Review Article

Covid-19, What Have We Learnt To Date?

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Abstract

Corona Virus Disease 2019 (Covid-19) was reported first in Wuhan, Hubei Province in China after patients presented with pneumonia of unknown etiology complicated with Severe Acute Respiratory Syndrome (SARS) reminiscent of SARS from 2002. The new virus was identified and described as SARS-CoV-2. The disease was declared as a pandemic in March 2020 with significant morbidity and mortality among particularly the elderly, those with chronic diseases and the immunocompromised. It impacted the healthcare services, economic systems, social and political systems in different parts of the world. The diagnosis is established through the identification of the RNA of the novel Coronavirus, SARS-CoV-2, using Reverse - transcriptase-polymerase- Chain- Reaction (RT-PCR). Clinical criteria and radiology using particularly CT- imaging assists in establishing the diagnosis. There is no cure for the disease, some of the medications are repurposed based on previous experience with the SARS virus and the Middle East Respiratory Syndrome (MERS) virus and other work related to other viruses. What is known to reduce the spread of the disease and "flatten the curve "of the pandemic is the well informed and supported public measures of mitigation and containment using testing, tracing, and treatment. The therapeutic options for Covid-19 are still limited.

Keywords: Covid-19, Sudan, PCR, SARS-CoV-2, CT chest

Introduction:

Since the early reporting of the pneumonia of unknown etiology in Wuhan in December 2019, it was clear the world was facing a new menace. More cases were reported with a severe respiratory disease which later led to the discovery of the novel corona virus-19, currently named SARS-SoV-2. It is related to the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) virus, being a beta-corona virus with a predilection to spread and to cause severe respiratory disease in susceptible hosts. Dr. Li Wenliang communicated with his colleagues on social media warning them of the increased cases of severe acute respiratory disease reminiscent of SARS. He was reprimanded by the Chinese government for spreading misinformation and later died from Covid-19. Within three months, it became a pandemic that led to significant mortality and a strain on healthcare, the world economy, and all aspects of human life.

Many organizations including the World Health Organization (WHO), the Center for Disease Prevention and Control (CDC), and the regional and local organizations worked in unison to combat the virus. It was clear that preventing the spread through mitigation and containment using physical (social) distancing, testing, tracing, and treating is the main approach to the treatment. Hand hygiene, public mask-wearing, personal protective equipment for healthcare workers, avoidance of public gatherings and sometimes regional lockdowns helped to slow the spread of the disease or “flatten the curve” while medical intensive care units and isolations center was being built to accommodate for the increased numbers of seriously sick patients. This review attempts to present what we know to date, despite it changes every moment as the numbers of the dead increase. Some useful websites are provided in Box 1, so that the reader can follow the pandemic statistics and gain access to guidelines for the prevention and management of Covid-19.

Epidemiology of Covid-19

China reported to the WHO cases of pneumonia of unknown etiology related to the Huanan seafood market in Wuhan, Hubei province on the 31st December 2019. By the 7th of January 2020, the Chinese authorities identified

the novel coronavirus (nCoV)(1). On 31st January 2020, the WHO declared the disease as a public health emergency calling it Corona Virus Disease-2019 (Covid-19) on the 11th of February 2020 and by March 11th declared it as a global pandemic. The first case in Africa was reported in Egypt on the 14th of February 2020. Sudan reported its first case of Covid-19 on the 13th of March 2020.

At the time of writing the manuscript (19th June 2020), the reported cases of Covid-19 worldwide are 8,242,999. The below data was sought from the CDC, Africa CDC, WHO, and WHO EMRO websites to describe the epidemiology of Covid-19 in terms of reported cases, death, recovery, and case fatality rate (CFR). The data changes every minute as more cases and more death are reported. Table 1, Table 2, and Figure 2 show the epidemiology of Covid-19 in different regions up to the 19th of June 2020.

The Northern region in Africa has the highest case fatality rate. Sudan is the fourth country in Africa in terms of CFR after Chad (8.67%), Algeria (7.09%), Niger (6.57%), and Liberia (6.4%). In the EMRO region, Sudan has the second-highest case fatality after Yemen (27%). Due to the variation in the healthcare systems among the different African and EMRO region countries, the variation in the reported cases and death may reflect differences in testing, reporting, and or the quality of healthcare. The CFR may be higher in certain countries like Sudan as the testing is mainly done in symptomatic patients who are moderate to severely sick and that may skew the results. The wider testing policy may reflect a bigger infection rate with lower death as has been reported in Wuhan. Africa is expected to be the hot spot of Covid-19 and so great effort is required by national and international organizations to support African governments to tackle the disease (2).

The last reported data from Sudan was on the 15th of June and included a total of 8,020 SARS-CoV-2 infections, 76.5% of them reported in Khartoum state. The first case of Covid-19 was reported on the 13th of March from a traveler who returned to Sudan from the United Arab Emirates. For a few days there were no reports and that may be due to the limited testing or reflects the actual time gap before the development of Covid19 community spread. It is clear in Figure 1 that the dips in the reported

cases may reflect delays in doing the tests, delays in reporting test results, or absence of testing facilities in certain areas in Sudan. The highest number of reported cases was on 21st May as 401 cases were reported in a single day and 10 days later Sudan reported the highest single-day mortality of 38 on the 30th May 2020. Some deaths may not have been reported as Covid-19, either due to the lack of availability of testing or avoidance of the stigma of the disease as some families might have avoided reporting to the Ministry of Health. Community based surveys coupled with testing after the pandemic may give insight into the epidemiology and impact of the disease.

Covid19 Resources

1. Centers for Disease Control and Prevention (CDC)
2. The World Health Organization (WHO)
3. Africa CDC (Centres for Disease Control and Prevention)
4. WHO Eastern Mediterranean Region
5. Sudan Health Observatory
6. Johns Hopkins University Corona Resource Center
7. European Clinical Trials Register
8. US National Library of Medicine (Clinicaltrials.gov)
9. Chinese Clinical trials Register
10. MedRxIV online archive of preprint of medical and related health science publications.

Box 1. Covid 19 Resources

Region	Total Cases	Died	Recovered	Case Fatality Rate
Worldwide	8,242,999	445,535	4,530,260	5.4%
Africa	268,391	7,217	123,139	2.6%
EMRO Region	848,100	18,725	511,292	2.2%
Sudan	8,020	487	2,966	6.1%

Table 2. COVID-19 Worldwide and in Africa, East Mediterranean Region (EMRO), and Sudan. The data is retrieved from the WHO and WHO-EMRO region websites on the 19th of June 2020.

Region	Total Cases	Died	Recovered	Case Fatality Rate
Central	26,000	568	9,800	2.1%
Eastern	29,300	880	11,500	3%
Western	55,600	1000	25,100	1.7%
Northern	73,200	3000	30,500	4%
Southern	84,300	1700	46,200	2%

Table 2. Covid-19 Cases in Africa according to the Region.The data is retrieved from Africa CDC Website accessed on 19th June 2020.

Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2)

The causative virus was initially called “novel coronavirus 2019” (2019-nCoV) by the World Health Organization (WHO), later to be renamed as “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) by the international committee of the Coronavirus Study Group (CSG). The

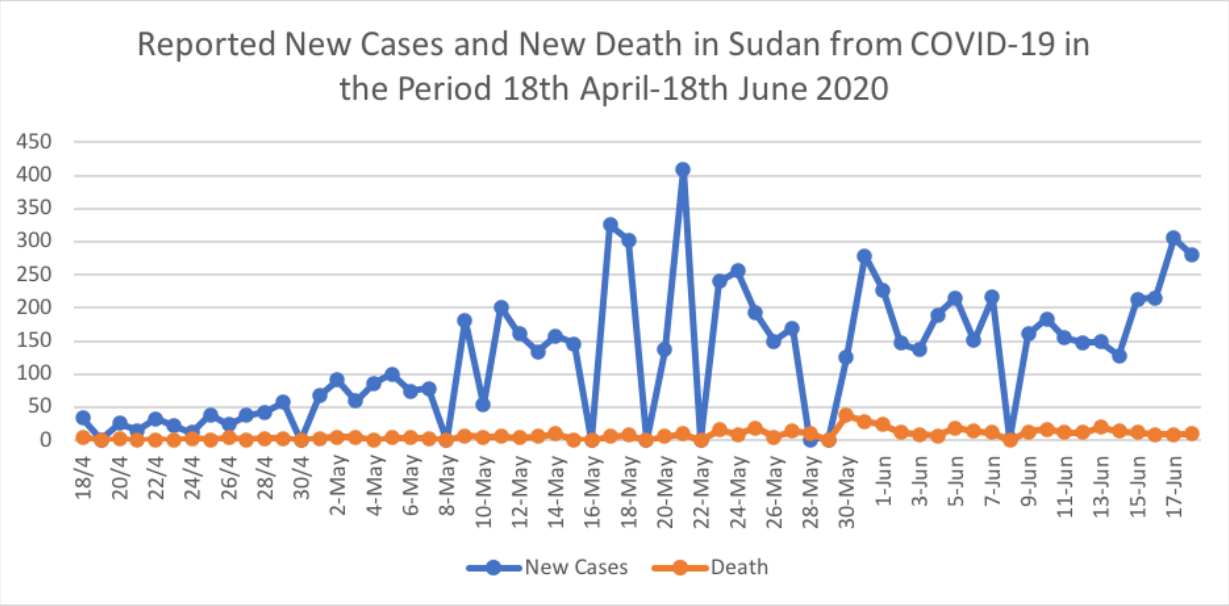

Figure 1. The data was retrieved from the WHO website and compared with the daily census of the Sudan Federal Ministry of Health which is available through the twitter account (@FMOH_SUDAN) and the Sudan Health Observatory Website http://sho.gov.sd/corona

disease is called “Coronavirus Disease 2019” (Covid-19) by the WHO(3).

It is an RNA-virus, the seventh reported coronavirus and belongs to the β-coronavirus subtype that causes infection in humans. It resembles MERS and SARS-CoV viruses, has a lower case fatality rate than both MERS (34.4%) and SARS (9.5%), but has more potential to spread as its basic reproductive number (Ro) is 2.0-2.5.

Similar to the SARS-CoV, Covid19 attacks the Angiotensin-Converting Enzyme 2 (ACE2) receptor which leads to most of the pathophysiological changes related to Covid-19 Disease (4). Inhibition of Angiotensin-converting enzyme 2 (ACE2) caused by the spike protein of SARS-CoV-2 is reported as a plausible mechanism of lung injury in Covid-19 (5).

The viral load is highest at the start of symptoms when the patient is more infectious. It is transmitted through droplet and direct contact and is higher in the nasal swabs rather than the oropharyngeal swabs. In addition to asymptomatic patients, some patients may be pauci-symptomatic with mild and atypical symptoms.

The pathogenesis of the disease is through inflammatory mechanisms namely: direct damage to the affected organs, a dysregulated immune

response (cytokine storm) or coagulopathy (Disseminated Vascular Coagulopathy, Deep Vein thrombosis, and Pulmonary embolism).

Clinical Presentation

The spectrum of the disease ranges from mild respiratory symptoms to Adult Respiratory Distress Syndrome (ARDS) and shock. The incubation period is between 3 and 14 days. When a patient deteriorates it is usually after day 9 from the onset of symptoms. Huang et al reported the first cases of Covid-19 from Wuhan. He reported 41 patients, 73% were men, the median age was 49 years, 66% were exposed to the Huanan seafood market and 32% had an underlying condition e.g. Hypertension, Diabetes, and other cardiovascular diseases. The common symptoms at the onset of illness were fever 98%, cough 76% myalgia/fatigue 44%. Within 8 days, 55% developed dyspnea. Less common symptoms were headache in 8%, hemoptysis in 5%, and diarrhea in 3%. 12 patients (29%) developed ARDS and of the 13 (32%) patients admitted to an ICU, 6 (15%) died (3). Frequency of symptoms from 3 early Case Series from China are outlined in Table 3 (3, 6, 7). A bigger sample of 72,413 patients from China showed that 80% developed only mild to moderate disease, 13-14% developed severe disease and 4-6% were critical requiring ICU admission(8).

Symptom	Frequency
Fever	67-98%
Cough	43-81%
Dyspnea	31-55%
Myalgia	11-44%
Confusion	9%
Headache	8%
Hemoptysis	5%
Diarrhea	3%

Table 3. Symptom frequency in Covid-19 patients.

Covid-19 and Cardiovascular Diseases

Hypertension, Diabetes and Coronary Artery Disease have been reported as risk factors for Covid-19. The disease also affects the cardiovascular system: arrhythmias affected 16.7% of hospitalized patients and 44% of patients admitted to the ICU(9), heart failure occurred in 23% of patients and is associated with increased mortality(10), acute myocardial injury and myocarditis in 7-17%(10, 11).

Pulmonary embolism is reported in 35-45% of patients with Covid-19

admitted to the hospital, higher in ICU patients, and is associated with poor prognosis. Kuster et al suggest that the increased mortality in patients with cardiovascular disease may reflect a dysregulated Renin-Angiotensin-Aldosterone System (RAAS) in favor of ACE/angiotensin II (ATII) signaling pathway. It has also been postulated that ARB and ACE-Inhibitors may have a protective effect through shifting the RAAS system from ACE/ATII to ACE2/Angiotensin 1-7 signaling pathway(12, 13).

Other Manifestations of Covid-19

Acute kidney injury is reported in 5.1% of hospitalized patients with Covid-19. Other manifestations of Covid-19 in adults include neurologic disease like Guillain Barre Syndrome, encephalitis, stroke, olfactory, and taste disorders. Skin rash was reported in 0.2% of Covid-19 patients and include erythematous rash, urticaria, chickenpox like vesicles, and localized petechial rash (14).

Diagnostic Approach and Investigations

Identification of the Virus RNA or antibodies to it

Clinical vigilance is required to: achieve early diagnosis and treatment of patients with Covid-19, tracing suspected cases, to avoid further spread of the disease. Currently, The WHO case definitions of Covid19 include confirmed (Demonstration of SARS-CoV-2 RNA on PCR), suspected, and probable. Most national health authorities have the same or minor adaptations to these definitions(15).

The WHO established clear guidelines on Covid-19 testing (16, 17). The Covid-19 is diagnosed through a demonstration of (SARS-CoV-2) RNA using reverse-transcriptase-polymerase-chain-reaction assay (RT-PCR). Samples are preferably taken from the nasopharynx and oropharynx. There are many molecular tests available, some of which have not been approved by the CDC or WHO. Rapid diagnostic tests are being developed. Serological assays are not used for the diagnosis of Covid-19 but may help in understanding the epidemiology of the disease(15).

Blood Tests

Patients with Covid-19 usually develop lymphopenia and in only 25-30% is leukocytosis reported at the time of diagnosis(18). Infected patients may have elevated Creatine Phosphokinase (CPK), Lactate Dehydrogenase (LDH),

transaminases (AST and ALT). Usually, the C-reactive Protein (CRP) is high with normal Procalcitonin. Acute kidney injury is commonly observed in severe cases. D-dimer is reportedly high in severe cases and may indicate the development of thromboembolic disease. Features of severe disease include high D-dimers, high creatinine, high lactate, leukocytosis, and agranulocytosis.

High levels of cytokines are associated with severe disease and have been described in cytokine “storm”(3). In spite not being measured routinely, IL-6 level is measured when considering the use of Tocilizumab.

Radiology

Abnormalities of Chest radiographs (CXR) include bilateral, peripheral Ground Glass Opacification (GGO), and Consolidation. In 1099 patients, Guan et al reported CXR abnormalities in 54.2 % of the less severe cases and 76.7% of the severe cases whereas the Chest CT demonstrated abnormalities in 84.4% of the less severe cases and in 94.6% of the severe cases(19). CT findings include GGO, consolidation, crazy paving, filling defects indicative of pulmonary thromboembolic disease. CT imaging may miss up to 3.9% of cases (20). This created interest to do early and wider CT imaging for patients, but this was limited due to the infection control requirements in radiology departments to reduce the spread of Covid-19.

Management of Covid-19

There is no cure for Covid-19. The spread of the disease can be reduced through proper handwashing, physical (social) distancing , public mask-wearing (21), wider access to testing , contact tracing , provision of proper personal protective equipment to healthcare workers (22) and isolation protocols of infected individuals (23) .These general measures proved very useful to limit the disease’s spread and its related mortalities in countries New Zealand, Singapore and South Korea. Shanghai, China did not suffer as much as Hubei province despite its proximity due to the above measures. Governments and individuals need to commit for the good of all. Unfortunately, it has been observed that due to religious and cultural norms these rules are not followed (24) and sometimes governments have provided erroneous messages through public platforms(25).

Dedicated units for testing and treatment of Covid-19 patients should be established. A move to telehealth helps provide care to non-Covid-19 patients and reduces the risk of delayed management of these conditions or getting infected if they attend the healthcare facilities during the pandemic. Standardized protocols for the treatment of Covid-19 are available (see Box 1 for more information) and are being regularly updated. The standard treatment of the disease includes empiric antibiotics in patients with pneumonia, oxygen and respiratory support in hypoxic patients, thromboprophylaxis and treatment of thromboembolic disease, management of shock and the use of renal replacement therapy in cases of severe acute kidney injury.

Many medications have been repurposed to use during the pandemic based on previous evidence of efficacy on SARS and MERS viruses or plausible mechanistic features to support their use. All medications should be used within the context of clinical trials and monitored for toxicity and benefit. The main drugs in use currently include Chloroquine/Hydroxychloroquine either alone or in combination with Azithromycin. There is no conclusive data regarding the benefit or lack off from the use of Chloroquine/Hydroxychloroquine in Covid-19 patients (26, 27). It has not been found to be effective as prophylaxis in high risk exposure (28).

Remdesivir is a new nucleoside analogue which inhibits the RNA-dependent RNA polymerase and the early data are positive showing reduced hospital stay and improved outcomes(29, 30). Tocilizumab is a recombinant human IL-6 monoclonal antibody and is being used in the presence of the cytokine storm or in extensive lung disease with high IL-6, the data related to its efficacy is pending. Other medications include antivirals like Arbidol, Fabiravir and Lopinavir/Ritonavir. Russel et made a bold statement that steroids have no place in the treatment of Covid-19 lung injury (31) but early unpublished data from the RECOVERY trial claims that the use of 6 mg dexamethasone daily reduced death by one third in ventilated patients and one fifth in patients requiring oxygen with no effect on patients with mild disease.

Convalescent plasma is used as part of clinical trials and is assumed to benefit

the patient through the presence of protective antibodies. Vaccines are being developed but they are not expected to be widely available for 12-18 months(32, 33).

Conclusion

There is a lot to learn about Covid-19 in a rapidly changing information landscape checked by sorrows and grievances of those who lost their loved ones and the loss of healthcare staff. Proper hand washing, physical (social) distancing and public mask-wearing are effective in reducing the spread of the disease and hopefully negate the arrival of the second wave. Remdesivir, and possibly dexamethasone, may have beneficial effect on the disease while the data pertaining to other medications and immunotherapy is awaited.

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