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Clinical Features and Predictors associated with Mortality in Non-Survived Patients of COVID-19 in a Referral Hospital in Rasht, North of Iran

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ABSTRACT

Background and Aim: In December 2019, a new type of Coronavirus (SARS-CoV-2) pneumonia (COVID-19) was reported in Wuhan and quickly spread worldwide. This study was designed to investigate the clinical symptoms of the COVID-19 patients.

Materials and Methods: In this retrospective study, we collected data of 132 COVID-19 dead patients. Demographic, epidemiological, and clinical data and laboratory test results were analyzed on days 1, 3, and 6 of admission.

Results: Most cases were in the 66-75 age group, 64.39% of which were males. Three days after admission, 55.3% of patients died. The most frequent clinical manifestations were dry cough (70.45%) and fever (54.54%), which increased during hospitalization. Diabetes and blood pressure were reported as the most prevalent underlying diseases. Lymphopenia and an increase in leucocyte number were observed in most patients. ESR (92.5%) and LDH (94.64%) levels were above normal. Furthermore, 42.85% and 44.73% of patients had elevated ALT and AST levels, respectively.

Conclusion: The results of this study revealed that males are more likely to be infected with SARS-CoV-19. Underlying diseases were common among patients and clinical and laboratory symptoms aggravated with a rise in hospitalization time.

Keywords: Clinical features, COVID-19, Epidemiology, Iran, SARS-CoV-2.

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1 Introduction

A newly emergent betacoronavirus causing respiratory tract infection, Coronavirus disease 2019 (COVID-19), was recognized in Wuhan, China, in December 2019 **(1)**. Genome sequencing of betacoronavirus revealed a close relationship with the SARS virus **(2)**. Infection of a human being with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), named by the International Committee of Taxonomy of Viruses (ICTV), can lead to COVID-19 disease, which is devastating particularly for the elderly **(3)**.

COVID-19 became a serious global issue in early 2020 and triggered an existential worldwide health crisis. WHO defined the epidemic of SARS-CoV-2 as a public health emergency of international concern. The SARS-CoV-2 could easily transmit via aerosols among the individuals of a society; additionally, it has been reported that this virus survives on surfaces, for instance, stainless steel and plastics, for up to three days facilitating its spread.

Despite the fairly thorough knowledge about the mortality of the clinical disease, its pathogenicity rem-

ains unknown (4). Six species of Coronavirus leading to disease are identified in humans (5). They cause infections in different systems, like respiratory, enteric, hepatic, and neurological organs (6). The SARS-CoV-2 virus binds to epithelial cells via its main receptor, ACE2, following inhalation in the nasal cavity and begins to replicate (7). In organs with a high expression of ACE2, such as the kidney and intestine, the virus proliferates, and the affected tissues are widely damaged when the protective immune response is impaired (8). Inflammation is induced in the lungs by damaged cells (9).

Patients with COVID-19 have been classified into mild, moderate, severe, and critical groups, based on clinical manifestations and radiographic score (10). The symptoms of COVID-19, such as fever, cough, fatigue, diarrhea, and vomiting, are similar to those of other respiratory viruses (11). The lungs have invasive lesions in radiographs presentation (12). Serious complications, including pneumonia, acute respiratory failure (ARF), acute respiratory distress syndrome (ARDS), acute kidney injury, acute cardiac or liver injuries, disseminated intravascular coagulation (DIC), and septic shock may be seen in certain cases facing-death (13).

The increasing number of patients with severe COVID-19 infection worldwide has led to investments in health care systems and medical supplies (14). There are some techniques to identify COVID-19; predominantly, Real-Time reverse-transcription polymerase chain reaction (rRT-PCR) is used to detect the target genes directly, S, N, E, and RdRp of the virus (15). The severity, mortality prediction, control plans, and treatment of the disease could be measured via several laboratory tests (16); for instance, white blood cell (WBC), lymphopenia, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) as hematological tests, as well as lactate dehydrogenase (LDH), creatine kinase (CK), and troponin as biochemical assays, were reported to be associate with the severity of COVID-19 (17).

Laboratory findings and their association with the complications caused by the disease could compromise important knowledge, as specific diagnostic significance, during the appearance of a novel infectious disease (18). Although the clinical characteristics of COVID-19 have been mainly defined, the development of severe conditions due to the damage of non-pulmonary organs may change the biochemical parameters' level of kidney and liver, such as creatinine, AST, and ALT to abnormal values (17).

Due to the high morbidity and mortality rate and the necessity of new methods for timely treatment and preventing the death of patients, this study aimed to investigate the changes in paraclinical parameters and their relationship with the death of hospitalized patients.

2.Materials and Methods

This retrospective-epidemiological study was performed in Razi hospital in Rasht, North of Iran. Razi hospital is a referral hospital during the COVID-19 epidemic in Rasht, and all patients are referred to this center. All the recorded patients had a unique national code, and there were no duplicate cases. A number of 132 hospitalized and non-survived patients from COVID-19 from March to August 2020 were included. Age, sex, and the hospitalization to death duration were measured. This study was evaluated and approved by the Ethics Committee of Guilan University of Medical Sciences (Ethical approval code: IR.GUMS.REC.1399.137). Ethical Review Board approved the consent taken from all the participants.

2.1. Real-Time PCR

To diagnose the disease using Real-Time PCR**,** swabs from Patients' nasopharynx and oropharynx were obtained and transferred to Viral Transport Medium (VTM). Viral RNAs were extracted from specimens using Sacace DNA/RNA extraction kit (Sacace Biotechnologies Co., Italy) according to the manufacturer's protocol. Extracted RNA was used as a template to One-Step Real-Time PCR for detecting N (nucleocapsid protein) and RdRp genes in COVID-19 using Real-Time PCR primer/probe kit (Pishtaz Teb Co. Iran). Patients with negative SARS-CoV-2 test results were excluded.

2.2. Clinical Data

The clinical data were obtained by the research team via the electronic medical record system (HIS). Clinical evidence included physical signs and symptoms, history of organ transplantation and surgery, underlying diseases, such as pulmonary disease, chronic obstructive pulmonary disease (COPD), cancer, asthma, blood pressure, diabetes, chronic renal disease, stroke history, and cardiovascular problems, and drug and smoke history. Moreover, several other clinical symptoms of patients were inclusive nausea, diarrhea, vomiting, headache, muscle pain, dry cough, anorexia, ageusia, and anosmia.

2.3. Laboratory Assays

Laboratory tests results, including complete blood counts (CBC), erythrocyte sedimentation rate (ESR), hepatic and renal enzymes tests, LDH, blood urea nitrogen (BUN), and serum creatinine, were collected from medical patients' records. Herein, Na, K, PT, and PTT levels, as well as pH, PaO_2, $PaCO_2$, HCO_3, and AO_2 saturation were measured.

2.4. Statistics

Categorical and continuous data were outlined as percentages and median with interquartile range (IQR), respectively. The variable between the groups was compared via χ2 test for categorical data and nonparametric comparative test for continual data. P-value<0.05 was considered to be statistically significant.

The variables recognized by univariate analysis (*P* <0.05) were put into the multivariate analysis, in which these variables were balanced according to three main factors (disease severity on admission, mechanical ventilation, and ICU transfer). SPSS version 21.0 software (SPSS Inc., Chicago, Il., USA) was utilized to carry out all the statistical analyses.

3.Results

A total of 132 death cases with confirmed COVID-19 were enrolled in this work. The number of male patients was higher than that of females (85 males versus 47 females). The subjects did not include the medical staff. The participants were categorized into seven age groups (25 to 95). Based on our results, most patients (17.42%) were in the age group of 66-75, which belongs to the males (Table 1).

Table 1. Frequency of patients based on their age

Age group	Sex	N (Percentage)
25-35	Female	0 (0)
	Male	3 (2.3)
36-45	Female	4 (3.03)
	Male	7 (5.3)
46-55	Female	5 (3.8)
	Male	9 (6.8)
56-65	Female	11 (8.33)
	Male	16 (12.12)
66-75	Female	9 (6.81)
	Male	23 (17.42)
76-85	Female	13 (9.84)
	Male	20 (15.15)
86-95	Female	5 (3.8)
	Male	7 (5.3)

The patients' symptoms were recorded at 1, 3, and 6 days after admission (Table 2); however, some patients died before days 3 or 6. It should be mentioned that 50% of the subjects were excluded in less than three days, and the rest were hospitalized for four days or longer.

As shown in Table 2, the patients' clinical symptoms were recorded on days 1, 3, and 6. Among all checked symptoms, only muscle pain was decreased from day 1 (50%) to 6 (41.2%). The other symptoms indicated an increasing rate from day 1 to day 6. Underlying diseases among the patients were also recorded after admission (Table 3). Based on our results, diabetes was the most prevalent underlying disease (16.66%), followed by blood pressure (13.63%). All the patients were checked for a history of asthma, allergy, HIV, immunodeficiency, and pregnancy in women. One female (80-85) with asthma and cardiovascular disease history died two days after admission.

There were other death cases in this study among the cases with underlying diseases; for instance, a man (age group: 45-50) with fauvism, a history of blood pressure, and cardiovascular disease died four days after admission. Another male subject (55-60) with rheumatism and a history of diabetes survived only one day after hospitalization. Lastly, a man (65-70) with pulmonary disease and chronic blood disease died five days after admission.

Table 2. Frequency of symptoms among studied patients at days 1, 3 and 6.

Symptoms	Day of record	N (%)
Muscle pain	Day 1	66 (50)
	Day 3	33 (47.8)
	Day 6	14 (41.2)
Dry cough	Day 1	93 (70.4)
	Day 3	48 (69.5)
	Day 6	26 (76.5)
Anorexia	Day 1	39 (29.5)
	Day 3	23 (33.3)
	Day 6	19 (55.9)
Anosmia and Ageusia	Day 1	56 (42.4)
	Day 3	31 (44.9)
	Day 6	18 (52.9)
Diarrhea	Day 1	54 (40.9)
	Day 3	30 (43.5)
	Day 6	19 (55.9)
Nausea and Vomiting	Day 1	43 (32.6)
	Day 3	35 (50.7)
	Day 6	24 (70.6)
Headache	Day 1	54 (40.9)
	Day 3	31 (44.9)
	Day 6	24 (70.6)
Shortness of breath	Day 1	56 (42.4)
	Day 3	41 (59.4)
	Day 6	26 (76.5)
Fever	Day 1	72 (54.5)
	Day 3	41 (59.4)
	Day 6	27 (79.4)

Note: Survived patients on day 1, 132 patients, day 3, 69 and day 6, 34 patients

Table 3. Frequency of underlying diseases among patients.

Underlying diseases	Frequency N (%)
Pulmonary diseases	12/132 (9.09)
Blood pressure	18/132 (13.63)
Diabetes	22/132 (16.66)
Cardiovascular disease	10/132 (7.57)
Chronic renal disease	7/132 (5.30)
Cancer	7/132 (5.30)

Moreover, 5.3% of patients had lung cancer, colon cancer, and leukemia. Additionally, two cases had a history of surgery, and one patient with a history of kidney transplantation died nine days after admission. Three days after admission, 55.3% of the studied patients died, and 21.5% lived longer than six days.

According to the result of complete blood count, on the first day of hospital admission, 45.52% of the patients and 54.05% of the survived patients on the third day showed a rise in their leucocyte number (>9.5). On the sixth day of admission, there was an increase in the leucocyte number of 71.42% of the survived patients. Subsequently, with a rise in hospitalization, the number of patients with elevated leucocytes counts was higher. Reduction in lymphocytes was frequently observed in the patients. On the first, third, and sixth day of hospitalization, 71.87%, 86.95%, and 100% of the patients showed lymphopenia, respectively. Therefore, lymphopenia was associated with an increase in hospitalization duration. Other laboratory findings included platelet counts, PT, and PTT were normal (Table 4).

Table 4. Laboratory results of patients' samples at day 1, 3 and 6.

Laboratory Parameters	Day 1	Day 3	Day 6
Leukocytes ($\times10^9$ /L; normal range 3.5-9.5)	9.1 (6.5-11.9)	9.6 (6.6-14.5)	17.4 (7.95-21.30)
Increased—No./total No. (%) (>9.5)	56/123 (45.52)	20/37 (54.05)	15/21 (71.42)
Lymphocyte percentage (%, normal range 20-50)	10 (10-21)	10 (8-15)	10 (5.5-13)
Decreased—No./total No. (%) (<20%)	23/31 (71.87)	20/23 (86.95)	9/9 (100)
Platelet ($\times10^3$ /uL; normal range 150-450)	205.5 (153.5-253)	217 (149.5-300)	201 (91.5-294)
PT (Sec; normal range 11 - 13.5)	12.5(12-13.58)	13.5(12-15.25)	12.5(12-13.35)
PTT (Sec; normal range 28-40)	30.5 (28-39)	36(28-45)	32.5(28.25-52.5)
BUN (mg/dL; normal range 13-43)	26.5(20-41)	27(17.5-39.5)	31(21-72)
Creatinin (mg/dL; normal range 0.6-1.3)	1.2(1.0-1.6)	1.07(0.86-1.92)	1.0(0.70-2.72)
Na (mEq/L; normal range 135-145)	134(132-138)	135(132-140)	138(133-143)
K (mEq/L; normal range 3.5-5.3)	4.2 (4-4.55)	4(3.9-4.3)	4.3(3.93-4.98)

According to Table 5, patients' LDH and ESR increased, with 94.64% of patients experiencing an LDH level above the normal range (>480) and 92.5% experiencing an ESR level above the normal range (>30). Furthermore, 42.85% and 44.73% had elevated ALT and AST levels, respectively. Finally, 89.47% of the patients underwent a PaO_2 level that was lower than normal, whereas 50% of them showed an increase in $PaCO_2$ (respiratory acidosis), and 62.5% represented a decrease in HCO_3 (Table 5).

Table 5. Base line Laboratory tests results according to patients' blood tests.

Laboratory tests	Results IQR: 50% (25% -75%)
LDH (U/L; normal range 230-480)	954.5 (757.5-1386.25)
ALT (SGOT) (U/L; normal range Up to 37)	32 (24-70)
AST (SGPT) (U/L; normal range Up to 41)	37.5 (25.75-54.75)
ALP (U/L; normal range 80-306)	199 (142-292)
Bilirubin (Total) (mg/dl; normal range	0.85 (0.50-1.92)

Laboratory tests	Results IQR: 50% (25% -75%)
0.3- 1.2)	
Ca (mg/dL; normal range 8.6-10.3)	8.3 (8.1-8.5)
Mg (mg/dL; normal range 1.53-2.5)	2.05 (1.9-2.3)
Blood pH (normal range 7.35-7.4)	7.27 (7.17-7.43)
PaO_2 (mmHg; normal range 80-100)	27.05 (1.00-57.80)
$PaCO_2$ (mmHg; normal range 35-45	43.85 (30.83-51.95)
HCO_3 (mEq/L; normal range 21-28)	19.5 (15.78-26.35)
ESR 1hr (mm/h ; Up to 30)	72 (56.50-91.75)

4.Discussion

In the present study, the data of 132 non-survived COVID-19 patients were collected from Razi Hospital in Rasht, Iran. The majority of subjects were in the age range of 66-75, which is older than patients' mean age stated by Zhang *et al*. (57 years) **(19)**, Wang *et al*. (56 years) **(19)**, and Chen *et al*. (55.5 years) **(20)**. According to M. Nikpour Aghdam *et al*. **(21)**, the majority of their cases were men, which is inconsistent with the results by Wan *et al*. **(22)**, Zhang *et al*. **(19)**, and S. Tian *et al*. **(22)**, reporting an equal range of male and female patients. Lower sensitivity to infection among women could be ascribed to the X chromosome and sex hormones, which have been suggested to play a role in innate and adaptive immunity **(23) (24)**.

On the contrary to other studies reporting fever as the most common symptom, dry cough (70.45%) was the most common symptom among studied patients herein. The prevalence of cough was similar to that in other reports **(19)**. Fever was observed in 54.54% of the patients, which is similar to that in the results of W. Guan *et al*. (25) (43.8%) and lower than that in the findings of Wang *et al*. **(19)**, Huang *et al*. **(26)**, and Zhang *et al*. **(19)**, reporting fever as the most prevalent symptom (>90%). In the present study, fever increased to 79.41% during hospitalization, which is in line with the report by Guan *et al*. **(25)** (88.7%).

Other symptoms, such as muscle pain and anorexia, were similar to those reported by Wang *et al*. **(19)**. Diarrhea (40.9%), vomiting, and nausea (32.57%) were common gastrointestinal signs in this study, while Wang *et al*. **(19)** stated that 20% to 25% of the patients experienced diarrhea. These symptoms developed during the course of the disease **(22)**.

Three patients had a history of surgery (2.27%); however, Zhang *et al*. **(27)** reported a 27.1% history of surgery among their studied patients. Diabetes was among the main underlying diseases (16.66%) in the studied patients, followed by high blood pressure (13.63%). Zhang *et al*. **(27)** stated high blood pressure (30%) and diabetes (12.1%) followed by cardiovascular disease as the most determining underlying diseases.

Leucocyte count increased in 45.52% of the patients, which reached 71.42% during hospitalization; this is not in line with the report of Zhang *et al*. **(27)** and Wan *et al*.**(22)** reporting that leucocyte count was in the normal range.

Lymphopenia was common in the studied patients herein (75.4%); this is in agreement with the study of Pingzheng Mo *et al*. (28) (73.5%). There was a positive correlation between hospitalization and increased lymphopenia among the subjects. In the current study, the platelet count was in the normal range. Nevertheless, Wan *et al*. **(22)** reported it to be 12% and 4% below and above the normal range, respectively.

Other laboratory findings, such as LDH, ALT, and AST levels, increased in the patients, which is in accordance with the study of Jin X, *et al*. **(29)** and Wan *et al*. **(22)**. ALP was also in the normal range among all the studied patients while ESR was elevated, indicating an impaired early liver function in the patients at a mild level; meanwhile, this impairment was more evident among severe cases.

This study had certain limitations; primarily, there were no data for all the studied days. Secondly, this work was conducted in a hospital; therefore, the results could be generalized if it were a multicenter study.

5. Conclusion

According to this study, the rate of mortality of COVID-19 was higher in older patients and males with a history of underlying diseases. The most prevalent underlying diseases were diabetes and blood pressure. The symptoms and clinical tests were exacerbated with a rise in hospitalization duration. Hepatic and renal enzymes were elevated during the

disease, indicating damage to the organs. Lymphopenia and the increase of leucocyte count were highly frequent among the non-survived patients. These factors can be used as predictors of death in COVID-19 disease. Some patients infected with Coronavirus die due to the disease despite not having shown clinical symptoms, such as fever or cough.

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Conflict of Interest

None declared.

Reference

1. Opriessnig T, Huang YW. Coronavirus disease 2019 (COVID-19) outbreak: Could pigs be vectors for human infections? Xenotransplantation. 2020;27(2). [DOI:10.1111/xen.12591]
2. Rockett RJ, Arnott A, Lam C, Sadsad R, Timms V, Gray KA, et al. Revealing COVID-19 transmission in Australia by SARS-CoV-2 genome sequencing and agent-based modeling. Nat Med. 2020;26(9):1398-404. [DOI:10.1038/s41591-020-1000-7] [PMID]
3. Bchetnia M, Girard C, Duchaine C, Laprise C. The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): A review of the current global status. J Infect Public Health. 2020;13(11):1601-10. [DOI:10.1016/j.jiph.2020.07.011] [PMID] [PMCID]
4. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and coronavirus disease 2019: what we know so far. Pathogens. 2020;9(3):231. [DOI:10.3390/pathogens9030231] [PMID] [PMCID]
5. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531-8. [PMID] [PMCID] [DOI:10.1007/s00392-020-01626-9]
6. Bohmwald K, Galvez N, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cellular Neurosci. 2018;12:386. [DOI:10.3389/fncel.2018.00386] [PMID] [PMCID]
7. Blume C, Jackson CL, Spalluto CM, Legebeke J, Nazlamova L, Conforti F, et al. A novel ACE2 isoform is expressed in human respiratory epithelia and is upregulated in response to interferons and RNA respiratory virus infection. Nature Genet. 2021;53(2):205-14. [DOI:10.1038/s41588-020-00759-x] [PMID]
8. Liaskou E, Hirschfield GM, Gershwin ME, editors. Mechanisms of tissue injury in autoimmune liver diseases. Seminars in immunopathology; 2014: Springer. [DOI:10.1007/s00281-014-0439-3] [PMID]
9. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204-18. [PMID] [PMCID] [DOI:10.18632/oncotarget.23208]
10. Li K, Fang Y, Li W, Pan C, Qin P, Zhong Y, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). Eur Radiol. 2020;30(8):4407-16. [PMID] [PMCID] [DOI:10.1007/s00330-020-06817-6]
11. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. J Chin Med Assoc. 2020;83(3):217-20. [PMID] [PMCID] [DOI:10.1097/JCMA.0000000000000270]
12. Fan L, Fang M, Li Z, Tu W, Wang S, Chen W, et al. Radiomics signature: a biomarker for the preoperative discrimination of lung invasive adenocarcinoma manifesting as a ground-glass nodule. Eur Radiol. 2019;29(2):889-97. [DOI:10.1007/s00330-018-5530-z] [PMID]
13. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46(6):1089-98. [DOI:10.1007/s00134-020-06062-x] [PMID] [PMCID]
14. Hopman J, Allegranzi B, Mehtar S. Managing COVID-19 in Low- and Middle-Income Countries. Jama. 2020;323(16):1549-50. [DOI:10.1001/jama.2020.4169] [PMID]

15. Younes N, Al-Sadeq DW, Al-Jighefee H, Younes S, Al-Jamal O, Daas HI, et al. Challenges in Laboratory Diagnosis of the Novel Coronavirus SARS-CoV-2. Viruses. 2020;12(6):582. [DOI:10.3390/v12060582] [PMID] [PMCID]

16. Sebastiani P, Nolan VG, Baldwin CT, Abad-Grau MM, Wang L, Adewoye AH, et al. A network model to predict the risk of death in sickle cell disease. Blood. 2007;110(7):2727-35. [PMCID] [DOI:10.1182/blood-2007-04-084921] [PMID]

17. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19-A systematic review. Life Sci. 2020:117788. [DOI:10.1016/j.lfs.2020.117788] [PMID] [PMCID]

18. Caliendo AM, Gilbert DN, Ginocchio CC, Hanson KE, May L, Quinn TC, et al. Better tests, better care: improved diagnostics for infectious diseases. Clin Infect Dis. 2013;57 Suppl 3(suppl 3): S139-70. [DOI:10.1093/cid/cit578] [PMID] [PMCID]

19. 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 (11):1061-9. [DOI:10.1001/jama.2020.1585] [PMID] [PMCID]

20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. [DOI:10.1016/S0140-6736(20)30211-7]

21. Nikpouraghdam M, Jalali Farahani A, Alishiri G, Heydari S, Ebrahimnia M, Samadinia H, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. J Clin Virol. 2020;127:104378. [DOI:10.1016/j.jcv.2020.104378] [PMID] [PMCID]

22. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. J Infect. 2020;80(4):401-6. [DOI:10.1016/j.jinf.2020.02.018] [PMID] [PMCID]

23. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Moller M. The X chromosome and sex-specific effects in infectious disease susceptibility. Hum Genomics. 2019;13(1):2. [DOI:10.1186/s40246-018-0185-z] [PMID] [PMCID]

24. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity Clin Rev Allergy Immunol, 56 (2019). Clin Rev Allergy Immunol. 308-21. [DOI:10.1007/s12016-017-8648-x] [PMID]

25. 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(18):1708-20. [DOI:10.1056/NEJMoa2002032] [PMID] [PMCID]

26. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. [DOI:10.1016/S0140-6736(20)30183-5]

27. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-41. [DOI:10.1111/all.14238] [PMID]

28. Mo P, Xing Y, Xiao Y, et al. Clinical Characteristics of Refractory Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2021;73(11):e4208-e4213. [DOI:10.1093/cid/ciaa270] [PMID] [PMCID]

29. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;69(6):1002-9. [PMCID] [DOI:10.1136/gutjnl-2020-320926] [PMID]