

Practical Guideline for Screening the Patients with SARS-CoV-2 Infection and Persian Gulf Criteria for Diagnosis of COVID-19

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Abstract

The new Coronavirus disease or COVID-19 is a contagious viral/immunological systemic disorder with predominantly respiratory features caused by human infection with SARS-CoV-2, which is rapidly spreading from person-to-person all around the world as a pandemic. The new outbreak of COVID-19 first appeared in Wuhan, China in December 2019. This virus is transmitted from human to human in various ways including air, aerosol, touching, and fecal-oral ways. The SARS-CoV-2 survives for several days in the environment. The SARS-CoV-2 virus multiplies within the cells of mouth-throat or nose-throat, and despite the production of antibodies by the human immune system, if the virus continues to multiply and progress, it will enter the bloodstream and reach its target organ, the lungs. It takes an incubation period of one to fourteen days for the initial symptoms/signs of disease to appear as fever, dry cough, and fatigue. Finally, shortness of breath due to pneumonia/pneumonitis with or without Acute Respiratory Distress Syndrome (ARDS) causes the patient to be hospitalized and transferred to ICU. Older people with underlying disorders account for the majority of deaths from COVID-19, while children under the age of 15 - 20 are the main carriers of the SARS-CoV-2. About 40% of patients with COVID-19 are asymptomatic and, 40% mild, 15%; severe, and 5% are critical COVID-19. COVID-19 Molecular Diagnostic Tests and COVID-19 Antibody Tests are two types of diagnostic kit tests for identification of the SARS-CoV-2 and the High Resolution Computerised Tomography (HRCT) scanning of lungs is the best imaging method for detecting pneumonia/pneumonitis and assessing its severity. This paper is intended to present a health system called COVID-19 Referral

System for screening and developing very sensitive diagnostic criteria as Persian Gulf Criteria for diagnosis of COVID-19. By using these two methods and performing the SARS-CoV-2 kit tests more and more widely, and performing accurate isolation of patients and virus carriers and complete quarantine of red zones, it is possible to successfully control the SARS-CoV-2 epidemics.

Keywords

COVID-19, SARS-CoV-2, Human Novel Co V, SARS-CoV-1, MERS-CoV, COVID-19 Referral System, Persian Gulf Criteria

1. Introduction

The new Coronavirus disease is a contagious viral/immunological systemic disorder with predominantly respiratory features caused by human infection with a novel and emerging virus from Beta RNA-Coronavirus group; that is rapidly spreading from person-to-person all around the world as a pandemic. The disease is referred to as COVID-19 by World Health Organization (WHO), where CO stands for Corona, VI stands for the virus, and D Stands for disease, and since it was first identified in late 2019, it has been granted the suffix 19. The new outbreak of novel Coronavirus disease or COVID-19 first appeared in Wuhan city, Hubei Province, China in December 2019. WHO declared a global emergency on January 30, 2020, and changed it to the global pandemic on March 11, 2020. The origin of the virus is an ant-eating animal call Pangolin, smuggled from the Malaysian desert to the Wuhan wildlife market and transmitted to humans by eating Pangolin; and of course, it looks like the new Coronavirus has been transmitted from bat to pangolin. However, another theory suggests that the origin of the novel Coronavirus epidemic has been a Viral Research Laboratory in Wuhan, China. Coincidentally, the virus was transmitted outside the laboratory following the infection of one of the personnel with the new Coronavirus. The authors of this article are of the opinion that the approval or rejection of these two above theories needs further investigation. This new (novel) Coronavirus is named Severe Acute Respiratory Syndrome-Corona Virus-2 or symbolically SARS-CoV-2 by International Committee on Taxonomy of Viruses (ICTV). It should be noted that SARS-CoV-1 was responsible for the SARS epidemic in China in the years 2002-2003, and MERS-CoV was responsible for Middle East Respiratory Syndrome epidemic in Saudi Arabia in the years 2012-2013. In general, Coronaviruses, including: SARS-CoV-1, MERS-Co V, are causing for 15 to 20 percent of Colds worldwide. Certainly, in the current situation in the world, at the height of the SARS-CoV-2 pandemic, most of the Colds should be caused by this emerging virus; SARS-CoV-2. The SARS-CoV-2 is transmitted from human to human in various ways:

- 1) Airway: After coughing and sneezing, the viruses are thrown out with ma-

cro droplets of saliva (5 - 10 micrometers) and landing on the ground immediately up to a distance of 1 meter.

2) Aerosol way or airborne transmission: while talking and breathing (exhaled phase) the viruses are released up to 4 meters in the air with tiny micro-droplets of saliva (<5 micrometers) and they can remain viable/float for up to 3 hours. It should be noted that micro-droplets of saliva can be thrown into the air up to 8 meters after sneezing [1] [2].

3) Touching way: close personal contact such as shaking hands, touching, and kissing. Touching objects or surfaces contaminated with the virus by hands and then, touching infected hands with the mouth, nose, or eyes before washing hands.

4) Fecal-oral: The virus exits through the anus and into the stool of the person carrying it. Contamination of surfaces, hands, or food with feces containing the virus will transmit the virus. It is even claimed that the intestinal gas passing from the anus is another way of transmission.

5) Mother to child: This vertical transmission can occur during childbirth or breastfeeding.

6) Hospital-acquired: The virus can be transmitted to hospitalized patients, medical staff, and all other hospital staff, patient companions, and other clients in the hospital.

7) Community-acquired: If based on history, there is no acceptable evidence to justify how the virus is transmitted, it is referred to as community-acquired.

Shortly after Wuhan/China, the virus spread to Qom city in Iran and then, South Korea, Japan, and especially; Italy, resulting in a Coronavirus epidemic in these countries and now the global Coronavirus-pandemic has begun to spread the most countries around the world especially; the USA, Brazil, Russia, Spain, UK, India, Italy, Peru, Germany, Iran, and The city of Wuhan (in China) was the first epicenter for the new Coronavirus epidemic in the world and shortly afterward Qom in Iran became the second epicenter of this epidemic due to the continuation of air navigation and exchange of passenger between the two countries. The human novel Coronavirus entered Iran on January 15, 2020, and the novel Corona epidemic began in Iran in late January 2020, particularly, the turning point was the holding of the International Shoe and Sandal Exhibition in Qom on January 21-24, with companies participating from 28 countries, especially Chinese merchants. China-Iran confrontation with the novel Coronavirus epidemic was the same and at least a month late in announcing its launch. The Chinese government acknowledged the start of a new Coronavirus epidemic in China when many countries around the world including Iran, USA, and many EU countries welcomed a large number of Chinese tourists due to the Chinese New Year holiday. In December 2019, Dr. Li Wenliang reported a new Coronavirus infection in Wuhan. At that time, no one, except Dr. Li W., knew that the virus was going to quickly invade the whole world, infect many people, and cause large death tolls. He warned that a national and then global catastrophe

would occur if the spread of the emerging virus was not stopped. The Chinese government realized the importance of Dr. Li W. warning too late. Dr. Li W. died of COVID-19 and a new Coronavirus epidemic spread. If China and then Iran, as well as all countries with the Corona epidemic, had acted only 3 to 4 weeks earlier, about 95% of the current catastrophe would have been prevented. Governments and the people of the world must remember Dr. Li W., and honor him every year on the anniversary of his death. In the pandemic, novel Coronavirus, all of the above countries are considered Red zones. Over time, as the virus spreads around the world, more and more countries will join the red zones. All areas in the novel Coronavirus pandemic that are; the outbreak center of the epidemic, spreading the epidemic to other areas, including the deaths of COVID-19, or in particular, those areas with higher rates of the incidence of new cases of COVID-19 are called Red zones. Areas, where novel Coronavirus has reached but do not meet the above criteria, are called yellow zones and Coronavirus-free areas, or areas where Coronavirus outbreaks were controlled and shut down in the early stages are white zones.

Because the virus looks like a crown under a microscope, it is called a Coronavirus. The RNA genome of virus codes for its proteins, including; structural proteins (SPs) and non-structural proteins (NSPs). The structural proteins, including; spike (S), membrane (M), envelope (E) and nucleo-capsid (N) aid the viral infection of host cells and the replication of virus. S-protein is responsible for attaching the virus to host cell receptors. M-protein helps shape the virus components and binds them to the N protein. E-protein plays a role in the assembly and release of virus particles. N-protein helps the virus's genome attach to the complex of replication-transcription, which is required to replicate the virus's genome

The novel Coronavirus has other names besides SARS-CoV-2, including Wuhan CoV, 2019-novel CoV and Human novel CoV.

2. Methods

2.1. Pathophysiology

From the time the virus enters the body to the time of initial symptoms of the disease, it is called the Incubation period which ranges from one day to fourteen days, however, in about 1% or more of patients the incubation period is more than 2 weeks [3]. The SARS-CoV-2 lasts for several hours to several days and survives in the environment, up to 9 days, and even up to 14 days? The SARS-CoV-2 survival time on different surfaces is: on plastic surfaces; up to 2 - 3 days, on stainless steel; up to 2 - 3 days, on cardboard; up to 1 day, and on copper; up to 4 hours [2] [4]. Metal and polished surfaces that are frequently and permanently touched by different people in the community play a major role in the contamination. The SARS-CoV-2 has a low resistance to temperatures above 56°C or 133°F and disintegrates at these temperatures. However, researchers at Nanjing Medical University have recently identified a specific type of Coronavi-

rus under the name of super-spreader Coronavirus. This virus has been able to infect a cluster of eight cases of COVID-19 in a warm water pool with a temperature of more than 41°C. A relative humidity (RH) range of 20% - 50% is required for stability of winter viruses, and about 80% for summer or all-year viruses. The SARS-CoV2 is expected to survive in all seasons. This novel Coronavirus or SARS-CoV-2 binds human Angiotensin-Converting Enzyme 2 (ACE2) receptors on mucous cells of the mouth, nose (\pm sinuses) or eyes by its Spike protein (aka. S) and enters the cells and RNA genome of the virus in the DNA of the cell orders its copy and production of the genome. The new Coronavirus has a greater tendency to bind to ACE2 receptors than older types, which is the main reason for the higher transmission of the SARS-CoV-2. After producing a large amount of the viral genome and Capsid protein, a large number of viruses multiply, rupturing the cell membrane and dropping it out to enter another cell, and this process is repeated. Monocytes/Macrophages in the front line of immune system cells fight the virus; Following the phagocytosis of the SARS-CoV-2, these cells isolate the main antigens of the virus and expose them to T Lymphocyte, and T Lymphocytes identify the antigens to B Lymphocytes. The B cells start making antibodies against the viral antigens. At this stage, if antiviral antibodies can control and shutdown the virus from entering and multiplying in the mucosal cells, then the disease will subside. But, in case of virus resistance and overcoming the immune system, whether through the mouth-throat or nose-throat, the virus multiplies and progresses and enters the bloodstream and reaches its target organ, the lungs; and then heart, kidneys, and intestines. Human ACE2 lowers blood pressure by catalyzing the cleavage of Angiotensin 2 (that is vasoconstrictor) into Angiotensin 1 - 7 (that is a vasodilator) and also acts as a receptor for SARS-CoV2 on the cell membrane of the cells within lungs, arteries, heart, kidney, and intestine. In the early phase of the disease, when the virus enters the upper respiratory tract, it produces symptoms similar to the common cold and common flu especially fever, dry cough, and fatigue. With the virus entering the main organ of the target, which is the lungs, due to severe damage to the alveolar cells, it causes edema and inflammation of the lungs; acute pneumonitis and secondary bacterial pneumonia, Acute Respiratory Distress Syndrome (ARDS), and finally respiratory failure and respiratory arrest. With renal, cardiac, arterial, and gastrointestinal involvement it can lead to kidney and heart failure, even vomiting, diarrhea, hypotension, and shock. Therefore, in critical situations; multi-organ dysfunction or failure along with septic shock occur and can lead to death. In parallel with the above processes, the SARS-CoV-2 activates the JAK-STAT signaling pathway and causes the production of IL-1 β from IL-1, inside the virus-infected cells. It is followed by cytokine storm due to too much production of cytokines especially TNF β , TGF β , and MMP. Cytokines travel through the bloodstream to the liver, producing large amounts of IL-6, which is followed by a sharp rise in CRP [5]. With the arrival of the new Coronavirus in all organs whose cells have ACE2 receptors for SARS-CoV-2, especially the lungs, heart and arteries, kidneys, and intestines, the main causes of severe in-

flammation in addition to cytokine storm is apoptosis of virus-infected cells.

Following severe COVID-19 disease, sometimes a severe systemic inflammatory syndrome called Hemo-phagocytic Lympho-Histiocytosis (HLH) occurs, with a high mortality rate especially in critical cases of COVID-19. The entry of SARS-CoV-2 into the body causes the immune system to work hard, especially in people with underlying Rheumatic disease or a primary immune system defect. In this case, lymphocytes and histiocytes become overactive and attack most cells in the body. Histiocytes phagocytose and engulf the body's cells, destroying them. There are two types of lymphocyte cells: T cells and NK cells. These are the main soldiers of the body, and after their over-activation, a cytokine storm occurs or the virus-infected cells are killed directly by apoptosis. Activated lymphocytes and histiocytes attack blood cells, especially in the bone marrow, as well as in the spleen, liver, lymph nodes, brain, and skin. The result of this attack on blood cells is a persistent high fever, rash, hepatitis, jaundice, spleen enlargement and enlarged liver, and a drop in all blood cells (pancytopenia) and even seizures and coma [5]. By destroying the red blood cells, the SARS-CoV-2 attacks the beta 1 chain of hemoglobin, hunts porphyrins, and releases iron into the bloodstream. Therefore, hemoglobin loses its ability to bind to and carry oxygen, and oxygen does not reach the major organs. This justifies hypoxia resistance to treatment and failure of various organs of the body. The iron released into the bloodstream is highly toxic and causes severe oxidative damage to the lungs. The body's response to this state; is to increase hemoglobin production, increase ferritin in the blood, reduce lymphocyte production in favor of increased monocyte production, high levels of D-Dimer and LDH and CPK in the blood. Excessive hemoglobin production and Iron load; increase blood viscosity and lead to numerous small and large thrombi in the bloodstream of most organs of the body, including the lungs, heart, kidneys, liver, spleen, brain, intestines, etc. This condition, similar to the Catastrophic Antiphospholipid Antibody Syndrome, leads to dysfunction and failure of various organs and justifies the sudden death and ineffectiveness of artificial respiration in some patients.

And, finally regarding the pathophysiology of COVID-19 we have to know that; at least six major subtypes of SARS-CoV-2 have been detected in less than six months since the onset of novel Coronavirus epidemics. This shows the fastest genetic mutation for a virus in the development of the disease [6].

2.2. Clinical Features

The clinical findings are divided into four major groups including; General features, ENT (Ear, Nose, and Throat) involvement, Lung involvement, and other organ's involvement. The following are the most important clinical findings in each group:

- 1) General features include; fever/chills, anorexia, fatigue/tiredness, arthralgia/myalgia or body ache, tingling all over the body
- 2) ENT involvement: includes; dry cough, sore throat, runny nose, anosmia,

lack of taste, sneezing, stuffy nose, and other findings mimicking common cold or flu: Ear: tinnitus, earache, Nose: anosmia, runny nose, stuffy nose, and epistaxis, Throat: unilateral sore throat, fever, drooling of saliva, foul-smelling breath, painful swallowing, hot potato voice, ipsilateral earache, and neck stiffness, torticollis and exudative erythematous enlarged tonsil due to tonsillitis and peri-tonsillar abscess (quinsy).

3) Lung involvement: It can be presented as high fever, severe dry cough and shortness of breath or dyspnea with or without, sputum expectoration, hemoptysis, and chest pain (pleuritic/non-pleuritic) which often indicate pneumonia. It is not possible to perform a deep breath, trap it, and perform a slow, long-term exhalation in a patient with COVID-19 lung involvement, or lead to a dry, recurrent cough. Older people especially with; diabetes mellitus, chronic heart and/or lung diseases, defects in the immune system, and chronic alcoholism are at higher risk for lung involvement following COVID-19. There are two types of COVID-19 lung involvement; benign phenotype and the malignant phenotype.

The benign phenotype of lung involvement: It is a pneumonia/pneumonitis and the lungs have type I failure. Despite its inability to receive oxygen, it can purify CO_2 from the blood. They improve with the administration of oxygen or the expansion of the pulmonary arteries. In this case, patients generally do not need an Intensive Care Unit (ICU) or artificial respiration, and if they do go to the ICU, they will be left out alive.

The malignant phenotype of lung involvement: In fact, it is a classic ARDS and/or diffuse small vessel-vasculitis of lungs and is more common in chronic lung underlying diseases. Both oxygen uptake and CO_2 clearance from the blood are impaired. They require artificial respiration by ventilator machine and must go to the ICU, but they do not necessarily come out of the ICU alive. Intractable cough accompanied by expulsion of blood from lungs and cyanosis along with respiratory distress are ominous features in this group of patients. Secondary bacterial pneumonia and respiratory failure (arrest) are the complications of this phenotype [7] [8].

4) Other organ's involvement:

a) Cardio-vascular involvements: They can be presented as fever, dyspnea, chest pain, and palpitation; due to acute myocarditis, pericarditis, acute coronary syndrome, cardiomyopathy, vasculopathy, and vasculitis. Acute heart failure, congestive heart failure, arrhythmias, acute myocardial infarction, cardiogenic shock, cardiac tamponade, disseminated intravascular coagulation (DIC), catastrophic antiphospholipid syndrome (APS) and small/medium-sized vessels vasculitis are the different clinical pictures in cardio-vascular involvements [9] [10].

b) Kidney involvement: Renal involvement is called Coronavirus nephropathy, which is an acute renal disorder due to acute tubular necrosis, induced by sepsis, dehydration, cytokine storm syndrome, hypoxia, and rhabdomyolysis. Its presentations are proteinuria, hematuria, and azotemia/uremia due to acute ren-

al failure [11] [12].

c) Gastrointestinal involvement: It can be presented as nausea, vomiting, abdominal pain, and diarrhea; due to invasion of ACE2 expressing enterocytes by the virus. Bowel obstruction due to blood clots (especially in people with blood group A) can be fatal. In about 50% of COVID-19 cases, SARS-CoV-2 can be detected in the intestinal mucosa, in fecal samples, and even in intestinal gas [13].

d) Liver involvement: includes; only abnormal liver function tests, hepatitis and hepatic failure; due to comorbidity, viral hepatitis, autoimmune hepatitis, drug-induced hepatitis, and hypoxia-induced fulminant hepatitis. In mild cases of COVID-19, liver damage is mild and reversible, but in critical cases, it can be irreversible and even fatal [14].

e) Central Nervous System (CNS) involvement: It can be presented as headache, tingling all over the body especially the hands and feet, dizziness, loss of speech, confusion, delirium, seizure, coma, muscle weakness and ataxia, loss of movement, sudden cerebrovascular accident (CVA) or stroke, loss of smell or taste as potential markers of COVID-19 and loss of involuntary control of breathing resulting in acute respiratory insufficiency. The SARS-CoV-2 can reach the brain; through the cribriform plate, or orbital fossa, or the bloodstream following lung involvement, and lead to meningitis or encephalitis. The CNS involvement in COVID-19 can occur secondary to; hypoxia, uremia, electrolyte disturbances, or respiratory/metabolic acidosis [15].

f) Psychological features: include anxiety, depression, sleep problems, and poor concentration due to losing health, job, income, and school/university uncertainty [16].

g) Skin involvement: includes; erythematous rash, generalized urticaria, and varicella-form exanthema, transient livedo-reticularis, petechial (Dengue-like) rash, eczematous lesions, Acute Generalized Exanthematous Pustulosis, frost-bite, Raynaud phenomenon. COVID toes is a purple or red bump on the tips and/or pads of digits or toes. Acro-ischemic lesions as cyanosis, blisters, and gangrene of fingers and toes can be seen in severe cases of COVID-19 due to vasculitis. Extensive darkening of the skin following hemosiderosis due to extensive destruction of red blood cells and the release of their hemosiderin, especially after HLH syndrome [17].

h) Ocular involvement: includes; bilateral acute follicular conjunctivitis or pink eyes. It manifests as; redness, foreign body sensation, and tearing in both eyes without blurred vision. The cornea, anterior chamber, fundus, and macula are normal in the ophthalmic examination [18].

i) Hemophagocytic lymphohistiocytosis (HLH): it manifests as; persistent high fever, rash, hepatitis, jaundice, hepatomegaly, splenomegaly, pancytopenia, seizures, coma, and DIC. It is similar to catastrophic APS and leads to multi-organ dysfunction and sudden death. The observation of Hemophagocytosis in the bone marrow, which are macrophages that have engulfed blood cells, especially RBCs, is the hallmark finding of HLH. These patients, if left alive, can

develop Hemosiderosis, which is caused by extensive destruction of RBCs and the release of hemosiderin and its deposition in the liver, lungs, kidneys, and skin [5].

If within two weeks of a person's SARS-CoV-2 entering, the body remains asymptomatic and healthy, he/she is the Carrier of SARS-CoV-2 [16]. Novel Coronavirus carriers are mainly children, and to a lesser extent, adult people. Infants and older people will rarely be carriers.

According to the opinion of American Lung Association; older people (age > 65) especially those with chronic lung disease or asthma, heart diseases, hypertension, diabetes mellitus, chronic kidney disease (CKD), cancers, immune deficiency, liver disease and morbid obesity (with BMI > 40) or people who live in a nursing home, will become more severely ill with higher mortality rate following novel Coronavirus infection includes 80% COVID-19 mortality.

Children less than 15 - 20 years old, however, occasionally develop COVID-19 following Coronavirus entering and they will often be carriers of SARS-CoV-2. In summary, the age distribution of COVID-19 is as follows: China: age < 15 years: 1%, 15 ≤ age < 50: 55%, 50 ≤ age < 65: 29%, age ≥ 65: 15%. Korea: age < 20 years: 6.7%, 20 ≤ age < 50: 51.8%, 50 ≤ age < 70: 30.5%, age ≥ 70: 11% [19]. Canada: age < 20 years: 5.4%, 20 ≤ age < 40: 26.5%, 40 ≤ age < 60: 32.5% & age ≥ 60: 35.6% [20].

Although early statistics showed that 60% - 70% of patients with COVID-19 were male and 30% - 40% were female [21] [22]. however, we think it was due to this fact that; there are more mild and asymptomatic cases in women and more severe cases in men. Indeed, according to reports available at the time of writing, there is no significant difference in gender regarding COVID-19, but the mortality rate for men is 50% higher than for women, simply put, 60 percent of COVID-19 deaths are men and 40 percent are women [23].

The best categorization for COVID-19 patients is generally as follows:

1) Asymptomatic COVID-19: About 40% of patients have no symptoms. If they still have no symptoms/signs and are all normal for lung imaging and laboratory tests, other than SARS-CoV-2 diagnostic tests, which are positive especially RT-PCR, they are carriers of SARS-CoV-2 or pre-symptomatic COVID-19 within the incubation period. If they are still clinically asymptomatic but abnormal lung image and/or elevated ESR/CRP along with low Lymphocyte count are seen, indeed, this group is subclinical COVID-19, accounting for about 50% of asymptomatic cases. Asymptomatic patients are almost all missed and they can carry the virus for about 2 weeks [16] [21] [22] [24].

2) Mild COVID-19: About 40% of patients have mild symptoms. The symptoms begin less than a week after the infection and will heal after a few days. All of the patients within this group respond well to the virus and become immune. these patients carry the virus for up to three weeks [16] [21] [22] [24]. In this group of patients, clinical findings are confined to the upper respiratory tract, or ENT, and mainly present with manifestations such as mild fever, dry cough, sore

throat, sneezing, and runny nose. This group of patients is often mistakenly diagnosed with a cold or flu [16] [21] [22] [24].

3) Severe COVID-19: About 15% of patients show severe symptoms/signs including: all the above features of mild COVID-19 but with severe presentation, shortness of breath, tachypnea with a respiratory rate of 30 or more in a minute, cyanosis or bluish lips, nose, ears, and extremities, persistent (pleuritic or non-pleuritic) chest pain or pressure in the chest, confusion, pneumonia/pneumonitis with infiltration of more than 50% of lung's zone in imaging within 24 - 48 hours, blood oxygen saturation <93% and PaO₂/FiO₂ ratio less than 300. Unfortunately, about 15% of this group of patients eventually die and all other patients carry the virus for approximately 4 weeks. All of the patients within this group must be hospitalized [16] [21] [22] [24].

4) Critical COVID-19: About 5% of patients develop extremely severe symptoms/signs after a few days, so they must be hospitalized and transferred directly to ICU before breathing becomes difficult. Most of these patients require artificial respiration by a ventilator machine and will eventually die in half and all other patients carry the virus for 6 weeks. The combination of respiratory failure and multi-organ dysfunction/failure is the predominant feature of this group of patients [16] [21] [22] [24].

The big problem with the SARS-CoV-2 epidemic is that asymptomatic patients and the majority of patients with mild symptoms are left uninvited and neither the patient him/herself knows that he/she is infected with SARS-CoV-2 nor the health system, and spreading the virus for two to three weeks.

Initial Cardinal presentation of COVID-19 is the combination of fever, dry cough, and fatigue or tiredness. Shortness of breath or dyspnea is the initial alarming/warning symptom for COVID-19 when it is new or worsening, for no other cause. The occurrence of this symptom in a patient with COVID-19 is a warning that the disease is severe or getting severe and the patient must be hospitalized. The emergency warning signs for COVID-19 are including; tachypnea with a respiratory rate of 30/minute or more, persistent chest pain or pressure in the chest, cyanosis or bluish discoloration of lips, nose, ears, and extremities, confusion, and loss of speech or movement. By observing any of these signs in a COVID-19 patient with shortness of breath, the patient should be transferred to the ICU for respiratory support with the help of a ventilator machine [16].

2.3. Paraclinical Features

There are two types of diagnostic tests for identifying the SARS-CoV-2 infection, including: COVID-19 Molecular Diagnostic Tests, and COVID-19 Antibody (Serology) Tests.

COVID-19 Molecular Diagnostic Test indicates a virus genomic map (by detection of SARS-CoV-2 RNA via cDNA sequencing) using swabs of oropharyngeal, or nasopharyngeal, or sputum, or tracheal secretion, or BAL (Broncho-Alveolar Lavage) sample. This test is also called the SARS-CoV-2 antigen kit test. In-

deed, it is Real-Time, Reverse Transcriptase-Polymerase Chain Reaction test, or in short RT-PCR Test. We have to know that the RT-PCR test is the Gold-standard diagnostic test, for the detection of active COVID-19. This can show the most accurate results early in COVID-19 presentation and is the test of choice for patients who have had fever, cough, and shortness of breath in the past 2 weeks. It is a labor-intensive test, which requires multiple additional reagents and specialized equipment. It can also show false-negative results in; late phase of inactive COVID-19, very early phase of COVID-19 in which the virus replication has not yet started, a case of COVID-19 in which the sample is taken from a site that does not contain the virus or sample is collected with errors [16] [25]. A positive RT-PCR test in a person who shows signs and symptoms of a viral disease indicates the presence of an active COVID-19. However, a positive RT-PCR test in a person who does not currently have any clinical signs or symptoms suggests; subclinical COVID-19, pre-symptomatic COVID-19 within the incubation period, and carrier state. It is clear that the above cases are contagious to others, so they should be isolated at home, that is Home quarantine or Self-isolation at home.

Another COVID-19 Molecular Diagnostic Test has been introduced under a new method called Loop-mediated isothermal Amplification (LAMP). Its operating speed is 2 to 3 hours, while RT-PCR takes 3 to 4 hours in the main laboratory and 6 to 8 hours in other laboratories due to sending samples to the main laboratory. The LAMP method is simpler/easier than RT-PCR with a little more sensitivity and specificity. It can be done in any laboratory but requires a few clinical trials to become popular or widespread [25].

COVID-19 Antibody Tests indicate antiviral antibodies in serum or plasma of blood samples. These tests are also called SARS-CoV-2 Antibody kit tests, and are including: COVID-19 IgM Antibody tests, and COVID-19 IgG Antibody tests.

These tests are generally recommended for people who feel healthy and have recently had no symptoms or who have had a previous COVID-19, however, in people who have had a fever, cough, and shortness of breath for the past two weeks, and RT-PCR test is recommended [16]. A positive COVID-19 IgM Antibody test shows that the person has recently developed COVID-19 and also indicates the onset of a person's immune response, therefore, it shows both active diseases and recently improved disease [16] [25]. IgG antibodies develop 7 to 10 days after the onset of COVID-19 symptoms, so a positive COVID-19 IgG Antibody test not only shows the recent previous disease but also reveals the body's immune protection against re-infection [16] [25]. The COVID-19 Antibody Test helps the physicians identify the safe time for termination of quarantine and the person to return to the workplace and school [16] [25]. Rapid antibody tests or Quick COVID-19 Tests can be used at point-of-care (with whole blood sample) or home (with finger prick sample) with fast results within 5 - 15 minutes and 15% false negativity. COVID-19 Antibody Test can be performed using the Lateral Flow Immunoassay (LFI) method, which, can identify; IgM, IgG, or both

IgM/IgG. Some diagnostic kits have low sensitivity, even about 30%; this means that kit is only able to identify 30% of patients with COVID-19 with 70% false-negative results. Now, some kits have a higher sensitivity, equals to 80 or 90%, and even 97%. However, Switzerland has already developed an Antibody kit test that is claimed to be 100% accurate.

As an unwritten rule in the SARS-CoV-2 epidemic, the ideal condition is that the entire population of the community is subjected to SARS-CoV-2 testing to identify carriers, patients within incubation period or pre-symptomatic cases, asymptomatic patients and mild cases of COVID-19 at the same time, to be isolated and quarantined. Because these four groups as silent spreaders play the most important role in the development of the SARS-CoV-2 epidemic in the community, and in the absence of a SARS-CoV-2 diagnostic test they are difficult to detect [16] [21] [22] [24] [26]. If there are not enough kits available, the priority for testing is as follows [22]:

- 1) Patients suspected of having COVID-19 hospitalized.
- 2) Symptomatic older people, especially those associated with underlying diseases.
- 3) People who have traveled to the Red zones or contacted a patient with COVID-19 for the past two weeks and even four weeks.
- 4) Health-care workers.

All symptomatic individuals who are suspected of having COVID-19, especially moderate to severe cases, should undergo Chest-X-ray, and even if Chest-X-ray is normal; HRCT scanning of lungs is recommended. All asymptomatic individuals who have a positive result for the SARS-CoV-2 kit test should undergo imaging too. Imaging of asymptomatic COVID-19 patients is abnormal in half of the cases. Normal imaging does not rule out the diagnosis, especially in the early days of the disease. Pulmonary involvement of COVID-19 patients in High-Resolution (HR) CT scanning of lungs follows 6 stages: Stage I: 0 - 4 days, Stage II: 5 - 9 days, Stage III: 10 - 14 days, Stage IV: 15 - 21 days, Stage V: 22 - 28 days and Stage VI: > 28 days [27]. HRCT scanning of the lungs is one of the main tools for screening, diagnosing, and evaluating the severity of COVID-19 disease. It may help us diagnose COVID-19 earlier than RT-PCR testing. The most common/classic lung imaging findings in COVID-19 are including:

- 1) Ground-Glass Opacification (GGO): hazy lungs without obscuration of the lung vessels.
- 2) Crazy-Paving Pattern: GGO with interlobular and intralobular septal thickening.
- 3) Consolidation: homogeneous opacification of the lungs with obscuration of the vessels.
- 4) Linear Opacities.

Air bronchogram, bronchiectasis, and pleural/pericardial effusion are the other findings, but cavitation and lymphadenopathies are not seen [27]. Imaging findings are peripheral when they are sub-pleural or involving mainly the peripheral

one-third of the lung. They are central or hilar, when involving mainly the central one-third of the lungs and diffuse when they are both peripheral and central. We have to know that, lung imaging findings in COVID-19 are peripheral at first and they finally become diffuse. There are 5 lobes and the imaging lesions can be involved in a single lobe, unilateral multi-lobe, and bilateral multi-lobe. A scoring system has been applied, including; Score 0: 0%, Score 1: < 5% involvement, Score 2: 5-25%, Score 3: 25-50%, Score 4: 50-75% & Score 5: \geq 75% with maximal CT Score for both lungs of 25 [27]. In most COVID-19 patients, the lung lesions are presented as bilateral multi-lobe with the lowest rate at stage I (42%) and the highest rate at stage IV (95.6%). In the stage, I; HRCT scans show single lung lobe involvement in 34% of lesions and 22% no lung involvement [27]. The diffuse bilateral lung involvement in COVID-19 is called White Lung in imaging.

The laboratory tests recommended for COVID-19 suspected patients are including; Group I: CBC/diff., ESR, CRP, BUN/Cr, Urinalysis, Liver Function Test (LFT), FBS, HbA_{1c}, Vitamin D₃. Group II: LDH, CK (MM, MB, BB), serum level of ferritin, D-Dimer, ABG, Cardiac troponins T and I, serum level of IL-6, CSF analysis, Bone Marrow microscopic examination, Electron Microscopic examination for SARS-CoV-2. This second group is considered in severe/critical cases of COVID-19. Elevated CRP/ESR along with low lymphocyte count is a compatible pattern with COVID-19.

A positive SARS-CoV-2 kit test or abnormal HRCT scan of lungs in a patient with compatible symptoms/signs or an asymptomatic case with the significant risk factor is sufficient to confirm the diagnosis of COVID-19, but two negative SARS-CoV-2 kit tests along with a normal HRCT scan of lungs are necessary to rule out the definite diagnosis of COVID-19 in an atypical or asymptomatic case.

History seems to be the mainstay in the diagnosis of COVID-19, and the SARS-CoV-2 kit test and HRCT scan of lungs are tools to confirm or reduce it.

3. Results

3.1. Screening Guideline

For screening the patients with COVID-19 we need to set up a referral health system called; COVID-19 Referral System. This referral system can include three levels. At the first level of this referral system, a list of clinical findings of COVID-19 and risk factors for SARS-CoV-2 infection through cyberspace, radio, and television or SMS is provided to all citizens.

1) List of Clinical findings: fever, dry cough, hoarseness, shortness of breath, fatigue, sneezing, runny nose, sore throat, nasal congestion or stuffy nose, sputum, chest pain, anosmia and lack of taste, cold or flu diagnosis over the past four weeks.

2) List of Risk factors:

- a) Contact with a COVID-19 patient within recent four weeks
- b) Travelling to Red zones within the recent four weeks

- c) Working in the live animal market
- d) Contact with a patient who has died due to unknown pneumonia within recent 4 weeks
- e) Contact with a live animal market workers
- f) Failure to follow the principles of prevention of becoming infected with SARS-CoV-2
- g) Contact with someone who has traveled to Red zones within recent four weeks
- h) Living in Red zone of the city
- i) Contact with someone who has contacted with a COVID-19 patient within recent four weeks
- j) Maybe close contact with pets???

Then, all citizens who have a positive case from the two lists, call the first level of the referral system through the announced telephone number and receive the necessary instructions.

The levels of COVID-19 Referral System:

Level One (I):

Step 1:

- 1) Take a history or medical advice by phone or Telemedicine
- 2) Quick COVID-19 test (finger-prick blood sample, at home)
- 3) Home quarantine of mild COVID-19 patients

Step 2:

- 1) Outpatient physical examination by General Practitioner
- 2) Quick COVID-19 test (whole blood sample, outpatient)
- 3) RT-PCR swab testing with both oropharyngeal and nasopharyngeal samples
- 4) Chest-X-Ray and routine laboratory testing (group I)
- 5) Home quarantine of mild COVID-19 patients

Level Two (II):

- 1) COVID-19 Antibody test (whole blood sample, inpatient)
- 2) Chest-X-ray and CT scan of lungs
- 3) Group I and group II laboratory testing
- 4) RT-PCR swab testing with both oropharyngeal and nasopharyngeal sample or sputum

5) Hospitalization of mild to moderate cases of COVID-19 who do not or cannot afford home quarantine, in semi-specialized or field hospitals.

Level Three (III):

- 1) Hospitalization of severe COVID-19 patients in Corona Hospital centers
- 2) ICU admission of severe COVID-19 cases who have to need ventilation.
- 3) COVID-19 Antibody test, and RT-PCR swab testing with oropharyngeal, nasopharyngeal, sputum, tracheal secretion or BAL sample
- 4) Group I and group II laboratory testing
- 5) HRCT scan of lungs, Abdominopelvic CT scanning, Brain MRI

- 6) Echocardiography, ECG and Cardiac monitoring
- 7) Electron Microscopy (EM) for identifying the SARS-CoV-2

3.2. Diagnostic Criteria

In addition to designing a referral system for COVID-19 patients, the corresponding author of this article also provides a Diagnostic Criteria (**Table 1**) for this disease includes two domains:

Table 1. Persian gulf criteria for diagnosis of COVID-19.

Persian Gulf Criteria for Diagnosis of COVID-19 ^{a,b}		
Domain (I)		
Clinical features:		up to 3 points
	Fever	2 points
	Dry cough	2 points
	Shortness of breath or dyspnea	2 points
	Loss of smelling and/or lack of taste	2 points
	Others ^c	1 point
	Abnormal CXR/HRCT scan of lungs compatible with pneumonia/pneumonitis ^d :	
	Single, central/upper lobe	1 point
	Single, peripheral/lower lobe	2 points
	Bilateral multi-lobe; peripheral or diffuse	3 points
Laboratory data:	Elevated CRP along with low lymphocyte count	1 point
Domain (II)		
Risk factors ^e		up to 3 points
Positive SARS-CoV-2 kit test		up to 3 points
	Positive RT-PCR test	3 points
	Positive IgM test	2 points
	Positive IgG test	1 point

^aFor each criterion in Domain (I): it must be new or worsening in the cases with other prominent disease or condition is likely to cause the presence of criterion. ^bclassification of diagnosis: 1) Definite (confirmed) COVID-19: patients with at least 4 points included at least one point from each of both Domains (I and II); 2) Highly suspected COVID-19: patients with only 3 points included at least one point from the first Domain (I); 3) Suspected COVID-19: patients with only 2 points including at least one point from the first Domain (I); 4) Possible COVID-19: patients with only 1 point from the first Domain (I); 5) Carrier of SARS-CoV-2: someone with a positive SARS-CoV-2 kit test with or without any risk factors but any Domain (I) points for at least two weeks. ^cincludes: fatigue/body ache, sneezing, runny nose, sputum, sore throat/hoarseness, nasal congestion, Cold/Flu Diagnosis and any other clinical features compatible with COVID-19. ^dincludes: Ground Glass Opacities (GGO), Crazy-paving pattern, consolidation and linear opacities. ^econtact with a COVID-19 patient within recent four weeks; 3.P./traveling to Red zones within recent four weeks; 3.P./working in the live animal market; 3.P./contact with a patient who has died due to unknown pneumonia within recent four weeks; 2.P./contact with a live animal market workers; 2.P./failure to follow the principles of prevention of becoming infected with the SARS-CoV-2; 2.P./living in Red zone; 1.P./contact with someone who has traveled to Red zones within recent four weeks; 1.P./contact with someone who has contacted with a COVID-19 patient within recent four weeks; 1.P.

Domain I includes: Clinical features, Imaging, and Laboratory data and
Domain II includes: Risk factors and SARS-CoV-2 kit testing.

4. Discussion

It is clear that, like other diseases in internal medicine, the clinical/para-clinical judgment of an expert Internist and/or Infectious Disease Specialist is the gold standard for diagnosis of COVID-19, of course in consultation with other medical professionals. We all know that a negative SARS-CoV-2 test does not rule out the diagnosis of COVID-19 and that a positive test does not necessarily indicate a COVID-19 diagnosis, and it is positive in carriers of virus too. Also, the normal lungs in HRCT scan, even with a negative SARS-CoV-2 test cannot rule out COVID-19. Many patients have COVID-19 without any risk factors. And many patients have no symptoms but have COVID-19. Therefore, it is simplistic for us to reject or confirm the diagnosis of COVID-19, only by performing a SARS-CoV-2 kit test and the HRCT scanning of lungs. For these reasons, the corresponding author concluded that to regulate the diagnosis of COVID-19 and to establish the same and coordinated decisions around the world regarding the diagnosis of COVID-19, it is necessary to provide a very sensitive and accurate Diagnostic Criteria for diagnosing this disease. The practical guideline and diagnostic criteria presented in this paper are the results of at least four months of extensive studies of published articles and review of various case reports regarding SARS-CoV-2/COVID-19 by the corresponding author; especially National Jewish Health Coronavirus Information and Resources [16] and WHO news and events regarding COVID-19 and SARS-CoV-2 [22]. Unfortunately, it is not possible to determine the exact sensitivity and specificity of this criterion in the country of my birthplace, Iran. Because more than five months have passed since the start of the novel Coronavirus epidemic in Iran. For the first month, the government and the nation were unaware of the SARS-CoV-2 epidemic in Iran, and according to the Deputy Minister of Research and Technology of the Ministry of Health and Medical Education of Iran, the COVID-19 cases were mistaken for Influenza. At first, there was no SARS-CoV-2 kit test in Iran, and then for a while, we only have 200 kits, which were used for specific individuals and groups. For almost two months now, Chinese kits have been used with a sensitivity of 30%, and of course along with a series of domestically produced kits, the sensitivity of which is not known. According to the head of the virology department of the Pasteur Institute of Iran, the Antibody kit test that is being used in Iran has no diagnostic value at all. Unfortunately, in Iran, only patients with a positive SARS-CoV-2 kit test are included in the official statistics of the country, which makes many patients forget. And of course, the very small number of diagnostic kit tests performed using very low-sensitivity kits complicates the story of many COVID-19 patients being missed in Iran. But the corresponding author believes that the sensitivity of these Criteria is close to 100% and its specificity is higher than 90%. Due to the especial global conditions, we present it, so that it

can be used as soon as possible if it is approved by a medical research team anywhere in the world.

In the cases with positive SARS-CoV-2 kit test but without any symptoms/signs or with mild clinical features, four options could be possible:

- 1) Carrier state for SARS-CoV-2
- 2) Subclinical COVID-19
- 3) Pre-symptomatic COVID-19 within the incubation period
- 4) Mild COVID-19

The above cases are silent spreaders, who have a major role in the spread of SARS-CoV-2.

Recovery (Discharge) Criteria for COVID-19: Patients with COVID-19 recover when [27]:

- 1) Afebrile for at least the last 72 hours, without using fever-reducing medications and;
- 2) Respiratory symptoms, especially coughing and shortness of breath, improved and;
- 3) More than one week has passed since the onset of symptoms
- 4) Significant improvement of acute lesions on chest HRCT,
- 5) Two consecutive negative RT-PCR tests at least 24 hours apart

Asymptomatic and mild COVID-19 patients, who make up 80% of cases, recover after 2 weeks. Moderate to severe COVID-19 patients usually recover within 3 to 6 weeks but the recovery in critical cases of COVID-19 varies with the person [16] [21] [22].

The principles of prevention of becoming infected with the SARS-CoV-2 as Ten Rules Preventing COVID-19 include:

- 1) Home quarantine of asymptomatic to mild COVID-19 patients and hospitalization of severe cases: Self-isolation of asymptomatic to mild COVID-19 patient from others in a specific room as sick room, with face-mask and with no visitors, and if available, with a separate bathroom, while his/her communication with the first level of COVID-19 Referral System or Family Physician could be continued by phone (telemedicine). Resting, warm-keeping, humidifier using and hot shower taking for cough and sore throat, hands cleaning after nose blowing or coughing or sneezing or use the bathroom and especially before eating or preparing foods, drinking plenty of fluids, a healthy nutritious diet and if needed symptomatic therapy are the only treatments available during this period. It is necessary to explain that home quarantine for parents with COVID-19 will not be effective without children's quarantine in another room at home [16] [21] [22] [27].
- 2) Physical (social) distancing:
 - a) Being away from others by more than 2 meters (acceptable) and, if possible, at least 4 meters (ideally)
 - b) Do not gather in groups
 - c) Prohibition of entering crowded places

d) Public transportation and taxis as ride-sharing cannot be used at all

3) Staying at home, especially for the elderly and children ages 15 to 20 years old or less than it, of course with the prohibition of coexistence of the elderly and children in a place under one roof, and also by establishing contactless meetings among residents.

4) Handwashing with water and soap for at least 20 seconds, and if they are not available, hand sanitizing with spray, gel or solutions containing at least 60% alcohol, especially before eating or preparing food and after nose blowing or coughing or sneezing or use the bathroom, and prohibition of face touching especially mouth, nose, and eyes with unwashed hands.

5) Cleaning and disinfecting high-touch surfaces every day including; door-knobs, handles, tables, light switches, countertops, desk, phone, keyboards, toilets, faucets, and sinks.

6) Face-Mask using:

a) Medical (Surgical) masks for the general population when forcing to leave the home and in the workplace and community

b) N95 masks for health care professionals

c) Hands should be washed or disinfected before and after applying the mask to the face, as well as before and after removing the mask.

7) Cough and sneeze covering with a tissue or inside of your elbow, whenever you don't have a mask on your face

8) Healthy nutritious diet along with the routine life activities and daily exercise

9) Have a video communication by phone/online with family and friends and regular daily schedule to watch movies

10) Practice to relieve stress/anxiety in these ways:

a) Think positive

b) Accept the existing reality

c) Follow novel Corona news, only once or twice a day

d) Deep breathing

e) Doing yoga/muscle relaxation

f) Meditation

g) Call your doctor or your best friend to ask for help

h) Conversation with God, alone and beyond the window of the room, looking at the sky or the mountain

The fate of the COVID-19 patients after home quarantine or self-isolation at home is as follows:

1) Asymptomatic patients can terminate home quarantine after 2 weeks because they carry the virus for up to 2 weeks.

2) Mild patients can terminate home quarantine after 3 weeks because they carry the virus for up to 3 weeks. Provided, of course, that there are criteria for recovery.

3) Hospitalization of mild to moderate cases of COVID-19 who do not or

cannot afford home quarantine, in semi-specialized or field Hospital of the level (II) of COVID-19 Referral System

4) With the occurrence of initial alarming/warning symptom, on the other hand, shortness of breath (new or worsening, for no other cause); the patient must be hospitalized in Corona Hospital Centre of the level (III) of COVID-19 Referral system

5) Severe to very severe patients should be quarantined in the Corona hospital and then at home for a total of at least 4 to 6 weeks. Provided, of course, that there are criteria for recovery.

Following a contact; the transmission probability of virus:

1) From a SARS-CoV-2 carrier without a mask, to a healthy person with a mask is 70%

2) From a SARS-CoV-2 carrier with a mask, to a healthy person without a mask is 5%

3) From a SARS-CoV-2 carrier with a mask, to a healthy person with a mask is 1.5%

4) From a SARS-CoV-2 carrier without a mask, to a healthy person without a mask is $\geq 90\%$

Therefore, according to the above principles, the occurrence of COVID-19 in the peoples with low socioeconomic classes will be much high, and also its prognosis will be too much worse. About 50% of COVID-19 deaths are due to pulmonary involvement, about 20% are due to cardio-vascular involvements and about 30% are due to concomitant cardio-pulmonary involvements. The Death Rate for COVID-19 patients is based on age and includes; old ages: 72%, middle ages (45 - 64 years): 23%, 18 - 44 years: 4.5%, 0 - 17 years: 0.5% [28]. COVID-19 Fatality Rate by age includes; + 80 years old: 15%, 70 - 79 years old: 8%, 60 - 69 years old: 3.6%, 50 - 59 years old: 1.3%, 40 - 49 years old: 0.4%, 30 - 39 years old: 0.2%, 20 - 29 years old: 0.2%, 10 - 19 years old: 0.2% and 0 - 9 years old: no fatalities [28] The Death Rate for COVID-19 patients regarding sex includes; male: > 60%, female: <40% [28]. COVID-19 Fatality Rate by sex includes; male: 4.7% for confirmed cases and 2.8% for all cases, female: 2.8% for confirmed cases and 1.7% for all cases [28]. COVID-19 Fatality Rate by comorbidity includes; Cardio-vascular diseases: 13.2%, Diabetes Mellitus: 9.2%, Chronic Lung Disease: 8%, Hypertension: 8.4%, Cancer: 7.6% [28]. Thus, older, illiterate, poor, and smoking men with comorbidity, account for the largest population of COVID-19 deaths. The outcome for COVID-19 depends on three parameters; the patient's age, the severity of the COVID-19, and underlying diseases.

We have to know that, the emergence of acquired natural immunity following COVID-19 may be questionable, because multiple reports of COVID-19 recurrence in patients, and multiple cases of lack of adequate antibody response to the virus have been observing.

Although the original image of COVID-19, which was introduced to the world from China, showed it to be much calmer than influenza, with far fewer death?!

But by looking at the SARS-CoV-2 epidemics in Europe and the United States, we find that we are facing a very deadly and pervasive disease, ten times more than influenza.

Certainly, if the world knew from the beginning what a dangerous and deadly disease it was facing and the flights of countries to China and vice versa and the exchange of passengers were stopped on time, and quarantine of the epicenter province/city in China began as soon as possible, now the world would not face this deadly pandemic.

The Persian scholar of medicine Ebne Sina (980-1037) suspected that some diseases were spread by microorganisms, and to prevent human to human contamination he came up with the method of isolating people for 40 days in Persian is called Cheleh. Traders from Venice saw his success and took this knowledge back to Italy and called it quarantine (forty in Italian). This is the origin of the word quarantine to fight pandemics, another bright idea coming from ancient Persia (Iran).

Comparing the clinical findings of COVID-19 with influenza (flu) and common cold, it is clear that;

- 1) A dry cough is severe and common in COVID-19 and flu but is mild and less common in colds.
- 2) Fever is common in COVID-19 and influenza, but less common in colds.
- 3) Stuffy nose is very common in colds and flu but is less common in the COVID-19.
- 4) The runny nose is very common in flu and colds, but less common in COVID-19
- 5) Sore throat is seen in all three diseases but is more common in colds and flu.
- 6) Dyspnea is a significant and alarming finding in COVID-19 and is seen in flu but not in colds.
- 7) Headache is very common in the flu and is also seen in COVID-19 but is less common in colds.
- 8) Body ache is seen in all three diseases.
- 9) Sneezing is common in flu and colds but is less common in COVID-19.
- 10) Exhaustion or fatigue occurs in all three diseases.
- 11) The loss of smelling and the lack of taste occasionally occur in flu and colds, while they are common and very important findings in COVID-19.

These three diseases have many common findings and are difficult to distinguish clinically [16]. Because COVID-19 is very dangerous, deadly, and pervasive, influenza is common and slightly dangerous, and the common cold is harmless; therefore; the corresponding author believes that in the SARS-CoV-2 epidemics in the Red zones, Cold and Flu diagnoses should be discarded in favor of COVID-19 diagnosis. By this decision, we are preventing the spread of the SARS-CoV-2 epidemic as much as possible and significantly reducing its mortality rate.

Because Allergic Rhinitis can lead to gradual dry coughs, they should be diffe-

rentiated from COVID-19. In Allergic Rhinitis sneezing, runny nose, nasal congestion and postnasal discharge, itchy eyes, and itchy skin are most common in the spring, while in COVID-19 itchy eyes and itchy skin are not seen and sneezing, runny nose, and nasal congestion are less common. Allergic Rhinitis do not cause weakness, body aches, fever, chills, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea, although they do occur in COVID-19, and fever is very common. Shortness of breath, the loss of smell, and the lack of taste occasionally occur in Allergic Rhinitis, while they are very important findings in COVID-19. People with the past medical history of Allergic Rhinitis; have allergies in this spring or year similar to previous years, not COVID-19, unless this time the symptoms are sudden, new, or more severe, and with previous conventional allergy treatment; don't give up and get even worse [16].

In patients who have previously had pulmonary disease, especially asthma, chronic obstructive pulmonary disease (COPD), or interstitial lung disease (ILD); if COVID-19 occurs, new respiratory symptoms/signs will be experienced especially along with new non-respiratory features, or previous respiratory problems will worsen and do not respond to previous conventional treatments [16].

Shortness of breath will usually be experienced after strenuous exercise, with going to high altitude, due to asthma, allergies, anxiety, strong emotional reaction, and nasal congestion or exposure to very high temperatures. It can also occur following diseases such as Asthma, COPD, ILD, Heart diseases, and morbid obesity. A new, sudden, severe, or worsening shortness of breath that cannot be justified by the above causes, especially accompanied by chest pain, fainting, nausea, high fever, chills, and cough can be due to COVID-19 [16].

New anosmia (loss of smelling) or dysgeusia (lack of taste) are considered important/key findings, so they can be proposed as a criterion for the diagnosis of COVID-19 [29].

Interpretation of the results of COVID-19 diagnostic tests in suspected COVID-19 cases include [25]:

- 1) (+) RT-PCR, (+) IgM, (+) IgG: Active COVID-19 and/or Carrier; Quarantine
- 2) (+) RT-PCR, (+) IgM, (-) IgG: Acute COVID-19 and/or Carrier; Quarantine
- 3) (+) RT-PCR, (-) IgM, (+) IgG: Late phase COVID-19 and/or Carrier; Quarantine
- 4) (+) RT-PCR, (-) IgM, (-) IgG: Window phase or incubation period and/or Carrier; Quarantine
- 5) (-) RT-PCR, (+) IgM, (-) IgG: Early phase or incubation period, no Carrier; no Quarantine
- 6) (-) RT-PCR, (+) IgM, (+) IgG: Recovery phase of COVID-19, no Carrier; no Quarantine
- 7) (-) RT-PCR, (-) IgM, (+) IgG: Previous COVID-19, recovery now, no Carrier; no Quarantine

Patients with severe COVID-19 who have a high fever, headache, and neck

stiffness with an impaired level of consciousness may be confused with cases of acute bacterial meningitis. Severe COVID-19 with; ENT, lung, and kidney involvement must be differentiated from Wegener's or Granulomatosis with Poly-Angiitis (GPA). Severe COVID-19 with; fever, body aches (arthralgia/ myalgia), lung involvement, skin erythematous rashes, headache and seizure, and kidney involvement along with pleurisy/pericarditis can be mistaken for Systemic Lupus Erythematosus (SLE). COVID-19 with; fever, arthralgia/myalgia, sore throat, coughing, hepatomegaly, splenomegaly, leukocytosis, neutrophilia, and rising ESR/CRP can be mistaken for Still's Disease in children and Adult-onset Still's Disease (ASD) in adults. COVID-19 in a patient over the age of 50 with, fever, recent headache, and high ESR may be mistaken for temporal arteritis or Giant Cell Arteritis (GCA). Due to the generalized arthralgia/myalgia and high ESR in a case of COVID-19 with the age of over 40 years, the diagnosis of Polymyalgia Rheumatica (PMR) is not far-fetched. Some cases of critical COVID-19 can lead to Hemophagocytic lymphohistiocytosis (HLH) and be included in the differential diagnosis of catastrophic Anti-Phospholipid Syndrome (APS). Microscopic Poly-Angiitis (MPA), and Behcet's Disease (BD) with medium to large vessel vasculitis or APS in adult, and Henoch-Schonlein Purpura and Kawasaki disease in children can also be considered in the differential diagnosis of critical COVID-19. There is no opportunity to discuss how these diseases differ from COVID-19 in this article, and it will be postponed to another article, however, certainly like other viruses, SARS-CoV-2 can cause many immunological disorders in human in an appropriate genetic and immunological background as a trigger, leading to the above-mentioned diseases.

We need to know that many treatments used in Rheumatology can have a therapeutic (?) and possibly preventive (?) aspect to the entry of SARS-CoV-2 into the body of a Rheumatic patient. Among them we can mention to; Antimalarial drugs especially Hydroxychloroquine, JAK inhibitors, IL-1 inhibitors, IL-6 inhibitors, IVIG, and Leflunomide. Hydroxychloroquine has been used to treat mild to moderate cases of COVID-19 in many medical centers of the world, and Actemra in severe cases. Indeed, Actemra or Tocilizumab is an IL-6 inhibitor.

We know that the incubation period of COVID-19 is a maximum of two weeks in about 99% of patients, and on the other hand, observations show that people with COVID-19 can carry the SARS-CoV-2 viruses for two to four weeks and pass it on to others. So instead of laying the groundwork for two weeks for risk factors and the length of the quarantine period and diagnosing the disease, it makes sense to use a four-week basis.

Possible causes of the higher prevalence of severe COVID-19 and its mortality in men include:

- 1) Women have a stronger immune system than men due to an extra X chromosome.
- 2) Men take the symptoms less seriously and go to the doctor later.
- 3) Men smoke a lot more than women.

- 4) Men are more likely to be in crowded places for work.
- 5) Men are more exposed to air pollutants.
- 6) Men are more likely to have heart disease, high blood pressure, lung, and liver disease.
- 7) Men drink far more alcohol.
- 8) Men follow health principles less than women.
- 9) Observations show that 90% of leading causes of death in the US are more common in men.
- 10) In some medical centers around the world, men with critical COVID-19 are injected with estrogen in the hope of rescuing them?!

We need to be aware that, Hospital-acquired COVID-19 that is called nosocomial COVID-19 is a severe form of COVID-19 disease because the virus originated in COVID-19 patients who were hospitalized and were usually severe or critical. Therefore, COVID-19 disease will appear in physicians, nurses, and hospital staff in a severe or critical form with a very high mortality rate.

Because asymptomatic COVID-19 patients, as well as the pre-symptomatic COVID-19 patients in the incubation period and carriers of SARS-CoV-2, are easily overlooked, by performing more and more SARS-CoV-2 diagnostic tests using high-sensitivity kits with very low false-negative results, in all people with or without any risk factors, with or without any symptoms and signs, if possible, we will alleviate this problem [26].

The reason for the growing number of COVID-19 in the United States and European countries is that more and more SARS-CoV-2 diagnostic tests are being performed, all using very high-sensitivity kits with very low false-negative results. For example, the number of SARS-CoV-2 diagnostic tests performed in the United States before writing this article was two times that of Germany, three times that of Italy, five times that of South Korea, and ten times that of Iran.

According to the corresponding author, if the diagnosis of COVID-19 is made only with the help of a set of clinical findings and SARS-CoV-2 diagnostic test, provided that the diagnostic kit is available everywhere and a SARS-CoV-2 test is performed for all suspected cases, between 6% and 20% of patients are diagnosed. Because only 20% of the patients have significant clinical findings, and the sensitivity of the kits varies from 30% to 100%. A study shows that 86% of patients with COVID-19 in China have been missed [27].

Now, if, in addition to clinical findings and SARS-CoV-2 diagnostic tests; risk factors, imaging, and laboratory tests are the founders of COVID-19 diagnosis, it is possible that up to 100% of patients can be diagnosed, which is the goal of Persian Gulf Diagnostic Criteria.

It is also suggested that in the Red zones of the SARS-CoV-2 epidemic, all deaths were unexpected and unjustifiable and all deaths due to unknown pneumonia and respiratory arrest, should be calculated as COVID-19 deaths.

According to the authors, in countries where quarantine is fully implemented during the SARS-CoV-2 epidemic, and governments support all sections of so-

ciety in terms of living costs, unemployment benefits, food, and health supplies, especially the lower strata of society; the role of low socioeconomic level in the occurrence and prognosis of COVID-19 disease is diminished. Vice versa, if the government does not support the lower strata of society, the likelihood of COVID-19 disease and a worse prognosis at low socioeconomic levels will increase dramatically.

The governments are easily able to show the official statistics of the COVID-19 and its mortality far below true statistics. This is done by performing a very small number of SARS-CoV-2 diagnostic tests per day using low-sensitivity kits.

Unfortunately, until this article is written, neutral experts in the world have not yet been allowed to enter China so that, they can conduct a comprehensive and independent investigation into the many questions in the world's awakened minds about this new Coronavirus and its pandemic, including:

- 1) The real source of the new Coronavirus?
- 2) The original story of the initial entry of the novel Coronavirus into the human body?
- 3) How to expand it in a limited area in China, but how to expand it quickly/widely in the world?
- 4) The main reasons for the delay in identifying and informing it in China?
- 5) Accurate statistics of new Coronavirus disease and its mortality in China?
- 6) The big difference between the initial reports of the disease (COVID-19) from China and the subsequent reports of the disease from the European Union, UK, and the US? And finally
- 7) Why the Chinese government treated Dr. Li Wenliang violently and how this precious physician, who deserved the Nobel Prize in Medicine died?

Identifying at least six major subtypes of SARS-CoV-2 in less than six months from the onset of novel Coronavirus epidemics indicates multiple genetic mutations [6]. Therefore, it is not possible to have a standard kit with high sensitivity to detect SARS-CoV-2 that can be used anywhere and anytime. Observing multiple reports of COVID-19 recurrence in patients, and multiple cases of lack of adequate antibody response to the virus along with multiple genetic mutations raises concerns about the development of an effective vaccine against the virus.

Do you think the following patients have COVID-19?

Case (1): A mother who suffered from fever and lethargy a week after visiting her son who has returned from a trip to China, has been hospitalized with shortness of breath. In a CT scan, both lungs are bleached, but the SARS-CoV-2 test is negative.

Case (2): An old man kept in a nursing home. He has diabetes mellitus. Without previous history, he suffers from lethargy and shortness of breath. In portable radiography, multiple opacities are evident in both lungs, so he is hospitalized, in blood tests, ESR and CRP are very high, along with low lymphocyte count, he died within 24 hours, despite being connected to a ventilator machine and prescribed broad-spectrum antibiotics. SARS-CoV-2 test is also negative.

Case (3): A 40-year-old woman who suffers from a dry cough and sore throat six days after meeting her Chinese boyfriend, who returned two weeks before from China. SARS-CoV-2 testing has not been performed due to a lack of access.

Case (4): A 45-year-old woman who was nursing her mother, who suffers from COVID-19, developed a high fever and cough a week later, but the SARS-CoV-2 test is negative.

Case (5): A 70-year-old man who visited a place of pilgrimage ten days ago has lost his sense of smell and taste. Due to chest pain and following a plain CXR and taking an ECG and a SARS-CoV-2 diagnostic test, only bilateral hazy lungs is evident.

Case (6): Occurrence of encephalitis with unknown cause in a physician is a member of the team of physicians at Corona Hospital for COVID-19: 1 point + 3 points

Case (7): Sudden death due to CVA with unknown cause + positive SARS-CoV-2 kit test

Case (8): Acute MI with unknown cause + traveling to Wuhan within 2 recent week

5. Conclusions

If we have a coherent and efficient patient referral system for screening people infected with SARS-CoV-2, and high-sensitivity diagnostic criteria should be used to identify COVID-19 patients. Also, along with these, more and more SARS-CoV-2 diagnostic tests should be performed using highly sensitive kits, and the principles of prevention of becoming infected with the SARS-CoV-2 should be followed carefully and as soon as possible; success in controlling and suppressing the SARS-CoV-2 epidemic will not be unexpected.

Governments can succeed against the SARS-CoV-2 epidemic when they prioritize the health of society and the lives of their citizens over economic, political, military, religious, and ideological issues. Providing accurate and real statistics regarding COVID-19, the number of patients and deaths, by the governments, and the existence of honesty and truthfulness in the thinking, expression, and performance of government officials, and the government's empathy with the nation and national determination and unity, are necessary for success in controlling SARS-CoV-2 epidemic. If a government falsely reports the statistics of COVID-19, it will not only fail to control the SARS-CoV-2 epidemic in the country but will also disrupt the control of the SARS-CoV-2 pandemic in the world.

Finally, according to the corresponding author of this article, effective medicine and vaccines for SARS-CoV-2 will not be made any time soon, and the only way to achieve global success in the face of novel Coronavirus pandemic is to unite all the states and nations of the world to establish a complete, synchronized and integrated quarantine for at least six weeks.

Applying a practical guideline such as COVID-19 Referral System for screen-

ing people infected with SARS-CoV-2, and having a Diagnostic Criteria such as Persian Gulf Criteria for diagnosing COVID-19 will be very useful and effective in this way.

The governments and nations of Vietnam, Singapore, Taiwan (China), Finland, Germany, South Korea, Japan, Canada, and Cuba are thought to be among the most successful countries in controlling the novel Coronavirus epidemic and receiving acceptable scores.

Authors Contribution

ISA conceptualized the study, overall guidance, and manuscript writing. SK reviewed the manuscript draft. FSA collected literature and references for the project. ASA contributed to data analysis. All authors were involved in the preparation of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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