

A New Perspective; Co-Infection of Influenza with COVID-19 During The COVID-19 Pandemic in Southern Iran

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Abstract

Background In the current COVID-19 pandemic, COVID-19 viral respiratory symptoms have been confused with other viral respiratory infections such as influenza. Given that both viruses cause respiratory diseases, there are important differences between these two viruses in terms of how they are spread, controlled and treated. Due to these differences, a definitive diagnosis of each infection has important implications for the public health measures that can be implemented in response to the treatment of each virus.

Method In this cross-sectional retrospective study from 4th September 2020 to 5th December 2020 (time period of influenza outbreak in Iran, a total of 455 Severe Acute Respiratory Infections (SARI) patients were included. Two nasopharyngeal and one oropharyngeal throat swab samples were collected from all participants and evaluated for COVID-19 by real-time reverse transcriptase–polymerase-chain-reaction (RT-PCR) assay using the E-Gene specific primers/FAM probe and S Gene primers/ROX probe (Covitech, Iran) for SARS-CoV-2. Due to the concurrence of the study in autumn and the history of influenza outbreak at this time in Iran. Nasopharyngeal samples were collected and tested for influenza viruses A (H1N1, H3N2, seasonal flu), and Influenza B by one step qRT-PCR Master Mix (Invitrogen, United States) and AG synthesis probe and primers (Metabion, Germany) for Influenza A (H1N1, H3N2, seasonal flu) and B.

Results In this study, 455 patients with SARI were hospitalized during September to December 2020. 203(44.61%) were infected with SARS-COV-2 and of these patients, one patient was positive for both COVID-19 and Influenza. The mean age was estimated 54.93 ± 17.00 and 50.65 ± 17.71 in COVID-19 and non-COVID-19 groups, respectively which was significantly different ($P < 0.001$). Sex distribution between two groups showed that most of COVID-19 patients were male, this is in contrast with the COVID-19 negative group, in which most of patients were female and these differences were statistically significant. ($P = 0.057$). Clinical outcomes of patients with diagnosed SARI were measured. The main parameters were discharge from ICU and death during hospital admission. There was no significant difference between the number of patients discharge from ICU who were COVID positive or COVID negative. In addition, there was no significant difference between the number of patients who died who were COVID positive or COVID negative.

Conclusion The decline in Influenza incidence and coinfection with COVID-19 in comparison to previous years appears to be significant due to its concurrence with the COVID19 pandemic and general population awareness on observing the instructions for personal respiratory protection e.g mask-wearing, hand washing, self-isolation and public health measures. Therefore, routine testing and empirical treatment for suspected influenza coinfection in COVID-19 patients is not recommended.

1 Introduction

COVID-19 is a novel respiratory disease caused by a new coronavirus called SARS-CoV-2. The WHO first became aware of this new virus on 31 December 2019, following the first report of a cluster of infected cases of 'viral pneumonia' in Wuhan, People's Republic of China. [1, 2] In the continuing COVID-19 pandemic, these viral symptoms have been confused with other viral respiratory infections such as influenza. Given that both viruses cause respiratory diseases, there are important differences between these two viruses in terms of how they are spread, controlled and treated. Due to these differences, a definitive diagnosis of each infection has important implications for the public health measures that can be implemented in response to the treatment of each virus. The World Health Organization's FluNet platform based on three Southern Hemisphere countries from Oceania (Australia), South America (Chile), and Southern Africa (South Africa) showed very low influenza activity during the typical Southern Hemisphere influenza season June–August 2020. Therefore, in the upcoming 2020–21 Northern Hemisphere influenza season, countries where widespread personal protective and public health measures are maintained (e.g., face masks, social distancing, school closures, and teleworking) may have decreased influenza circulation. According to the Infectious Diseases Society of America (IDSA) guidelines, nucleic acid amplification test (NAAT) is a recommended procedure for detection of infectious diseases (such as SARS-CoV-2) in symptomatic individuals and in the suspected infected population. [3] Currently, Quantitative real-time-PCR (RT-PCR) is widely used for NAAT due to its large dynamic range, high sensitivity, high sequence specificity, little to no post amplification processing, and sample throughput. [4–6] Co-infection may cause the disease to become more complicated and may increase the mortality rate. [2, 7] Presently, diagnosis of the infectious agents is based on nucleic acid amplification is the gold standard technique and is very useful in the exact diagnosis of infectious diseases with similar presentations. Currently, a major concern is the co-concurrence of influenza and COVID-19 in the current epidemic, the co-infection of COVID-19 with different infections is evaluated in several studies. Many studies have shown a pattern of decrease in influenza incidence in 2020 due to public health measures. With respect to the importance of identifying the viral etiology in clinical practice, and for health policymakers in crisis management and supply of required protective equipment and medicines this study was designed to evaluate the co-infection of COVID-19 with influenza virus type A (H1N1) in patients with the Severe Acute Respiratory Syndrome in Ali Asghar Hospital, Shiraz, Iran.

2 Material And Methods

In this cross-sectional retrospective study from 4th September 2020 to 5th December 2020 (time period of influenza outbreak in Iran, a total of 455 Severe Acute Respiratory Infections (SARI) patients were included. All patients were hospitalized in Ali Asghar Hospital, Shiraz, Iran which is affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. Two nasopharyngeal and one oropharyngeal throat swab samples were collected from all participants and evaluated for COVID-19 by real-time reverse transcriptase–polymerase-chain-reaction (RT-PCR) assay using the E-Gene specific primers/FAM probe and S Gene primers/ROX probe (Covitech, Iran) for SARS-CoV-2. Nasopharyngeal samples were collected and analyzed for influenza. Due to the concurrence of the study in autumn and the history of influenza outbreak at this time in Iran. All nasopharyngeal samples were tested for influenza viruses A (H1N1,

H3N2, seasonal flu), and Influenza B by one step qRT-PCR Master Mix (Invitrogen, United States) and AG synthesis probe and primers (Metabion, Germany) for Influenza A (H1N1, H3N2, seasonal flu) and B. All tests were performed under standard procedures in the referral laboratories of Fars Province, Iran.. Demographic data and clinical specifications of the patients include age, sex, comorbidities, presenting symptoms, travel history, and contact history were collected in standard questionnaires and analyzed.

Informed consent was obtained from all participants of this study, in case of dead participants informed consent was obtained from legally authorized representatives. This study was approved by Shiraz University of Medical Sciences Ethical Committee, with ethics code IR.SUMS.REC.1398.1173. In addition, all methods were carried out in accordance with the relevant hospital clinical and ethical guidelines and regulations

3 Results

In the current study, 455 patients with SARI were hospitalized during September to December 2020. 203(44.61%) were infected with SARS-COV-2 and of these patients, one patient was positive for both COVID-19 and Influenza. The mean age was estimated 54.93 ± 17.00 and 50.65 ± 17.71 in COVID-19 and non-COVID-19 groups, Table 4 - 1, respectively which was significantly different ($P < 0.001$).

Table 4-1
Demographic Details of Patients with Severe Acute Respiratory Infections.

Variables	COVID-19 Positive (n = 203)	COVID-19 Negative (n = 252)	P-value
Age Distribution			
18–25 years old	5 (2.47%)	14(5.55%)	0.03
26–35 years old	32 (15.84%)	48(19.04%)	
36–45 years old	29 (14.35%)	51(20.23%)	
46–55 years old	26(12.87%)	34(13.49%)	
56–65 years old	58(28.71%)	41(16.26%)	
66–75 years old	31(15.34%)	40(15.87%)	
76–85 years old	17(8.8%)	22(8.73%)	
More than 86 years old	5(2.47%)	2(0.79%)	

Sex distribution between two groups showed that most of COVID-19 patients were male, Fig. 3 - 1, this is in contrast with the COVID-19 negative group, which most of patients were female, Fig. 3 - 2, and these

differences were statistically significant. ($P = 0.057$).

Fever ($P < 0.001$), cough ($P < 0.001$) and muscle pain ($P < 0.001$) symptoms were significantly different between the two study groups as shown in Fig. [3](#).

4 Discussion

The current study evaluated the co-infection of SARS-CoV-2 and Influenza virus in flu epidemic season during the first year of COVID-19 pandemic in the Southern Iran, in 455 patients with a SARI. In this study total of 203 patients were positive for COVID-19, only one patient was infected with Influenza H1N1 simultaneously (co-infected with COVID19). It was expected that other respiratory illnesses, such as the influenza, would be significantly reduced due to preventive policies related to the current COVID-19 crisis. Our study is consistent with several studies in other parts of the world. [8] In Kim et al study in California, of 1206 patients, a total of 116 patients was positive for COVID-19, while concomitantly only one patient was positive for Influenza type A. [9] In another study by Chaomin et al, only one patient of 201 COVID-19 positive individuals in the study was concomitantly positive for Influenza A virus. [10, 11] In the first large case series study in the US, a total of 5700 patients hospitalized with COVID-19 in the New York City Area were considered where it was shown that the rate of respiratory virus co-infection is only 2.1 percent. [12] In a study in Japan by Sakamoto et al. it was shown that seasonal influenza activity was lower in 2020 than in previous years in that region. [13] On the other hand, Yue and his research team have found that co-infection of SARS-CoV-2 and influenza viruses were common in Wuhan, China, between 12th January and 21st February 2020 during the COVID-19 outbreak. They have found that co-infection of SARS-CoV-2 and influenza viruses is highly prevalent during the early time of the COVID-19 outbreak in Wuhan (12th January-21st February 2020). [14] But it should be noted that this difference might be caused by other factors such as underlying diseases in infected patients or the different geographical circulation of respiratory viruses which may change during the COVID-19 epidemic continues as we exit out of the classical influenza season. [15] Another important point in reducing respiratory diseases, including influenza, is to follow the guidelines related to global COVID-19 risk control, which includes mask-wearing, hand washing, self-isolation as well as social distancing between symptomatic individuals. [14, 16] Because of these results, it is not yet clear whether initial testing should include both COVID-19 and influenza viruses especially at the time of influenza outbreak or whether the influenza testing can be added after the SARS-CoV-2 negative results return. Concerning COVID-19 risk factors, in agreement with our findings and previous studies, it can be suggested that COVID-19 has more effect on males than females, and increasing age is associated with increased odds of a positive SARS-Cov2 test result. [17–20] Also in systematic reviews, it has been shown that chronic comorbidities such as hypertension and diabetes mellitus especially uncontrolled forms are more at risk for severe COVID-19 disease [21, 22] Based on this information and the aggregation of results obtained so far, it seems that the current policies on respiratory diseases, especially in the field of diagnosis and vaccination, should be revised.

5 Conclusion

The decline in Influenza incidence and coinfection with COVID-19 appears to be significant due to its concurrence with the COVID-19 pandemic and general population awareness on observing the instructions for personal respiratory protection e.g mask-wearing, hand washing, self-isolation and public health measures. Therefore, routine testing and empirical treatment for suspected influenza coinfection in COVID-19 patients is not recommended.

Abbreviations

COVID-19 - Corona Virus Disease 2019

RT PCR - Reverse Transcriptase Polymerase Chain Reaction

ICU – Intensive Care Unit

SARI - Severe Acute Respiratory Infections

NAAT - nucleic acid amplification test

IDSA - Infectious Diseases Society of America

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all participants of this study, in case of deceased participants informed consent was obtained from legally authorized representatives. This study was approved by Shiraz University of Medical Sciences Ethical Committee, with ethics code IR.SUMS.REC.1398.1173. In addition, all methods were carried out in accordance with the relevant hospital clinical and ethical guidelines and regulations.

Consent for publication: Not applicable

Written informed consent was obtained from the patient for publication of this retrospective study. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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Patient data, lab data collected by: OE, AE, AH, MA, AS

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All authors have read and approved the final manuscript

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Figures

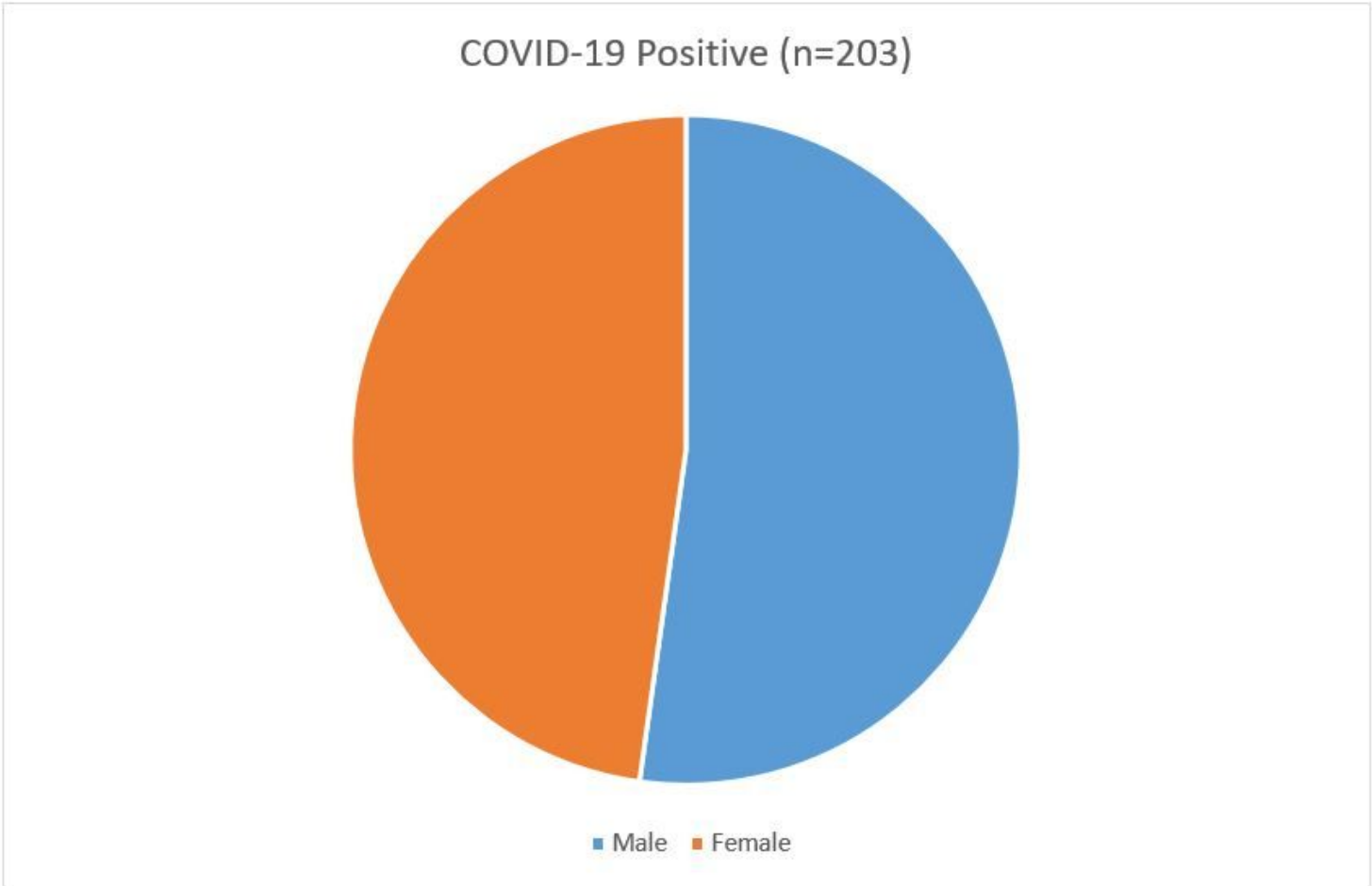


Figure 1

Sex distribution between two groups showed that most of COVID-19 patients were male, figure 3-1

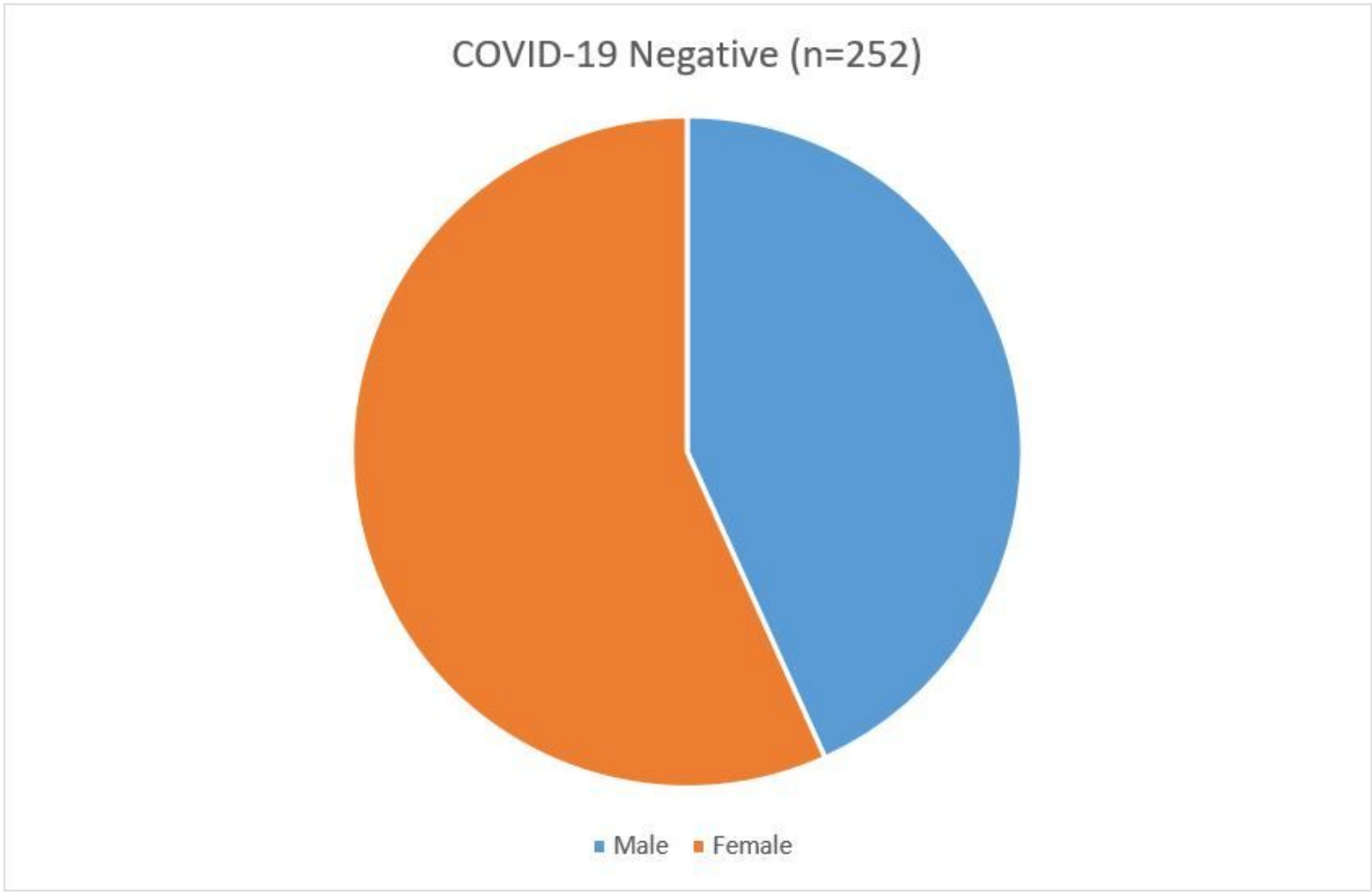


Figure 2

this is in contrast with the COVID-19 negative group, which most of patients were female, figure 3-2, and these differences were statistically significant. (P=0.057).

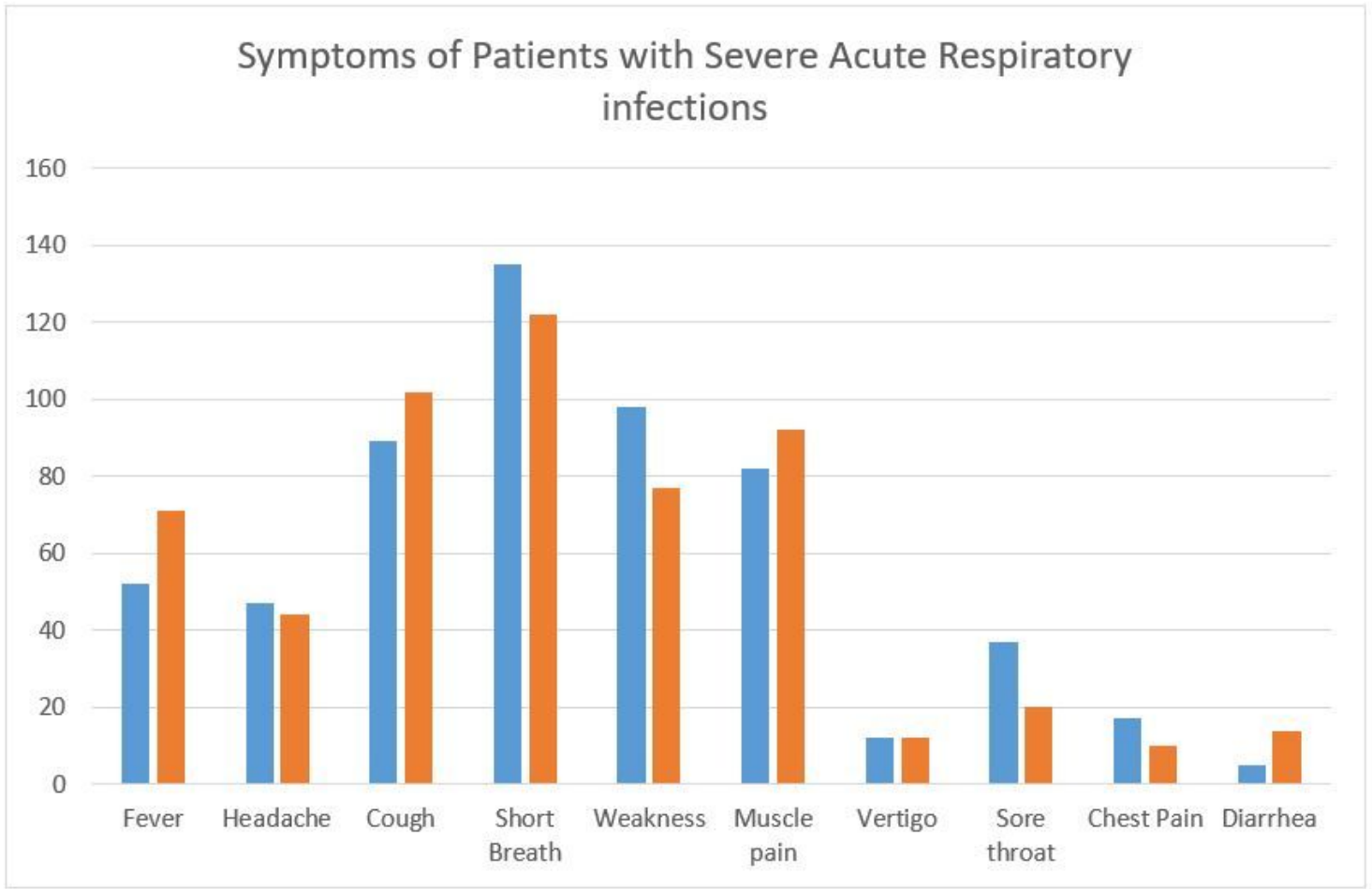


Figure 3

Fever ($P < 0.001$), cough ($P < 0.001$) and muscle pain ($P < 0.001$) symptoms were significantly different between the two study groups as shown in figure 3-3.

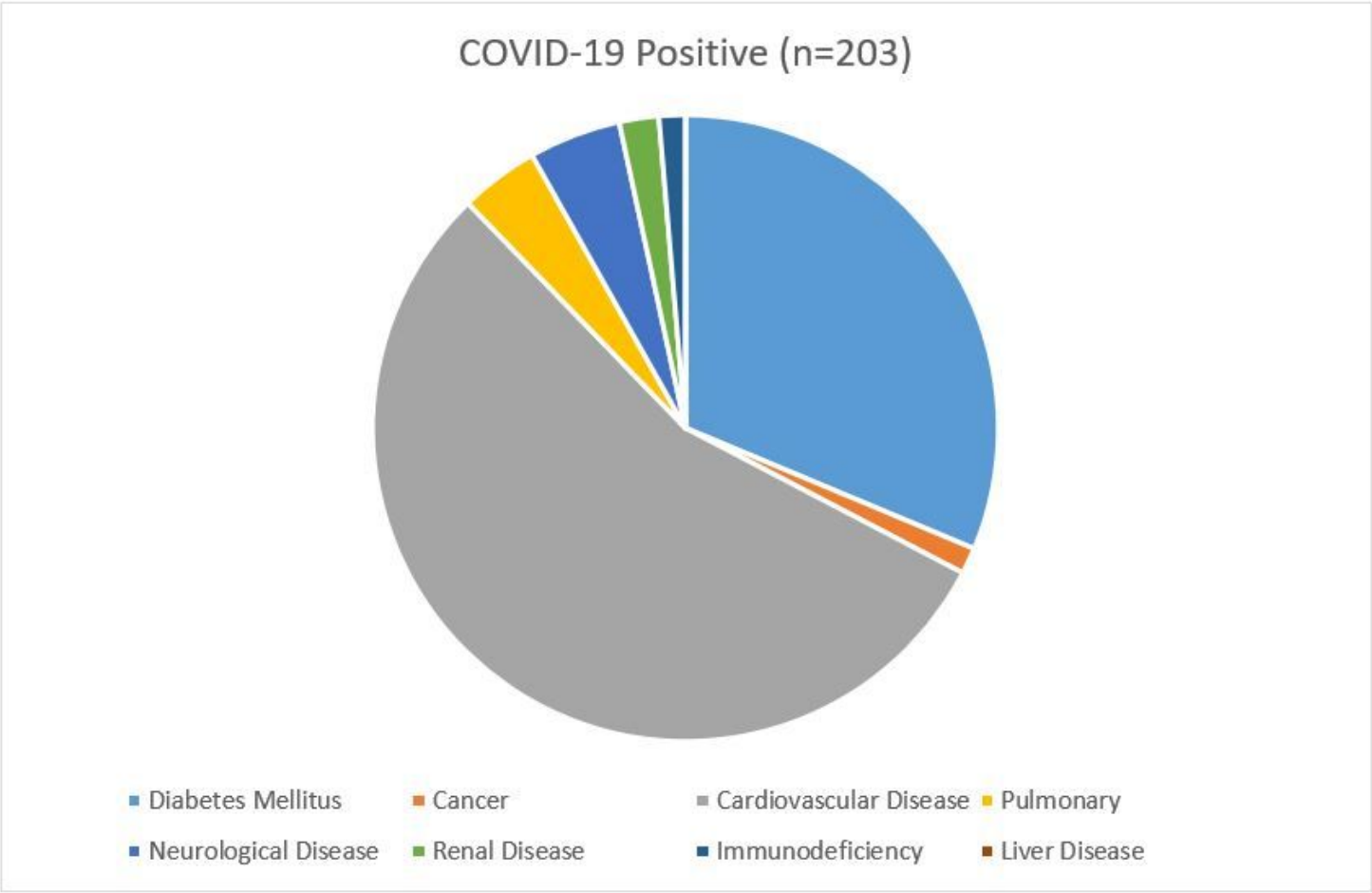


Figure 4

SARS-CoV-2 infection is related to underlying comorbidities as shown in figure 3-4

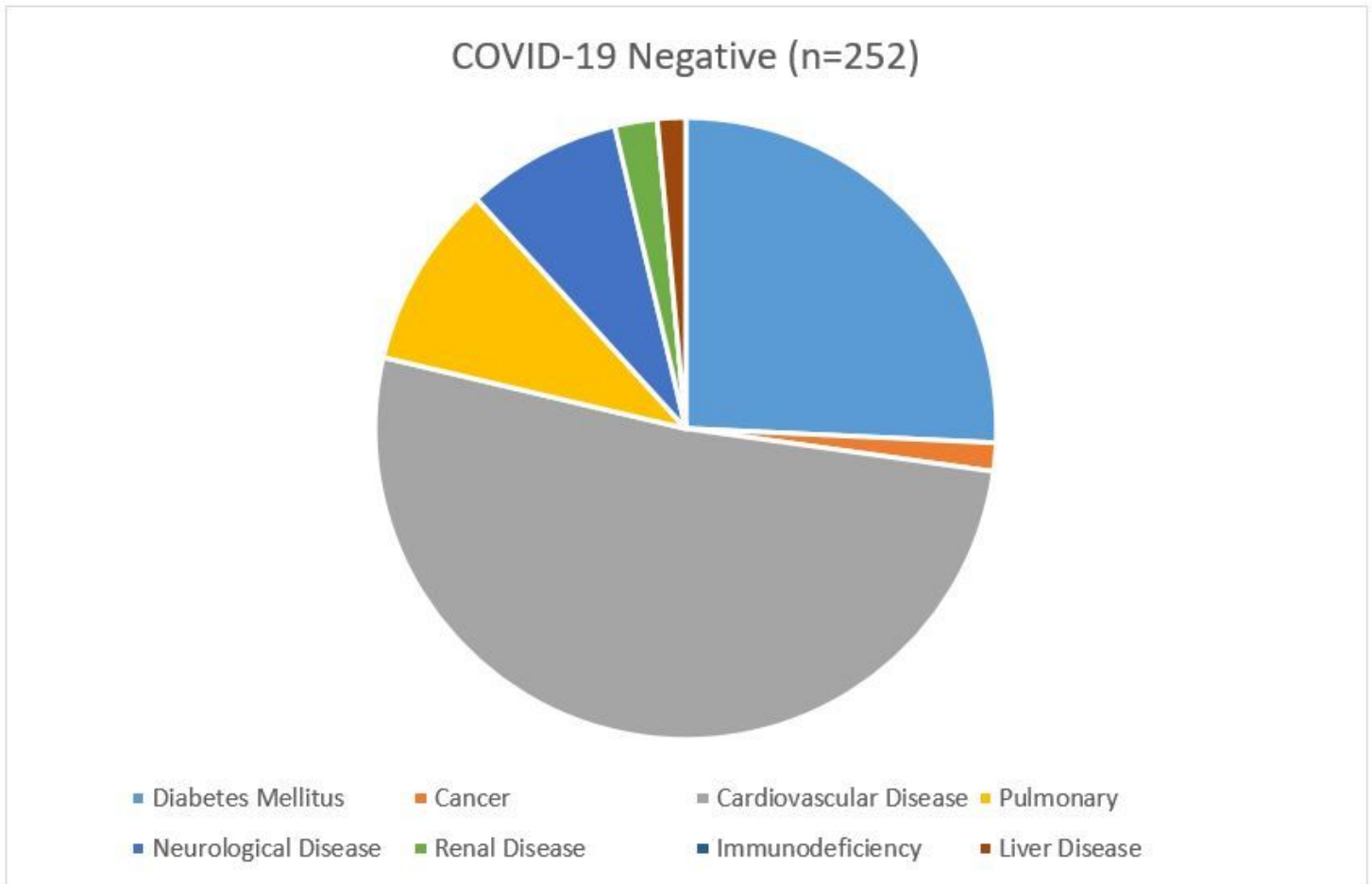


Figure 5

figure 3-5, of which, diabetic mellitus (P=0.015) and cardiovascular disease (P<0.001) were significantly different between two groups.

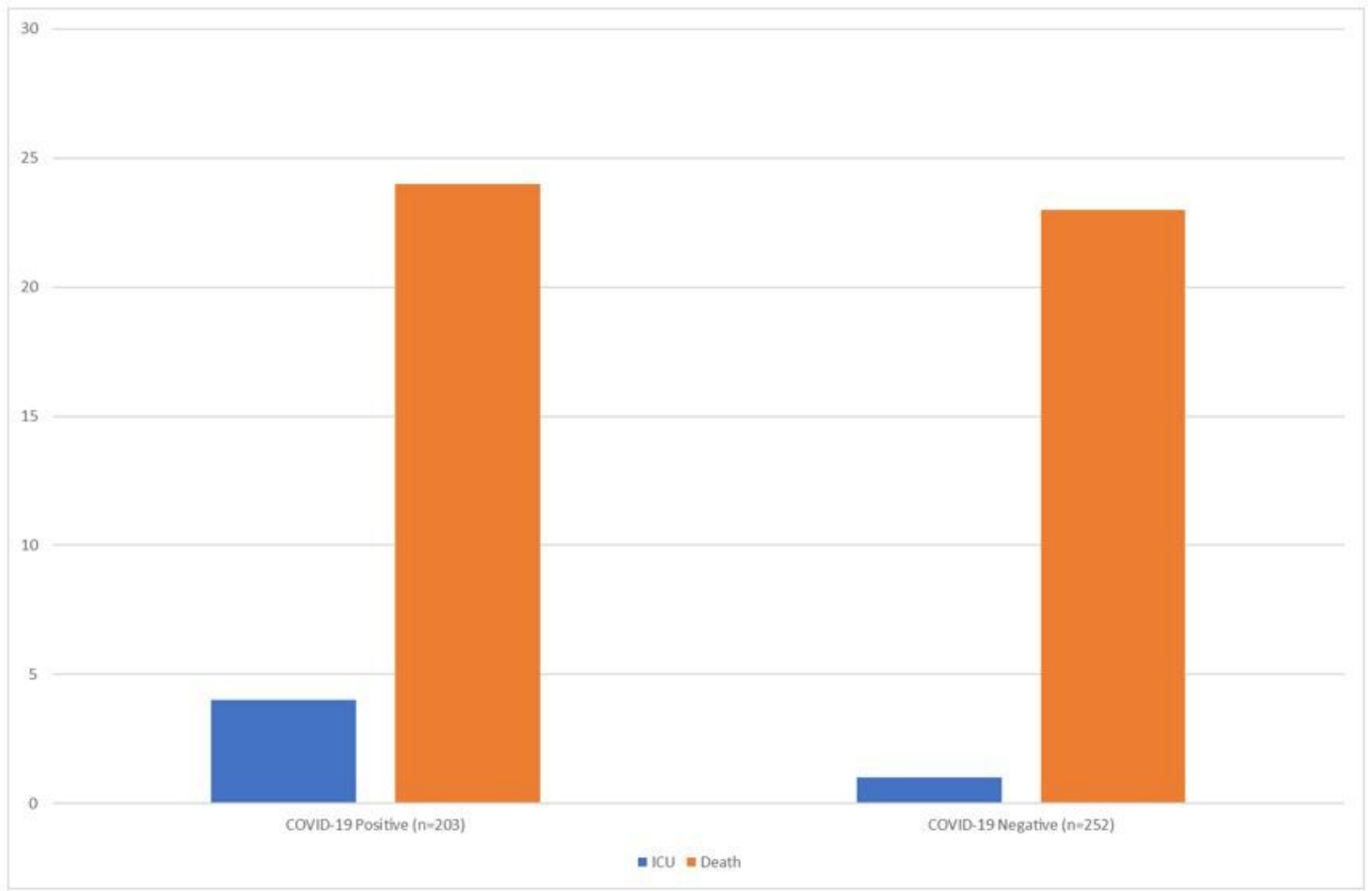


Figure 6

Clinical outcomes of patients with diagnosed SARI were measured. The main parameters were discharge from ICU and death during hospital admission. There was no significant difference between the number of patients discharged from ICU who were COVID-19 positive (4 patients) or COVID-19 negative (1 patient) as shown in figure 3-6.