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## RESEARCH ARTICLE

### CLINICAL MANagements FOR SEVERE COVID-19 PATIENTS WITH PNEUMONIA AND ACUTE RESPIRATORY DISTRESS: BASIC RECOMMENDATION TO REDUCE COMMUNITY MORTALITY

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#### ABSTRACT

Coronavirus Disease 2019 (COVID-19), caused by a novel corona virus (SARS-CoV-2), is a highly contagious disease. Most of the infected patients have mild symptoms including fever, fatigue and cough. But in severe cases, patients can progress rapidly and develop to the acute respiratory distress syndrome, septic shock, metabolic acidosis and coagulopathy. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of corona virus disease 2019 (COVID-19), which was declared a global pandemic by the World Health Organization on 11th March 2020. The treatment guidelines for COVID-19 vary between countries, yet there is no approved treatment to date. To report any evidence of care and therapeutics used for the management of patients with COVID-19 in clinical practice since emergence of the virus to reduce mortality. A systematic review protocol was developed based on the PRISMA statement. Articles for review were selected from Embase, Medline and Google Scholar. Readily accessible peer-reviewed, full articles in English published from 1st December 2019 to 26<sup>th</sup> March 2020 was included. The search terms included combinations of: COVID, SARS-COV-2, glucocorticoids, convalescent plasma, antiviral and antibacterial. There were no restrictions on the types of study eligible for inclusion.

#### INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019. Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus. By way of definition, a symptomatic COVID-19 case is a person who has developed signs and symptoms suggestive of COVID-19. Symptomatic transmission refers to transmission of SARS-CoV-2 from persons with symptoms. Epidemiology and virologic studies suggest that transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces [1-4]. Clinical and virologic studies that have collected repeated biological samples from confirmed patients demonstrate that shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease<sup>5-7</sup>, within the first 3 days from onset of symptoms [7-9]. The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5-6 days, but can be up to 14 days. During this period, also known as the "presymptomatic" period, some infected persons can be contagious, from 1-3 days before symptom onset<sup>9</sup>.

It is important to recognize that presymptomatic transmission still requires the virus to be spread via infectious droplets or by direct or indirect contact with bodily fluids from an infected person. An asymptomatic case is a person infected with SARS-CoV-2 who does not develop symptoms. While most people with COVID-19 develop only mild (40%) or moderate (40%) disease (see Table 1), approximately 15% develop severe disease that requires hospitalization and oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury [10]. COVID-19 is associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningo-encephalitis, impaired sense of smell or taste<sup>11</sup> anxiety, depression and sleep problems. In many cases, neurological manifestations have been reported even without respiratory symptoms. A number of pneumonia cases of unidentified causative agent was reported in December 2019 in Wuhan, capital city of Hubei governorate of China, and after that it was identified to be caused by the 2019 novel coronavirus SARS-CoV-2, and the medical problem that occurred due to this novel virus is known as Coronavirus Infectious Diseases-19 (COVID-19) [12-15]. Coronaviruses belong to a large family of viruses that have the adversity in both phenotypic and genotypic characteristics and possess an envelope containing positive sense RNA and it is about 27-32 kb that is responsible for encoding of essential proteins for viral lifecycle, including both structural and non-

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structural proteins. For instance, membrane (M), envelope (E) protein, nucleocapsid (N) protein and spike protein (S), which are belong to structural proteins have an important role in both viral entry and viral growth within the host cell and able to cause infection in birds, mammals and humans<sup>16-18</sup>. In the earlier time, two types of animal originated coronaviruses were recognised with a highly pathogenic ability, which are Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV-2) and Middle East Respiratory Syndrome-Coronavirus (MERS-CoV-2) in China 2003 and in Saudi Arabia 2011 respectively that caused a broad epidemic infection and deaths in a large number of countries in the world. SARS-CoV-2 is considered as the third identified human coronavirus with a highly pathogenic infection in the respiratory system<sup>14</sup>. Even though there is a belief that it is to be from bats or pangolin origin<sup>19</sup>. However, the defined source of this novel coronavirus, its intermediated hosts and even enzootic patterns of transmission still not completely understood.

It was declared by The World Health Organization (WHO) that the novel coronavirus SARS-CoV-2 is considered as a pandemic viral infection on March 11, 2020 [20]. Till now, World Health Organization (WHO) in May 29, 2020, reported that there were globally 5701,337 confirmed SARS-CoV-2 cases with 357,688 deaths from many countries in the world. From which Americas and Europe revealed with higher numbers of confirmed cases and fatalities, which are 2613,092 cases, 151,212 deaths and 2102,574 confirmed cases, 178,378 deaths respectively [21]. A report that declared by The Centers for Disease Control and Prevention (CDC) stated 17% of the United States total population is individuals with greater than 65 years, 31% of them composed of COVID-19 infections, 45%, 53% and 80% of them make up of hospitalizations, intensive care unit admissions, and deaths caused by this novel viral disease respectively [22]. This proposes that the individuals in older age group are seemed more probably to infect with SARS-CoV-2 and suffer from worse consequences compared with other age groups in the population. The aims of conducted this scoping review are to provide a summary information on the relation of COVID-19 fatality with age groups among infected patients. Moreover, to determine whether ethnicity has a role in COVID-19 prevalence in various regions in the world. Also, to assess the association of nutrition and immune system impacts in fighting against this new viral infectious disease. Finally, to find out the effect of other comorbidities among infected patients on COVID-19 fatality.

Despite of that SARS-CoV-2 has the ability to infect all age groups, the median age reveals around 47-59 years old, and it normally has a greater infection rate especially among severe and non-survival cases. Even though there is no specific gender bias appears to be found with the novel viral infection, whereas a higher tendency of COVID-19 cases seems to be in males than female individuals<sup>23-25</sup>. Among children and infants, a few numbers of cases has been recognised with COVID-19. Furthermore, in a report that declared by the center for Disease Control and Prevention (CDC) on massive cases of SARS-CoV-2 in China, which involving 72,314 infected individuals, from which just only 2% of them was higher than 20 years old<sup>26</sup>. The pandemic COVID-19 death rate in older age group has been significantly noticeable. Regarding to the joint mission of WHO and China, in which there was a decrease in the total Case Fatality Rate (CFR) for COVID-19 from 17.3% in January to 7% in February; however,

among elderly age group (> 80 years old), there was an increase of CFR (21.9%)<sup>27</sup>. Furthermore, a meta-analysis of 72,314 cases showed total CFR of 2.3%, whereas in patients (aged with 70 – 79 years old) reveals a CFR of 8% and 14.5% in elderly patients (> age 80)<sup>28</sup>. Moreover, in a survey investigation on 355 SARS-CoV-2 infected patients showed that the average of 79.5 years among death patients (29). In addition, a surveillance that performed in the United States on 4,226 SARS-CoV-2 cases showed a very low CFR (< 1%) in patients within age group (<54 age years), whereas among patients with ages between 65 – 84, a higher CFR of 3% - 11% was recorded and even a higher CFR (10% - 27%) in those elderly patients (>85 years old) and a higher percentage of mortality (>80%) was observed among older adult patients (> 65 years old) occurred in those older than age 65<sup>30</sup>. Till to date, nearly all the death cases of SARS-CoV-2 have been recorded especially among older adults and patients with comorbidities [31-32].

Nearly almost of elderly patients with COVID-19 suffer from some sort of impairment of body organs because of this novel coronavirus, in which 17% of them have severe acute respiratory syndrome (SARS), 20% with acute renal damage, and 33%, 15% and 67% of them have heart injury, hepatic dysfunction and required intensive care unit administration for therapy support respectively (33). In all age groups, chest computed tomography imaging of patients with SARS-CoV-2 revealed ground glass opacities (GGOs) (87%), mixed GGOs and consolidation (65%), vascular enlargement (72%), and traction bronchiectasis (53%). Among these, lesions had peripheral distribution (87.1%), bilateral lung involvement (82.2%), lower lung predominance (54.5%), and multifocality (54.5%) (34). Comparatively, chest radiograph findings in older adults showed bilateral reticular-nodular opacities (58%), GGOs (48%), pleural effusions (about 33%), peribronchial thickening (about 25%), and focal consolidations (20%) [33].

In spite of the pathophysiological pathways of COVID-19 are still not clearly understood, while nearly the majority of critical, severe and death cases of SARS-CoV-2 has been noticed among older adult patients or those patients who suffer from other underlying comorbid conditions; for instance, cardiovascular diseases (CVD), hyperglycaemia, chronic respiratory and kidney disease, cancer and higher blood pressure<sup>34-37</sup>. In the United States, a large number of older adults suffer from underlying chronic medical conditions; for example, 17% of them have CVD, and 63.1%, 38%, 26.8% and 23.7% of those elderly patients have blood hypertension, chronic renal diseases, hyperglycaemia and chronic obstructive pulmonary disease respectively<sup>38-41</sup>. An analysis by the joint WHO-China fact-finding mission found that patients older than age 60 and those with comorbidities had the highest risk for severe disease and death. The CFR in patients without comorbidities was 1.4%, whereas the CFR was 13.2% for patients with cardiovascular disease, 9.2% for patients with diabetes, 8.4% for patients with hypertension, 8% for patients with chronic respiratory disease, and 7.6% for patients with cancer<sup>42</sup>. One study on 46 fatal cases of SARS-CoV-2, in which 84% of patients were older than age 60, found that diabetes is likely associated with increased mortality<sup>43</sup>. Another study on critically ill older patients with SARS-CoV-2 found that 86% of patients had comorbid conditions such as CKD, congestive heart failure, COPD, and diabetes<sup>44</sup>. This likelihood of having multiple comorbidities places older adults at an even greater risk of increased mortality from SARS-CoV-2.

Table 1. Clinical presentation and risk factors for COVID-19 in severe cases

Clinical presentation	Risk factors for severe disease
Presenting signs and symptoms of COVID-19 vary. Most persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, have also been reported. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported. Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, and reduced mobility, and diarrhea, loss of appetite, delirium, and absence of fever. Symptoms such as dyspnea, fever, GI symptoms or fatigue due to physiologic adaptations in pregnant women, adverse pregnancy events, or other diseases such as malaria, may overlap with symptoms of COVID-19. Compared with adults, children are less likely to present with fever, cough and shortness of breath.	Age more than 60 years (increasing with age). Underlying noncommunicable diseases (NCDs): hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, diabetes, immunocompromising conditions, and cancer have been associated with higher mortality. Smoking.

One Chinese meta-analysis including 1527 patients showed that the most prevalent cardiovascular metabolic comorbidities with COVID-19 were hypertension (17.1%, 95% CI 9.9 - 24.4%) and cardio-cerebrovascular disease (16.4%, 95% CI 6.6 - 26.1%), followed by diabetes (9.7%, 95% CI 6.9 - 12.5%). In this report, patients with diabetes or hypertension had a 2-fold increase in risk of severe disease or requiring intensive care unit (ICU) admission, while those with cardio-cerebrovascular disease had a 3-fold increase<sup>39</sup>. In a sub-set of 355 patients with COVID-19 in Italy who died, the mean number of pre-existing underlying conditions was 2.7, and only 3 subjects did not have any comorbidity<sup>40</sup>. Many older adults in the United States have cardiovascular disease (17%), diabetes (26.8%), hypertension (63.1%), COPD (23.7%), and CKD (38%)<sup>9,34,37</sup>. An analysis by the joint WHO, China fact finding mission found that patients older than age 60 and those with comorbidities had the highest risk for severe disease and death and COVID-19 also risky and leads to severe complications.

The CFR in patients without comorbidities was 1.4%, whereas the CFR was 13.2% for patients with cardiovascular disease, 9.2% for patients with diabetes, 8.4% for patients with hypertension, 8% for patients with chronic respiratory disease, and 7.6% for patients with cancer<sup>29</sup>. One study on 46 fatal cases of SARS-CoV-2, in which 84% of patients were older than age 60, found that diabetes is likely associated with increased mortality<sup>25</sup>. Another study on critically ill older patients with SARS-CoV-2 found that 86% of patients had comorbid conditions such as CKD, congestive heart failure, COPD, and diabetes<sup>27</sup>. This likelihood of having multiple comorbidities places older adults at an even greater risk of increased mortality from SARS-CoV-2. The clinical spectrum of COVID-19 can be very heterogeneous. Most adults and children present mild flu-like symptoms, but some may rapidly develop acute respiratory distress syndrome (ARDS), respiratory failure, arrhythmias, acute cardiac injury, shock, multiple organ failure and death<sup>12, 28</sup>. The most commonly reported symptoms are fever, cough, fatigue, sputum production and shortness of breath. However, headache, upper respiratory symptoms (e.g., sore throat and rhinorrhoea) and gastrointestinal symptoms (e.g., nausea and diarrhoea) occur less often [1217, 28]. Although not described in the initial Chinese studies, smell and taste disorders (e.g., anosmia and dyspepsia) have also been found frequently in patients with COVID-19 in Italy [31].

Many older adults in the United States have cardiovascular disease (17%), diabetes (26.8%), hypertension (63.1%), COPD (23.7%), and CKD (38%) [23,34,37]. An analysis by the joint WHO-China fact-finding mission found that patients older than age 60 and those with comorbidities had the highest risk for severe disease and death. The CFR in patients without comorbidities was 1.4%, whereas the CFR was 13.2% for patients with cardiovascular disease, 9.2% for patients with diabetes, 8.4% for patients with hypertension, 8% for patients with chronic respiratory disease, and 7.6% for patients with cancer<sup>29</sup>. One study on 46 fatal cases of SARS-CoV-2, in which 84% of patients were older than age 60, found that diabetes is likely associated with increased mortality [25]. Another study on critically ill older patients with SARS-CoV-2 found that 86% of patients had comorbid conditions such as CKD, congestive heart failure, COPD, and diabetes<sup>27</sup>. This likelihood of having multiple comorbidities places older adults at an even greater risk of increased mortality from SARS-CoV-2.

## METHODOLOGY

A literature review was carried out to search for articles in PubMed and Google Scholar databases till 02 April 2020. The following keywords were used: “SARS-CoV-2”, “COVID-19”, “infection”, “pathogenesis”, “incubation period”, “transmission”, “clinical features”, “diagnosis”, “treatment”, “diabetes”, with interposition of the Boolean operator “AND”. We also retrieved the full text of the relevant cross references from the search results. Furthermore, any methods; additional references, nature research reporting summaries, source data, extended data, supplementary information, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at scientific literature and recommendations in the WHO and United States Centers for Disease Control and Prevention (CDC) websites. Also depending of the following table the finding recommendations were accepted.

## Recommendations

Concerning over all of the above screening and review we suggested that the following recommendations were important to decrease fatality rate and decrease severity of the disease in order to get best management and give the patient good practices:

We recommend that COVID-19 care pathways be established at local, regional and national levels. COVID-19 care pathways are for persons with suspected or confirmed COVID-19. We recommend screening all persons at the first point of contact with the health system in order to identify individuals that have suspected or confirmed COVID-19.

**We recommend for Mild disease** Symptomatic patients (Table 1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.

**We recommend for Moderate disease:** Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia.

### We recommend Severe disease

Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO<sub>2</sub> < 90% on room air (54). Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following:

- Central cyanosis or SpO<sub>2</sub> < 90%; severe respiratory distress (e.g. fastbreathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions (55, 56).
- Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 (55).
- While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

### We recommend for Critical disease like; Acute respiratory distress syndrome (ARDS):

**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms.

**Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.

**Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present.

### Oxygenation impairment in adults (57, 59):

- Mild ARDS: 200 mmHg < PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH<sub>2</sub>O).**b**
- Moderate ARDS: 100 mmHg < PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 200 mmHg (with PEEP ≥ 5 cmH<sub>2</sub>O).**b**
- Severe ARDS: PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 100 mmHg (with PEEP ≥ 5 cmH<sub>2</sub>O).**b**

**Oxygenation impairment in children:** note OI and OSI.**c** Use OI when available. If PaO<sub>2</sub> not available, wean FiO<sub>2</sub> to maintain SpO<sub>2</sub> ≤ 97% to calculate OSI or SpO<sub>2</sub>/FiO<sub>2</sub> ratio:

- Bilevel (NIV or CPAP) ≥ 5 cmH<sub>2</sub>O via full face mask: PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 300 mmHg or SpO<sub>2</sub>/FiO<sub>2</sub> ≤ 264.
- Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5.
- Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3.
- Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3.

### We recommend for Critical disease like; Sepsis

**Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fastbreathing, low oxygen saturation, reduced urine output (3, 60), fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.

**Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count. Other complications that have been described in COVID-19 patients include acute, life-threatening conditions such as: acute pulmonary embolism, acute coronary syndrome, acute stroke and delirium. Clinical suspicion for these complications should be heightened when caring for COVID-19 patients, and appropriate diagnostic and treatment protocols available.

### About mechanism of therapy

**Mild:** We recommend that patients with suspected or confirmed mild COVID-19 be isolated to contain virus transmission according to the established national COVID-19 care pathway. This can be done at a designated COVID-19 health facility, community facility or at home (self-isolation). We recommend patients with mild COVID-19 be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition and appropriate rehydration. Counsel patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care. We recommend against antibiotic therapy or prophylaxis for patients with mild COVID-19.

**Moderate:** We recommend that patients with suspected or confirmed moderate COVID-19 (pneumonia) be isolated to contain virus transmission. Patients with moderate illness may not require emergent interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases. We recommend for patients with suspected or confirmed moderate COVID-19, that antibiotics should not be prescribed unless there clinical suspicion of a bacterial infection. We recommend close monitoring of patients with moderate COVID-19 for signs or symptoms of disease progression. Provision of mechanism for close follow up in case of need of escalation of medical care should be available.

**Severe (pneumonia):** We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs and to any patient without emergency signs and SpO<sub>2</sub> < 90%. Closely monitor patients for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock and respond immediately with supportive

care interventions. Use cautious fluid management in patients with COVID-19 without tissue hypoperfusion and fluid responsiveness.

**Critical cases:** In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) may be used. Refer to Table 1 for definitions of mild, moderate and severe ARDS. We recommend prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support. We recommend that endotracheal intubation be performed by a trained and experienced provider using airborne precautions. We recommend implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH<sub>2</sub>O). In adult patients with severe ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> < 150) prone ventilation for 12–16 hours per day is recommended.

Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness. Avoid disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis and increased risk of infection of health care workers. In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxaemia despite lung protective ventilation. Critical cases (septic shock) Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP)  $\geq$  65 mmHg AND lactate is  $\geq$  2 mmol/L, in the absence of hypovolaemia. Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] < 5th centile or > 2 SD below normal for age) or two or more of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia. Do not use hypotonic crystalloids, starches or gelatins for resuscitation. In adults, administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP  $\geq$  65 mmHg in adults and improvement of markers of perfusion. In children, administer vasopressors if signs of fluid overload are apparent or persists after two fluid bolus.

**For older people:** Older age has been reported as a risk factor for increased mortality in those affected by COVID-19. We recommend that older people be screened for COVID-19 at the first point of access to the health system, be recognized promptly if they are suspected to have COVID-19 and treated appropriately according to local COVID-19 care pathways. This should occur in all settings where older people may seek care; included but not limited to facility-based emergency units, primary care, prehospital care settings and LTCFs. Identify if there is an advance care plan for patients with COVID-19 (such as desires for intensive care support) and respect his/her priorities and preferences. Tailor the care plan to be in line with patient's expressed wishes and provide the best care irrespective of treatment choice. We recommend a review of medication prescriptions to reduce polypharmacy and prevent medicine interactions and adverse events for those

being treated with COVID-19. Ensure multidisciplinary collaboration among community workers, physicians, nurses, pharmacists, physiotherapists, occupational therapists, social workers, mental health and psychosocial providers and other health care professionals in the decision-making process to address multimorbidity and functional decline. Finally we recommend collecting standardized clinical data on all hospitalized patients to improve understanding of the natural history of disease and contribute data to the WHO Global COVID-19 Clinical Data Platform.

## Conclusion

In conclusion, this is the first systematic review of medication used to treat patients with COVID-19. Only 41 research articles were eligible for inclusion in this review, mainly conducted in China, of which only three were clinical trials. The use of corticosteroids to treat patients with COVID-19 was reported most frequently in this review, despite safety alerts issued by WHO and CDC, followed by lopinavir, oseltamivir and arbidol hydrochloride. Although further research is warranted as the amount of the evidence increases, this review presents the current picture of treatment modalities used for COVID-19. Efficacy and safety profiles of treatments for COVID-19 will need to be characterized in future studies.

Conceder to the clinical practice and initial management of COVID-19 patients the treatment guidelines and gratefully acknowledgment is the basic and dependant process leading to decrease occurrence of complications and decrease mortality rate of COVID-19. As with any patient in intensive care unit successful clinical management of patients with COVID-19 depends on attention to the primary and early detection process leading to support health system to evaluate and fix the regulatory strategies. Use decision support tools bear in mind that these discussion may need to take place remotely. Be aware that older people, or those with comorbidities, frailty, impaired immunity or a reduced ability to cough and secretion, are more likely to develop severe pneumonia in COVID-19 patients. As COVID-19 pneumonia is caused by virus antibiotics are ineffective. In our country we follow the WHO guidance for treatment by using and give the patients nutritional supplements such as vitamin C and Zink and advice the patients to take rest at home and follow taking more sufficient water and fluids for mild cases, but for moderate cases increasing the immune system of the patients is an important point we depend on it, also for severe cases should admit the patients in critical care unit inside the hospital and we add antibiotic such as Azithromycin and give the patients plasma of cured patients as a local guidance to improve health care and increase the rate of recovery.

**Conflict of Interest:** We declare that we have no conflict of interest.

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