Review Article

Asian Jour Hosp Phar, Vol: 2, Issue: 3, 2022; 70-76

Asian Journal of Hospital Pharmacy

Available at www.ajhp.online ISSN: 2583-0724

Risk factors assessment and therapeutic drug management of sars covid-19 virus

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Received: 29 June 2022 Revised: 15 July 2022 Accepted: 16 August 2022

Abstract

Severe acute respiratory syndrome corona virus (COV)-2(SARS-COV-2) previously called 2019 novel cov emerged from china. This virus causes cov disease-19(COVID-19), favipiravir (1000mg) is an oral anti-viral that inhibits RNA polymerase that is a pproved in Russia during phase 2/3 clinical trials for the treatment of covid. Ivermectin an antiparasitic drug showed an in-vitro reduction of viral RNA in vero-hslam cells 2hr post-infection with SARS-COV-2.corticosteroids include dexamethasone (6mg), Methyl Prednisolone (80mg) can induce harm through immunosuppressant effects during treatment of infection and a study in the Netherlands showed a 5-day course of high dose corticosteroids accelerated respiratory recovery lowered hospital mortality rates and reduced the likelihood of mechanical ventilation in patients with severe COVID-19 associated cytokine storm syndrome. Use of convalescent PLASMA after a multicentre study conducted by Mayo clinic indicates transfusion of ABO-compatible human covid-19 is safe and effective in hospitalized adults. NAK and JAK inhibitors may mitigate systemic and alveolar inflammation in patience with covid-19 pneumonia by inhibiting essential cytokine signaling drugs include baricitinib (4mg), fedratinib (100mg), ruxolitinib (5mg). Statins decrease the inflammatory processes of atherosclerosis. Vitamins and mineral supplements have been promoted for the treatment of respiratory viral infections. Hydroxychloroquine(400mg) and chloroquine (600mg) are widely used anti-malarial drugs that elicit immunomodulatory effects based on PBPK models recommended loading dose of HCQ is 400mg (BID) followed by 200mg (BID) for four days. In a randomized controlled, open-label trial of hospitalized adults with conformed SARSCOV-2, recruited patients had 02 saturation of 94% less than ambient air or pao2 of less than 300mmhg were randomized to receive Lopinavir/Ritonavir 400mg/100mg for 14 days, Adjunctive nutritional therapies also recommended.

Keywords: SARS-COV2,COVID-19, pneumonia,respiratory illness,therapeutic regimens.

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Introduction

Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. These patients were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China [1,2]. Early reports predicted the onset of a potential Coronavirus outbreak given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, named by WHO on Feb 11, 2020) which was deemed to be significantly larger than 1 (ranges from 2.24 to 3.58) [1, 2].

The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019 [4]. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died. By January 2, 2020, 41 admitted hospital patients had been

identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension, and cardiovascular disease [6]. These patients were presumed to be infected in that hospital, likely due to nosocomial infection. It was concluded that the COVID-19 is not a super-hot spreading virus (spread by one patient to many others), but rather likely spread due to many patients getting infected at various locations throughout the hospital through unknown mechanisms. In addition, only patients that got clinically sick were tested, thus there were likely many more patients that were presumably infected. As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (COVID-19) were reported in 25 provinces (districts and cities) in China . The China National Health Commission reported the details of the first 17 deaths up to January 22, 2020. On January 25, 2020, a total of 1975 cases were confirmed to be infected with the COVID-19 in mainland China with a total of 56 deaths . Another report on January 24, 2020 estimated the cumulative incidence in China to be 5502 cases . As of January 30, 2020, 7734 cases have been confirmed in China and 90 other cases have also been reported from a number of countries that include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany. The case fatality rate was calculated to be 2.2%

(170/7824) .The first case of COVID-19 infection confirmed in the United States led to the description, identification, diagnosis, clinical course, and management of this case. This includes the patient's initial mild symptoms at presentation and progression to pneumonia on day 9 of illness . Further, the first case of human-to-human transmission of COVID-19 was reported in the US on January 30, 2020 . The CDC has so far screened >30,000 passengers arriving at US airports for the novel coronavirus. Following such initial screening, 443 individuals have been tested for coronavirus infection in 41 states in the USA. Only 15 (3.1%) were tested positive, 347 were negative and results on the remaining 81 are pending . A report published in Nature revealed that Chinese health authorities concluded that as of February 7, 2019, there have been 31,161 people who have contracted the infection in China, and more than 630 people have died of infection. At the time of preparing this manuscript, the World Health Organisation (WHO) reported 51,174 confirmed cases including 15, 384 severe cases and 1666 death cases in China. Globally, the number of confirmed cases as of this writing (February 16, 2020) has reached 51,857 in 25 countries [6,13].

EPIDEMIOLOGY

With regard to the Perspective article by Lipsitch et al. (published Feb. 19 at NEJM.org),1 cases of Covid-19 (the illness caused by SARS-CoV-2 infection) with no epidemiologic link to travel to China or known cases outside China have caused international concern about undetected introduction of the virus from subclinical infection. It is also possible that local zoonotic spill over of this coronavirus from an intermediate animal reservoir or reservoirs into human populations might have occurred, particularly in Southeast Asia [3,7].

SYMPTOMS

The main symptoms include:

- Fever
- Coughing
- Shortness of breath
- Trouble breathing
- Fatigue
- Chills, sometimes with shaking
- Body aches
- Headache
- Sore throat
- Loss of smell or taste
- Nausea
- Diarrhea

According to researchers in China, these were the most common symptoms among people who had COVID-19:

- Fever 99%
- Fatigue 70%
- Cough 59%
- Lack of appetite 40%
- Body aches 35%
- Shortness of breath 31%
- Mucus/phlegm 27%

RISK FACTORS

Anyone can get COVID-19, and most infections are mild. The older you are, the higher your risk of severe illness.

You also a have higher chance of serious illness if you have one of these health conditions:

- Chronic kidney disease
- Chronic obstructive pulmonary disease (COPD)
- A weakened immune system because of an organ transplant
- Obesity
- Serious heart conditions such as heart failure or coronary artery disease
- Sickle cell disease
- Type 2 diabetes

Conditions that could lead to severe COVID-19 illness include:

- Moderate to severe asthma
- Diseases that affect your blood vessels and blood flow to your brain
- Cystic fibrosis
- High blood pressure
- A weakened immune system because of a blood or bone marrow transplant, HIV, or medications like corticosteroids
- Dementia
- Liver disease
- Pregnancy
- Damaged or scarred lung tissue (pulmonary fibrosis)
- Smoking
- Thalassemia
- Type 1 diabetes

TRANSMISSION

The spread of COVID-19 is rapid. Transmission is from close contact and droplet. There is scarce evidence to suggest airborne transfer. Very minimal to no RNA concentration is found in airborne samples. No RNA is detected in urine or serum samples of positive patients. Viral RNA can be detected on fomites including plastic. The mean incubation period is about 3–9 days with a range between 0–24 days. The mean serial interval is about 3–8 days, presenting sooner than the end of incubation. This suggests that one becomes contagious before symptoms present (about 2.5 days earlier from the start of symptoms). About 44 % of transmission is estimated to occur before symptoms arise. Close contact with someone during their infectious period puts one at risk for acquiring the infection. However, the certainty of becoming infected is still unpredictable. Burke et al. tested 445 people that were in close contact (at least 6 feet from the source for a minimum of 10 min) with 10 COVID-19-confirmed patients. After two weeks of testing, only two subjects became positive. Both subjects were household members that practiced isolation from the infected individuals. Five subjects continued to expose themselves constantly with the infected individuals and never became positive. No healthcare workers (222 subjects) became positive. These findings coincide with two other studies. Evaluation of all positive cases from mainland China showed 3.8 % being from healthcare workers (1716/44672). About 18 % of cases remain asymptomatic. The potential of asymptomatic patients infecting others is proven by multiple studies concerning clusters. They can be asymptomatic and contagious regardless of lab or CT scan findings. Younger patients tend to remain asymptomatic (even if constantly around an infected individual), while the elderly usually show symptoms. It is calculated that about 86 % of infections have remained undocumented, and about 55 % of those cases were contagious. This may be because of the infectious period presenting before symptoms, the frequency of asymptomatic cases, and the poor documented sensitivity of nasopharyngeal RT-PCR. Symptoms tend to resolve after 10 days. However, viral shedding continues despite symptoms disappearing. COVID-19 RNA viral shedding persists for about 18 days (by nasopharyngeal swab) or 19 days (via feces). Mild and asymptomatic cases tend to shed 10 days (between 8–15 days) after symptom resolution, with 90 % resolving after 10 days and nearly all cases resolving after 15 days. Severe cases continue shedding up until 25 days after initial symptoms arise. Severe cases also have 60 times more viral load than mild cases. However, the infectious potential based on severity has not been discovered. Due to these findings, the Chinese Municipal Health Commission has recommended against discharging patients until the patient has remained afebrile for three days and RT-PCR becomes negative(4,9).

LABORATORY FINDINGS

COMMON LABORATORY TESTS

Laboratory values that suggest COVID-19 infection include lymphopenia, prolonged prothrombin time (PT), elevated lactate dehydrogenase (LDH), elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), elevated D-dimer, elevated neutrophils, eosinopenia, elevated C-reactive protein (CRP), and elevated troponin (including high-sensitivity troponin) displays the frequency of most suggested labs. The most common findings are eosinopenia (<0.02 × 10^9/L) and lymphopenia (<1.5 × 10^9/L) with 78.8 % and 68.7 %, respectively.

COMMON COVID-19 LABORATORY FINDINGS

LABORATORY FINDING	RATE
Eosinopenia	78.8 %
Lymphopenia	68.7 %
Elevated AST	63.4 %
Elevated C-reactive protein	60.7 %
Elevated PT	58.0 %
Elevated LDH	47.2 %
Elevated D-dimer	46.4 %
Thrombocytopenia	36.2 %
Elevated ALT	21.3 %
Elevated HS-Troponin	12.5 %

LDH – Lactate Dehydrogenase; AST – Aspartate Aminotransferase; PT – Prothrombin time; HS-Troponin – High-sensitivity Troponin. While eosinopenia is linked with COVID-19 infection, its sensitivity and specificity are low at 82 % and 64 %, respectively. This equates to small positive and negative likelihood ratios of 2.29 and 0.28. The combination of lymphopenia and eosinopenia change the sensitivity and specificity to 38.5 % and 75.5 %. Positive and negative likelihood ratios worsen with 1.57 and 0.81, respectively. Troponin elevation is suggestive of infiltration of cardiac tissue. While respiratory-compromising symptoms are present in most cases, cardiac chest pain is also a possibility [11].

REVERSE TRANSCRIPTASE-POLYMER CHAIN REACTION

RT-PCR remains the gold standard for diagnosing COVID-19. While its specificity is nearly 100 % from having no reported false positive cases or cross-reactivity with other viruses or estranged oligonucleotides, the sensitivity is low at 64 %. This correlates with a high positive likelihood ratio of 64, but a poor negative likelihood ratio of 0.3. Studies have started performing two sequential RT-PCRs to ensure true negative cases. RT-PCR tends to present negative-to-positive at a mean of 5.1 days, and positive-to-negative at 6.9 days. Recommendations are to acquire a repeat RT-PCR 3 days after an initial negative result. Factors that may contribute to the low sensitivity of one RT-PCR may be from immature technology, variation of detection by

manufacturers, low initial viral load, and improper sampling. While studies recommend two sequential RT-PCRs to ensure true negativity, testing kits are sparse during the pandemic. Some studies suggest employing chest CT scans if the initial RT-PCR is negative. CT scans have a sensitivity of 98 %, despite a lower specificity. The Chinese General Office of National Health Committee initially allowed positive CT scan findings to be diagnostic for COVID-19 without RT-PCR, but this recommendation was removed in a more recent list of recommendations [13,12].

IMAGE FINDINGS

Imaging modalities may serve as a surrogate to diagnose COVID-19. Chest x-ray abnormalities present in 33 %–60 % of patients, despite most having CT scan findings. Chest CT scans hold more potential to diagnose COVID-19 cases. Chest CT scans of COVID-19 cases present with bilateral ground-glass opacification or consolidation. Ground-glass opacification is dominant during early stages and consolidation presents at later stages. More than two lobes are frequently affected with most patients presenting with infiltration in all five lobes. Consolidation rarely present without ground-glass opacification. The opacifications typically are rounded and present peripherally in the subpleural area. Some studies suggest lower lobe predilection. Severe cases present with more consolidation along with architectural distortion, traction bronchiectasis, lymph node enlargement, and pleural effusions.

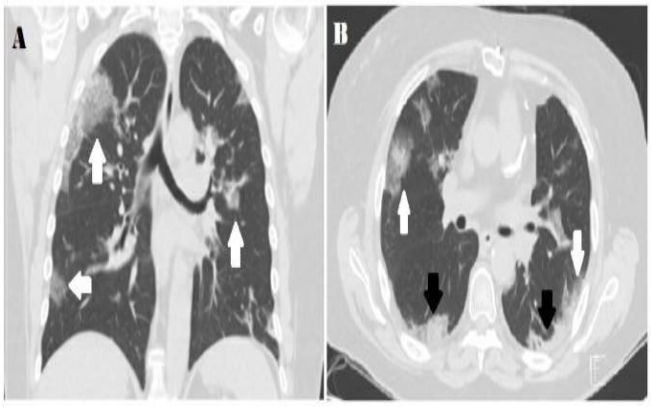

Fig 01: Coronal thin-section unenhanced CT image showing ground-glass opacities with a rounded morphology (arrows). B) Axial thin-section unenhanced CT scan showing diffuse bilateral confluent and patchy ground-glass (white arrows) and consolidative (black arrows) pulmonary opacities. Note the peripheral propensity.

CT scan findings, compared to RT-PCR, show a sensitivity of 84 %–98 % and specificity of 80.5 %–25 %. Combining the data from two studies, the sensitivity and specificity for CT scans are 88 % and 25 %, respectively. This presents a positive likelihood ratio of 1.17 and a negative likelihood ratio of 0.48. CT scan interpretation by radiologists hold a sensitivity of 70–80 % and specificity of 90–100 %. Bai et al. studied whether radiologists could discern COVID-19 cases based on CT scan findings. Using the medians from the study (sensitivity 80 %, specificity 93 %), the positive predictive value and negative predictive value are 92 % and 82 %, respectively. This suggests that during this pandemic, a radiologist stating a CT scan is COVID-19-positive is likely correct; however, if the CT scan is deemed negative, it only can be stated with moderate confidence [8].

THERAPEUTICS\TREATMENT OPTIONS

ROLE OF IMMUNOMODULATORS

Baricitinib is a Janus Kinase inhibitor which has already got FDA approval for treating moderate-to-severe rheumatoid arthritis patients nonresponsive to TNF inhibitor therapies. AP2-associated protein kinase 1 (AAK1) is a known regulator of endocytosis, and the entry of most of the viruses is dependent on the receptor mediator endocytosis. Hence, the disruption of AAK1 may block the virus entry into the cells. Baricitinib has shown to inhibit AAK1 with therapeutic dosing and may be a promising therapy for the patients.The trials are underway where baricitinib is being given in COVID-19 patients (NCT04320277, NCT04321993).

Eculizumab

It is believed to modulate the activity of terminal complement to inhibit the formation of membrane attack complex. Therefore, it is believed to be beneficial in patients with ARDS/lung injury. A trial is ongoing for evaluating eculizumab in COVID-19 patients (NCT04288713).

Interferons

In a study by Huang et al., out of the 41 COVID-19 patients admitted, six died from ARDS. ARDS is believed to be one of the main causes of death in COVID-19.Cytokine storm is one of the proposed mechanisms for ARDS. It is characterized by the release of large amount of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-12, IL-1β, IL-18, IL-33, IL-6 TNF-α, transforming growth factor-beta, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells.The trigger in immune response attacks the body, leading to ARDS and multiorgan failure, ultimately death in SARS-CoV-2 infection.With previous experience of SARS outbreak, the chief pathogenesis of organ dysfunction is cytokine dysregulation. The same is noted even in case of worsening of SARS-CoV-2-infected individuals, characterized by a decline in peripheral lymphocyte counts and elevated cytokines indicative of a triggered immune response.[15] Remdesivir (initially named GS-5734) is an adenosine analogue that has a broad-spectrum antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus (EBOV), Middle East respiratory syndrome (MERS-CoV), and Severe Acute respiratory Syndrome Coronavirus-1 (SARS-CoV-1) [16] Pharmacologically, remdesivir has been designed to efficiently deliver the monophosphate nucleoside analogue GS-441524 into cells. Inside the cells, the GS-441524 monophosphate undergoes rapid conversion to the pharmacologically active nucleoside triphosphate form GS-443902. Nucleoside triphosphate GS-443902 acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate to selectively inhibit viral RNA-dependent RNA polymerase (RdRp). The primary mechanism of inhibition is the incorporation of the nucleoside triphosphate GS-443902 into nascent RNA chains by viral RdRp, causing delayed RNA chain termination during the process of viral replication [4]. In summary, remdesivir is a prodrug and inhibits viral RNA polymerases, when intracellularly metabolized to an ATP analogue. According to Awadhesh Kumar Singh et.al preclinical studies conducted on Remdesivir appears to have optimal safety profile although its efficacy in the treatment of COVID-19 appears to have a mixed outcome at the moment. Jury is still out and future trials should further enlighten its cost-effectiveness, in particular when the results of head-to-head trial with other low-cost repurposed drugs is available [16]. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available. The treatment that have so far been attempted showed that 75 patients were administrated existing antiviral drugs. The course of treatment included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days. Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. These antiviral compounds have been used in human patients with a safety track record. Thus, these therapeutic agents can be

considered to treat COVID-19 infection. Furthermore, there are a number of other compounds that are in development. These include the clinical candidate EIDD-2801 compound that has shown high therapeutic potential against seasonal and pandemic influenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection. Along those lines, until more specific therapeutics become available, it is reasonable to consider more broad-spectrum antivirals that provide drug treatment options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), RNA synthesis inhibitors. It is clear however, that more research is urgently needed to identify novel chemotherapeutic drugs for treating COVID-19 infections.

In order to develop pre-and post-exposure prophylaxis against COVID-19, there is an urgent need to establish an animal model to replicate the severe disease currently observed in humans. Several groups of scientists are currently working hard to develop a nonhuman primate model to study COVID-19 infection to establish fast track novel therapeutics and for the testing of potential vaccines in addition to providing a better understanding of virus-host interactions [14].

PROGNOSIS

RISK STRATIFICATION AND SURVIVAL RATE-

The case-fatality rate (CFR) continues to change as the pandemic continues. Table presents the CFR in China via age group. Age greater than 60 years is considered a mortality risk factor. Case-Fatality Rate Organized by Age Group.

AGE GROUP (YEARS)	CASE-FATALITY RATE
Overall	1.6 %
0–9	0.0094 %
10–19	0.022 %
20–29	0.091 %
30–39	0.18 %
40–49	0.4 %
50–59	1.3 %
60–69	4.6 %
70–79	8.0 %
80+	14.8 %

Table 01: represents the risk stratification commonly used in studies. About 81 % are mild cases, 14 % are severe, and 5 % are critical. Mortality for mild, severe, and critical cases are 98 %, 52 %, and 6 %. Severe cases have an unpredictable prognosis solely based on clinical presentation. Laboratory markers including LDH, high-sensitivity CRP, and lymphocyte count estimate the prognosis for these cases.

RISK STRATIFICATION OF COVID-19 CASES

SEVERITY	DESCRIPTION
Mild	COVID-19 positive
Severe	COVID-19 positive + RR > 30 or SaO_2<93 %
Critical	COVID-19 positive + mechanical ventilation, evidence of multiorgan failure, or shock

RR-Respiratory Rate; SaO_2-Oxygen Saturation; COVID-19-coronavirus infectious disease 2019.

PROGNOSIS PREDICTORS

Comorbidities associated with severe COVID-19 cases include elderly age, hypertension, cardiovascular disease, cerebrovascular disease, and chronic kidney disease. Cardiovascular disease presents with a 10.5 % CFR. Other diseases that present with a high CFR include diabetes (7.3 %), chronic lung diseases (6.3 %), hypertension (6.0 %), and cancer (5.6 %).

Laboratory values contribute to survival prediction. These include elevated LDH, elevated high sensitivity-CRP, and lymphopenia. A significantly elevated LDH (>365 units/L) presents a positive likelihood ratio of 58 for mortality based on the results by Yan et al. High sensitivity-CRP also has a positive likelihood ratio of 17, but a negative likelihood ratio of 0. Lymphopenia presents a small positive likelihood ratio of 2.65 and a small-moderate negative likelihood ratio of 0.37. Other laboratory values that suggest a high mortality risk if elevated include aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, neutrophil count, prothrombin time,

procalcitonin, and high-sensitivity and regular cardiac troponin. Low monocytes, platelets, and albumin also suggest high mortality risk.

Some chest CT scan findings, although rare with COVID-19 respiratory disease, suggest a high-risk case. These include architectural distortion, traction bronchiectasis, intrathoracic lymph node enlargement, and pleural effusions [10].

CONCLUSION

The COVID-19 pandemic is rapidly spreading. Case rates and CFRs continue to change. Identifying clinical characteristics, developing and identifying pertinent diagnostic criteria, and providing effective treatment and care are vital for overcoming the pandemic(12).Globally, hundreds of clinical trials are ongoing to evaluate the efficacy of these old drugs in SARS-CoV-2 infection. The WHO has also planned a large global trial known as "Solidarity Trial" mainly to generate a robust clinical evidence to combat this pandemic. As there is no specific

treatment till date, prevention is the only measure to contain the infection. Even a small negligence in following the preventive measures would be very expensive for the mankind. The ICMR has given some recommendations regarding COVID-19 prevention and treatment. However, these recommendations are based on the present current evidence and may change once robust clinical data is generated. The famous quote says "United we stand and divided we fall." Therefore, it is the duty of every citizen of India to abide by the rules and regulations led by our government, let's come together and fight against this pandemic.

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