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Prevalence of SARS-CoV-2 in Patients with Severe Pneumonia in Khuzestan Province, Iran

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ABSTRACT

The emergence of a highly pathogenic virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) accounts for severe pneumonia throughout the world. More than 7 million world population have been infected with SARS-CoV-2, and the number of deaths is increasing every day. This study aimed to evaluate the frequency of SARS-CoV-2 in hospitalized patients with acute respiratory infection (ARI).

During an outbreak of the SARS-CoV-2, the nasopharyngeal and oropharyngeal swabs were collected from 909 hospitalized patients with severe pneumonia, including 517 (56.9%) males and 392 (43.1%) females. All the collected samples were from different cities of Khuzestan province from 19 February to- 27 March 2020. The RNA was extracted from samples and subjected to real-time polymerase chain reaction (PCR) tests for the detection of the SARS-CoV-2. Simultaneously, the computerized tomography (CT) scan was tested for the presence of ground-glass opacity in the lung among the patients.

Of the total number of 909 specimens, 328 (36.08%) cases, including 185 (20.35%) females and 143 (15.73%) males, were positive for the SARS-CoV-2 while, 581 (63.9%) cases, including 374 (41.14%) males and 207 (22.77%) were negative for the SARS-CoV-2 by

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real-time PCR (p=0.001).Four hundred sixteen (45.76%) cases were positive for ground-glass opacity in the lung by CT scan, while 328/909 (36.08%) trials proved positive for SARS-CoV-2 by the real-time PCR (p=0.003).

In this study, 36.08% of patients were positive for SARS-CoV-2. Although the results of positive cases by CT scan showed higher than real-time PCR, screening the SARS-CoV-2 with a real-time PCR method is the first line of choice.

Keywords: Nucleocapsid protein; Pneumonia; Real-time polymerase chain reaction; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in adult patients with unexplained severe pneumonia in Wuhan, China, in December 2019.[1] Rapidly the virus has spread with high morbidity and low mortality in china and now it has become a pandemic.[2,3] According to the world health organization (WHO) reports, the overall mortality rate for SARS-CoV-2 varies between 3% and 4.3%.[2,4,5]

Coronaviridae has been divided into four genera, alpha-coronavirus, beta-coronavirus, gamma-coronavirus , and delta-coronavirus. Among them, alpha (229E, NL63) and beta coronavirus (OC43, HKU1, Middle East respiratory syndrome coronavirus(MERS-CoV), SARS-CoV, and SARS-CoV-2) are zoonotic and cause ARI in humans.[6-13]

SARS-CoV-2 is enveloped, 60–140 nm in diameter, and comprised of single-stranded RNA approximately 30 kb in length.[14] The Genome contains 10 open reading frame (ORFs), among them ORF 10 encodes four main proteins: S, M, E, N proteins, and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein.[15,16] SARS-CoV-2 can be inactivated by ethanol, chlorine, peroxyacetic acid, and chloroform.[17,18]

The transmission of SARS-CoV-2 to humans happens via wild animals, droplets during coughing and sneezing by patients or asymptomatic individuals.[19,20]
It may also occur via touching the nose, mouth, and eyes by contaminated hands.[21] The transmission of the SARS-CoV-2 via the fecal-oral route has also been reported.[22]

The incubation period is about 2 to 14 days. The SARS-CoV-2 enters the respiratory mucosa cells via angiotensin-converting enzyme 2 (ACE2). Antigenic peptides are presented by major histocompatibility complex (MHC or HLA) and then recognized by virus-specific cytotoxic T lymphocytes (CTLs).[23] Eventually, antigen presentation evokes virus-specific B (IgM followed by IgG) and T cells responses ($CD4^+$ and $CD8^+$).[24] Common symptoms include fever, fatigue, and dry cough, always followed by anorexia, myalgia, dyspnea, lymphopenia and the prolonged prothrombin time is also noticed as the most common characteristic.[19,20]

Severe cases cause the immune defenses to overshoot with a "cytokine storm" (IFN-α, IL-1β, IFN-γ, TNF-α, TGFβ, IL-18, IL-12, IL-6, i.e.) and chemokines CXCL10, CXCL9, CXCL8, CCL5 CCL3 CCL2).[25] White blood cells are misdirected to attack and inflame healthy tissue, leading to failure of the heart, lungs, intestines, liver, kidneys, and genitals multiple organ dysfunction syndrome, (MODS). WBC may shutdown the lungs due to acute respiratory distress syndrome (ARDS) which makes absorption of oxygen difficult. Most deaths due to coronavirus disease 2019 (COVID-19) are, therefore, due to respiratory failure.[26]

The respiratory samples, including sputum, nasopharyngeal swab, throat swab, and Bronchoalveolar lavage, can be used for diagnosis of the SARS-CoV-2 by real time-PCR.[19,20] Presently, real-time polymerase chain reaction (PCR), computerized tomography (CT) imaging, and some hematology parameters are used for clinical diagnosis of the SARS-CoV-2 infection.[27,28]

Concerning the quick global outbreak of the coronavirus, this study was conducted to determine the prevalence of SARS-CoV-2 among hospitalized patients with severe pneumonia in Khuzestan province, Iran.

PATIENTS AND METHODS

Sampling

For this cross-sectional study, the nasopharyngeal and oropharyngeal swabs samples were received from different hospitals of Khuzestan province, Iran, from 19 February 2020 to 27 March 2020. The hospitalized patients were aged <10 years to <80 years with clinical severe viral pneumonia. Most patients had symptoms such as fever, fatigue, dry cough, anorexia, myalgia, dyspnea, lymphopenia, prolonged prothrombin time, and fevers over 38°C. All samples were then transferred to the reference laboratory and were storedin storage refrigerators at -80°C before RNA extraction.

This study has been approved with Ethical Code number IR.AJUMS.REC.1399.005 by the ethics committee of Ahvaz Jundishapur University of Medical Sciences, Iran. According to the Declaration of Helsinki's ethical standards, all experiments were achieved in conformity with relevant laws and institutional guidelines.

RNA Extraction

Viral RNA was extracted from 909 samples by a high-pure nucleic acid extraction kit (Roche Diagnostic, Manheim, Germany), according to the manufacturer's instructions.

Primers and Real-time PCR

The multiplex RT-q PCR test kit was manufactured by DAAN Gene.co. China was used to detect conserved regions of N and ORF1ab of SARS-CoV-2. The 5 µl amount of extracted RNA was added to theOne-Step RT-PCR Buffer (enzymes, primers, and probes). The patient samples, positive and negative controls, and internal control (RNAse P gene) were subjected to Real-time PCR (Qiagen rotor-gene q, Germany) according to the manufacturer's instructions test kit. The thermal cycling conditions were programmed: one cycle 50ºC for 15 min, one cycle 95ºC for 15minutes, and 45 cycles: 94ºC for 15 sec, 55ºC for 45seconds.

Statistical Analysis

The records were evaluated by SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The chi-square test was run to study the variables, such as sex, distribution of viral infections in genders, and diverse age groups. p values<0.05 were considered statistically significant.

RESULTS

Overall, 909 samples [392 (43.1%) females and 517 (56.9%) males] with severe viral pneumonia cases were registered from 19 February 2020 to 27 March 2020. The Mean patients' ages: 49.2±20.49 years (ranged from 1 month to 99 years). Of the total number of 909 specimens, 328(36.08%) cases, including 185 (20.35%) females and 143 (15.73%) males, were positive for the SARS-CoV-2. While 581(63.9%) cases, including 374 (41.14%) males and 207 (22.77%) females, were negative for SARS-CoV-2 by real-time PCR (p=0.001) (Table 1).

Table 1. Frequency of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), lymphopenia, and C-reactive protein (CRP) in gender

Parameter	Female	Male	Total	*p*
Total patients	392 (43.1%)	517 (56.9%)	909 (100%)	
Positive COVID-19*	185 (20.35%)	143 (15.73%)	328 (36.08%)	***p*<0.001**
Negative COVID-19	207 (22.77%)	374 (41.14%)	581 (63.9%)	
Lymphopenia positive**	83/185 (44.86%)	53/143 (37.6%)	136/328 (41.46%)	0.155
CRP* positive**	164/185 (88.64%)	116/143 (81.11%)	280/328 85.36%	0.056

The numbers of positive cases in females and males were 53.4% and 43.6%, respectively. The chi-square test showed a significant gender difference (p<0.001). The distribution of lymphopenia among females and males with positive SARS-CoV-2 was not significant (0.155). The distribution of positive CRP among the females was higher than males but not significant (0.056). * COVID-19, ** Lymphopenia: below 1.0 x 10(9)/L , *** C-reactive protein (CRP)

Table 2. The distribution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in different age groups

Age (years)	Number	SARS-CoV-2 Positive	SARS-CoV-2 Negative
0-9	27	0	27(100%)
10-19	34	1(2.9%)	33(97.1%)
20-29	89	23(25.8%)	66(74.2%)
30-39	166	49(29.5%)	117(70.5%)
40-49	147	77(52.4%)	70(47.6%)
50-59	153	69(45.1%)	84(54.9%)
60-69	142	59(41.5%)	83(58.5%)
70-79	74	37(50%)	37(50%)
+80	77	13(16.9%)	64(83.1%)

The distribution of SARS-CoV-2 in different age-groups 20-29(25.8%), 30-39(29.5%), 40-49(52.4%), 50-50(45.1%), 60-69(41.5%), 70-79 (50%) and > 80 years (16.9%). It is noted that there is an increasing rate of positive SARS-CoV-2 as age-group increases.

Of the total number of 909 specimens, 390 (42.9%) cases, including [219 (56.15%) females and 171 (43.84%) males], were positive for ground-glass opacity in the lung by CT scan. The number of 390 (42.9%) positive ground-glass opacity by CT scan was compared with 328/909(36.08%) cases proved by the real-time PCR as significant (p=0.003).

The distributions of SARS-CoV-2 in different age-groups were 20-29(25.8%), 30-39(29.5%), 40-49(52.4%), 50-50(45.1%), 60-69(41.5%), 70-79 (50%) and > 80 years (16.9%) (Table 2). No SARS-CoV-2 was detected in the age group below ten years of age.

DISCUSSION

The pandemic SARS-CoV-2 has led to a public health concern and economic challenges throughout the world.[29] Although the origin of SARS-CoV-2 is ambiguous, several factors including low environmental humidity, dry and cold climate, natural host (bat) intermediate hosts (bamboo rat, and pangolin) are noted as influencing factors to spread COVID-19.[30]

The early detection of COVID-19 by real-time PCR is the first line of choice established as a decisive method to control community transmission able to provide appropriate treatment.[31]

In our study, out of 909 specimens, 328(36.08%) cases, including 185 (20.35%) females and 143 (15.73%) males, were positive for the SARS-CoV-2 by real-time PCR (p=0.001). These results showed that the females were more susceptible to be infected with SARS-CoV-2 than males.

Chest CT scan imaging is sensitive but less specific in diagnosing the COVID-19 (32). In the present study, 390 (42.9%) cases were positive for ground-glass opacity in the lung by CT scan, which appeared significant (p=0.003) compared with 328/909 (36.08%) cases diagnosed by the real-time PCR. The presence of ground-glass opacity in the lung by CT Scan has also been seen in other viral infections such as influenza virus H1N1, respiratory syncytial virus (RSV), parainfluenza virus,[33,34] military tuberculosis (MT)[35], and streptococcus pneumonia.[36] In the present study, the mentioned viruses and bacteria infections have not been investigated among the patients.

Furthermore, the obtained results indicated that the age group above 20 years was at risk of SARS-CoV-2 infection, in addition to the age group> 40 years who were much more susceptible to contract SARS-CoV-2 due to underlying conditions such as cardiovascular disease, diabetes, and hypertension.[37] In this research, no SARS-CoV-2 was detected in the age group < 10 years. Usually, SARS-CoV-2 causes mild respiratory infections in children.[38] The SARS-CoV-2 have been confirmed in China, Japan, Singapore, Hong Kong, Thailand, South Korea, Taiwan, Australia, Malaysia, Germany, Vietnam, the USA, Macao SAR, the United Arab Emirates, Canada, France, the Philippines, the UK, Italy, India, Russia, Finland, Sweden, Sri Lanka, Cambodia, Nepal, Spain, and Belgium.[39]

Treatment is mainly supportive and symptomatic. Antibiotics and antifungals may be required if co-infections are confirmed.[27,40] The role of corticosteroids is not evidenced, but it was recommended that low-to-moderate doses of corticosteroids were effective for short- term therapy in SARS-CoV-2 ARDS.[41,42] Antiviral drugs such as ribavirin, lopinavir, and ritonavir have been taken against SARS and MERS. The treatment of patients with the SARS-CoV-2 with lopinavir-ritonavir and ribavirin has shown better outcomes as compared with ribavirin alone.[19] Evidence

has shown that the use of remdesivir, interferons, chloroquine, and plasma may be effective to treat patients with the SARS-CoV-2.[43,44]

Presently no approved vaccine is available against the SARS-CoV-2. Therefore, preventive measures should be implemented to stop the outbreak of SARS-COV-2 within communities. The generalization of our results is limited as the role of other coronaviruses such as 229E, NL63, OC43, HKU1, MERS-CoV SARS-CoV, and other viruses or co-infective viruses which can cause pneumonia were not investigated; thus, further investigation is required.

The newly emerged coronavirus in Ahvaz city is a tremendous public health problem. The rates of SARS-CoV-2 among females and males were 20.35%and 15.73%, respectively (p=0.001). The results revealed that there was an increasing rate of positive SARS-CoV-2 as age increased. Preventive measures should be considered for the elder age group.

The analysis of positive SARS-CoV-2 416/909 (45.76%) cases by CT scan compared with 328/909 (36.08%) cases by the real-time PCR proved significant (p=0.003). In conclusion, Although the results of positive trials by CT scan were higher in frequency than real-time PCR, the screening of SARS-CoV-2 with a real-time PCR method is still the first line of choice. At present, no definitive treatment and approved vaccine are available against COVID-19.

CONFLICT OF INTEREST

All the authors declare that there is no conflict of interest

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REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P. China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020 ;382(8):727-33.
2. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020 ;323(11):1061-1069.
3. Cowling BJ, Leung GM. Epidemiological research priorities for public health control of the ongoing global novel coronavirus (2019-nCoV) outbreak. Euro Surveill. 2020 ;25(6):2000110.
4. Xie M, Chen Q. Insight into 2019 novel coronavirus—an updated interim review and lessons from SARS-CoV and MERS-CoV. International Journal of Infectious Diseases 94 (2020) 119–124
5. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-269.
6. Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology. 2018 ;23(2):130-137.
7. Drosten C, Günther S, Preiser W, Van Der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348(20):1967-76.
8. Zaki AM, Van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814-20.
9. Elfiky AA, Mahdy SM, Elshemey WM. Quantitative structure-activity relationship and molecular docking revealed a potency of anti-hepatitis C virus drugs against human corona viruses. JMV. 2017;89(6):1040-7.
10. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol. 2009;7(6):439-50.
11. Báez-Santos YM, Mielech AM, Deng X, Baker S, Mesecar AD. Catalytic function and substrate specificity of the papain-like protease domain of nsp3 from the Middle East respiratory syndrome coronavirus. JVI. 2014;88(21):12511-12527.
12. Hemida MG, Alnaeem A. Some One Health based control strategies for the Middle East respiratory syndrome coronavirus. One Health. 2019; 8:100102.

13. German M, Olsha R, Kristjanson E, Marchand-Austin A, Peci A, Winter AL, Gubbay JB. Acute Respiratory Infections in Travelers Returning from MERS-CoV–Affected Areas. Emerg infect Dis. 2015 ;21(9):1654–1656
14. Masters PS. The molecular biology of coronaviruses. Adv Virus Rev. 2006 ;66:193-292.
15. Ziebuhr J, Snijder EJ, Gorbalenya AE. Virus-encoded proteinases and proteolytic processing in the Nidovirales. J Gen Virol. 2000 ;81(Pt4):853-79.
16. Hussain S, Chen Y, Yang Y, Xu J, Peng Y, Wu Y, Li Z, Zhu Y, Tien P, Guo D. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. JVirol. 2005;79(9):5288-95.
17. Kratzel A, Todt D, V'kovski P, Steiner S, Gultom M, Thao TT, et al. Inactivation of severe acute respiratory syndrome coronavirus 2 by WHO-recommended hand rub formulations and alcohols. Emerg Infect Dis. 2020; 26(7): 1592–1595.
18. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. Journal of Hospital Infection. 2020;104(3):246-51.
19. 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. The Lancet. 2020;395(10223):507-513.
20. Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr. 2020;87(4):281–286.
21. Li H, Wang Y, Ji M, Pei F, Zhao Q, Zhou Y, Hong Y, Han S, Wang J, Wang Q, Li Q. Transmission Routes Analysis of SARS-CoV-2: A Systematic Review and Case Report. Front Cell Dev Biol..2020 ;8:618.
22. Cha MH, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. World J Gastroenterol. 2020;26(19):2323–2332.
23. Cheng ZJ, Shan J. 2019 novel coronavirus: where we are and what we know. Infection. 2020; 48:155–163
24. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: current state of the science. Immunity. 2020 52(6): 910–941.
25. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020; 53: 25–32
26. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet. 2020 ;395(10229):1014-1015..
27. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil. Med. Res. 2020;7(1):4.
28. Huang P, Liu T, Huang L, Liu H, Lei M, Xu W, Hu X, Chen J, Liu B. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology. 2020;295(1):22-3.
29. Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int J Biol Sci. 2020; 16 (10):1678-1685
30. Sun Z, Thilakavathy K, Kumar SS, He G, Liu SV. Potential factors influencing repeated SARS outbreaks in China. In J Environ Res Public Health. 2020;17(5):1633.
31. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA.2020 ;323(18):1843-1844.
32. He JL, Luo L, Luo ZD, Lyu JX, Ng MY, Shen XP, Wen Z. Diagnostic performance between CT and initial real-time RT-PCR for clinically suspected 2019 coronavirus disease (COVID-19) patients outside Wuhan, China..Respir Med.2020;168:105980
33. Lee JE, Choe KW, Lee SW. Clinical and radiological characteristics of2009 H1N1 influenza associated pneumonia in young male adults. Yonsei Med J. 2013;54(4):927–34.
34. Kim MC, Kim MY, Lee HJ, Lee SO, Choi SH, Kim YS, et al. CT findings in viral lower respiratory tract infections caused by parainfluenza virus, influenza virus and respiratory syncytial virus. Medicine (Baltimore).2016;95(26):(e4003).
35. Lee J, Lim JK, Seo H, Lee SY, Choi KJ, Yoo SS, et al. Clinical relevance of ground glass opacity in

105 patients with miliary tuberculosis. RespirMed. 2014;108(6):924-30.
36. Haroon A, Higa F, Fujita J, Watanabe A, Aoki N, Niki Y, et al. Pulmonary computed tomography findings in 39 cases of Streptococcus pneumoniae pneumonia. Intern Med. 2012;51(24):3343-9
37. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with SARS-COV-2in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395:1054–1062
38. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020;382(17):1663-1665.
39. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges.. Int J Antimicrob Agents. 2020;55(3):105924.
40. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, Lin R, Tang LF, Wang TL, Wang W, Wang YS. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr. 2020:16(3):240-246
41. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. The Lancet. 2020;395(10223):473-475.
42. Zha L, Li S, Pan L, Tefsen B, Li Y, French N, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust. 2020;212(9):416-420.
43. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-271.
44. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20(4):398-400.