IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 7 Ser.1 (July. 2020), PP 28-41
www.iosrjournals.org

Overview of Epidemiology, Pathogenesis and Clinical Aspects of COVID-19: A Libyan Perspective

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Abstract
Libya has an estimated population of 6,871,292 million which is relatively small compared to its very large surface area with a density of four people per one Km^2.
Libya is one of the latest countries to be infected by a coronavirus (COVID-19). The first case of coronavirus was reported on March 24th, 2020, since then 24 cases were recorded with only mild symptoms, eight cured and one died. The delay of the infection possibly attributed to several explanations. Most of the people live in single-family homes, 68.32% of the population ranged between 15-54 years of age and only 5% of the Libyans are aged over 65 years according to Bureau of Statistics and Census Libya .

Unlike Libya, Italy ranked one of the first countries infected with the coronavirus (February 21st, 2020). It is located on the other side of the Mediterranean Sea cross from Libya. It has an area of 301,340 Km^2 with a density of 206 people per 1 Km^2 .

Italy reported 156,363 cases infected with COVID-19 and a death toll of 19,901. As of 13thApril 2020 (41). The age group of 65+ years representing 23.1% of the total Italian population as compared to the same age group in Libya which representing less than 5 %. This may contribute to the differences in the death rate between the two countries, the differences continue in the other young age groups, children (0-14) and youth (15-24 years).
Another important factor was the civil war leading to the isolation of Libya with flights restricted to countries such as Tunisia, Turkey, Jordan and Egypt which reported COVID-19 infection later than all other countries. There were no direct flights from China or USA or NATO countries.
Apart from that travelers were inspected and screened in those countries before departure to Libya and were screened again upon arrival at the Libyan airports.
(https://en.wikipedia.org/wiki/Libyan_Civil_War_(2014–present) #cite _note-guardianbriefing- 92)
The Libyan government has taken very early precautions steps. In early March, the ministry of education adjourned all schools and universities. On March 16, all borders, airports, and seaports were closed for safety measures to avoid any infections coming from abroad. Mosques ordered to shut down and all social congregations were eliminated. On March 20, limited curfew was applied (6:00 pm to 6:00 am) and only grocery stores and pharmacies were kept open.
Libya provides a unique situation in which Nature has played its role through its geographical and regional locations. Civil war and its impact have indirectly made ordinary citizens to stay back home and avoid crowding in the streets. There are no big malls or theatres to take extra measures of shut down. Yet the civil war has put Libya with scarce resources for diagnosis, monitoring and treatment apart from social distancing. It remains to be seen how the big picture unfolds in the days to come. This review explains the general nature of COVID-19 and other related infectious diseases. It also provides a bird's eye view of the COVID-19 pandemic in Libya, one of the unique nations of Africa.

Key words: *Libya; COVID-19, Corona Virus, AIDS, Other related infectious diseases*

Date of Submission: 18-06-2020 Date of Acceptance: 04-07-2020

I. Introduction

Coronaviruses were first discovered in the 1930s in domesticated chickens, and in the 1940s, it was discovered in animals. In the 1960s, Human Coronaviruses (CoVs) were discovered and they were classified under the family Coronaviridae, which is the largest RNA virus family within the order Nidovirales. The family Coronaviridae encompasses two subfamilies: subfamily Orthocoronavirinae and subfamily Torovirinae (ICTV). Coronaviridae is a family of enveloped, non-segmented, positive-sense, and single-stranded RNA viruses (ssRNA) with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope (ICTV) (1). The viral genome was about 29,881 nucleotides in length, which is encoding a total of 9860 amino acids. Coronaviruses cause diseases in mammals and birds. Unexplained low respiratory infections of unknown etiology were detected in Wuhan, China. In December 31, 2019, a new coronavirus genome (CoV) was found. The Chinese authorities identified and characterized the novel coronavirus (2019-nCoV) as the causative agent of the outbreak. The outbreak appears to have started from a single or multiple zoonotic transmission events in a wet market in Wuhan where wild animals, fish, and meat were sold. It was temporarily given the name 2019 novel coronavirus (2019-CoV) (2,3). The virus was subsequently renamed as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2), which caused the disease named Corona Virus Disease-2019 (COVID-19).

In January 30, 2020, the WHO declared a global public health emergency. The virus is transmitted from human to human. In February 11, 2020, the WHO Director-General, Dr. TedrosAdhanom, announced that the disease caused by this new CoV is called (COVID-19). The SARS-CoV-2 belongs to the genus Beta-coronavirus (4,5). Phylogenetic analysis revealed that the SARS-CoV-2 is closely related, with 88-89% similarity, to the bat-derived Severe Acute Respiratory Syndrome (SARS)-like coronaviruses. Also, it is more distant from SARS-CoV and MERS-CoV, with about 79% and 50% similarities, respectively (4). CoV circulating in Horseshoe bats, had 98.7% nucleotide similarity to the partial RNA, dependent RNA polymerase gene, of the bat coronavirus strain BtCoV/4991 (GenBank KP876546, 370 nucleotide sequences of RdRp) and had 87.9% nucleotide similarity to bat coronavirus strain (bat-SL CoVZC45 and bat-SL-CoVZXC21) (4). CoVs were further divided into four genera: alpha-CoVs, beta-CoVs, gamma-CoVs and delta-CoVs, among which alpha- and beta-CoVs can infect mammals while the other two genera infect birds and could infect mammals too. Seven coronaviruses have been found to infect humans and cause respiratory diseases (6). Four out of seven are common human viruses CoVs (HCoVs), which usually lead to common self-limited upper respiratory disease: HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. These viruses can occasionally cause more serious symptoms in the elderly, diabetic, heart-disease patients, and immunocompromised individuals. MERS-CoV, which was isolated in 2012 is similar to the SARS-CoV. Both can infect the lower respiratory tract and usually cause severe respiratory syndrome in humans with a fatality rate of 35% (3). In September 2003, more than 8,000 patients suffered from Severe Acute Respiratory Syndrome (SARS) due to the coronavirus. 774 virus-related deaths with a fatality rate of 9.5% were reported to the WHO. Since September 2012, there were 2,494 laboratory-confirmed cases of infection with Middle East Respiratory Syndrome Corona Virus (MERS-CoV). 858 virus-related deaths were reported to the WHO. All these emerging infectious diseases were caused by beta-coronaviruses.

Respiratory RNA viruses

Influenza A H1N1, and H5N1 Viruses

Influenza A virus (IAV) is a single-stranded, negative-sense RNA virus that belongs to the Orthomyxoviridae family. It's the causal agent of flu and the main pathogen responsible for worldwide epidemics and pandemics. It has high antigenic flexibility and mutates more rapidly than the other two subtypes of influenza viruses (B and C). IAV is classified into subtypes based on two surface proteins hemagglutinin (HA) and neuraminidase (NA) and is given 18 known HA subtypes and 11 known NA subtypes(7). Accordingly, influenza A viruses can be classified into (H1N1) virus subtypes A, which is the most common cause of swine influenza; and virus subtypes A (H5N1) that cause avian influenza, among other animal influenzas types. Generally, all these animal influenza types A viruses do not easily transmit among humans. In May 2009, a pandemic outbreak of H1N1 occurred as a result of the progression and reintegration of avian, swine, and human influenza viruses in pigs. H1N1 showed an excellent example of evolution by their sudden ability to jump from pigs to humans and then sustain human to human transmission (8,9). The mode of transmission of this virus is similar to the seasonal flu virus. H1N1 viruses are spread mainly from person to person through sneezing, coughing or talking to people carrying the virus. Sometimes people may become infected by touching an object contaminated with flu viruses followed by touching their mouths or/and noses.

Most of the serious cases of H1N1 influenza manifested in older children, young adults and pregnant women with a mortality rate of approximately 1%(10).

On the other hand, (H5N1) known as Asian Highly Pathogenic Avian Influenza (HPAI) A virus pathogenies are mainly for birds and cause high mortality among poultry. In 1997, the first human case was

reported during a poultry outbreak in Hong Kong (11). Most human infections with H5N1 viruses have been associated with close contact with infected live or dead birds. Unlike H1N1, H5N1 shows rare human-to-human spread. The infected population may reach 60 mortality rate as the virus causes severe damage to the human respiratory system(12).

Regarding the pathogenicity of the H1N1 virus, many studies have found that 2009 H1N1 preferred the ciliated epithelial cells of the upper respiratory tract (12). The mild cases of the 2009 H1N1 exhibited mild inflammatory lesions of the upper respiratory tract (laryngitis and rhinitis) and had self-healing properties. The virus mainly adheres to the upper respiratory tract, trachea, and bronchial ciliary epithelial cells without severe symptoms. On the other hand, the severe cases of the 2009 H1N1 can cause death to individuals. The results of the autopsy of the lung tissues have shown diffused alveolar damage (DAD). DAD refers to a pathology-based on the diffuse injury of the capillary endothelium and alveolar epithelium and enhanced vascular permeability caused by serious diseases inside and outside the lung (including viral infection), with pulmonary edema and transparent membrane formation as the main morphological manifestations. The clinical manifestations are acute respiratory failure syndrome characterized by progressive respiratory distress and refractory hypoxemia (13,14).

Autopsy results of a small number of death cases with H5N1 virus infection have been reported in the literature, showing that lung lesions are centered on alveoli and bronchioles with rare tracheal or bronchial lesions(15–18). The lung tissues of H5N1 death cases showed DAD changes, which showed early changes in the exudate phase, showing clear membrane formation, vascular congestion, and interstitial lymphocyte infiltration

Despite the differences between the H1N1 and H5N1 viruses, there are some important similarities particularly in severe and fatal cases especially the histopathological findings for these cases. It appears to have similarities for both diseases in terms of damage and severity(19). Also, it is hard to distinguish between H1N1, H5N1 and seasonal flu due to the resemblances of most of the symptoms. The most common flu tests are called "rapid influenza diagnostic tests," where swab samples from the nose or the back of the throat are tested for antigens. These tests can provide results in about 15 minutes. Unfortunately, the outcomes of these tests can vary greatly and are not always accurate. Currently, the more sensitive and accurate flu tests are the ELISA and the Real-Time Polymerase Chain Reaction (PCR) (20).

SARS-CoV virus

This virus belongs to the family of Coronaviridae with genera beta-coronavirus. The SARS-CoV was first identified in November 2002 following an outbreak in Guangdong Province, China. Phylogenetic analysis of these viruses had indicated with a high degree of probability that the virus was originated in bats and spread to humans either directly or through an intermediate host. Examples of intermediate hosts included masked palm civets, raccoon dogs, and domestic cats held in Chinese markets. In March 2003, the infection quickly spread to Beijing, Hong Kong, Vietnam, Singapore, and Canada. This disease proved highly infectious via respiratory droplets released from the body when an infected person coughs or sneezes close to another person. The incubation period of this disease is up to 14 days and the fatality rate is 9.5% (3,21).

MERS-CoV

The MERS virus also known as camel flu, belongs to the family Coronaviridae, beta-coronavirus genera. It was first identified in 2012 in an old Saudi patient who had acute pneumonia and renal failure. This person later died from complications of the disease. The virus was originated in bats and spread to humans through an intermediate host, Dromedary camel, which are believed to be involved in its spread to humans. MERS is a highly fatal respiratory disease with a higher fatality rate of 35%, higher than SARS. In 2015, this virus caused large outbreaks in Saudi Arabia and the Republic of Korea in 2015 (3).

SARS-CoV-2

In late December 2019, the third zoonotic coronaviruses rapidly spread in Wuhan, China. It was a new beta-coronavirus that belonged to the family Coronaviridae. The genome of this virus has 86.9% similarities to a previously identifies and published bat SARS-like CoV genome (bat-SL-CoVZC45, MG772933.1). It is different from the human SARS-CoV and the MERS-CoV. It is originated in bats with the possibility of intermediate hosts, such as snakes and pangolin. (3,6). SARS-CoV-2 is a contagious disease just like any other respiratory pathogens (the flu) that can be transmitted by coughing and sneezing as well as close interaction between individuals.

The spread is primarily limited to family members, healthcare facilities, and other close contacts. Infected Individuals with COVID-19 usually suffer fever and lower respiratory tract symptoms. The incubation period is from 2- 14 days (21). Patients infected by the SARS CoV- 2 showed symptoms such as fever, severe headaches, sore throat, rhinorrhea, cough, diarrhea, dyspnea, and lymphopenia. In severe cases, patients develop life- threatening complications, such as respiratory failure, shock, and multiple organs dysfunction. In addition to bilateral lung involvement ground-glass opacity by radiological pictures, reduced or normal white blood cells, and lymphopenia (3).

This review aims to understand the unique features of SARS-CoV-2 and relationship with other coronavirus respiratory viral infections. We also discussed COVID-19 outbreak in Libya with detailed analysis

of the current situation and causes of slow spread. We also reviewed the latest treatments and ongoing clinical trials worldwide.

Clinical Manifestations of coronavirus respiratory infections

Most patients of COVID-19 haveflu-like symptoms including fever (83-98%), cough (77-82%), chills, fatigue and 31-64% had shortness of breath. Other symptoms include Myalgia, headache,confusion, chest pain, and diarrhoea(22,23). Many patients presented with organ failure, including ARDS, acute respiratory failure, acute renal failure, cardiac injury,septic shock or pneumothorax (22,24)..

Table 1. Comparison between SARS -CoV- 2, MERS- CoV, and SARS- CoV viruses

Characteristics	SARS CoV- 2	MERS-CoV	SARS-CoV
Virus	non-segmented, +ssRNA viruses	non-segmented, +ssRNA viruses	non-segmented +ssRNA viruses
Receptor	ACE2	DPP4 (CD26)	ACE2
Primary Host	Bats	Bats	Bats
IntermediateHost	Pangolins, Snakes,Seafood?	Camels	Raccoon dogs, civet cat
Speed of spread	High	Low	Moderate
Incubation Period	2 - 14 days	2 - 14 days	2 – 10 days
Number of Cases	1,970,225 (As of 6 April, 2020)	2506	8098
Number of deaths	124,544 as of 6 April, 2020	862	774
Fatality rate	6.3 %	35 %	9.5 %
Recovered cases	469,926	1644	7324
Seasonal occurrence	Winter (Dec- to date)	Summer (May-July)	Winter (Dec-Jan)
Possible complications	Multiple organ failure	Multiple organ failure	Acute renal failure Rhabdomyolysis Gastrointestinal bleeding
Clinical manifestations	Fever, Cough, Shortness of breath. Fatigue and malaisePneumonia is common	Fever, cough and shortness of breath. Pneumonia is not always present	Flu-like symptoms (fever, malaise, myalgia, headache, and shivering) and diarrhoea. Severe cases often evolve rapidly, progressing to respiratory distress and requiring intensive care

These symptoms are similar to those of SARS-CoV and MERS-CoV respiratory infections with flu-like symptoms are the hallmarks of disease. It is generally difficult to distinguish between them on clinical basis alone, and hence molecular testing by RT-PCR is needed to establish the diagnosis. Table 1 summarizes the epidemiological and clinical features of coronaviruses

Co- infection of SARS- CoV- 2 with HIV

Human Immunodeficiency Virus

The human immunodeficiency virus (HIV) is a single-stranded, enveloped RNA lentivirus of the retrovirus family (*retroviridae*) and is the etiological agent of acquired Immunodeficiency Syndrome (AIDS). The family name (retroviridae) comes from the concept that they replicate by the reverse transcription of their genomic RNA (gRNA) into a linear double-stranded DNA copy and the subsequent covalent integration of this DNA into the host cell genome (25). Furthermore, the AIDS is characterized by state of low immunity that leads to several illnesses due to a wide range of opportunistic infections and neoplasms (26,27).

However, The unique pattern related to outbreak of peumocystiscarinii pneumonia (PCP) and Kaposi sarcoma (KS) in 1981, leads to the first clinical AIDS(28,29). The Centers for Disease Control and Prevention (CDC) named these patterns of conditions the AIDS as these conditions of a rare opportunistic infection and neoplasm were known to be associated with severely suppressed immune status.

Moreover, the first clue to AIDS etiology came in 1983 after the isolation of the virus from lymph nodes of a patient suffering from cervical lymphadenopathy (30,31).

At the end of 2012, the WHO/UNAIDS reported a prevalence of 35.3 million [32.2 million–38.8 million] people estimated to be living with HIV, of which about 430,000 are children below the age of 15.

The majority of HIV-1 infections, accounting for about 80%, are acquired through unprotected sexual contacts, either heterosexual (70%) or homosexual (10% of the total percentage). Additionally, the susceptibility of HIV infection increases considerably with the presence of ulcerative genital lesions due to other sexually transmitted diseases (32). Second mode of infection is associated with transfusion of contaminated blood and blood products that account for 5% of all transmissions (33). Lastly, maternal transmission of HIV is also responsible for more than 90% of all HIV infections in infants and children (34).

The lowering of CD4+ T lymphocyte count to <500 per µl (normal value 600–1200 cells/µl) referred as AIDS related complex (ARC) formation and the loss of cell-mediated immunity. Further decrease in CD4+ T-cell counts (<200 cell/µl) leads the onset of frank AIDS. At this point, the infected individual becomes susceptible to a variety of opportunistic infections and neoplasms and death usually proceeds within an average time interval of 9 months.

Moreover, the highly active antiretroviral therapy regimen (HAART) reduces considerably HIV morbidity and mortality (35). HAART regimens combine three drugs belonging to at least two classes of the 35 commercially available Anti-RetroViral (ARV) agents: typically, two nucleoside analogues reverse transcriptase inhibitors (NRTIs), plus either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI) (36,37). However, HIV is known for its drug resistance due to high error rate of reverse transcriptase enzyme that represents a major barrier to the development of effective antiviral therapy(35).

Incident of HIV infection in Libyan Children

In Libya, the HIV was rare until 1998 when over 400 children were deliberately infected with HIV by six foreign medical workers, causing an epidemic at El-Fatih Children's Hospital in Benghazi, Libya (38). By August 2007 about 56 of the infected children had died.More recently data from The Libyan Health Ministry's Center for Disease Control have reported more than 10,000 infections by the end of 2018 (39).

Co- infection of SARS- CoV- 2 and HIV

Currently, we have no specific information about the risk of COVID-19 in people with HIV. Our information is based on early data from small studies that demonstrated the Co- infection of SARS- CoV- 2 in immunocompromised patient, practically HIV patient, appear to increase the risk for major complications that include admission to intensive care (ICU) and even death. Moreover, the risk for people with HIV is greatest in elderly people and people with low CD4 cell count, people who are not on HIV treatment (The highly active antiretroviral therapy regimen HAART), and those who have other medical condition(40).

Epidemiology and transmission

Globally, about 1,776,867 confirmed cases of COVID-19 have been reported at the time of writing this review (14/4/2020)(41). Since the first reports of cases from Wuhan, COVID-19 cases have been recorded in Wuhan China, and most of the cases were from Hubei and adjacent provinces. The peak of pandemic period was between late January and early February 2020 (42), and the rate of new cases declined significantly by early March 2020. Then, COVID19 widely spread and reported in several continents,gradually increasing in numerous countries (43).

The transmission of SARS-CoV-2 was not completely understanding. Epidemiologic investigation in Wuhan at the beginning of the outbreak identified an initial association with a seafood market that sold live animals, where most patients had worked or visited, and which was subsequently closed for disinfection (44). Several studies suggested that bat may be the main reservoir of SARS-CoV-2 (45,46). Bats are also considered as a natural reservoir of several types of CoVs, including SARS-CoV and MERS-CoV(47). Current study has showed that several bat CoVs are capable of invading human cells directly without the need for intermediate host (48). Upon virus genome sequencing, the COVID-19 was analyzed throughout the genome to Bat CoV RaTG13 and showed 96.2% overall genome sequence identity (49), indicating that bat CoV and SARS-CoV-2 might had a similar ancestor, also bats are not offered for sale in Whuan seafood market (50). Moreover, no specific animal has been correlated with SAR-CoV-2. The supposed intermediated host of SARS-CoV-2 is pangolins as the coronavirus genetic sequences were 99% match between these animals the infected patients, as recorded at a press conference on February 7, 2020 (51). Researcher are investigating the origin of COVID-19 including supposed intermediate animal vectors. However, person-to-person spread became the major pattern of infections. Person-to-person spread of (SARS-CoV-2) is thought to occur mainly through respiratory droplets, resembling the spread of influenza which supported by the incidents that occurred among families and between persons who did not visit the seafood market in Wuhan (52). Further information's stated that person to person transmission occurs mainly among family members, including relatives and friends who directly contacted infected persons (53). The infected patients can release the viruses via respiratory secretions when sneezing, directly talking or coughing. Droplets typically do not travel more than two meters and do not exists in the aerosol. For that, recent study indicating that, SARS-CoV-2 persisted viable in air under experimental circumstances for three hours at least (54).

Immunopathology of COVID-19

The location of initial infection with SARS-CoV-2 is unclear and the pathogenesis mechanism of COVID-19 is still under study. For majority of patients, COVID-19 might affect only the lungs because it is basically classified as a respiratory disease. The first pattern of infection is person to-person transmission via direct contact, which arises through droplets from an infected patient due to cough or sneeze. COVID-19 has a

probable asymptomatic incubation period between 2 and 14 days (55). Hence, the rapid spread of SARS-CoV-2 has occurred with a basic R0 of 2.2-2.6, meaning that on average each individual has the potential to spread the infection to 2.2 other people (22). Based on previous hospital data obtained from patients infected with COVID 19, the majority (80%) of cases presented with mild symptoms or with asymptomatic while the remainder (20%) are presented in severe cases (56,57). As compared with SARS and MERS, the severity and mortality rate of COVID-19 is considered mild(50). Moreover, recent study of 41 hospitalized cases with high levels of proinflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα was observed in the COVID-19 critical cases (56). These results are compatible with MERS and SARS in that the existence of lymphopenia and "cytokine storm" may have a significant factor in the pathogenesis of COVID-19(58,59). The increase level of cytokines factor can trigger viral sepsis causing lung injury which leads to other complications including pneumonitis, acute respiratory distress syndrome, respiratory failure, shock and potentially death.

Recently, few data are presented on the host innate immune status of SARS-CoV-2 infected patients. Previous study conducted in Wuhan, 99 cases were examined, decreased total level of lymphocytes (35%), neutrophils level were increased (38%), %), increased serum IL-6 (52%) and increased c-reactive protein (84%) were detected (60). Moreover, other study from Wuhan, indicated that in 41 patients, total number of neutrophils were increase, decreased total number lymphocytes in patients of intensive care unit (ICU) in contrast of non-ICU care were found to be statistically different. raised neutrophils and decreased lymphocytes also correlate with disease severity and death (50). Furthermore, infected persons needing ICU care posse higher plasma levels of numerous innate cytokines, (56).

The effective innate immune response against viral infection relies heavily on the interferon (IFN) type I responses and it reduce cascade that terminates in controlling viral replication and trigger of effective adaptive immune response. While SARS-CoV and SARS-CoV-2 appears to share the same entry receptor of ACE2, but in terms of MERS-CoV, dipeptidyl peptidase (DPP)-4 used as a specific receptor (49). The assumed receptor of SARS-CoV-2, ACE2, is mostly expressed in a small subset of cells in the lung called type 2 alveolar cells (Zhu et al, 2020b). SARS-CoV-2 infects any immune cells that are still unknown. Only minimal percentages of monocytes/macrophages in the lung expressed ACE2 (60). If ACE2 is minimally expressed in the potential target immune cells, other receptors may exist, or another cellular entry mode is utilized such as antibody-dependent enhancement as presented in Figure 1.

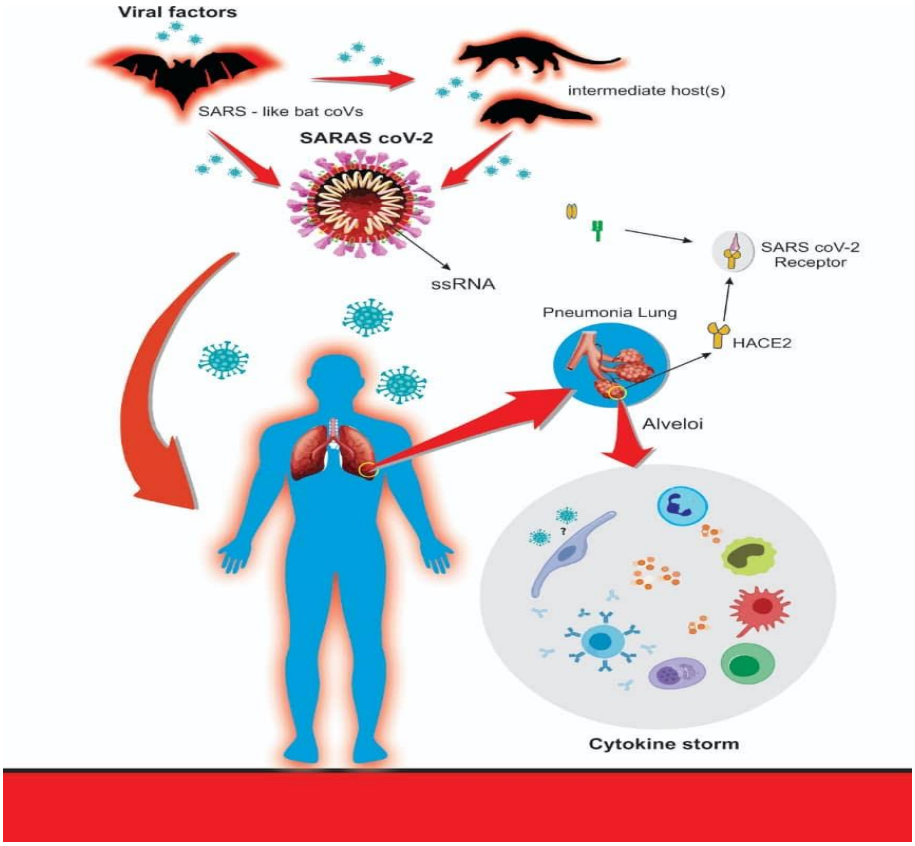

Figure 1. Proposed host immune response during SARS-Cov-2 infection

Possible causes of slow spread of Covid-19 infection in Libya

Libya is one of the Middle Eastern countries in North Africa. It is ranked the 17th in the world in terms of area and 4th in Africa, with an area size of about 1,759,540 Km^2(61). It has a 1,955 km seashore which is the longest coastal strip in the Mediterranean Sea (Figure2). According to the UN data (61), Libya has an estimated population of 6,871,292 million which is relatively small compared to its very large area with a density of four people per one Km^2.

Libya is one of the latest countries to be infected by a coronavirus (COVID-19). The first case of coronavirus was reported on March 24th, 2020, since then 24 cases were recorded with only mild symptoms, eight cured and one died. The delay of the infection possibly attributed to several explanations. Most of the people live in single-family homes, 68.32% of the population ranged between 15-54 years of age and only 5% of the Libyans are aged over 65 years according to Bureau of Statistics and Census Libya(Figure 3).

Unlike Libya, Italy ranked one of the first countries infected with the coronavirus (February 21st, 2020). It is located on the other side of the Mediterranean Sea cross from Libya. It has an area of 301,340 Km^2 with a density of 206 people per 1 Km^2 (Figure 2)(62,63).

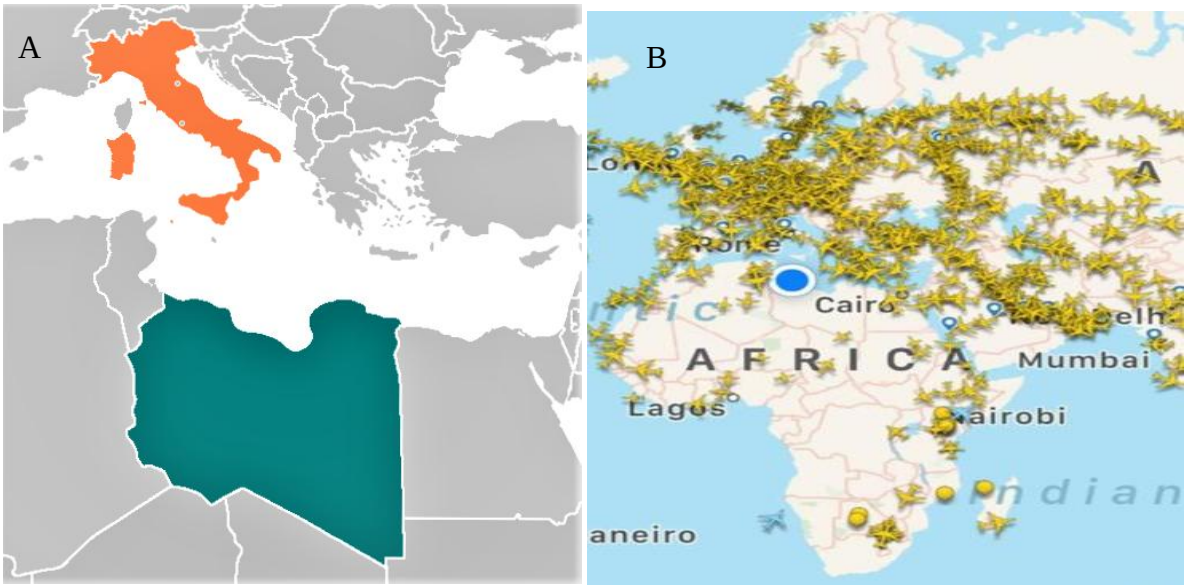

Figure 2. A. Map showing Libya (green)and Italy (Orange) B. Photo from Flightradar24 application showing air traffic over Europe versus Africa on 13th April 2020. The air traffic density highly matches COVID-19 spread in these countries

Italy reported 156,363 cases infected with COVID-19 and a death toll of 19,901. As of 13th April 2020 (41).The age group of 65+ years representing 23.1% of the total Italian population as compared to the same age group in Libya which representing less than 5%(62,64). This may contribute to the differences in the death rate between the two countries, the differences continue in the other young age groups, children (0-14) and youth (15-24 years) (Figure 2).

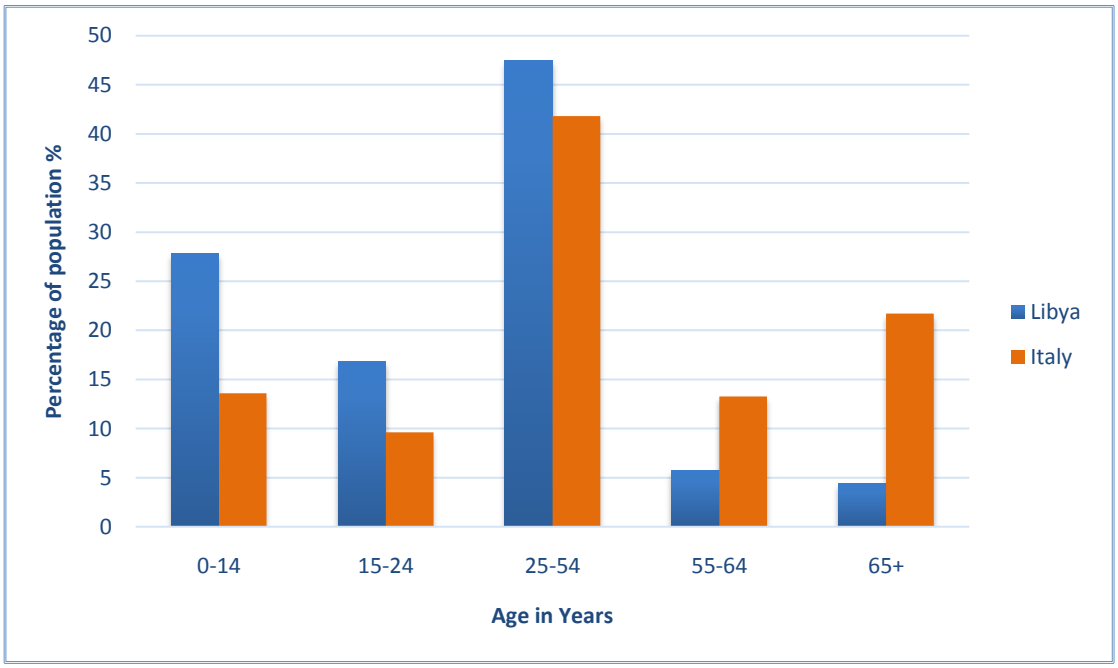

Figure 3. Comparison of population structureby Age groupinLibyaand Italy.

The Impact of Civil War

Since the eruption of the civil war in 2014, Libya became isolated, international flights were restricted to only local airlines and to only limited countries such as Tunisia, Turkey, Jordan, and Egypt which most of them infected with COVID-19 lately. There are no direct flights from China and Italy to Libya. Travelers were inspected and screened in those countries before departure to Libya and were screened again upon arrival at the Libyan airports. (https://en.wikipedia.org/wiki/Libyan_Civil_War_(2014–present) #cite_note-guardianbriefing-92)

Government Mitigation efforts

The Libyan government has taken very early precautions steps. In early March, the ministry of education adjourned all schools and universities. On March 16, all borders, airports, and seaports were halt for safety measures to avoid any infections coming from abroad. Mosques ordered to shut down and all social congregations were eliminated. On March 16, all borders, airports, and seaports were halt as a safety measure. On March 20, limited curfew was applied (6:00 pm to 6:00 am) and only grocery stores and pharmacies allowed to open during the permitted hours to restrict movement. These precautions were executed 9 days before the appearance of the first case of COVID-19 on March 24th. In comparison, Tunisia has imposed a limited curfew (6:00 pm to 6:00 am) on March 18th, 2020 after the number of infected peoples reached 29 cases and one case had died(65,66).

Libya Infrastructure

Most of the housing in Libya are lacking central air-conditioning and central heating systems which promote contamination between apartments. Several reports stated that Legionnaire's disease caused by Legionella bacteria was transferred through central hot water systems between apartments (1, 2 and 3). Most of the buildings consist of not more than 12 floors, installed with single air-conditioning units that eliminate the contamination between apartments by any microbes of the same buildings.

The impact of the civil war and limited health resources resulted in a shortage of personal protective equipment and other medical supplies in the hospitals to confront the coronavirusoutbreak. Furthermore, the National Centre for Disease Control (NCDC) was unable to test all individuals for the COVID-19 virus even for older ages (65+). The NCDCcurrently tests only COVID-19 suspected individuals and their contacts using Real-time Reverse transcriptase Polymerase Chain Reaction test (RT-PCR).

Culture and food behaviors

Other aspects may contribute to the reasons of why the infected cases in Libya appeared late as compared to Italy and the neighboring countries; All sports activities including football leagues which are attended by a large number of fans were suspended since 2018 (67). Also, absence of large shopping malls,

movie theaters, and public transport such as trains or buses lessen the chances of direct contact between individuals and reduce the spread of disease.

As the COVID-19 outbreak worldwide, people went through self-isolation and are stockpiling disinfectant and food. Although there is no one way to dodge infection exclusively, health professionals recommend strengthening the immune system with certain foods and spices which can go a long way to improve the health overall and to reduce the risk of contamination. Among the food ingredients that are part of the Libyan diets is Onion, it is consumed daily in different types of dishes. It acts as antioxidant-rich food which is essential for building up the immune system. It contains Vitamin C, B and E which assist fight off infections (68). Eggplants, pumpkins, and carrots are also an effective antioxidant that is eaten more frequently in Libya. Turmeric is an anti-inflammatory rich spice that is normally added to most of the Libyan diets. Eating several types of vegetable daily assist along with the addition of turmeric in the ingredients have extra benefits. Eggs play an important role in Libyan diets. They are extremely nutritious food containing more than 20 essential vitamins and minerals especially selenium which is important for cell health. A single egg can provide 25% of the daily selenium requirement. Green tea, which is the traditional drink among the Libyan society, contains flavonoids that assisting the production of virus-spreading enzymes. Garlic contains Allicin compound which is known to boost the white blood cells in response to sickness(69).

Correlation between BCG vaccination and spread of COVID-19 infection

A large number of epidemiological studies have shown nonspecific effects of BCG vaccination against infections other than tuberculosis (70). In addition, recent literature has suggested a role of BCG vaccine in trained immunity and immunomodulation (71–73).

BCG vaccination in patients vaccinated by live attenuated yellow fever vaccine reduces the level of YFV viremia after vaccination and induces genome-wide histone changes in monocytes and cytokine responses indicative of trained immunity (73). Another non-specific protective effects through induction of innate immunity are provided by the use of BCG vaccine for treatment of bladder cancer and melanoma.

Hence it is postulated that people in countries receiving BCG vaccination could have protection against a number of viral infections including SARS-CoV2. This theory is partly supported by the slower spread of the COVID-19 infection in these countries especially among children (74).

Smoking Practice

It is doubtful that anyone understands for sure yet how smoking might affect the susceptibility to COVID infection. Smoking could pose a renewed risk among the patients, leaving many cases at a higher threat of complications. Chinese research on COVID-19 patients reported that smoking was linked with 14-fold higher odds of the disease progression. Lung damage my impact patient's response to the virus and warning was issued to smokers for their susceptibility to the hazardous effect of the virus due to weakened lung function.

Almost half of the Libyan population is females and the smoking habit among them is rare which may attribute to the reason why most of the infected cases reported were males.

Treatment Of COVID-19 and current clinical trials

On initial examination patients are evaluated for severity of symptoms and subsequently categorised for therapeutic options. Patients with mild disease do not require hospital interventions; but isolation is necessary to contain virus transmission and will depend on national strategy and resources. These patients are usually given symptomatic treatment such as anti-pyretics for fever and headaches and close monitoring for development of signs and symptoms of severe disease. Asymptomatic individuals who were in contact with a confirmed COVID-19 case are isolated for 14 days and if they develop symptoms are managed accordingly (75).

Laboratory testing using RT-PCR of viral RNA extracted preferably from nasopharyngeal swabs should be performed on all symptomatic patients depending on availability of resources. Priority testing is however given to healthcare workers and hospitalized patients, patients ≥65 years of age and patients with comorbidities to ensure proper triage of these categories (76).

Management of patients with moderate and severe disease (receiving supplemental oxygen or requiring mechanical ventilation) consists of infection prevention and control (IPC), and supportive care (Yang et al, 2020). World health organization issued detailed guidelines on IPC based on prior experience of SARS and MERS infection outbreaks and data from China and other countries (77). Investigational antiviral drugs were given to most cases in China including oseltamivir, Remdesivir, Lopinavir/ritonavir and Favipiravir (6,22,24).

There are currently 68 recruiting interventional clinical trials registered in *Clinicaltrials.gov* at the time of writing this paper. Table 2. summarizes the trials of drug therapies used in different hospitals worldwide for COVID-19 infections.

The only FDA approved drug (off label) for COVID-19 is hydroxychloroquine and azithromycin combination therapy. In addition to being antimalarial drugs, chloroquine and hydroxychloroquine are also used

in the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus due to its immunomodulatory activity (78). The use of HCQ in treatment of COVID-19 stems from studies on its inhibitory effect on SARS-CoV-2 infected Vero cells and other RNA viruses (78–80). Results from clinical studies in China involving more than 100 patients have shown that chloroquine phosphate reduced disease severity and shortened its course, led to negative seroconversion and improved pulmonary scans in comparison with control arm (81). An open label non-randomized clinical trial was also conducted in France including 36 patients with confirmed COVID-19 infection; respiratory viral load was cleared on day 6 post-treatment compared with control (82). However, a study of 11 patients with COVID-19 who have poor prognosis showed no clinical benefit nor viral clearance 6 days post-treatment using the same dosing regimen in the French study by Gautret et al (83).

"SOLIDARITY" is an international randomized, multicenter, adaptive clinical trial to help find an effective treatment for COVID-19, launched by the World Health Organization and partners. The SOLIDARITY trial currently involving 45 countries will assess relative effectiveness of four drugs against standard of care in COVID-19 patients in multiple countries aiming to rapidly determine whether any of the drugs show clinical benefit or improve survival. The study treatments are remdesivir, chloroquine or hydroxychloroquine, lopinavir plus ritonavir, and interferon-beta (84).

Remdesivir (GS-5734) is a 1′-cyano-substituted adenosine nucleotide analog prodrug and shows broad-spectrum antiviral activity against several RNA viruses. Based on findings from studies on in vitro cell line and mouse models, remdesivir could inhibit viral NSP12 polymerase (85,86). The first covid-19 patient in the United States has received Remdesivir on the 7^{th} day of admission and started to improve on the 8^{th} day (87).

During the SARS outbreak in 2003, several drugs were studied and used to treat patients. Treatment of SARS prototype virus (HKU-39849 isolate) with Lopinavir/ritonavir in *in vitro* antiviral susceptibility testing showed an inhibitory effect compared with other tested antiviral agents but only at 48hrs. Lopinavir/ ritonavir treatment was also associated with a better clinical outcome (88). These results along with lack of available therapy for SARS-CoV-2 encouraged clinicians to use these drugs in the treatment for COVID-19 infection (89,90).

However, a study by Sheahan et al, demonstrated that remdesivir and interferon-beta have better improved lung function and reduced viral load in MERS-CoV infected mice compared with Lopinavir/ ritonavir (91). In addition, a randomized trial of lopinavir–ritonavir in adults hospitalized with severe covid-19 showed no benefit with lopinavir/ritonavir treatment beyond standard care (92). Therefore, further randomized clinical trials are needed to explore the clinical effects of its use in SARS-CoV-2 pneumonia.

Use of convalescent plasma has been used to treat other viral infections including the SARS-CoV-1, H1N1 influenza virus, MERS-CoV and Ebola viral infection, without the occurrence of severe adverse events (93,94).

Convalescent plasma donated from patients who have recovered from the disease were used to treat severely ill patients in US and China hospitals (95,96). In an uncontrolled trial of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS), administration of convalescent plasma containing SARS-CoV-2 specific IgG antibody binding titer greater than 1:1000 was followed by an improvement in clinical status (96).

Convalescent plasma has not yet been approved for use by FDA, but it is regulated as an investigational product through either randomized clinical trials or An IND application for expanded access is an alternative for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomized clinical trials (97). The viral specific IgG passive antibody therapy mostly works by neutralizing the virus and possibly also by inducing antibody-dependent cellular cytotoxicity and/or phagocytosis (98).

Two other drugs are now being studied in phase 3 clinical trials and are previously approved by FDA for rheumatology indications: tocilizumab and sarilumab.

Ivermectin is another drug studied for treatment of COVID-19 which reduces viral replication of SARS-CoV-2 Vero/hSLAM cell line within 24-48 hr through inhibiting IMPα/β1- mediated nuclear import of viral proteins (99).

Other antivirals being tested against COVID-19 are arbidol, darunavir, favipiravir, oseltamivir, and various protease-inhibitor combinations in trials in China and Thailand.

II. Conclusions:

Libya provides a unique situation in which Nature has played its role through its geographical and regional locations. Civil war and its impact have indirectly made ordinary citizens to stay back home and avoid crowding in the streets. There are no big malls or theatres to take extra measures of shut down. Yet the civil war has put Libya with scarce resources for diagnosis, monitoring and treatment apart from social distancing. It remains to be seen how the big picture unfolds in the days to come. This review explains the general nature of

COVID-19 and other related infectious diseases. It also provides a bird's eye view of the COVID-19 pandemic in Libya, one of the unique nations of Africa.

Acknowledgement: We thank Mr. Nabil Mustafa for designed the Figure 1.

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Dhastagir Sultan Sheriff, et. al. "Overview of Epidemiology, Pathogenesis and Clinical Aspects of COVID-19: A Libyan Perspective." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(7), 2020, pp. 28-41.