The Seybold Report

ISSN 1533-9211

DOI 10.17605/OSF.IO/B5HWS

SYSTEMATIC INVESTIGATION OF CARDIO VASCULAR & CLINICAL PROBLEM IN PATIENTS WITH COVID-19 WITH NEUROLOGICAL AND PATHOLOGICAL POINT

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Abstract

This study has systematically investigated cardiovascular and clinical problems in patients with Covid-19 with neurological and pathological symptoms. The coronavirus, the cause of acute respiratory syndrome, appeared in December 2019 in the Chinese city of Wuhan. The disease spread rapidly throughout the world and was considered a pandemic disease. Every day, many people around the world die due to this disease. Respiratory viruses are a serious threat to the health security of people internationally and can lead to global epidemics with high mortality and financial burden for treatment. An example of these viruses that have always brought many challenges are coronaviruses. Coronaviruses are a large family of viruses that are responsible for causing approximately one quarter of common colds. Some coronaviruses, such as SARS and MERS, are more dangerous and cause more severe symptoms that may lead to fatal cases of pneumonia (lung infection), kidney failure, and death. Evidence shows that the main target of the corona virus is the lungs, but it can also affect the heart; Especially a heart that has failed. According to initial reports, 40% of the patients with the corona virus who were admitted to hospitals had cardiovascular disease or cerebrovascular disease. Evidence shows that the possibility of contracting Covid-19 or worsening symptoms is higher in the elderly with coronary artery congestion or high blood pressure. A person suffering from heart disease may also have a weakened immune system. Some heart patients, such as heart transplant patients, pregnant women with serious cardiovascular disease (including congenital diseases) are at a very high risk if infected with the corona virus.

Keywords: Corona, Heart, Lung, Blood Pressure, Death

INTRODUCTION

Corona virus is one of RNA viruses (Ribonucleic acid) and belongs to Corona family order and is widely seen in humans and other mammals [1]. Although most human coronavirus infections are mild, epidemics of beta coronavirus, SARS-COV [2] and Middle East respiratory syndrome coronavirus (MERS-COV) [3] have caused more than 10,000 cases in the past twenty years.

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ISSN 1533-9211
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The disease has a mortality rate of 10% for SARS-COV and 37% for MERS-COV [4]. Corona viruses that have been identified before may be only the tip of the mountain covered with ice and will be revealed in potentially new and more severe human and animal events [1]. Elderly, meaning age over 60 years, is one of the important risk factors for increasing disease severity and mortality in patients with Covid-19 [7-9]. Co-occurrence of chronic diseases in the elderly is a common problem in the field of healthcare worldwide [10-12]. In countries where life expectancy is high and non-communicable diseases are more common than communicable diseases, it has been reported that more than half of the elderly have at least two chronic diseases with different pathologies [13-15]. The most common co-morbidities in the elderly with Covid-19 are hypertension, diabetes, obesity, cardiovascular diseases and respiratory system diseases [16]. Studies have shown that patients with multiple chronic diseases have a worse prognosis than patients with one disease [17-19]. However, the relationship between the type of disease and the number of co-morbidities with the prognosis of elderly patients with Covid-19 is not definitely known. On December 31, 2019, China reported an outbreak of a disease with acute pneumonia manifestations from the city of Wuhan to the World Health Organization (WHO) [20].

In a short period of time, the disease caused by the new corona virus (Covid-19) spread from China to other countries and faced the people of the world with various health, economic, social and political problems [21]. On January 30, 2020, WHO declared the 2019 novel coronavirus pandemic as a Public Health Emergency of International Concern (PHEIC). On February 11, 2020, the World Health Organization chose the official name for the new coronavirus disease as "Covid-19" [8] and the International Committee on Taxonomy of Viruses (ICTV) on the same day, the name of the virus The causative agent of this disease changed from 2019-nCoV to SARS-CoV-2 [9]. The number of people who can be infected by a person infected with Covid-19 in the society is 3.5 people on average, which means that more than 70% of the society will be infected [10]. The fatality rate in hospitalized patients is between 4-11% and the overall fatality rate is reported between 2-3% [11]. According to the announcement of the World Health Organization, until March 30, the number of infected people in the whole world is 248349127, and the number of deaths due to Covid-19 in the world has been reported as 5937872 [12]. It is stated that most of the infected people recover spontaneously within 7 to 10 days. While other sufferers suffer from fatal complications such as organ failure, septic shock, severe pneumonia, pulmonary edema and acute respiratory distress syndrome (ARDS). Older people and people with underlying diseases are more at risk of severe disease and death [13]. Clinical symptoms such as fever and cough have been widely described in published articles [14]. Studies have shown that in older people who are more likely to be men and have two diseases at the same time such as diabetes, high blood pressure, cardiovascular diseases or respiratory diseases, the risk of hospitalization and death increases. Other risk factors including smoking and obesity have been reported [15]. Regarding the investigation of the factors related to hospitalization of patients with Covid-19 in the hospital, several preliminary studies have been conducted [22].

But these studies were conducted in a small environment and have a smaller sample size. There are also contradictions between their results. Considering that a comprehensive study that

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evaluates and summarizes their results was not found; Therefore, it seems necessary to review these articles to get an overview of the factors related to the hospitalization of patients with Covid-19. Therefore, the aim of the present systematic review study is to determine the factors related to the hospitalization of patients with Covid-19 in the hospital and to identify the increased risk of hospitalization of these patients. Due to the special nature of the articles published in this regard, in order to fully gather the relevant reliable information, in the continuation of the processes related to the systematic review, other practical findings are also presented under thematic axes.

Definition, symptoms and how to spread Covid-19

Covid-19 is an infectious disease whose most common symptoms are fever, fatigue and dry cough. Some patients may have pain and discomfort, nasal congestion, runny nose, sore throat, or diarrhea. These symptoms are typically mild and have a gradual onset [23]. Some people are infected but do not show any symptoms and do not feel uncomfortable. Most people (about 80%) recover from this disease without needing specific treatment [24]. 1 out of every 6 people who get Covid-19 becomes seriously ill and has trouble breathing. Older people and people with underlying medical conditions such as high blood pressure, heart problems, or diabetes are more likely to develop serious illness. Infected people who develop fever, cough and breathing problems should seek medical attention. This disease can be transmitted from one person to another through tiny droplets released from the nose or mouth when the sick person coughs or sneezes and exhales. These drops fall on surrounding objects and surfaces. Then other people get this disease by touching these objects or surfaces and then their eyes, nose or mouth. People can also get the disease if they inhale droplets from a person with Covid-19 who coughs or sneezes. The risk of contracting Covid-19 from people who have no symptoms is very low. However, many affected people experience only mild symptoms. The risk of contracting Covid-19 from the feces of an infected person also appears to be low. While preliminary research suggests that the virus may be present in feces in some cases. The onset of clinical symptoms of this disease is from 1 to 14 days and its average is usually around five days.

Laboratory diagnosis of new coronavirus (nCoV-2019)

It is important to have the travel history of people to the centers of contamination or the history of their contact with people affected by the disease. Most of the time, the patient's problem is diagnosed as a cold and he is sent home, but if the symptoms of the disease are severe, the medical team may prepare samples of nasal secretions or throat mucus or the person's blood for a more accurate diagnosis of the disease (Figure 1). Currently, the only method of laboratory detection of the new coronavirus is RT-PCR molecular detection test. There are various commercial kits to perform this test. However, only limited laboratory centers have the ability to perform this test. These centers follow the protocols recommended by the World Health Organization.

ISSN 1533-9211

DOI 10.17605/OSF.IO/B5HWS

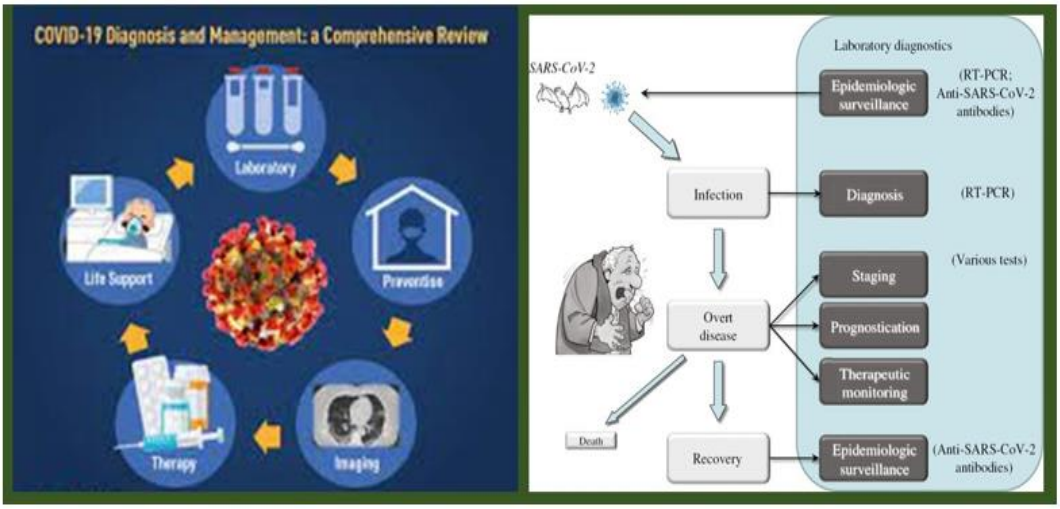

Figure 1: Laboratory diagnosis of new coronavirus (nCoV-2019)

In Iran, the National Influenza Laboratory (Faculty of Health, Tehran University of Medical Sciences) and the Rapid Response Laboratory of the Pasteur Institute of Iran are the reference laboratories for testing the new coronavirus. However, at present, the early detection kit of Covid-19 by immunoassay method according to the antibody and brand Viva Diad TM IgM, IgG Rapid Test was first designed by Chinese scientists, which can detect the presence of antibodies against Covid-19 in the body of a suspected person. evaluated so that if there is an antibody and the test is positive, the suspected person is considered to be infected with Covid-19 [25]. However, considering that there is still not enough information about the life cycle of the virus and also that antibody production occurs at least two days after the virus enters the body, this method cannot be very reliable and a negative test does not indicate the health of the suspected person. In these cases, if there is clinical suspicion and there are suspicious lesions in CT-SCAN, the final diagnosis is made by RT-PCR. This kit is more than being used for definitive diagnosis, it can be used in the screening of people suspected of this disease and the diagnosis of asymptomatic carriers, especially in deprived areas, considering its conditions, cheap price. In addition, one of the major problems of this disease, which has created a great challenge, is the high percentage of asymptomatic carriers that play a major role in the spread and epidemic of this disease [26]. The Infectious Diseases Management Center is responsible for assessing the need to conduct a diagnostic test for nCoV-2019 in all or some of the laboratories of the influenza laboratory network or in other public and private laboratories, as well as making a decision on this matter. The main samples for molecular diagnosis of the new coronavirus are the upper respiratory tract sample, including nasopharyngeal swab or oropharyngeal swab, and the lower respiratory tract sample, including sputum/induced sputum, endotracheal aspiration, and broncho alveolar lavage. Also, to increase the probability of identifying the virus, taking two nasopharyngeal and oropharyngeal swabs at the same time and placing both in a tube containing special transfer medium or VTM can give better results. In addition, sterile Dacron, nylon or polyester swabs and special VTM medium should be used to prepare samples from the upper part of the respiratory tract (Figure 2).

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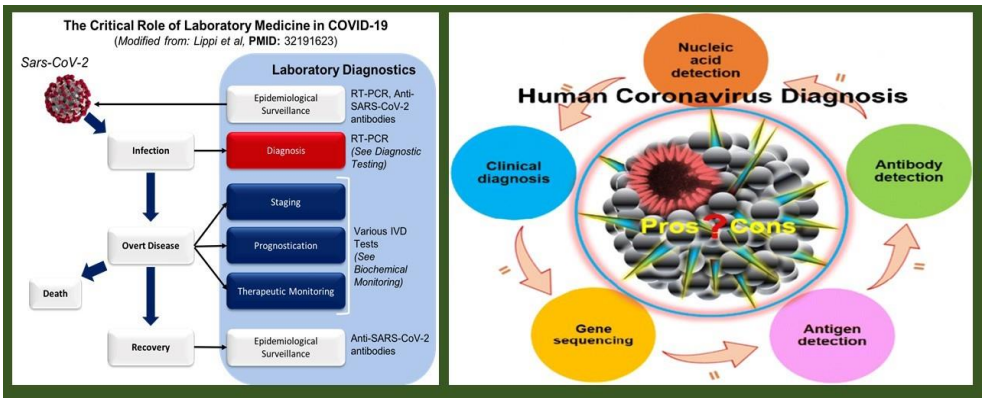

Figure 2: Sterile Dacron, nylon or polyester swabs and special VTM medium should be used to prepare samples from the upper part of the respiratory tract

Heart failure

Heart failure is a complex clinical syndrome caused by dysfunction of the left ventricle, and due to the reduction of cardiac output, the body's metabolic needs are not met [27]. Chronic heart failure is considered one of the most important health problems in today's societies due to the high rate of hospitalization, mortality and high costs, and it is known as a life-threatening problem in the last century [28]. It is predicted that by 2030, the increase in deaths caused by this disease in the world will be more than 23.3 million people [29]. The nature of heart failure causes a decrease in functional capacity, shortness of breath and disability in sufferers, and it has faced them with numerous and annoying problems such as fatigue [30]. Fatigue is defined as an unpleasant feeling caused by a decrease in physical and mental capacity, followed by a decrease in the ability to perform daily physical and mental activities [31-33]. A review of the evidence shows that the prevalence of fatigue in patients with heart failure is variable from 28 to 59% [34-36]. Considering that heart failure is a pathophysiological condition in which the heart is not able to discharge enough blood according to the metabolism of body tissues [37], these patients show signs of exercise intolerance, shortness of breath, and fatigue [38], because the dysfunction of the heart leads to poor perfusion to the body organs, the accumulation of waste materials and the feeling of fatigue [39]. Although fatigue is a significant symptom in heart failure, there is little knowledge about its severity and predictive factors [40]. It seems that the complications and symptoms of heart failure, such as fatigue, can be influenced by the nature of the disease, treatments, and even lifestyle. Improving the lifestyle of cardiovascular patients can be done with the simplest and perhaps the least expensive of these solutions, among which physical activity is one of them [41]. Physical activity is defined as any body movement performed by skeletal muscles and associated with energy expenditure [42-44] and modifies risk factors in heart patients [44]. A review of evidence shows the lack of long-term and regular physical activity in patients with heart failure [45], so that their physical activity is less than that of normal people [46]. On the other hand, insufficient physical activity is a worrying health problem in Iranian society, especially Iranian adults, and it has been decreasing in recent years [47].

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Like other people in Iranian society, 30 to 70 percent of Iranian heart patients do not have proper physical activity [47]. It seems that fatigue caused by heart failure reduces self-care and limits physical activities [48]; Therefore, it is necessary to follow up the problems of heart patients and pay attention to health promotion in order to prevent and control complications in them, and it can be effective in reducing disease complications, reducing frequent hospitalizations, increasing quality of life and even reducing mortality [49]. Previous studies have reported conflicting results. Sheshadari et al showed in patients undergoing hemodialysis in America that for every thousand steps per day, their fatigue intensity decreased by 0.2 units [20], but in the study of Karan et al., the level of fatigue in women with myocardial infarction There was no significant relationship with their participation in physical activities. The results of the present study showed that in terms of fatigue, most of the research units were not at an optimal level. In past studies, fatigue has been reported as a common symptom in heart failure patients, and their experience of fatigue was at a high level [4, 26]. In different results, Williams et al. have considered fatigue variable in newly diagnosed heart failure patients and stated that its origin may be in both psychological and physiological factors [6]. The reason for the difference can be seen in the fact that this study was conducted in patients who were recently diagnosed with heart failure, and according to the degree and severity of the disease, patients may experience varying degrees of fatigue. Based on the findings of the research, there was an inverse and significant relationship between physical activity and fatigue in heart failure patients. So that with the increase of physical activity, the fatigue of the patients decreased significantly. Previous investigations showed that in cross-sectional studies that investigated the relationship between fatigue and physical activity in heart failure patients, it was not found, but sports tests and physical activity were able to reduce fatigue in heart failure patients [28, 27]. In other chronic diseases, a systematic review conducted by Newland et al. showed that fatigue is challenging in adults with multiple sclerosis (MS) and cardiovascular diseases and was negatively related to physical activity [29].

Razazan et al showed that physical exercise can significantly reduce fatigue in patients with multiple sclerosis. The reason can be seen in the fact that various factors such as lack of physical activity, muscle weakness and neurological problems play a role in the fatigue of MS patients. A decrease in endurance and muscle resistance usually leads to premature fatigue and as a result, a decrease in the activity level of patients [30]. Based on the results of the study, the variables of drug use, history of heart surgery and degree of illness were predictors of patients' fatigue. Beta coefficients showed that fatigue was significantly lower in patients with no history of heart surgery, lower degree of disease and drug use than other patients. A number of studies have shown that as the degree of disease increases in heart failure patients, their fatigue worsens [26]. In patients with heart failure, Polikandrioti et al. at two higher university hospitals in Athens and Najafi et al. in a review study [31] showed that as the degree of heart failure increased, the patients' fatigue worsened. Contrary to the results of the present study, where there was no relationship between fatigue, level of education and suffering from other chronic diseases, Ziyaee Raad et al. showed that patients with congestive heart failure with a higher level of education reported significantly less fatigue [33]. The reason for this difference can be related to the difference in measurement tools and research samples. It seems that the two

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variables of physical activity and fatigue have a negative effect on each other, and just as a decrease in physical activity can cause an increase in fatigue, an increase in fatigue also causes a decrease in self-care and limitations in performing physical activities; Therefore, patients may be able to overcome their fatigue as a result of continuing physical activity [18]. According to the results and the review of the relevant literature, it seems that one of the symptoms that should be taken into consideration by the treatment and care team in patients with heart failure is fatigue, because the heart is not able to discharge enough blood in accordance with the metabolism of the body tissues, and the patients cause of this cardiac dysfunction is that they experience annoying symptoms such as fatigue [8]; Therefore, in order to reach the desired level of well-being, it is necessary to take timely measures to reduce fatigue in heart failure patients by the health team, especially nurses, to increase the quality of life in these patients, and to conduct studies on the impact of tests on the management of fatigue symptoms. It seems necessary in these patients. This study contained several limitations. Considering that temporal and seasonal factors affect fatigue and physical activity, this cross-sectional study cannot provide objective information about them and only reflects the patients' understanding of their fatigue and physical activity. The second limitation is the self-report questionnaire, which can affect the generalizability of the results, and the other limitation was conducting the research during the Corona era.

Psoriasis and heart problems

Psoriasis can be an independent risk factor for heart attack, especially in young people who have severe psoriasis. But you should know that only young people are exposed to this disorder. Researchers analyzed various medical findings in more than 680,000 patients and concluded that people with severe psoriasis at the age of 40 have twice the risk of heart attacks compared to people without skin disease. The researchers say: Our findings are very new and therefore more research and experiments should be done to confirm them. On the other hand, patients with psoriasis should be encouraged to boldly seek treatment for their modifiable and cardiovascular risk factors (Figure 3). Although new research confirms the connection between psoriasis and cardiovascular disease, all the findings so far based on clinical and hospital research show that there is no control over cardiovascular risk factors [50].

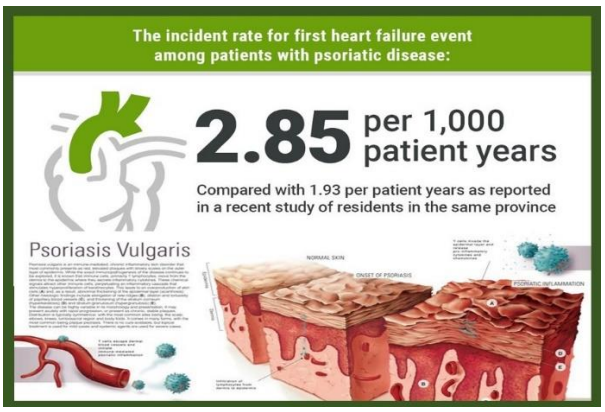

Figure 3: Psoriasis and heart problems

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ISSN 1533-9211
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Diagnosis of heart disease

The human heart is composed of many muscles, valves, vessels and cavities. Whenever one of these components is damaged, complications arise for the patient, but it is almost impossible to diagnose the type of damage in the heart without using various medical tools. Fortunately, modern medical equipment has made the work of doctors easier in early diagnosis and treatment of heart diseases:

ECG (electrocardiography)

The electrocardiogram records the electrical activity of the heart and shows how the heart rhythm works. With ECG, evidence of heart attack can be determined to a great extent. This method is available and cheap, but the problem of this device is to give general information and it is not possible to find out the details of heart disorder with ECG.

X-ray of the chest

It is the same simple photograph of the chest in which the size of the heart, the shadow of the heart and the tissue of the lungs and bones are determined. The review with this tool is also general.

Eco cardiography

A device called echocardiography can be used to find out about the condition of heart valves and cavities, pumping function and congenital heart disorders. The working mechanism of this device is using ultrasonic waves. The advantage of this tool is its safety (even for pregnant women) and its high power in diagnosis.

M.R.I

The MRI device can show the vessels, function, anatomy and cavities of the heart well, and it seems to be the best method for diagnosing heart diseases in the future.

Angiography

It is one of the invasive methods for examining the heart. In the angiography method, the patient must be hospitalized and thin catheters are sent to the heart from the groin artery or hand, and an injection is made into the coronary arteries to check the heart vessels and cavities.

MATERIALS AND METHODS

The current systematic review study was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, including steps: identification, screening, eligibility and inclusion [51-53]. In order to avoid errors and mistakes, all the steps of searching articles, selecting studies, qualitative evaluation and extracting data were done independently by two researchers. If there was a difference of opinion between the researchers regarding the inclusion of the article in the study, in order to avoid the risk of bias for specific studies, a final agreement was reached first by discussion and in some cases with the participation and opinion of a third person. In order to find related

ISSN 1533-9211

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studies, MagIran, SID, ISI, Embase, ProQuest, PubMed, and Scopus databases were searched. In order to finalize the scientific search engine, Google Scholar was reviewed. To find the desired articles using the keywords "2019-nCoV", "Covid-19", "SARS-CoV-2", "Coronaviruses", "Hospitaliz*", "Factor*" and all possible combinations of these words with the help of and or operators, the search strategy was determined for each of the desired databases. No time limit was considered in the search process and all possible related studies were identified until April 2021 and the information of these studies was transferred to EndNote X8 software. For example, the search strategy in PubMed is given below: ((((2019-nCoV [Title/Abstract]) OR (Covid-19[Title/Abstract])) OR (SARS-CoV-2 [Title/ Abstract])) OR (Coronaviruses [Title/Abstract])) AND (Hospitaliz [Title/Abstract])) AND (factor*[Title/Abstract]) (Figure 4) [54].

with Neurological and Pathological Point

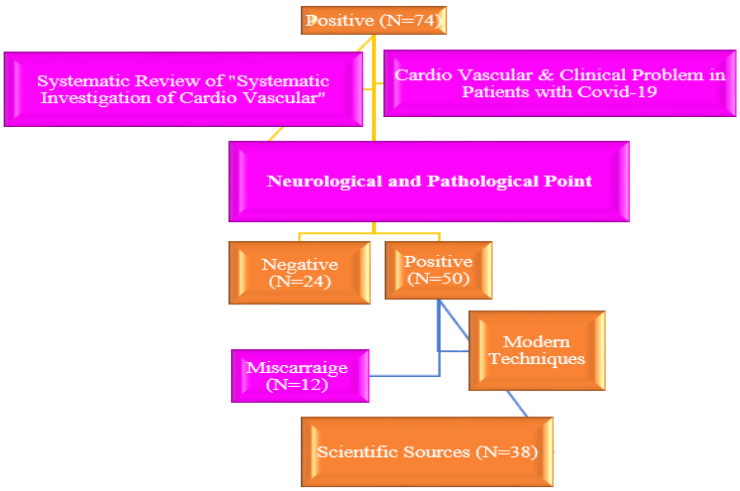

Figure 4: Flow chart of included subjects

In order to access the latest studies published on a number of important databases such as PubMed and Scopus, an alert was created to check if new articles were published during the study. Also, in order to access all related studies, the sources of articles that met the inclusion criteria were checked manually. Inclusion criteria include:

- Studies that investigated the factors related to hospitalization of patients with Covid-19 in the hospital,
- Studies that were observational (descriptive, analytical, descriptive-analytical, etc.) and
- Studies whose full text was available. Exclusion criteria include:

1- Studies unrelated to the topic,
2- Interventional studies (due to the impact of interventions on the factors of hospitalization of patients with Covid-19), theses, systematic review studies and meta-analysis (if the systematic review study and the meta-analysis overlapped with

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the present study, its primary studies were examined and if they met the inclusion criteria, they were included in the present systematic review study (although there was no such case in the present study), case report, letter to the editor, and conferences,

3- Studies whose full text was not available,
4- Studies that were repeated in different databases and
5- Studies that were in the form of preprints. The information of all articles found in each database was transferred to EndNote X8 software. After completing the search in all the databases, duplicate articles were deleted. Then, in order to avoid the risk of bias in the selection of studies, the names of the authors and the title of the journals of the articles were removed and a checklist was prepared based on the title and abstract of the studies. In the next step, two of the authors independently examined the titles and abstracts of the studies and excluded studies not related to the research based on the inclusion and exclusion criteria. Studies whose full text could not be found were also excluded from the systematic review process. Then the full text of all remaining articles was evaluated. Studies that did not meet the inclusion criteria were excluded.

The qualitative evaluation of the studies was done using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist, which is a suitable tool for the qualitative evaluation of observational studies. This checklist has 22 general items, each of which has partial items (32 partial items in total) and for evaluating different parts of a study including: Title and abstract, study objectives, statement of the problem, type of study, sampling method, statistical population of the study, the sample size, the definition of variables, the means of collecting study data, statistical analysis, findings and discussion. In order to score the articles, if each of the articles mentioned the items considered in the checklist, a score of 1 was given and if it was not mentioned, a score of zero was given. The minimum and maximum score in this checklist is 0 and 32, respectively. Articles with a score of 16 and above were considered high and medium quality studies, and articles with a score below 16 were considered as poor-quality studies [30]. After selecting the studies to enter the systematic review process, data was extracted and the studies were summarized. For this purpose, an electronic checklist was prepared.

DISCUSS

The Covid-19 disease has caused a severe pandemic that has affected people of all ages. However, this disease is recognized more like a health disaster in the elderly [51-53]. Despite the high mortality rate of having several diseases at the same time and the high severity of this disease in the elderly, the data available in this age group are few. This study was conducted with the aim of describing the demographic and clinical characteristics and investigating the relationship between underlying diseases and the severity and mortality caused by Covid-19 in the elderly. Many studies have shown that the death rate in the elderly with Covid-19 is much higher than the death rate in young people. The results of our study also showed that about 23% of the elderly with Covid-19 died, which was higher than the mortality rate in China, Korea

ISSN 1533-9211

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and Italy. Chronic diseases have become a global economic burden [20]. Our study showed that 70% of the elderly participants in this study had at least one underlying disease. In a study conducted by Atkins et al. among English elderly patients with Covid-19, the most common diseases among the patients were hypertension (4.44%) and diabetes (1.17%) [28]. In the participants of this study, the most common diseases were high blood pressure (47%) and diabetes (6.35%). Patients with Covid-19 usually die for various reasons, such as multiple organ failure, shock, respiratory failure, heart failure, arrhythmias, and kidney failure. It was previously shown that older age and suffering from several diseases at the same time can cause defects in the response of the body's immune system to pathogens, dysfunction of body organs [54], acceleration of inflammation and ultimately lead to death and multiple organ failure and death in ICU [55]. In previous studies, it has been shown that co-occurring with other diseases may cause weakness in the immune system and dysfunction of the body, this issue has had a greater impact on negative outcomes in elderly patients than in young patients with Covid-19 [56]. Previous studies have reported cardiovascular diseases, obstructive pulmonary disease, blood pressure and diabetes as the most important risk factors for disease severity and death due to Covid-19 [57]. The results of the present study also showed a significant relationship between cardiovascular diseases and death caused by Covid-19, as well as between cardiovascular diseases and stroke with hospitalization in ICU as a proxy of disease severity (Figure 5 & 6). Having high blood pressure had a borderline significant relationship with hospitalization in ICU, and these results were in line with the results of some previous studies. Regarding the relationship between the negative consequences of Covid-19 and co-morbidity with stroke, in previous studies, the relationship between infectious agents and blood coagulation has been shown [58].

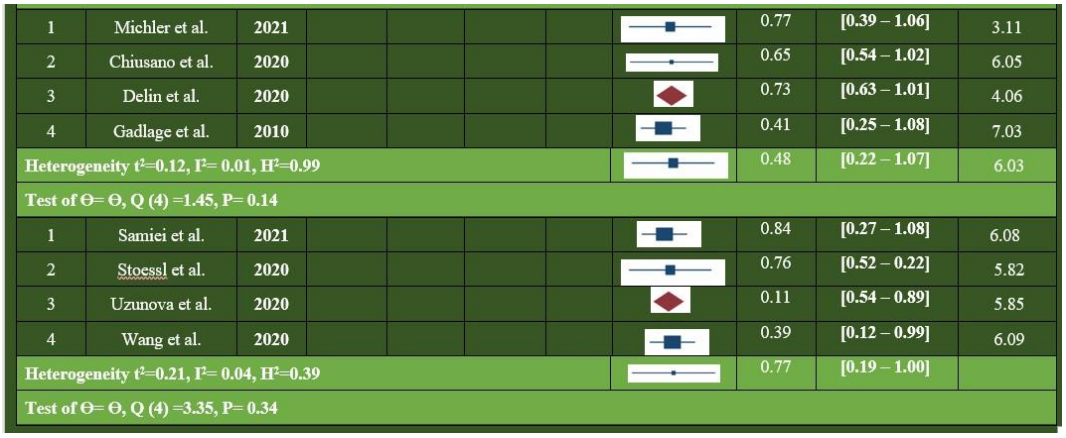

Figure 5: Forest plot showed Systematic Investigation of Cardio Vascular & Clinical Problem in Patients with Covid-19 with Neurological Point

ISSN 1533-9211

DOI 10.17605/OSF.IO/B5HWS

Figure 6: Forest plot showed Systematic Investigation of Cardio Vascular & Clinical Problem in Patients with Covid-19 with Pathological Point

The coagulation property/enhancement of blood coagulation seems to be one of the important mechanisms of the clinical effects of Covid-19 [59]. However, its possible effect on the cause of stroke is still unknown [60-61]. It seems that by increasing the risk of this disease in patients, Covid-19 causes negative consequences such as death or hospitalization in ICU. Blood pressure is also one of the diseases that worsens the prognosis of the disease in the elderly, and on the other hand, a high percentage of patients who have had a stroke also have blood pressure [44]. A study by Sun et al., which was conducted on 3400 patients, also reported similar results to the results of this study [45]. Also, the study of Roan et al., which was conducted among 150 patients with Covid-19, showed that cardiovascular diseases and blood pressure were more common in patients who died due to this disease than in patients who were discharged (19% vs. 43%; P<0.001) [46]. In a systematic review and meta-analysis that included 16 studies and 3994 patients, it was shown that hypertension (OR=2.95), diabetes (OR=3.07), cardiovascular diseases (OR=4.58) and chronic diseases kidney (OR=5.32) leads to a higher risk of serious events; However, only diabetes (OR=2.78) had a significant effect on mortality [61].

The relationship between diabetes and negative outcomes of Covid-19 has also been investigated in meta-analysis studies [17]. Studies have shown that having age-adjusted diabetes (independent of the effect of age) is an important risk factor for the severity of the disease of Covid-19, which was in line with the results of our study [5]. In the present study, we estimated a 70.1-fold increase in the odds of ICU admission and a 1.30-fold increase in mortality associated with Covid-19 in patients with diabetes. Diabetic patients had worse prognosis in other common infections such as severe acute respiratory syndrome and Middle East respiratory syndrome (MERS-COV) [52].

Affecting the immune system of people with diabetes due to chronic high blood sugar [62] and severe fluctuations in blood glucose levels in diabetic patients may be factors affecting the rehabilitation and response to treatment [54]. Also, irregular pro-inflammatory cytokine responses may be the main reason for the severity of Covid-19 in diabetic patients [63]. In previous studies, it has been shown that diabetic patients have dysregulated levels of pro-

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ISSN 1533-9211
DOI 10.17605/OSF.IO/B5HWS

inflammatory cytokines, especially interleukins 1 and 6 (IL-1 and IL-6) and tumor necrosis factor (α-TNF) [7]. Various markers including C-reactive protein, fibrinogen and D-dimer are also increased in diabetic patients with Covid-19 [64].

Therefore, this situation may increase the cytokine storms in Covid-19, which leads to an increase in the severity of the disease. Cardiovascular diseases were one of the most common chronic diseases among the elderly. The results of this study showed that patients with cardiovascular disease are prone to severe Covid-19 disease and the occurrence of negative consequences, including hospitalization in ICU and death. The results of our study were consistent with previous studies and meta-analyses [9]. The mechanism involved in the relationship between severity and mortality of Covid-19 is still under investigation. Studies conducted in people infected with other coronaviruses such as severe acute respiratory syndrome (SARS-COV) and Middle East respiratory syndrome (MERS-COV) have reported an increased risk of mortality in patients with cardiovascular diseases [65].Early reports have also shown similar results in the severity of illness and death due to Covid-19 [60]. One of the potential mechanisms of association between pneumonia and cardiovascular events is inflammation [61]. In particular, the inflammatory response following lung diseases can lead to changes in plaque levels and damage to blood vessels. Evidence for increased local inflammation in coronary arteries and cardiac arrhythmia following acute systemic infections has been shown in many studies [61]. On the other hand, suffering from cardiovascular diseases can cause a malfunction of the body's immune system and increase the expression of the angiotensin-converting enzyme receptor 2, as a result of which the lethality or severity of the Covid-19 disease increases [64]. In three other studies, increasing age was mentioned as one of the factors related to hospitalization in patients with Covid-19. The results of eight studies show that the rate of hospitalization in men is more than women [26], while the results of the study by Telle et al. No significant relationship has been reported between men and women in terms of the rate of hospitalization ($P > 0.05$) [28]. The results of four studies reported that blacks are hospitalized more than whites as a result of contracting Covid-19 [20]. Also, from the total of studies included in this review, four studies reported that smoking has a direct relationship with hospitalization due to Covid-19 ($P<0.05$) [17]. In total, five studies stated that obesity is one of the factors related to hospitalization of patients with Covid-19 [16]. Also, our review shows that three studies investigated body mass index and the amount hospitalization of people with Covid-19 [27, 22, 18] and the results of these studies have shown that with increasing body mass index, the rate of hospitalization increases, but Bhasin et al. [23] reported that no correlation was found between hospitalization due to Covid-19 and patients' body mass index.

Hamer et al. [17] reported alcohol consumption and Almazeedi et al. [24] having asthma among the factors related to hospitalization due to Covid-19. The results of four studies reported that diabetes is one of the factors related to the hospitalization of patients with Covid-19 [16]. Also, the results of four studies show that cardiovascular diseases are among the factors related to the hospitalization of patients with Covid-19. In examining the relationship between high blood pressure and hospitalization of patients with Covid-19, five studies reported that the rate of hospitalization due to Covid-19 has a direct relationship with high blood pressure [17]. Also,

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the results of three studies introduced kidney diseases as factors related to the hospitalization of patients with Covid-19. Knowing the factors related to hospitalization of patients with Covid-19 is effective for planning treatment, therefore, the present systematic review study was conducted with the aim of determining the factors related to hospitalization of patients with Covid-19.

In general, 9 studies [16] reported increasing age as a factor associated with hospitalization of patients with Covid-19. Many physiological changes occur in the body tissue with aging. Among the changes in this period, we can mention muscle wasting, decreased endurance capacity and muscle weakness [31], increased sensitivity to infectious agents, decreased immune system function [32], hormonal changes and decreased ratio of anabolic to catabolic hormones [33]. The increase in the risk of infection in old age is due to impaired cellular and humoral immune function, nutritional deficiencies, bacterial colonization in some mucosal surfaces, a decrease in the physiological defense reflexes of the body such as cough, wound healing, and an increase in the prevalence of chronic diseases with infections [34]. Therefore, older age and suffering from several diseases at the same time can cause defects in the response of the body's immune system to pathogenic agents, dysfunction of the body's organs as a result of the highest mortality rates, hospitalizations, hospitalizations in the intensive care unit, and complications caused by this disease in the elderly. Also, 5 studies [16] reported obesity and 3 studies [18] increased body mass index as factors related to hospitalization of patients with Covid-19. Obesity and increase in body mass index may cause diabetes, cancer, cardiovascular diseases, high blood pressure, respiratory and digestive problems such as reflux [36]. Obesity and an increase in body mass index are associated with a dysfunction of the immune system, which is associated with an increase in the number of infections [37]. Also, a number of reports were related to the reduction of antibodies in obese patients [38]. Obesity and increasing body mass index may cause damage to people's immune response [66]. In general, by reviewing the studies, it can be said that obesity reduces the activity level of the immune system and obese people are more susceptible to the risk of infection and various diseases, including corona disease.

In general, one study [17] alcohol consumption, one study asthma, 4 studies [16] diabetes, 4 studies cardiovascular diseases, 5 studies high blood pressure and 3 studies introduced kidney diseases as factors related to hospitalization of patients with Covid-19. Therefore, suffering from underlying diseases is one of the most important risk factors in patients with Covid-19. Studies on people with underlying diseases indicate that in these people, not only the risk of contracting the disease is higher, but also the probability of death due to the disease is higher [39]. The presence of underlying diseases can affect the symptoms, diagnosis, course of treatment and prognosis [40]. The response of the immune system is less effective in people with underlying diseases. Therefore, the risk of contracting Covid-19 is higher in these people, and in case of infection, it leads to a severe type of disease with hospitalization and the risk of death [41].

Also, 4 studies [16] introduced smoking as a factor associated with hospitalization of patients with Covid-19. Since Covid-19 is an acute respiratory disease, the initiation or continuation of

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smoking during the Covid-19 pandemic may lead to worse outcomes for people infected with the virus [42]. In fact, early indications show that the proportion of current and former smokers is higher among people with severe illness and among people who are in intensive care and require ventilation [43]. Overall, 8 studies [16] reported that more men than women are hospitalized due to infection with Covid-19. In their systematic review, Galbadage et al. reported that more men than women suffer from severe clinical symptoms caused by Covid-19, and the mortality rate of men is higher than that of women [66].

According to the review of various studies; Increasing age, male gender, black race, obesity, high body mass index, smoking, diabetes, cardiovascular diseases, kidney diseases, high blood pressure are among the factors related to hospitalization of patients with Covid-19. But regarding alcohol consumption and asthma, more research is needed in this field. Due to the high prevalence of the Covid-19 pandemic, it is now necessary to carry out programs for the prevention and early diagnosis of this disease, especially in the elderly, obese people and people with underlying diseases (such as diabetes, high blood pressure, cardiovascular diseases, etc.). In addition, necessary intervention programs to reduce body mass index and blood pressure should be implemented. It is also necessary to provide the necessary training in the field of prevention to all members of the society so that, in addition to preventing the transmission of the disease, the field of disease control in high-risk people can be provided. it is suggested; Studies with more people in different parts of the world should be designed and implemented. It is also suggested that more studies be conducted in different parts of the world with a larger sample size regarding some factors such as alcohol consumption and asthma in order to determine the relationship between these factors and hospitalization. Among the limitations of this research, some samples were not based on random selection. We can also mention the non-uniformity of the implementation method, the lack of standardization and the unavailability of the full text of the articles presented in the conference. Also, due to the large number of factors related to the hospitalization of patients with Covid-19 and the heterogeneity of the data obtained from the articles (different methodologies used in the studies, different pooled effect sizes and lack of uniform reporting of the articles), it is possible there was no statistical analysis by meta-analysis method.

CONCLUSION

The results of the present study showed that the risk of being hospitalized due to Covid-19 disease is significantly related to male sex and old age because increasing age leads to defects in the body's immune system response to pathogens and increases the rate of hospitalization. Also, the current research showed that blacks, obese people and smokers, as well as people with underlying diseases such as diabetes, cardiovascular diseases, kidney and high blood pressure, have the highest number of hospitalizations due to Covid-19. They are because the efficiency of the immune system response in these people is low. Therefore, it leads to severe illness and hospitalization. Therefore, the results of the present study can be of interest to experts and policymakers in this field. Coronaviruses are the source of common infections of the upper respiratory tract, gastrointestinal tract, and central nervous system in humans and other mammals. In the last two decades, two beta-coronaviruses named SARS and MERS

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caused continuous public panic and became the most important public health events. At the end of the last decade, on December 31, 2019, a new coronavirus called nCoV-2019 from the same beta coronavirus family caused a large pneumonia outbreak from Wuhan, China, with a high number of patients. The intensity of transmission of this virus was so high that it became a major global challenge in just 3 months. So far, the routes of infection and the exact mechanism of infection of the respiratory tract by Covid-19 are not known. In this study, we gathered the information obtained from the researches about Covid-19 and it was found that the expression level of ACE2, which is the receptor of nCoV-2019, in AT2 cells of the lung, upper epithelial cells and esophagus, absorptive enterocytes has increased greatly from the ileum and large intestine and the cells of the oral cavity and especially the tongue, and this increase in expression has caused an increase in the level of contamination and, as a result, a high percentage of infectivity of this virus. The high level of ACE2 expression in the cells of different organs indicates that not only the respiratory system but also the digestive system is part of the possible route of infection and disruption by this virus. In addition, the intestinal symptoms of 2019-nCoV may appear following the high expression of ACE2 in enterocytes. Having said that, since there is still no definitive treatment for infections caused by coronaviruses, it seems that the best way to deal with a severe infection of Covid-19 is to control the source of infection, early diagnosis, supportive treatments and timely dissemination of correct information. Far from creating terror, it is a way to deal with the epidemic. However, researchers around the world are developing more than 165 vaccines against the corona virus, and 27 vaccines have reached the human testing phase.

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