-77.
5. Scaldaferri F, Ianiro G, Privitera G, Lopetuso LR, Vetrone LM, Petito V, et al. The Thrilling Journey of SARS-CoV-2 into the Intestine: From Pathogenesis to Future Clinical Implications. Inflamm Bowel Dis 2020; 26: 1306-14.
6. Wong MC, Huang J, Lai C, Ng R, Chan FKL, Chan PKS. Detection of SARS-CoV-2 RNA in fecal specimens of patients with confirmed COVID-19: A meta-analysis. J Infect 2020; 81: e31-8.
7. Parasa S, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients with Coronavirus Disease 2019: A Systematic Review and Meta-analysis. JAMA Netw Open 2020; 3: e2011335.
8. van Doorn AS, Meijer B, Frampton CMA, Barclay ML, de Boer NKH. Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for faecal-oral transmission. Aliment Pharmacol Ther 2020; 52: 1276-88.
9. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020; 158: 1831-3.
10. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020; 382: 1708-20.
11. Ghahramani S, Tabrizi R, Lankarani KB, Kashani SMA, Rezaei S, Zeidi N, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res 2020; 25: 30.
12. Xu L, Mao Y, Chen G. Risk factors for 2019 novel coronavirus disease (COVID-19) patients progressing to critical illness: a systematic review and meta-analysis. Aging (Albany NY) 2020; 12: 12410-21.
13. Liu J, Cui M, Yang T, Yao P. Correlation between gastrointestinal symptoms and disease severity in patients with COVID-19: a systematic review and meta-analysis. BMJ Open Gastroenterol 2020; 7: e000437.
14. Tariq R, Saha S, Furqan F, Hassett L, Pardi D, Khanna S. Prevalence and Mortality of COVID-19 Patients with Gastrointestinal Symptoms: A Systematic Review and Meta-analysis. Mayo Clin Proc 2020; 95: 1632-48.

15. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical Characteristics of COVID-19 Patients with Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol 2020; 115: 766-73.

16. Suresh Kumar VC, Mukherjee S, Harne PS, Subedi A, Ganapathy MK, Patthipati VS, et al. Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19. BMJ Open Gastroenterol 2020; 7: e000417.

17. Zhang J, Wu J, Sun X, Xue H, Shao J, Cai W, et al. Association of hypertension with the severity and fatality of SARS-CoV-2 infection: A meta-analysis. Epidemiol Infect 2020; 148: e106.