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RESEARCH ARTICLE

The Role of Secondary Infections and Underlying Diseases in the Mortality of Patients with COVID-19

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Abstract:

Background:

Coronavirus disease (COVID-19) caused by coronavirus is a respiratory infection, that has spread worldwide in the past few months. Considering the necessity and importance of the COVID-19 pandemic, determining the importance of the secondary infection of COVID-19 patients and the death of these patients is one of the main issues considered in the study. Common bacterial infections are often found in viral respiratory infections and are major causes of death. This study investigated the cause of death from COVID-19 within a year.

Methods:

In this cross-sectional study from March 2020 and March 2021, 1600 patients with secondary infection were enrolled based on their characteristics, symptoms and signs, laboratory data and presence of other underlying diseases. Chi-square test analysis were used to check the effectiveness of other comorbidities on the mortality outcome among patients with COVID 19.

Results:

Of the 1,600 COVID 19 patients with secondary infection who have died, 900 (56.25%) had underlying diseases, such as 380 (42.22%) with COPD, 80 (8.89%) with cardiovascular disease and hypertension, 25 (2.78%) with Obesity and smoking, 265 (29.44%) with age over 60 years, 150 (16.67%) with diabetes. 700 (43.75%) patients had no underlying disease.

Conclusion:

The most important causes of death in COVID-19 patients were secondary infections caused by important nosocomial bacteria. High mortality rates in COVID-19 patients indicate the importance of secondary infections.

Keywords: Coronavirus, Secondary infections, COVID-19, Underlying diseases, COPD, Nosocomial.

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1. INTRODUCTION

Coronavirus is the latest challenge and threat to the living things of the world right now. The coronavirus was recognized by the international community in December 2020. In a short time, it became a widespread pandemic within the world. SARS-CoV-2 is a highly pathogenic and transmissible virus; the virus is spread mainly through droplets in the air and close contact with infected persons [1, 2].

The clinical symptoms of SARS-CoV-2 infected patients range from mild non-specific symptoms to severe pneumonia with organ dysfunction. The clinical symptoms of COVID-19 caused by the new SARS-CoV-2 are age-related [3, 4].

Respiratory problems occur in adults, which can turn into very severe acute respiratory distress syndrome, while children are largely immune to respiratory diseases but can have multisystem inflammatory syndrome [4].

Fever, headache, cough, fatigue, shortness of breath from breathing, body aches in some cases, gastrointestinal symptoms, and occasionally in the most severe stages of involvement of various organs of the body such as the kidney,

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liver, and retina a higher percentage of the lungs and respiratory system, central nervous system, etc. are the most prevalent early symptoms in the majority of patients [4]. Bacterial infections are common in patients with respiratory tract infections such as influenza. Patients with respiratory tract infections and secondary infections have a high mortality rate, which requires early diagnosis and appropriate antibiotic treatment [5 - 7].

Information on the prevalence of concomitant bacterial infections in SARS-CoV-2 infected patients is not generally available, and in these critical situations, the identification and diagnosis of antibiotic resistance are essential in the treatment of secondary infections [7 - 11].

Antibiotics are ineffective in treating COVID-19. Doctors prescribe COVID-19 testing to patients with suspected or definitive diagnoses for a variety of reasons. During the influenza epidemic, to prevent high mortality, guidelines were established for the use of antibiotics in patients with secondary infections. Because the role of secondary infections is not being ignored during the COVID-19 pandemic, the aim of this study was to examine the relationship between secondary infections and mortality in COVID-19 patients at the Ayatollah Alimoradian Hospital in Nahavand.

2. MATERIALS AND METHODS

2.1. Data Collection

In this cross-sectional retrospective study (March 2020 and March 2021), 2500 patients with confirmed SARS-CoV-2 infection were evaluated according to the inclusion criteria of the study. These patients were admitted to Ayatollah Alimoradian Hospital, affiliated with Hamadan University of Medical Sciences (UMSHA), Nahavand Province, Iran.

2.2. The Selection Conditions of Patients Studie

In this study, inclusion criteria for this study were based on a questionnaire that each suspected COVID-19 patient completed after additional testing lactate dehydrogenase (LDH), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) at the Ayatollah Alimoradian Hospital Medical Center in Nahavand, Hamadan. The positive results of the tests were real-time PCR or the presence of ground glass opacity in the CT-scan. All information was recorded by the Laboratory Information Management System (LIS). Patients with suspected COVID-19 disease had a real-time PCR test negative. They were excluded from the study [12]. The collected clinical data include age, gender, main symptoms, history of underlying disease, and patient demographics.

2.3. Definition

A positive COVID-19 case was defined as a person with a confirmed positive result on a nasopharyngeal and tracheal swab tested using RT-PCR testing for SARS-CoV2. Secondary infections were identified by bacterial infections. Secondary bacterial infections in COVID-19 patients are typically referred to as superinfections.

2.4. Statistical Analysis

Categorical variables were expressed as frequency and percentages (%), and continuous variables were expressed as mean. Categorical variables between the groups were compared by using the $\chi 2$ test. Continuous variables were analyzed by employing Student's t-test. All statistical analyses were conducted using the IBM SPSS Statistics Version 22.0 software and Microsoft Excel 2010. P value <0.05 was considered statistically significant.

3. RESULTS

During the study time, of 2500 hospitalized confirmed positive patients for COVID-19, 1600 (64%) individuals with secondary infection criteria were considered. The included patients were categorized into two groups: The first group with underlying diseases; 900 (56.25%); the second group with no underlying diseases; 700 (43.75%).

The rate of mentioned underlying diseases in the first group was as follows: 380 (42.22%) with COPD, 80 (8.89%) with cardiovascular disease and hypertension, 25 (2.78%) with Obesity and smoking, 265 (29.44%) with age over 60 years, 150 (16.67%) with diabetes.

Comparison of the two groups showed an association in the presence of secondary infection in the group of patients who died with and without the underlying disease (p-value<0. 01). According to the analysis of the underlying diseases among the dead, those with COPD and disorders associated with advanced age (over 60) had higher fatality rates than those without these conditions (p-value<0.001, p value-<0.001) (Table **1**).

Table 1. The relationship between demographics, underlying disease, and mortality rate in patients with diabetes and COVID-19.

Variables		Total COVID 19 patient N % =1600	Death (%)	Alive (%)	P value
Sex	Man	1100(68.7)5	800 (72.73)	200 (27.27)	0.05
	woman	500(31.25)	350 (70)	150 (30)	
Age	30-40 Years	300(18.75)	50 (16.67)	250 (83.33)	0.123
	40-60 Years	800(50)	250 (31.25)	550 (68.75)	0.108
	Up to 60 Years	500(31.25)	450 (90)	50 (10)	<0.001
Underlying Disease	Yes	900(56.25)	750 (83.33)	150 (16.67)	<0.01
	NO	700(43.75)	540 (77.14)	160 (22.85)	

(Table 1) contd.....

Type of Underlying Disease	COPD	500(31.25)	420 (84)	80 (16)	<0.001
	Cardiovascular disease and hypertension	**200(12.5)**	70 (35)	130 (65)	0.157
	Age over 60 years	500(31.25)	450 (90)	50 (10)	0.01
	Obesity and smoking	100(6.25)	40 (40)	60 (60)	0.421
	Diabetes	300(18.75)	220 (73.33)	80 (26.64)	0.042
Cause of Death	Secondary infection with underlying disease	900(56.25)	750 (83.33)	150 (16.67)	0.01
	Secondary infection without underlying disease	700(43.75)	420 (84)	80 (16)	

4. DISCUSSION

Recent research have revealed that COVID-19, a viral pneumonia with an unusually high prevalence, is an animal-derived pathogen. Due to the prolongation of the COVID 19 pandemic and the high mortality rate, it has become a global public health problem threatening the entire world [13]. Seasonal viral infections and hospitalization of COVID-19 patients that affect the respiratory tract have been shown to be associated with an increased risk of common bacterial infections and the transmission of multidrug-resistant organisms to these patients, resulting in increased antimicrobial use and mortality in these patients [14 - 16].

In studies of the COVID-19 patients admitted to hospitals in Wuhan city conducted by Wang et al. and Zhang et al., the rates of secondary infections were reported to be 7.1% and 43%, respectively [16 - 18].

Many secondary infections reported in COVID-19 patients indicate that these hospitalized patients are infected with resistant bacteria, including *Pseudomonas aeruginosa, Klebsiella pneumonia,* which produces broad-spectrum β-lactamase, *Escherichia coli* resistant to several drugs, *Acinetobacter* and *Enterococcus* [17].

Due to the long-term hospitalization of COVID-19 patients in the intensive care unit (ICU), there is a possibility of secondary infections. Limited data suggests that hospital-acquired infections are associated with increased COVID-19 severity and risk. Significant predictions for an increase in bacterial and fungal nosocomial infections in COVID-19 patients include catheters, diabetes, combination antibiotic therapy, and corticosteroid therapy [18].

Zhang et al. reported that secondary infections were the cause of death in 37% of COVID 19 patients. In another study by Yang et al., 52 patients with SARS-CoV-2 pneumonia in Wuhan City were analyzed and their results showed that seven patients (13.5%) developed hospital-acquired infections and four of these patients eventually died [19].

Bacterial and fungal infections are common complications of viral pneumonia and are more common in severely ill patients. These conditions have increased the need for intensive care and increased mortality [19]. In influenza patients, bacterial co-infection occurs in about 0.5% of young people and at least 2.5% of elderly people [20]. Research by Ripa et al. COVID-19 patients reported a high positive blood culture rate (7.9%) caused by coagulase-negative staphylococci. This result may reflect the high exposure to catheter infection. However, several factors may indicate the presence of coagulase-negative staphylococci in the culture [21].

In their study, the researchers described the causes of bacterial infections in COVID-19 patients as follows: First, at the epicenter of the COVID-19 pandemic, and given the unprecedented pressure on healthcare systems in countries, highly malignant patients are treated using different devices outside the country [21].

ICU can lead to an increase in positive blood cultures due to bacteria in the normal skin flora. Secondly, pandemic conditions can reduce adherence to strict aseptic conditions, especially in critically ill patients monitored outside of the temporary or overcrowded ICU [21]. According to the results of the research, the presence of underlying diseases such as high blood pressure, diabetes, cardiovascular diseases, chronic liver and kidney diseases, cerebrovascular diseases, chronic lung failure, malignant neoplasms, and autoimmune diseases are higher in the elderly with COVID-19 than in other ages [21].

In the current study, it has been indicated that COPD, hypertension, cardiovascular and chronic kidney diseases, and diabetes are the most prevalent comorbidities in infected patients with COVID 19. These results were similar to studies in other parts of the world [22, 23]. In one meta-analysis study report, the most hazardous comorbidities in fatal cases were hypertension, diabetes and cardiovascular diseases [24].

The presence of underlying diseases can affect symptoms, diagnosis, course of treatment, prognosis, as well as survival and mortality. Studies in patients with COVID-19 have shown that the majority of patients who died had underlying illnesses related to secondary illnesses. In this study, the most common underlying disease was chronic obstructive pulmonary disease and the age over 60 years [21].

The elderly are the most vulnerable group in society for many reasons, including weak immune systems, inattention, and inability to fully observe the principles of personal hygiene and self-care [21].

A study of 1,099 COVID-19 patients found that 15.1% of all patients and 27% of critically ill patients were 60 years of age [21]. In another large study of 4,021 confirmed coronavirus cases, the results showed that 1,051 people (26.2%) were over 60 years old [25]. Ferguson *et al*. reported that the mean case fatality rate for people under 60 is estimated to be less than 0.2%, while this range for people over 80 is 9.3% [26].

Regarding the consequences and complications observed in the elderly with COVID-19 disease, bacterial infections, acute kidney damage, acute respiratory distress syndrome, liver

enzyme disorders, acute heart damage, arrhythmias, heart failure, and shock can be mentioned as the most common complications [27].

It is recommended that a comprehensive database be created to record the incidence, clinical symptoms, complications, and mortality of COVID 19 disease. In addition, the report obtained from this database is analyzed and published so that it is available to doctors and health centers. The nations' health systems can be more comprehensive and informed about the treatment of disease.

CONCLUSION

The most important causes of death in COVID-19 patients were secondary infections caused by important nosocomial bacteria. High mortality rates in COVID-19 patients indicate the importance of secondary infections. From the recent study, we can conclude that older-aged patients with underlying diseases and some comorbidities like chronic kidney diseases and COPD are more at risk of mortality during the COVID-19 crisis. Since the role of symptom screening of underlying diseases in the current new crisis is vital.

LIST OF ABBREVIATIONS

LDH	=	Lactate Dehydrogenase
CRP	=	C-reactive Protein
ESR	=	Erythrocyte Sedimentation Rate

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The project was approved by the Ethics Committee of Hamadan University of Medical Sciences with the ethics code (IR.UMSHA.REC.1399.914).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. The study on humans was conducted in accordance with the ethical standards of the Helsinki Declaration and Good Clinical Practice.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants of this study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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