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Short Communication

Verifying Extra-Pulmonary Manifestation of COVID-19 in Firoozgar Hospital in 2020

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Abstract

Background: COVID-19 is a newly emerging disease that causes a pandemic situation in the world. Coronavirus can enter into the body in several ways and it damages other organs of the body in addition to the respiratory system. This study aimed at verifying extra-pulmonary manifestation of COVID-19.

Methods: The present study was conducted as cross-sectional in a single center from March 1 to May 1 2020 at Firoozgar educational Hospital in Tehran, Iran. 107 patients with confirmed COVID-19 pneumonia according to WHO interim guidance were recruited in this study. Extra-pulmonary manifestations of COVID-19 were recorded. SPSS version 26 was used for all the analyses.

Results: The mean (SD) and the median age were 59.3 (17.4) and 62.0 years, respectively and 58 (54.2%) were men. Body temperature of the patients who were equal or less than 60 years was significantly higher than other patients (39.02 *vs*. 38.08°C, p=0001). The most common extra-pulmonary manifestation was GI symptoms including nausea, vomiting, abdominal pain, diarrhea, hepatocellular Liver Function Test (LFT) abnormality, cholestatic LFT abnormality, and amylase lipase incensement [37 patients (34.6%]. Ophthalmological, cardiac, neurological and dermatological manifestations were shown in 6.5, 6.5, 14.9 and 14.0% of the patients, respectively.

Conclusion: Investigating the clinical and radiological symptoms of COVID-19 showed that SARS-CoV-2 infection may also be associated with extrapulmonary symptoms. Therefore, clinicians and radiologists should be familiar with such symptoms of the disease.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, Gastrointestinal symptom, Neurological symptom

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Introduction

A new coronavirus causes COVID-19 infection. COVID-19 cases suffer from mild-to-moderate respiratory disease and they recovered with no special treatment. Older cases and people with underlying medical diseases, such as cardiovascular disease, diabetes, chronic respiratory disorder, and cancer are at higher risk for developing serious illnesses.

Respiratory symptoms have been investigated in this disease (1). Along with respiratory and other typical symptoms such as fever, cough and muscle ache, extra-pulmonary manifestations have been reported in some cases requiring special care and attention. Neurological (2), cardiac (3), Gastrointestinal (GI) (4), dermatological (5) and ophthalmological (6) manifestations have been less evaluated, which should be considered more.

Coronaviruses (CoVs) are able to go into the CNS via the bloodstream or neuronal retrograde pathway and cause meningitis, encephalitis, related morbidity, and risk of death. It is usually hard to diagnose viral encephalitis due to light or lack of symptoms; however, it is possible to detect some symptoms of the serious viral encephalitis including changed mental status and body temperament, unusual behavior or speech, unusual motor movement and focal neurological dysfunctions, like flaccid paralysis, paresthesia, hemiparesis, or seizures (7).

Gastrointestinal (GI) symptoms have been reported in several patients. Some COVID-19 patients with GI symptoms were found as the only manifestation of the disease with no respiratory disorders (8,9). It has been reported that from 67 COVID-19 cases with diarrhea, 13 patients had no other symptoms (10). Although GI symptoms in COVID-19 are not specific, they are more common in cases with approved SARS-CoV-2 infection.

Cardiovascular symptoms of COVID-19 are also challenging for physicians. Identification of the damage by COVID-19 to the cardiovascular system and the underlying mechanisms are crucial since treating these cases is timely and effective with reduced mortality (3).

Recent studies have verified skin symptoms of COVID-19. The results of evaluating 88 COVID-19 cases show that skin symptoms are erythematous rash, widespread urticaria, and chickenpox-like vesicles. Trunk skin lesions as the main area affected were not somewhat itchy (5).

The transmission of COVID-19 is done through droplets, however, other methods of transmission have been documented, for instance, transmitting via infected ocular tissue or fluid (11,12). The nasolacrimal system may pave the way for viruses to travel from the upper respiratory tract to the eyes. Consequently, ocular tissue and fluid are probably a likely source of coronavirus. This study aimed at verifying extra-pulmonary manifestation of COVID-19.

Materials and Methods

The present study was conducted as cross-sectional in a single center from March 1 to May 1 2020 at Firoozgar educational Hospital in Tehran, Iran. 107 patients with confirmed COVID-19 pneumonia according to WHO interim guidance were recruited in this study.

This study was approved by Ethics Committee of Iran University of Medical Sciences and all the patients signed the written informed consent. Two attending doctors separately examined the patients for neurological, cardiac, GI, ophthalmological and dermatological manifestations. Lung CT involvement was categorized into mild, moderate and severe based on the CT severity score (CTSS) (13). Presence of cough, dyspnea, chest pain, anosmia and dysgeusia were recorded. Past medical history such as suffering from diabetes, Hypertension (HTN), Ischemic Heart Disease (IHD), Chronic Kidney Disease (CKD), Immuno-compromised status, myalgia and other diseases were collected from all the patients.

Statistical analysis

Continuous measurements reported as mean ± standard deviation (SD) for normally distributed data and categorical variables were described as number of patients (percent). SPSS version 26 was used for all the analyses. Continuous variables were compared using independent sample t-test, and proportions for categorical variables were compared using the $\chi 2$ test, whereas the Fisher exact test was conducted when the data were limited.

Results

The study participants included 107 hospitalized patients with confirmed Covid-19 pneumonia. Basic

characteristics of the study participants according to age groups are illustrated in table 1. The mean (SD) and median of age was 59.3 (17.4) and 62.0 years, respectively and 58 (54.2%) were men. Body temperature of the patients who were equal or less than 60 was significantly higher compared to other patients (39.02 *vs*. 38.08, p=0001). Of the patients older than 60 years old, 16 (28.6%) and 55 (98.2%) had HTN and dyspnea, respectively. Surprisingly, patients who were equal or less than 60 years of age, had significantly more underlying comorbid systemic disease than other patients (9 (17.3%) *vs*. 2 (3.6%), P=0.019). Figure 1 shows comorbidities of the patients on admission.

Extra-pulmonary manifestations associated with COVID-19 patients are shown in table 2. The most common extra-pulmonary manifestation was GI symptoms including nausea, vomiting, abdominal pain, diarrhea, hepatocellular Liver Function Test (LFT) abnormality, cholestatic LFT abnormality and amylase lipase incensement (37 patients (34.6%)). Ophthalmological (7 patients (6.5%)) and cardiac (7 patients (6.5%)) manifestations were the lowest clinical involvement related to COVID-19 pneumonia. Neurological manifestations consist of ischemic Cerebrovascular Accidents (CVA), Intracerebral Hemorrhage (ICH), Guillain–Barré Syndrome (GBS), and encephalitis were observed in 16 patients (14.9%). Of 107 patients who participated in the present study, 15 patients (14.0%) showed dermatological symptoms such as erythema, macula, papule, morbid form rash, urticarial and patch (Figure 2).

Table 1. Baseline characteristics of participants by age group

Baseline characteristics	All patients (n=107)	Age ≤ 60 years (n=51)	Age > 60 years (n=56)	p-value***
*Continues variables**				
Hospitalization duration	9.98±6.3	9.53±7.06	10.50±5.60	0.431
Body temperature	38.53±0.65	39.02±0.39	38.08±0.51	0.0001
*Categorical variables***				
Sex				
Female	49 (45.8)	24 (49.0)	25 (51.0)	0.848
Male	58 (54.2)	27 (46.6)	31 (53.4)	
Diabetes	29 (27.1)	11 (21.0)	18 (32.1)	0.142
Ischemic heart disease	21 (19.6)	7 (13.5)	14 (25.0)	0.101
Chronic kidney disease	4 (3.7)	2 (3.8)	2 (3.6)	0.662
Hypertension	19 (17.7)	3 (5.8)	16 (28.6)	0.002
Immuno-compromised status	2 (1.9)	1 (1.9)	1 (1.8)	0.773
Other diseases	11 (10.3)	9 (17.3)	2 (3.6)	0.019
Opium use	2 (1.9)	1 (1.9)	1 (1.8)	0.733
Smoking	14 (13.1)	7 (13.5)	7 (12.5)	0.554
Myalgia	2 (1.9)	2 (3.8)	0 (0.0)	0.658
Lung CT involvement				0.076
Mild	22 (20.5)	11 (21.2)	11 (19.6)	
Moderate	45 (42.1)	19 (36.5)	26 (46.4)	
severe	33 (30.1)	14 (26.9)	19 (33.9)	
Cough	98 (91.6)	46 (88.5)	52 (92.9)	0.325
Dyspnea	99 (92.5)	44 (86.3)	55 (98.2)	0.022
Chest discomfort	65 (60.7)	29 (56.9)	36 (64.3)	0.279
Anosmia	12 (11.2)	8 (15.7)	4 (7.1)	0.137
dysgeusia	11 (10.3)	8 (15.7)	3 (5.4)	0.075

*data reported as mean±SD

**data reported as number of patient (percent)

*** p-value of difference between two age groups

Table 2. Extra-pulmonary manifestation related to covid-19 patients

Variables	All patients (n=107)	Age ≤ 60 years (n=51)	Age > 60 years (n=56)	p-value*
Neurological manifestations	16 (14.9)	10 (19.6)	6 (10.7)	0.155
Ischemic CVA	2 (1.9)	0 (0)	2 (3.6)	0.496
ICH	0 (0)	0 (0)	0 (0)	-
GBS	1 (0.9)	1 (2.0)	0 (0)	0.477
Encephalitis	2 (1.9)	2 (3.9)	0 (0)	0.225
Cardiac manifestations	7 (6.5)	4 (7.8)	3 (5.4)	0.448
Myocardial infarction	4 (3.7)	2 (3.9)	2 (3.6)	0.655
Pulmonary embolism	1 (0.9)	0 (0)	1 (1.8)	0.523
Pericarditis	2 (1.9)	1 (2.0)	1 (1.8)	0.728
Myocarditis	2 (1.9)	1 (2.0)	1 (1.8)	0.728
GI manifestations	37 (34.6)	21 (41.2)	16 (28.6)	0.122
Nausea, vomiting	34 (31.7)	20 (39.2)	14 (25.0)	0.085
Abdominal pain	26 (24.3)	14 (27.5)	12 (21.4)	0.308
Diarrhea	19 (17.7)	11 (21.6)	8 (14.3)	0.232
Hepatocellular LFT abnormality	23 (21.5)	13 (25.5)	10 (17.9)	0.506
Cholestatic LFT abnormality	0 (0)	0 (0)	0 (0)	-
Amylase lipase incensement	3 (2.8)	3 (5.9)	0 (0)	0.105
Ophthalmologic manifestations	7 (6.5)	5 (9.8)	2 (3.6)	0.491
Ocular irritation	5 (4.7)	4 (7.8)	1 (1.8)	0.154
Ocular itching	5 (4.7)	4 (7.8)	1 (1.8)	0.154
Epiphora	1 (0.9)	1 (2.0)	0 (0)	0.477
Foreign body sensation	6 (5.6)	4 (7.8)	2 (3.6)	0.296
Ocular secretion	2 (1.9)	1 (2.0)	1 (1.8)	0.728
Conjunctival hyperemia	6 (5.6)	4 (7.8)	2 (3.6)	0.296
Shirmer left	7 (6.5)	5 (9.8)	2 (3.6)	0.491
Shirmer right	7 (6.5)	5 (9.8)	2 (3.6)	0.491
Tear or secretion PCR test	0 (0)	0 (0)	0 (0)	-
Eye side involvement	7 (6.5)	5 (9.8)	2 (3.6)	0.491
Dermatologic manifestations	15 (14.0)	10 (19.6)	5 (8.9)	0.163
Erythema	9 (8.4)	6 (11.8)	3 (5.4)	0.200
Macula	6 (5.6)	4 (7.8)	2 (3.6)	0.296
Papule	6 (5.6)	4 (7.8)	2 (3.6)	0.296
Patch	3 (2.8)	3 (5.9)	0 (0)	0.105
Plaque	3 (2.8)	2 (3.9)	1 (1.8)	0.604
Nodule	0 (0)	0 (0)	0 (0)	-
Pustule	0 (0)	0 (0)	0 (0)	-

Contd Table 2

Vesicle	2 (1.9)	1 (2.0)	1 (1.8)	0.728
Urticarial	4 (3.7)	3 (5.9)	1 (1.8)	0.274
Scaling		2 (3.9)	1 (1.8)	0.604
Itching		2 (3.9)	1 (1.8)	0.604
Irritation or pain		1 (2.0)	2 (3.6)	1.000
Secretion PCR test		0 (0)	0 (0)	-
Morbid form rash		4 (7.8)	2 (3.6)	0.421
Petechial		2 (3.9)	1 (1.8)	0.604
Acral syansis		0 (0)	2 (3.6)	0.496
Livedoreticularis		1 (2.0)	0 (0)	0.477

All data reported as number of patient (percent)

*p-value of difference between two age groups

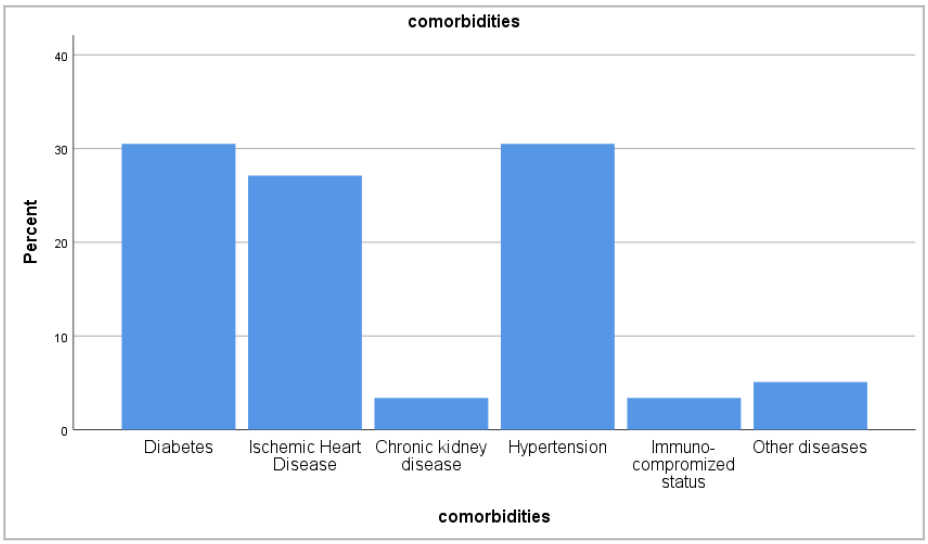

Figure 1. Comorbidities of patients on admission.

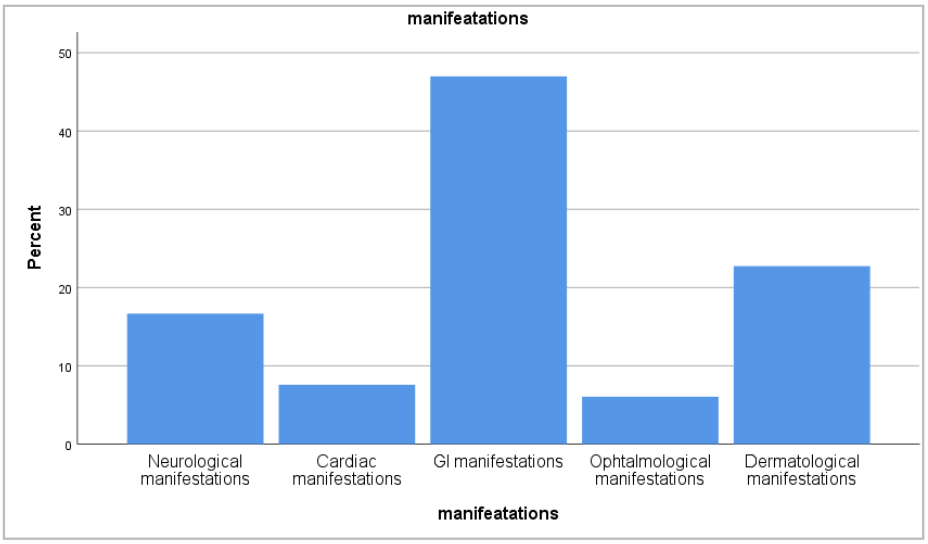

Figure 2. Some manifestations of patients with COVID-19.

Discussion

The current study focuses on the epidemiology and clinical characteristics of 107 COVID-19 cases referred to Firoozgar hospital. Human coronavirus is an important cause of respiratory tract infection. SARSCoV and MERSCoV lead to severe respiratory syndrome in humans, and HCoVOC43, HCoV229E, HCoVNL63, and HCoVHKU1 as other human coronaviruses cause mild upper respiratory disorder.

There was no significant difference between the number of male and female subjects. In many studies evaluating COVID-19 cases, the number of men was more compared to women (1,14,15). The decreased vulnerability of women to viral infections may be associated with the protection from X chromosome and sex hormones that are crucial in innate and adaptive immunity (16). Approximately, 30% of cases affected by coronavirus were found with hypertension, diabetes and ischemic heart disease, which is also true for MERS-CoV.19 (14). Our findings indicated that younger cases had remarkably more underlying comorbid systemic disease compared to older cases, which can be associated with underlying diseases that weaken the immune system and increase the risk of infection with coronavirus (17).

GI symptoms are more prevalent among the extrapulmonary manifestations. Nausea, vomiting, abdominal pain, diarrhea, Hepatocellular liver function test abnormalities, cholestasis, and Amylase lipase incensement have been reported in approximately 45% of cases. Some cases of COVID-19 have been observed with GI symptoms as the only manifestation of the disease with no respiratory dysfunctions (8). GI wall permeability is enhanced to foreign pathogens while infected with the virus, GI symptoms, such as diarrhea, are observed due to mal-absorption of infected enterocytes (18). Cohort studies have also consistently announced GI symptoms in Covid-19 cases. Another study on 1,099 patients from 552 hospitals in China reported nausea or vomiting in 55 (5.0%) and diarrhea in 42 (3.8%) patients (19). Many cohort studies have revealed diarrhea (2.0–10.1%) and nausea and/or vomiting (1.0–10.1%) in these patients (18,20,21). Consistent with the current study, in a cohort study of 140 Covid-19 cases in Wuhan, up to 39.6% of them had GI symptoms, such as nausea (24,17.3%), diarrhea (18, 12.9%), and vomiting (7,5.0%) (22). The receptor-binding domain on SARS-CoV-2 is capable of binding to human ACE2 with strong affinity, which is believed to help spread the virus among human population effectively (23,24). Significant expression of ACE2 in Alveolar cells Type II (AT2) in the lungs has been reported, and the receptor can be also extensively expressed in the GI tract, chiefly in the small and large intestines (25). Staining of the virus nucleocapsid protein was observed in cytoplasm of gastric, duodenal, and rectal epithelium (26). Thus, it is possible to consider that receptor-mediated entry into the host cells can reveal a basis for its probable transmission way via the fecal contents.

Dermatological symptoms have been recorded in nearly 20% of 107 COVID-19 cases. Erythema has been the most common manifestation, particularly in the patients ≤ 60 years old. It has been reported that patients with confirmed SARS-CoV-2 infection might develop cutaneous involvement. In another study on 88 COVID-19 patients, it was observed that erythematous rash, widespread urticaria, and chickenpox-like vesicles are the skin symptoms of the COVID-19. Trunk skin lesions as the main area affected were not somewhat itchy (5).

CoVs are capable of going into the CNS via the bloodstream or neuronal retrograde route causing meningitis and encephalitis along with morbidity and risk of mortality. It is hard to diagnose viral encephalitis due to subtle or lack of symptoms, however, symptoms in severe viral encephalitis are changed mental status and body temperament, unusual behavior or speech, abnormality in motor movement and focal neurological dysfunctions, including flaccid paralysis, paresthesia, hemiparesis, or seizures (7). Assessing 214 patients with COVID-19 indicated that 78 patients (36.4%) had neurological manifestations, like headache, dizziness, acute cerebrovascular diseases, and disturbed consciousness (27).

Studies on the neurological attack in COVID-19 pneumonia revealed that SARSCoV-2 was capable of attacking the CNS and finding the way throughout the systemic circulation or through the cribriform plate of the ethmoid bone. It could then damage the neuronal tissues via interaction with ACE2 receptors. COVID-19 cerebral participation through the cribriform plate can cause more complications, like hyposmia or anosmia (28,29). Some investigations have reported

the likely cerebrovascular endothelial rupture leading to bleeding and irrepressible consequences (28). Due to intracerebral hemorrhage, cerebrovascular accidents have been declared as the rare COVID-19 neurological consequence (30). COVID-19-related acute hemorrhagic necrotizing encephalopathy was found in an individual with changed mental status with nasopharyngeal swab positive for SARS-CoV-2. According to the imaging results, symmetric hypo attenuation in the bilateral medial thalami was detected by the head CT, as well as hemorrhagic ring-enhancing lesions in the bilateral thalami, medial temporal lobes, and sub insular areas detected by brain MRI (31). Nevertheless, more investigations should be conducted for the causation link.

Cardiac and ophthalmological symptoms have been reported in less than 10% of the COVID-19 cases in our study. Of 107 studied patients, only 4 cases showed myocardial infarction. ACE1 is the target receptor for SARS-CoV-2 expressing remarkably in the heart. This transmembrane aminopeptidase is linked with developing hypertension, and heart function is essential in the cardiovascular system. Therefore, it is possible to consider cardiovascular injury or myocarditis a COVID-19 manifestation (32). Zheng *et al* studied 5 COVID-19 cases with myocardial injury through the course of the disease. Myocardial injury is typically manifested as an elevated level of biochemical markers, such as cardiac), Troponin I (cTnI creatine kinase (CK), α-hydroxybutyrate dehydrogenase (HBDB), and Lactate Dehydrogenase (LDH) (33). The impact of COVID-19 on acute Myocardial Infarction (MI), such as STEMI and NSTEMI was reported in the new protocols of acute MI (34).

According to the American Academy of Ophthalmology report, conjunctival infection and chemosis are some extrapulmonary symptoms of the infection with SARS-CoV-2 (35). Transmitting by infected ocular tissue or fluid should be more studied and is debated (11,12). Nasolacrimal system may pave the way for the viruses to travel from the upper respiratory tract to the eyes. Consequently, it is possible to consider ocular tissue and fluid as likely source of SARS-CoV-2. However, in the present study, tear or secretion PCR test for detecting coronavirus was not positive.

Conclusion

COVID-19 leads to viral pneumonia with some clinical symptoms. According to the clinical and radiological symptoms of COVID-19, SARS-CoV-2 infection might also be associated with extrapulmonary symptoms. Consequently, clinicians and radiologists are advised to be aware of such symptoms of this disease. It is essential to perform more studies to verify the causal link between SARS-CoV-2 infection and the reported extrapulmonary symptoms of COVID-19.

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Availability of the data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Iran University of Medical Sciences. Written informed consent was obtained from all the participants.

Conflict of Interest

All authors declare no competing interests.

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