Republic of Iraq
Ministry of Higher Education
and Scientific Research
Diyala University
College of Medicine

The Percentage of Candidiasis Among Covid -19 Patients

Presented by
Fatima Jaffer Reda
Supervised by
Prof Dr. Luma T. Ahmed

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Praise be to God, who made praise a price for his bounties, a refuge from his misfortune, and a reason to increase his benevolence, a praise greater than the praise of the thankful, and a thank you that exceeds the thanks of the thankful, and prayers be upon His Messenger, our master Muhammad, the Prophet of mercy and his good and pure family. **The Prof Dr. Luma T. Ahmed** for her distinguished supervision, continuous follow-up, care and generosity, and scientific support for the completion of this research, he has all respect and gratitude from us, and I ask God Almighty to .grant him health and wellness, and perpetuity of giving and success

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He makes excuses for me." Everyone I missed mentioning his name, and I ask God to help everyone

1. Introduction

Candidiasis is an opportunistic infection caused by *Candida*, a type of fungi. Fungi are eukaryotic organisms found in the form of yeast, molds, or dimorphic fungi (Vanani *et al*.,2019).

Like other living organisms, fungi form a complex group with a wide range of life cycles, metabolisms, morphogenesis, and ecology including mutualism, parasitism, and commensalism. The fungal kingdom has historically been divided into four phyla, two of which share a monophyletic origin (the dikarya: Ascomycota, Basidiomycota) and two which are considered the basal fungi (Zygomycota, Chytridiomycota) (Stajich *et al*., 2009).

The genus *Candida* is a form of yeast, belongs to the phylum Ascomycota. It is considered one of the most important opportunistic pathogenic yeast-like organisms through human pathogens. This broad genus includes more than 200 species, the most prevalence of which is *Candida albicans* (Williams and Lewis, 2011, Behzadi and Behzadi, 2012).

These fungi present in healthy individuals as a commensally organisms by inhabiting various body surfaces such as oral cavity, gastrointestinal tract, vagina and healthy individual's skin. such as impaired immune system, underlying disease states, and prolonged use of antibiotics (Martins *et al*., 2014). They become pathogenic and cause infections only when favorable conditions arise (Vanani *et al*., 2019) .

Candidiasis may be classified by its location into oral candidiasis (oral thrush), oropharyngeal candidiasis, genital (vulvovaginal) candidiasis, cutaneous candidiasis and invasive candidiasis (candida in the bloodstream). The most danger is invasive candidiasis or candidemia because it has the highest mortality rate among other types of *Candida* infections (CDC, 2016).

Corona virus disease 2019 (COVID-19) infections may be associated with a wide range of bacterial and fungal co-infections. *Candida* and *Mucor* are the common fungus encountered during this pandemic. *Candida* is one of the commonly encountered opportunistic fungi that cause superficial mucosal infections usually, but can invade tissue and can be a source of life-threatening infections (Ruhnke and maschmeyer,2002). Common predisposing factors for Candidiasis are diabetes, malignancy and prolonged use of antibiotics (kamali and sarvtin ,2016). The incidence of fungal infection has increased significantly, contributing to mortality and morbidity. The increasing frequency can be attributed to factors such as the use of potent chemotherapeutic agents that alter the host's immune response, the advent of HIV/AIDS, intravenous drug abuse and the success of intensive care unit in prolonging the survival of highly compromised patients, *Candida albicans* is the most common cause of candidiasis, and affect almost all the systems of the body starting from skin to Central nervous system (Jayant *et al* ., 2021).

Candida also occurs as commensal flora in healthy individuals on mucosal oral cavity, Gastro intestinal tract, vagina etc. With changes in environmental and host conditions this commensal can act as endogenous opportunistic pathogen. The emergence of non-albicans *Candida* spp. becomes a challenge for clinicians. C.*glabrata* is less susceptible and *Candida krusei* is intrinsically resistant to Fluconazole. C.*tropicalis* has the highest adherence rate to inanimate materials such as urinary and vascular catheters, and is often involved in biofilm formation, that is more resistant to Antifungal agents (Segal and Elad ,2007). So, it becomes an immense important to identify the species of *Candida*. Speciation of *candida* play an important role in preliminary treatment because different species is intrinsically resistant to different antifungal drugs and have different antifungal susceptibility pattern which vary from area to area (geographical distribution) (Arora *et al*., 2011).

2. Literature Review

2.1. Taxonomy of Genus *Candida*

Dean and Burchard (1996) classified *Candida spp.* as:

Kingdom: Fungi.

Phylum: Ascomycota.

Sub phylum: Saccharomycotina.

Class: Saccharomycetes.

Order: Saccharomycetales.

Family: Saccharomyceteae.

Genus: *Candida*.

The term *Candida* derives from the Latin word *Candida* which means white. *Candida's* spores are a commensal, harmless type of fungi that become invasive and pathogenic when the flora balance or the host homeostasis is disrupted. This genus contains about 200 species and is the largest medically important yeast genus. At least 30 species of *candida* were identified as the causative agent of candidiasis and the number continues to grow (Miceli *et al.* 2011). However, only five species cause around 95% of infections including *Candida ablicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei* (Turner and Butler, 2014, Gabaldon *et al*., 2016).

C. albicans is among the several species of *Candida*, the most common fungal pathogen of candidiasis (65.3%), followed by *C. glabrata* (11.3%), *C. tropicalis* (7.2%), *C. parapsilosis* (6.0%) and *C. krusei* (2.4%) (Pfaller *et al.*, 2010, Giri and Kindo, 2012).

2.2. Pathogenesis

Candida species have some characteristics that permit them to adapt to different environments and act as an opportunistic pathogen. These factors include adaptation to pH changes, permitting to survive in blood or some alkaline environments, as well as in the acidic environment of the vaginal tissue; these species have adhesins, mannoproteins with capacity to adhere to different cells and cell products (Cortés and Corrales,2018).

These adherence proteins allow the isolates to survive in tissues, but also over inanimate surfaces that have been exposed to plasma or inflammatory host proteins like urinary or endotracheal catheters. *Candida* species have also important enzymes as virulence factors, since some of them have keratinolytic, peptidase, hemolysin, and other effects. One of the most frequently mentioned virulence factors include the possibility of a morphologic transition, which has been extensively studied. It refers to the possibility of morphologic changes of blastoconidia to pseudohyphae to real hyphae. These changes are stimulated by environmental conditions. The filamentous forms are related to active infection in the host, except for C. *glabrata*. Other factors related to pathogenicity or virulence also include a phenotyping change, the possibility of adopting different phenotypes in the cultures (color or aspect of the colonies), and biofilm formation. A biofilm is a large community of symbiotic microorganisms adhered to a surface. This conformation allows the microorganisms to have a highly defensive capacity, persistence, and a highly antimicrobial resistance. As mentioned before, *Candida* might be part of the human flora. The majority of infections are due to the interplay between the risk factors, that pose a risk to the individual, the interaction with other microorganisms presents in the skin or mucosa and the total quantity of microorganisms present. This was demonstrated some years ago in an experiment (Cortés and Corrales,2018). An individual ingested directly from a C. *albicans culture*. After some hours, this immunocompetent individual began to have fever. After 12 hours, *Candida* isolates were found in the bloodstream and, after 16 hours, they were found in the urine. After 24 hours, *Candida* isolates were cleared from the body and the individual returned to the normal state. This experiment proved the importance of colonization. With posterior evidence, it has been demonstrated that the first step to have an infection is colonization by *Candida* especially in the gastrointestinal tract, but otherwise in contact with indwelling catheters, the skin, or wounds that may permit the entry of the yeast into the bloodstream. In another critical observation, patients in the ICU were followed with cultures. The colonization index (it is the proportion of positive cultures for the same *Candida* species taken from different anatomical places) increased over time and was correlated to the probability of developing an invasive candidiasis (Cortés and Corrales,2018). These studies suggest that in individuals with *Candida* colonization, those factors that promote the grow of the yeast, by eliminating the bacteria that can compete for the environment, that alter or facilitate the penetration of the yeast to the bloodstream (lesions in the gastrointestinal mucosa, indwelling catheters) will promote the entry of *Candida* yeast to the blood, while the net state of compromise of the immune system will affect the probability of fungal clearance and the possibility of seeding on specific organs(Cortés and Corrales,2018).

2.3. Epidemiology

2.3.1. Risk factors

2.3.1.1. Candida infection in the intensive care unit

Patients in the ICU have the highest rate of *Candida* infections in the hospital. In comparison with patients in other wards, patients in the ICU have more frequent abdominal surgery, stay longer in the hospital, and are more severely ill (Ylipalosaari *et al*., 2012). They also have a worse prognosis in the long term, with increased mortality after one year of the event.

2.3.1.1.1. Vascular devices

Patients in the ICU have higher rates of *Candida* infection in comparison with patients in other wards. Critically ill patients often require multiple vascular and other indwelling devices for their management and candidemia has been related to catheter colonization in 20–80% of the cases. As mentioned, *Candida* colonization of the catheter might provide a route for entering into the bloodstream without a heavy gastrointestinal colonization. Studies have shown that *Candida* catheter-related bloodstream infections have a shorter time to grow in comparison with those from other sources (Ben *et al*.,2008). One study in Japan identified the presence of a solid tumor, the use of total parenteral nutrition, and the administration of anti-anaerobic agents as the main risk factors for the development of *Candida* infections (Nagao *et al*., 2014). With a breakpoint of 30 hours, the time to grow in patients with *Candida* bloodstream infection might identify 100% of those catheter-related infection. Probably, patients with catheter-related infection have a higher inoculum, which would explain the faster time to grow and the fact that observational studies have shown a lower mortality when catheter is removed, On the other hand, patients with non-catheter-related candidemia were more seriously ill, had a higher mortality, and the removal of the catheter did not affect the outcome (Arias *et al*., 2017).

2.3.1.1.2 Parenteral nutrition

Another commonly identified risk factor is the use of parenteral nutrition or the length of its use (Chow *et al*., 2008). This group of patients shares several risk factors, but parenteral nutrition has been identified in multivariate analysis (Leon *et al*.,2006). Usually, they have an abdominal procedure (see below) and they require parenteral nutrition for several days. Lack of appropriate measures to handle the nutrition, colonization of the catheter or the ports used to infuse it, and probably the availability of optimal growing conditions are conditions related to its use. But clearly, the use of parenteral nutrition leads to the development of mucosal atrophy and a loss of mucosal epithelial barrier function (Yang *et al*., 2009). which might affect the relationship between microorganisms in the gut and the possibility of gaining access to blood vessels. Total parenteral nutrition has also a profound effect in the gastrointestinal microbiome (Pierre, 2017).

2.3.1.1.3 Surgical procedures

Several studies have shown the relationship between candidemia and a previous surgical procedure (Ortiz *et al.*, 2016). specially an abdominal surgery. There are several explanations to this observation, but gut manipulation, and the effect of resected sections over the gut microbiology, microbiota abundance, and epithelial function might contribute to the possibility of candidemia. Studies have shown that patients with high anastomotic leak, as well as those with recurrent gastrointestinal perforation, or acute necrotizing pancreatitis, have a higher risk of candidemia (Cortés and Corrales,2018).

2.3.1.1.4 Antibiotic use

They contribute to the observed increased colonization over time observed in patients in the ICU. With more antibiotic effect, there is a net decrease in the number of species in the gastrointestinal tract, an increase in the number of patients colonized, and the proportion of them being heavily colonized (Guyton and Alverdy, 2016). Almost all studies of candidemia have shown an extremely high use of antibiotics previous to the identification of bloodstream or tissue infection. The proportion of patients with antibiotic use is over 80% , The number and spectrum of the antibiotics used might affect the risk of candidemia. Antimicrobials also have an effect over gut microbiota, and some studies have shown some impact from antibiotics with anti-anaerobic effect, and those with higher gastrointestinal concentration (Cortés and Corrales, 2018).

2.3.1.1.5 Other risk factors

Studies have identified several risk factors that alone, or in combination, might increase the probability of having candidemia. The presence of renal failure, the use of antihistaminic blockers, the severity of illness, and the length of stay in the ICU contribute to colonization and development of candidemia (Cortés and Corrales, 2018).

2.3.1.2. Hematological malignancy, solid organ transplantation, and other immunosuppressive states

These disorders share a common factor: immunosuppression. However, different types of immunocompromise entail different risks for the patients. The incidence of candidemia among patients with cancer is higher in comparison with other patients in the hospital. In a multicenter study in Greece, patients with hematological disease had an incidence of candidemia of 1.4 cases per 1000 admissions, while other patients hospitalized had an incidence of 0.83 cases per 1000 admissions (Gamaletsou *et al*.,2014). An Italian multicenter study from a surveillance network showed a diminishing trend for candidemia among patients with cancer, especially among those with acute myeloid leukemia (Pagano *et al*., 2017). Whether this trend can be inferred to other European countries or not is not known, and the most likely explanation for this decrease in the number of cases could be related to the use of prophylaxis among those patients with acute leukemia with posaconazole. In general, non-albicans *Candida* species are more frequently found among these groups of patients (Gamaletsou *et al*.,2014). A multicenter European study found an incidence of 1.2% cases of candidemia among patients with bone marrow transplantation (BMT) and leukemia (Cesaro *et al*., 2018).

2.3.1.2.1. Neutropenia

Neutropenia, a count of leukocytes in peripheral blood below 500 cells per µl, is the common risk factor among patients with hematological disorders (i.e., leukemia, lymphoma, multiple myeloma among others) as well as those with bone marrow transplantation (BMT). Neutropenia might be a consequence of the activity of the hematological disease, an effect of chemotherapeutic strategies or side effect of multiple medications including antimicrobials. It also is a marker of the intensity of chemotherapy. A study that looked for risk factors identified underlying leukemia as one of the major risk factors, together with chronic lung disease (Fernandez *et al*., 2015). Several studies have shown that isolates of C. *tropicalis* are more frequently found among patients with cancer (Wu *et al*., 2017). Patients with chemotherapy-induced neutropenia accumulate various risk factors: they usually receive wide spectrum antibiotics for several days, they have serious gastrointestinal epithelial tissue dysfunction, usually with diarrhea and signs of mucosal damage, and the use of vascular catheters for the infusion of chemotherapeutic drugs and antibiotics (Cortés and Corrales, 2018).

2.3.1.2.2. Concurrent conditions in patients with cancer

In patients with cancer and candidemia, several factors were identified in comparison with those with cancer and bacterial infections (Li *et al*., 2017). Total parenteral nutrition over 5 days, urinary catheter for more than 2 days, distant metastasis of cancer, and gastrointestinal cancer were independent risk factors. Patients with solid tumors might accumulate factors as patients in critical care, since they have abdominal surgery (gastrointestinal neoplasm), require vascular catheters for extended periods of time (for chemotherapy or antibiotics), total parenteral nutrition and received antibiotics frequently (Tang *et al*., 2014). A study to identify factors predicting catheter-related infections with *Candida* identified solid tumors and the use of antianaerobic antibiotics as risk factors (Nagao *et al.*, 2014). Among patients with leukemia and BMT, the risk factors for occurrence of candidemia included bone marrow or cord blood stem cell source, T-cell depletion, use of total body irradiation, and acute graft versus host disease (Cesaro *et al*., 2018).

2.3.1.3. Neonates

Neonates in the intensive care unit usually have limited breastfeeding, indwelling vascular catheters, total parenteral nutrition, and antibiotics (Chen *et al*., 2016). Newborns have no gastrointestinal flora at birth and have to be colonized by enterobacteria and other microorganisms, which is made via maternal breast feeding. Any alteration in the normal process can lead to colonization by pathogenic microorganisms, including yeasts (Ortegon *et al*., 2017). Some studies have illustrated this relationship with proportion of candidemia between 3 and 10% among those with a weight of less than 1000 g while showing an incidence of less than 1% for those weighting over 2500 g. In this scenario, disseminated candidemia can be found and near 10% of those with invasive disease can compromise the central nervous system. Another important risk factor includes the time that the patient has been in the unit, clearly, patients with low weight, lower gestational age, and more comorbidity tend to spend more time in the neonatal ICU and to accumulate other risk factors (surgery, indwelling catheter, antibiotics, etc.), There are some high-risk units, in which the incidence of candidemia traditionally has been high, usually over 10% of the admitted cases. In this scenario, prophylaxis has been suggested for the prevention of infection (Cortés and Corrales, 2018). Such combination of risk factors put. this group of patients at a higer risk of infection, reaching over 10% of patients in units with extreme prematures and low weight at birth (the group that requires more invasive interventions) (Benjamin *et al.*, 2020).

2.3.2. Global epidemiology

The real incidence of candidemia is difficult to calculate due to differences in the approach. While studies based on hospitals might overestimate the importance of some groups of high-risk patients, they are difficult to compare. Data from population studies might reflect better the real situation, but this kind of information is scarce. Studies have shown ample differences in the incidence in some regions and at specific times (Arendrup ,2010). Since 2013, the Leading International Fungal Education (LIFE) portal has facilitated an important effort to know the epidemiology and burden of fungal infections around the world and allowed a better understanding of their epidemiology in different countries (Bogomin *et al*.,2017).

2.3.2.1.Changing trend for non-albicans Candida

Traditionally, C. *albicans* had been the most frequently isolated species. However, a trend toward non-albicans species has been observed around the world in the last 15 years. In United States, C. *glabrata* has been identified as second in frequency, while C. *parapsilosis* or C. *tropicalis* dispute this place in other regions. Table (1) shows the proportion of isolates in some studies around the world in the last 10 years. They found differences between the countries that include the frequency of C. *tropicalis* isolation, being more commonly found in hematology-oncology wards and in tropical areas. This study confirmed the observed trend for a lower frequency of C. *albicans* isolates. The other study is the Latin-American surveillance study (Nucci *et al.*, 2013). Two studies deserve a detailed description. The first one is a multicenter study from the Southeast Asia region, including 25 hospitals from 6 countries: China, Hong Kong, India, Singapore, Taiwan, and Thailand (Tan *et al.*, 2015).

Table (1) : Proportion of *Candida* species in selected studies of candidemia around the world.

Area and publication year	*C. albicans* (%)	*C. glabrata* (%)	*C. tropicalis*	*C. parapsilosis*	References
USA 2012	38	29	17	10	[49]
Latin America 2013	37.6	6.3	17.6	26.5	[48]
Spain 2014	45.4	13.4	7.7	24.9	[50]
Asia-Pacific region 2016	20–55	5–22	2–20	8–27	[51]
France 2014	56	18.6	9.3	11.5	[52]

It involved patients from 20 centers in 7 seven countries: Argentina, Brazil, Colombia, Chile, Honduras, Mexico, and Venezuela. Important differences were seen among institutions, reflecting difference in healthcare systems, access, population types, and risk factors. However, in these two studies, the incidence of candidemia is higher than in developed countries in Europe and North America. In Latin America, C. *parapsilosis* frequency is over 30% of the isolates while this place is occupied by C. *tropicalis* in the Asian countries (Cortés and Corrales,2018).

2.3.2.2.Epidemiology in Europe and North America

There are data from some population surveillance surveys in Europe and United States. In general, the incidence might be lower than in some other areas of the world. Table (2) shows the incidence from data from North America and European countries (Lagrou *et al*.,2015). In Europe, the highest incidence has been observed in Hungary, while in North America the highest incidence has been seen in some cities in United States(Cortés and Corrales,2018).

Table (2): Estimated incidence of invasive candidiasis or candidemia in countries of the European or North American regions.

Country/region	Publication Year	Incidence (per 100.000 inhabitants)	References
Belgium	2015	5	[54]
Denmark	2008	10.4	[55]
Finland	2010	2.8	[56]
Germany	2015	4.6	[57]
Hungary	2015	11	[58]
Ireland	2015	7.3	[59]
Norway	2018	3.8	[60]
Portugal	2017	2.57	[61]
Romania	2018	6.8	[62]
Russia	2015	8.29	[63]
Serbia	2018	10	[64]
Spain	2015	8.1	[65]
Sweden	2013	4.2	[66]
Ukraine	2015	5.8	[67]
Canada	2017	2.91	[68]
México	2015	8.6	[69]
USA	2015	9.5–14.4	[70]

2.3.2.3.Epidemiology in Central and South America and the Caribbean

This region has profound differences in healthcare systems, access to care, and medical technology development. With a transition toward a higher income, a growing number of institutions with capacity to attend cancer patients, and more complex medical needs, the number of candidemia cases seems to be higher than in developed countries. Ample information exists about the problem in Brazil, where a number of studies have been carried out in high-complexity hospitals in the main cities of the country (Colombo *etal*.,2006). These studies show a higher frequency of invasive candidiasis in comparison with developed countries, an increased isolation of C. *glabrata* for the last period and an important exposition to fluconazole (which might have increased the selection for non-albicans species) (Colombo *et al.*, 2014).

2.3.2.4.Epidemiology in Africa and Asia

A multicenter in Asia gathered information from various countries, including nine hospitals from China. The incidence rate among patients hospitalized was 0.38 per 1000 region with 1.08 cases per 1000 admissions (Nucci *et al.*, 2013). admissions, which is lower than that observed in the Latin-American The numbers for the African countries are lacking and for some countries like Algeria, Burkina Faso, Cameroon, Egypt, Malawi, Mozambique, and Tanzania, the estimated incidence is 5.8 cases per 100,000 inhabitants, a standard calculation based on previously reported incidence in other countries (faini *etal*.,2015).The estimated incidence of candidemia in countries in Asia is shown in Table (3) (Tilavberdiev *et al*., 2017). In Asia, the highest incidence has been observed in Pakistan, followed by Qatar and Israel. In China, geographic variations in the causative species and susceptibilities were noted, with increasing isolates resistant to fluconazole (Xiao *et al*., 2018).

Table (3): Estimated incidence of invasive candidiasis or candidemia in countries of Africa and Asia.

Country/region	Publication year	Incidence (per 100,000 inhabitants)	References
Bangladesh	2017	5	[83]
Israel	2015	11	[84]
Jordan	2018	5.75	[85]
Kazakhstan	2018	4.3	[86]
Korea	2017	4.57	[87]
Malaysia	2018	5.8	[88]
Pakistan	2017	21	[89]
Philippines	2017	2.25	[90]
Qatar	2015	15.4	[91]
Thailand	2015	13.3	[92]
Uzbekistan	2017	5.93	[93]

2.4 Etiology of Candidiasis

Candidiasis is an opportunistic infection. *C. albicans* is present in healthy persons colonizing the oropharyngeal, esophageal, and gastrointestinal mucosa. *C. albicans* can cause mucosal candidiasis in these areas where they usually are present in an immunocompromised host (Dabas,2013). In patients who have leukemia, lymphoma because of the consumption of corticosteroids or cytotoxic drugs, their immunity is compromised, leading to *candidal* infection. Antibiotic usage is commonly associated with candidiasis. Cancer cytotoxic chemotherapy may result in fungemia caused by *C. albicans*, which develop from fungal translocation through compromised mucosal barriers. Fungal commensals in the upper and lower GI tract can transform into opportunistic pathogens due to changes in endogenous bacterial population size or composition, as well as changes in the host environment (Bertolini and Dongari-Bagtzoglou, 2019). Vaginal colonization increases in diabetes mellitus, pregnancy, and the use of oral contraceptives. Oral candidiasis is very closely associated with HIV patients. More than 90% of HIV patients present with candidiasis. Other predisposing factors of candidiasis include TB, myxedema, hypoparathyroidism, Addison's disease, nutritional deficiency (vitamin A, B6, Iron), smoking, poorly maintained dentures, IV tubes, catheters, heart valves, old age, infancy, and pregnancy (AN and Rafiq, 2020).

2.5 Gender of covid- 19

2.5.1 Gender Sensitivity in COVID-19 Infection

Clinical data regarding COVID-19 show no significant sex differences in susceptibility to COVID-19 infection. An analysis of the public data set from the Chinese Public Health Science Data Center contained the first 37 fatalities from COVID-19 and 1,109 cases of COVID-19 survivors. The analysis showed that male and female patients displayed the same susceptibility to COVID-19 infection (Jin et al., 2020). In a study of 44,672 confirmed cases taken from China’s Infectious Disease Information System through February 11, 2020 ,it was found that 51.4% of patients with confirmed cases of COVID-19 were male (Team ,2020). In a contracttracing effort in the United States, the Maine Center for Disease Control and Prevention (CDC) enrolled 1,622 contacts of 614 patients with COVID-19 in an automated symptom-monitoring tool between May 14, 2020 and June 26, 2020. Among these enrollees, 190 developed COVID-19; and, among these patients, 52.1% were female, and 47.9% were male (Krueger *et al*., 2020). Furthermore, an analysis of the 1,320,488 confirmed COVID-19 cases in the United States reported from January 22, 2020 to May 30, 2020 found that the incidence of cases was similar between females and males. Among the total reported patients, 646,358) (48,9%) were male, and 674,130 (51.1%) were female. Furthermore, the cumulative incidence for males was 401.1 cases per 100,000, and that of females was 406.0 cases per 100,000 (Stokes *et al.*, 2020). Interestingly, this particular report from the United States shows a higher percentage of cases in females than males. Data regarding confirmed COVID-19 cases, as of April 1, 2020, from China, Italy, Spain, France, Germany, and Switzerland showed that there were no significant sex disparities in the absolute number of cases of COVID-19. However, it was noted that this could indicate a higher incidence of COVID-19 among older males, as the absolute number of older males is less than that of females. Data from Germany and Switzerland support this assertion; it was found that there was an increased incidence of COVID-19 infection in males greater than 60 years old (Gebhard *et al*., 2020).

2.5.2 Gender Sensitivity in COVID-19 Mortality

There is substantial evidence that points to gender and sex sensitivities in COVID-19 severity, and males experience more severe COVID-19 cases. In addition to increased severity, several studies have shown that male COVID-19 patients have a higher fatality rate than female patients (Mukherjee and Pahan,2021).

2.5.3 Greater Death Among Males Than Females From COVID-19 in China

A case series analysis of 43 patients in Wuhan, China found that male patients' cases of COVID-19 were more likely to be serious than those of female patients. The median age of these patients was 62 years old, and there was no significant difference in the ages of the male and female patients. Furthermore, among this data set, 37.2% had underlying disorders including hypertension, cardiovascular diseases, diabetes, and lung diseases; however, there were no significant differences in comorbidities between the male and female patients (Huang *et al.*, 2020). Additionally, an analysis of COVID-19 cases from the Chinese Public Health Science Data Center found that, among the deceased patients, the number of male patients was 2.4 times greater than that of female patients. The median age for the deceased patients was 70.3 years old, and there were no significant differences in ages between the male and female patients in this data set. Furthermore, among the deceased patients, 64.9% had comorbidities (Jin *et al*., 2020). Analysis of a data set of 41 COVID-19 patients from December 16, 2019 to January 2, 2020, found that there was a greater proportion of male patients admitted to the intensive care unit (ICU). The median age of these patients was 49 years old. Furthermore, 32% of the patients had underlying conditions, including diabetes, hypertension, and cardiovascular disease. Among all the patients in this data set, 30 were male(%73) and 11 were female (27%). However, among the 13 patients admitted to the ICU, 11 were male (85%) and 2 were female(15%) (Huang *et al.,* 2020)

A study of 262 COVID-19 patients in Beijing between January 20, 2020 and February 10, 2020 also found that males made up a greater percentage of those with severe cases. The age range of patients was from 6 months to 94 years old, and the median was 47.5 years old. Additionally, 77.4% of the patients were aged between 13 and 64 years old. Among the total cases, 48.5% were male; however, among the 46 severe cases, 56.5% were male patients (Tian *et al.,* 2020). A retrospective study was conducted regarding 191 patients diagnosed with COVID-19 in Wuhan, China between December 29, 2019 and January 31, 2020. The age range for all of the patients was 18 to 87 years old, and the median age was 56 years old. Nearly half (48%) of the patients had comorbidities, the most common being hypertension. Additionally, while 62% of the total patients were male, the study found that males made up 70% of the deceased patients (Zhou *et al.,* 2020). In the study of 44,672 COVID-19 cases from China's Infectious Disease Information System, taken through February 11, 2020, a total of 1,023 deaths occurred. Among these patients, 77.8% were between the ages of 30 and 69 years old. Furthermore, data regarding comorbidities was collected for 20,812 patients, and about 25.5% of those patients had comorbidities. Furthermore, while 51.4% of the total patient population was male, 63.8% of the deceased population was male. Additionally, it was found that the case fatality rate for males was higher than that of females: 2.8% versus 1.7%, respectively (Team ,2020).

2.5.4 Gender Difference in COVID-19-related Deaths in USA

These gendered differences are also observed in the United States. In one study, the COVID-19-Associated Hospital Surveillance Network (COVID-NET) monitored COVID-19-related hospitalizations between March 1, 2020 and March 28, 2020. Majority of the patients that were hospitalized were over the age of 50 (74.5%). Data regarding underlying conditions was only collected for 178 hospitalized patients, and 89.3% of those patients had one or more underlying conditions. Furthermore, among the 1,482 patients hospitalized with COVID-19, 54.4% were male. The population makeup of the COVID-NET area is about 49% male and 51% female, showing that males were disproportionately hospitalized with COVID-19 in comparison to females (Garg *et al.*, 2020). Between February 12, 2020 and May 18, 2020, 52,166 deaths from 47 jurisdictions were reported to the CDC. In this data set, majority of the patients were above 65 years old (79.6%), and the median age was 78 years old. Data regarding comorbidities was not collected for this data set. Among the deceased patients, 55.4% were male. Furthermore, the CDC collected data regarding 10,647 deaths from 56 public health departments regarding deaths related to COVID-19 between February 12, 2020 and April 24, 2020. In this report, the median age was 75 years old, and at least one comorbidity was reported for 76.4% of the patients. Among these deceased patients, 60.6% were male. In both cases, male patients made up a larger percentage of the deceased patients (Wortham *et al.*, 2020). Furthermore, an analysis of 1,320,488 cases of COVID-19 in the United States reported between January 22, 2020 to May 30, 2020 was conducted. The median age of the patients was 48 years old, and 22% of these cases were associated with underlying conditions. The most common conditions were cardiovascular disease, diabetes, and chronic lung disease; and, the proportion of these comorbidities in male and female patients were comparable. Analysis of these cases found that male patients experienced more severe outcomes than female patients. The report showed that males had a higher rate of hospitalization than female patients (15.6% vs. 12.4%, respectively); males had a higher rate of admission to the ICU than female patients (2.8% vs. 1.7%, respectively); and, males had a higher fatality rate than female patients (6.0% vs. 4.8%) (Stokes *et al.*, 2020).

2.5.5. COVID-19 is More Deadly Among Males Than Females in Europe

These trends are seen in European countries, as well. In Switzerland and France, data regarding COVID-19-related hospitalization find that, although there is no displayed gender or sex sensitivity in incidence of COVID-19, there are 50% more male patients hospitalized than female patients. In Switzerland, incidence of COVID-19 in males and females is similar across age groups, but hospitalization is 1.5 times higher for male patients. Furthermore, composite COVID-19 data from Germany, Italy, Spain, and Switzerland, comprising of 14,364 deaths, consistently show that the case fatality rate for males is higher than that of females across all age groups. This greater case fatality in male patients was observed across all age groups (Gebhard *et al.,* 2020). In the Lombardy region of Italy, a retrospective study of ICU patients in 72 hospitals was conducted. Among the 1591 patients treated between February 20, 2020 and March 18, 2020, 82% were male and 18% were female, displaying a higher proportion of males among the ICU patients. In this data set, the median age was 63 years old, and the relative proportions of males and females in each age group was similar. Furthermore, of the patients on whom data regarding comorbidities were collected, 68% had at least one comorbidity (Grasselli *et al.*, 2020). Finally, reports from Germany as recent as September 2, 2020 show that male patients represent a greater proportion of deceased patients. Though males make up 49% of total cases in Germany, they make up 55% of the total deaths related to COVID-19)COVID-19 daily situation report of the Robert Koch Institute 2020) (Mukherjee and Pahan,2021).

2.6 Chronic disease

2.6.1 COVID-19 Related Comorbidities

The studies of patients with COVID-19 infection have shown that people with underlying diseases not only have a higher risk of developing the disease but also are more likely to die from the virus infection (Table 4) (Verity *et al.,* 2020). Another factor influencing the mortality rate of COVID-19 is the old age, especially over 60. Still, the World Health Organization (WHO) emphasizes that young people are not safe, and theymust also follow health principles to prevent the spread of the virus

(Murthy *et al.*, 2020). People with diabetes can help control their immune systems by controlling their blood sugar and prevent COVID-19 as much as possible.

Table (4). Effect of COVID-19 Infection on Underlying Health Conditions

Disease	Study Design	Number of Confirmed COVID-19	Target Group	Outcomes	Main Findings
Mixed	Cross-sectional	571,678	Adults	Prevalence of underlying health conditions	The most commonly reported conditions were diabetes mellitus, chronic lung disease, and cardiovascular disease
Mixed	Retrospective	54	Adults	Prevalence of underlying health conditions	The most commonly reported conditions were hypertension, diabetes, coronary heart disease, and previous cerebral infarction
Diabetes	Special communication				Keeping patients safe, functional, and at home during pandemics
Cardiovascular diseases	Cross-sectional	150	Adults	Myocardial injury	COVID-19 can lead to myocardial injury
Diabetes	Cross-sectional	174	Adults	Symptoms, laboratory findings, chest computed tomography (CT), and treatment	Diabetes should be considered a risk factor for COVID-19
Cardiovascular diseases	Meta-analysis	1527	Adults	Association	Previous cardiovascular metabolic diseases lead to a greater risk of COVID-19
Diabetes	Perspective			Potential mechanisms by which diabetes interacts with COVID-19	

2.6.2 Diabetes

High blood sugar levels can damage a person's immune system. The weaker the body's immune system, the lower the ability to fight infections, such as COVID-19; thus, the virus can cause more damage to the body (Ma and Holt ,2020). People living with diabetes, like everyone else in the community, need to take precautions against the COVID-19 disease. They should also be more careful about controlling their blood sugar and avoiding changing their medications without consulting a physician. Some vitamins and minerals play a role in improving the function of the immune system, but the arbitrary and indiscriminate use of supplements containing these micronutrients may cause disorders in the body's function (Haybar and Kazemnia,2020). Therefore, if a person is not nutrient-deficient, it is better to provide nutrients by food sources and avoid taking supplements without consulting a doctor. Recent studies show that there is no specific way to prevent the immune system from infecting people with the COVID-19, especially people with diabetes (Maddaloni and Buzzetti,2020). In general, relaxation, adequate sleep, and proper nutrition can improve the immune system.

2.6.3 Cardiovascular Diseases

It seems that viral diseases, including COVID-19, are responsible for about 5% of the cases of acute heart failure. In addition to new cases of heart disease, COVID-19 infection in patients with a history of cardiovascular problems can change the course of the underlying disease and increase mortality in the patients (Guo *et al*., 2019). Infectious diseases, including viral infections such as COVID-19, are one of the leading causes of cardiovascular disease, which can lead to heart failure with pericarditis, myocarditis, and cardiac conduction (Vuorio *et al*., 2020). Patients with cardiovascular disease and over the age of 60, with a history of high blood pressure, obesity with a BMI above 25, and a history of smoking are at a higher risk of COVID-19 infection. Researchers at the Wuhan University of China found that of 416 patients admitted to the hospital, about 20% had severe muscle heart damage due to a severe COVID-19 infection, of whom more than half died (Chen *et al.*, 2020). The findings show that patients with heart damage have a very high risk of death. One of the researchers' hypotheses is that the immune system reacts to the COVID-19 infection, which, if not controlled, can cause a condition called "cytokine storm" and damage organs (Zhang *et al.*, 2020). Another possibility is that in people with cardiovascular disease, the overall stress caused by the infection can damage the heart muscle. Finally, COVID-19 may attack the heart directly. According to research, the virus binds very strongly to angiotensin converter enzyme 2 (ACE2) receptors. These receptors are expressed not only in the lungs but also in other parts of the body, such as the heart and digestive tract (South *et al.*, 2020). Some hypotheses suggest that common blood pressure medications, such as ACE inhibitors and angiotensin receptor blockers, can be very harmful to people with COVID-19 infection (Chen *et al* ., 2020). However, another study claimed that RAS inhibitors might be a good therapeutic choice in patients with COVID-19 infection (Sun *et al.*, 2020). Therefore, it is highly recommended that cardiovascular patients adhere to the principles of prevention, personal hygiene, isolation, social distancing, and regular use of cardiac drugs. Researchers emphasize the importance of preventive measures in the current situation and suggest that people with cardiovascular disease and a history of stroke consider themselves to be at high risk. These patients should not stop taking any of their medications without consulting a doctor (Haybar and Kazemnia,2020).

2.6.4 Gastrointestinal Diseases

Dysfunction of other organs is seen in severely ill people but it can also occur in any other serious infection. This damage to organs is not always directly caused by an infection, but can be caused by the body's reaction to the infection. Epidemiological studies have shown less common symptoms of COVID-19 such as sputum production, headache, bleeding, and some gastrointestinal symptoms (Jin *et al.*, 2019). Surprisingly, recent cellular data from two independent groups showed the significant enrichment of ACE2 expression in cholangiocytes (59.7% of cells) instead of liver cells (2.6% of cells), indicating that COVID-19may cause direct damage to the intrahepatic ducts (Chai *et al* ., 2019). Therefore, the possibility of fecal-oral transmission should be considered in COVID-19 infection. According to previous and recent studies, COVID-19 may be associated with gut microbiota through the ACE2 receptor; thus, we speculate that COVID19 may be related to gut microbiota (Gao *et al.,* 2019). Some people with COVID-19 have reported gastrointestinal symptoms such as nausea or diarrhea, although these symptoms are much less common than lung problems. As COVID-19 appears to enter the body more easily through the lungs, they can also enter the intestine. In the past, SARS and MERS were detected in intestinal and fecal samples. New studies have also shown that fecal samples from some people with COVID-19 contain the virus. Research is ongoing on the possibility of transmitting the virus from feces (Nouri and Alizadeh , 2020 and Gu *et al .,* 2020). Other studies have reported an association between COVID-19 and inflammatory bowel disease (IBD) (Turner *et al* ., 2020) . surveyed 102 PIBD centers using an electronic reporting system of pediatric patients with IBD infected with COVID-19, and reported only eight cases of IBD with COVID-19 infection globally. Other studies revealed that patients with IBD may have no increased risk of COVID-19 infection, which is possibly due to using cytokine blockers to treat these patients (Monteleone and Ardizzone , 2020). Therefore, targeting the gut microbiome may be a new potential treatment option for treating COVID-19-related pneumonia. Overall, we have to work hard to be aware of the early signs of COVID-19 for detection, separation, and intervention in the early stages of the disease. Finally,more attention should be paid to hand hygiene and disinfection and the control of vomiting, feces, etc. We can overcome COVID-19 infection soon withjoint efforts and ex cellent support (Haybar *etal*.,2020).

2.6.5 Respiratory System Disease

A new study of 138 patients admitted to the hospital for COVID-19 found that, on average, people had difficulty in breathing five days after the onset of symptoms. Respiratory distress syndrome also began, on average, eight days after the onset of symptoms (Wang *et al.*,2019). Like other respiratory disease-inducing viruses, such as SARS, MERS, and community-acquired pneumonia (CAP), COVID-19 usually first affects the lungs. Early symptoms include fever, cough, and shortness of breath. These symptoms can appear within two days or up to 14 days after contact with the virus. The COVID-19 severity varies from mild or asymptomatic to severe or sometimes fatal. Older people and those with chronic diseases appear to be at a higher risk of serious symptoms. This variability is also seen in the effect of COVID-19 on the lungs (Haybar and Kazemnia,2020). Some people may have only mild respiratory symptoms while others may develop pneumonia, which does not threaten a person's life. Some people also suffer from severe lung damage. According to research, what we often see in people who are severely infected with COVID-19 is respiratory distress syndrome (Hase *et al* .,2020 and Kim *et al .,* 2020). These conditions are not caused by the virus alone and can be triggered by a variety of events, including infections, trauma, sepsis, and anemia. These conditions damage the lungs, leading to fluid leakage from small blood vessels in the lungs. While there is a lack of information about the type of damage caused by COVID-19 in the lungs, a new report has shown that similar damage can occur with SARS and MERS (Yi *et al.,* 2020). The treatment for respiratory distress syndrome involves the use of oxygen and mechanical respiration to absorb more oxygen into the blood. There is no specific treatment for respiratory distress syndrome and medical staff must do their best to support the patient during this process so that the body recovers and the immune system takes care of underlying events (Haybar *etal*.,2020).

2.6.6 Liver and Kidneys

When liver cells are inflamed or damaged, they can secrete excessive amounts of enzymes into the bloodstream. An increase in liver enzymes is not always a sign of a serious problem, but this laboratory finding has been seen in people with SARS or MERS. New reports showed the signs of liver damage in patients with COVID-19, but it was not clear if the virus or the used drugs to treat the patients induced the damage (Cui *et al*., 2020 and Xu *et al*., 2020). Some people with COVID-19 hospitalization have also had acute kidney damage, which sometimes requires kidney transplantation. The same thing happened with SARS or MERS. However, according to the World Health Organization (WHO), there is little evidence that the virus directly causes kidney damage. Accordingly, kidney damage may be caused by other changes that occur during COVID-19 infection. When a person has pneumonia, less oxygen circulates through the body, which can damage the kidneys (Haybar and Kazemnia,2020).

2.6.7 Immune System Disorders

With any infection, the immune system reacts by attacking the virus or external bacteria. While this immune response can help eliminate infection, it can sometimes cause side effects in the body. It can occur in the form of a severe inflammatory reaction, sometimes called the "cytokine storm" (Chen *et al* ., 2020, Wu and Yang , 2020). Immune cells produce cytokines to fight inflammation, but if too many of them are released, these conditions can cause problems in the body. Many of the damages caused by COVID-19 in the body are caused by a condition called sepsis syndrome, which results from complex immune responses (Alhazzani *et al* ., 2020). The infection itself can cause an acute inflammatory reaction in the body, and such conditions can affect the functioning of various organs. Another thing about the immune system is that so far there have been almost no cases of COVID-19 in children under nine years of age. Researchers are not sure if children get the infection or if they have mild symptoms that no one notices. In other types of infections, including measles and pneumococcal infections, children experience less severe symptoms than adults do. This may be because children have a direct immune response while older people can sometimes experience an over-immune response (Cristiani *et al* ., 2020 and Dong *et al*.,2020). An over-immune reaction may cause some damage during infections. This was evidenced during the outbreak of SARS, which may be true of COVID-19 infection (Haybar and Kazemnia,2020).

3 .Conclusions

Candidiasis is an opportunistic infection caused by *Candida*, a type of fungi. Fungi are eukaryotic organisms found in the form of yeast, molds, or dimorphic fungi. These fungi present in healthy individuals as a commensally organisms by inhabiting various body surfaces such as oral cavity, gastrointestinal tract, vagina and healthy individual's skin. such as impaired immune system, underlying disease states, and prolonged use of antibiotics. They become pathogenic and cause infections only when favorable conditions arise.

Corona virus disease 2019 (COVID-19) infections may be associated with a wide range of bacterial and fungal co-infections. *Candida* and *mucor* are the common fungus encountered during this pandemic. Common predisposing factors for Candidiasis are diabetes, malignancy and prolonged use of antibiotics. The increasing frequency can be attributed to factors such as the use of potent chemotherapeutic agents that alter the host's immune response, the advent of HIV/AIDS, intravenous drug abuse and the success of intensive care unit in prolonging the survival of highly compromised patients, *Candida albicans* is the most common cause of candidiasis, and affect almost all the systems of the body starting from skin to Central nervous system.

4 . Recommendations

1- We recommend that studying the effect of COVID- 19 on oropharyngeal candidiasis.

2- We recommend Molecular diagnosis of patients with COVID- 19.

3- We recommend further Study of the IgM, IgG of patients with COVID- 19.

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