A Systematic Literature Review of Current Therapeutic Approaches for COVID-19 Patients

Saber Soltani[1,2,3], Amir Mohammad Zakeri[4], Mohammad Reza Karimi[2],
Sara Akhavan Rezayat[5], Fateme Zomorodi Anbaji[6], Alireza Tabibzadeh[7],
Parastoo Yousefi[7], Armin Zakeri[8], Ali Jafarpour[1], Mehdi Norouzi[1],
Yousef Erfani[9] and Vahdat Poortahmasebi[10,11,12*]

[1]*Department of Virology, School of Public Health, Tehran University of Medical Sciences,*
Tehran, Iran.
[2]*Research Center for Clinical Virology, Tehran University of Medical Sciences, Tehran, Iran.*
[3]*Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran.*
[4]*Pediatric Surgery Research Center, Research Institute for Children's Health,*
Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[5]*Department of Health Care Management and Economics, School of Public Health,*
Tehran University of Medical Sciences, Tehran, Iran.
[6]*Department of Cell and Molecular Biology, School of Biology College of Science,*
University of Tehran, Tehran, Iran.
[7]*Department of Virology, Iran University of Medical Sciences, Tehran, Iran.*
[8]*Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran.*
[9]*Department of Medical Laboratory Sciences, School of Allied Medical Sciences,*
Tehran University Medical Sciences, Tehran, Iran.
[10]*Infectious and Tropical Diseases Research Center, Tabriz University of Medical Sciences,*
Tabriz, Iran.
[11]*Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences,*
Tabriz, Iran.
[12]*Department of Bacteriology and Virology, Faculty of Medicine,*
Tabriz University of Medical Sciences, Tabriz, Iran.

Review Article

*Corresponding author: E-mail: poortahmasebiv@tbzmed.ac.ir, vahdat2011@gmail.com;

ABSTRACT

Background: In December 2019, the pneumonia outbreak reported in Wuhan, Hubei Province, China. WHO introduced a novel coronavirus and the virus named *Severe acute respiratory syndrome-related coronavirus-2* (SARS-CoV-2) in January 2020. There are not any specific antiviral agents for coronavirus disease 19 (COVID-19).

Objective: Our review aimed to discuss treatment options and the efficacy of currently prescribed drugs and supportive care in COVID-19 patients.

Study Design: A literature review of the articles in the Web of Science, PubMed, Scopus and EMBASE conducted.

Results: Lopinavir/ritonavir combination was the most frequently used drug, followed by Arbidol and Oseltamivir and Methylprednisolone. Lopinavir/Ritonavir outcome showed the fever and respiratory infection improve in day two and day eight, respectively. Also, negative PCR of SARS-CoV-2 in days six and 7day was seen and finally these patients discharged in 10 days.

Conclusions: Lopinavir/Ritonavir was the most improving administrated antiviral combination, which might be a good option for COVID-19 due to its availability. Although supportive care such as O_2 supplementary and IV fluid therapy has improved outcomes. There are not evidence for suggesting a new treatment or a new drug, which mean the necessity of further investigations for drug research in a clinical trial for a conclusion about the optimum treatment.

1. INTRODUCTION

In the past two decades, there were two coronavirus outbreak includes *Severe acute respiratory syndrome-related coronavirus* (SARS-CoV) and *Middle East respiratory syndrome-related coronavirus* (MERS-CoV) in 2002 and 2012, respectively [1]. In December 2019, patients suffering from pneumonia with unknown reason detected in Wuhan, Hubei Province, China. Investigations lead to the introduction of a novel coronavirus by world health organization (WHO) [2] and the virus named *Severe acute respiratory syndrome-related coronavirus-2* (SARS-CoV-2) in January 2020 [3]. SARS-CoV-2 and SARS-CoV classified in the *betacoronavirus* genera which belong to *Coronaviridae* family. These enveloped viruses are positive-sense RNA [4] and because of their sequence similarity to bat SARS-CoV like coronaviruses, they thought to originate from bats. The sequence of a coronavirus isolated from a *Rhinolophus affinis* bat, named RaTG13, shows 96% similarity to that of SARS-CoV-2 [5]. Coronavirus spike glycoproteins (S) enables the virus to enter the cells via binding to ACE2 (Angiotensin-converting enzyme 2) receptors [6]. The spike glycoprotein's receptor-binding domain (RBD) which is a part of the subunit S1, binds directly to ACE2 [7]. The amino acid sequence homology of RBDs in SARS-CoV and SARS-CoV-2 is 73.7% and the head to head comparison of SARS-CoV-2 and SARS-CoV showed a similar virus-cell interaction which leads to less different infectivity [8]. SARS-CoV RBD specific antibodies may cross-react with SARS-CoV-2 RBD, which may be a valuable option for the prevention of these two viruses [9]. Between November 2002 and July 2003, the SARS-CoV epidemic leads to 9.6% reported case fatality rate with 8096 confirmed cases and 774 death [10]=. Before December 2014, the case fatality rate for MERS-CoV reported being 35% [11]. After that, from July 2016 to July 2017, 249 patients diagnosed with MERS-CoV including 75 deaths were reported in Saudi Arabia (30% case fatality rate) [12] and it is still in circulation in the Middle East region [13,14]. According to WHO, by the time this draft was prepared, April 24 2020, it was declared that SARS-CoV-2 took 181938lives with 2626321confirmed cases (~3.4% case mortality rate by the WHO as of March 3) all around the world in countries, territories and areas [2]. Notwithstanding the unavailability of a promising drug to cure severe acute respiratory infection (SARI), there have been loads of advances made in the process of developing useful drugs. Investigation showed that Chloroquine an anti-malarial drug inhibits the SARS-CoV-2 [15]. Various non-specific antiviral drugs are taking for inhibiting SARS-CoV-2 in patients such as Remdesivir, Ribavirin, Favipiravir [15,16]. Furthermore, Lopinavir inhibits SARS-CoV-2

replication in Vero E6 cells [17]. Recently Ivermectin, an anti-parasitic agent showed in vitro activity against SARS-CoV-2 [18].

Despite many effort, there is no specific antiviral treatment available for SARS-CoV-2 yet. The current literature review discusses the efficacy of current and various prescribed drugs and supportive care especially in patients with coronavirus disease 19 (COVID-19), which can be useful for evaluating treatment options and outcomes against SARS-CoV-2.

2. METHODS

2.1 Search Strategy

For the current literature review, a comprehensive search on the therapeutic strategy in the treatment of COVID-19 patients was carried out in multiple electronic databases including Web of Science, PubMed, Scopus and EMBASE according to the title, abstract and author keywords. The exact keywords used in this study include "Wuhan coronavirus", "New coronavirus", "Novel Coronavirus 2019", "nCoV-2019", "Coronavirus disease 2019", "COVID-19", "*Severe acute respiratory syndrome-related coronavirus 2*", "SARS-CoV-2" and "SARS-2". To avoid missing articles, the "OR" used between all of the keywords in the search query.

2.2 Inclusion and Exclusion Criteria

The criteria considered in the current literature review and the English online COVID-19 paper from outbreak time evaluated. The cohort, cross-sectional and case series studies in COVID-19 treatment field included. The full-text articles that conducted in therapeutic approaches, supportive care and antiviral usage for the treatment COVID-19 patients included for additional assessment. Also, those studies reporting duplicate or irrelevant data and studies not meeting eligibility criteria such as review articles excluded.

2.3 Study Screening and Data Collection Process

The reports were reviewed and managed by EndNote X9 (Thomson Reuters). Duplicated documents removed and papers independently screened to verify that inclusion criteria met. The intended data of the selected articles recorded in the data extraction table prepared. From each eligible study the first author, location, study design, number of patients, mean age, background medical condition, symptoms of patients, intervention used with dose, supportive care, administration, drug outcome were extracted. Also, all studies screened by two independent authors, and the third expert person solved the conflicts.

3. RESULTS

3.1 Search Result

Conducted search by using keywords leads to the 1414 documents. Fig. 1 illustrates the selection process. These documents screened by titles and abstracts by considering the inclusion and exclusion criteria which it relived 146 studies. All of the screened studies meet the inclusion criteria and assessed full text. After the full-text assessment, we included 11 studies for data extraction. The data extractions on 11 included studies summarized in Table 1. Furthermore, 8 of the conducted studies focused on the case presentations while there were three original articles with larger sample size.

3.2 Clinical and Demographical Characteristics

In all included studies, there were 265 assessed cases. The minimum mean age was 35 and the maximum mean age was 59.7 In clinical presentations, the fever and cough were the most repeated symptoms in all studies. Most of the included studies conducted in China (8 studies) and the rest of them were from the USA, Taiwan and Korea. Patients in the primary studies show a wide range of background conditions, including Diabetes, Hypertension, Chronic Obstructive Pulmonary Disease (COPD), hypertriglyceridemia, Hypo-thyroidism, Cardiovascular disease and malignancies.

3.3 Therapeutic Drugs

Lopinavir/ritonavir combination was the most frequently used drug as mentioned in 7 out of 11 studies and it follows by Arbidol and Oseltamivir by four different studies and methylprednisolone was used in 3 different studies for the treatment of the COVID-19 patients. Between recovered patients that received Lopinavir/Ritonavir, the fever and respiratory infection improve in day two and day eight, respectively. Also, negative PCR

of SARS-CoV-2 in days six and seven days reported, and finally, these patients discharged in 10 days. The dosage of prevalent Prescribed Antiviral drugs such as Lopinavir/Ritonavir, Arbidol, Oseltamivir and Methylprednisolone were 100-800 mg, 0.2-200 mg, 75 mg and 40-120 mg, respectively. The routine administration of Lopinavir/Ritonavir and Arbidol was PO q8h-q12h, PO q8h. Among the supportive therapies, oxygen supplementation was the most common among the six included articles. In addition, the details of other prescribed drugs with more information on the mentioned drugs summarized in Table 1.

4. DISCUSSION

As the newly emerged novel coronavirus 2019 has almost spread and infecting more than 200 countries and territories around the world and may become a severe threat to humanity, an efficient treatment protocol should be considered to face it. Until April 24 2020, COVID-19's victims have risen to near 181938; unfortunately, no definitive drug has been reported, and few are undergoing clinical trials. Studying COVID-19's genome sequence may help to provide the proper treatment and vaccines, but as it may take months, studying the better-known
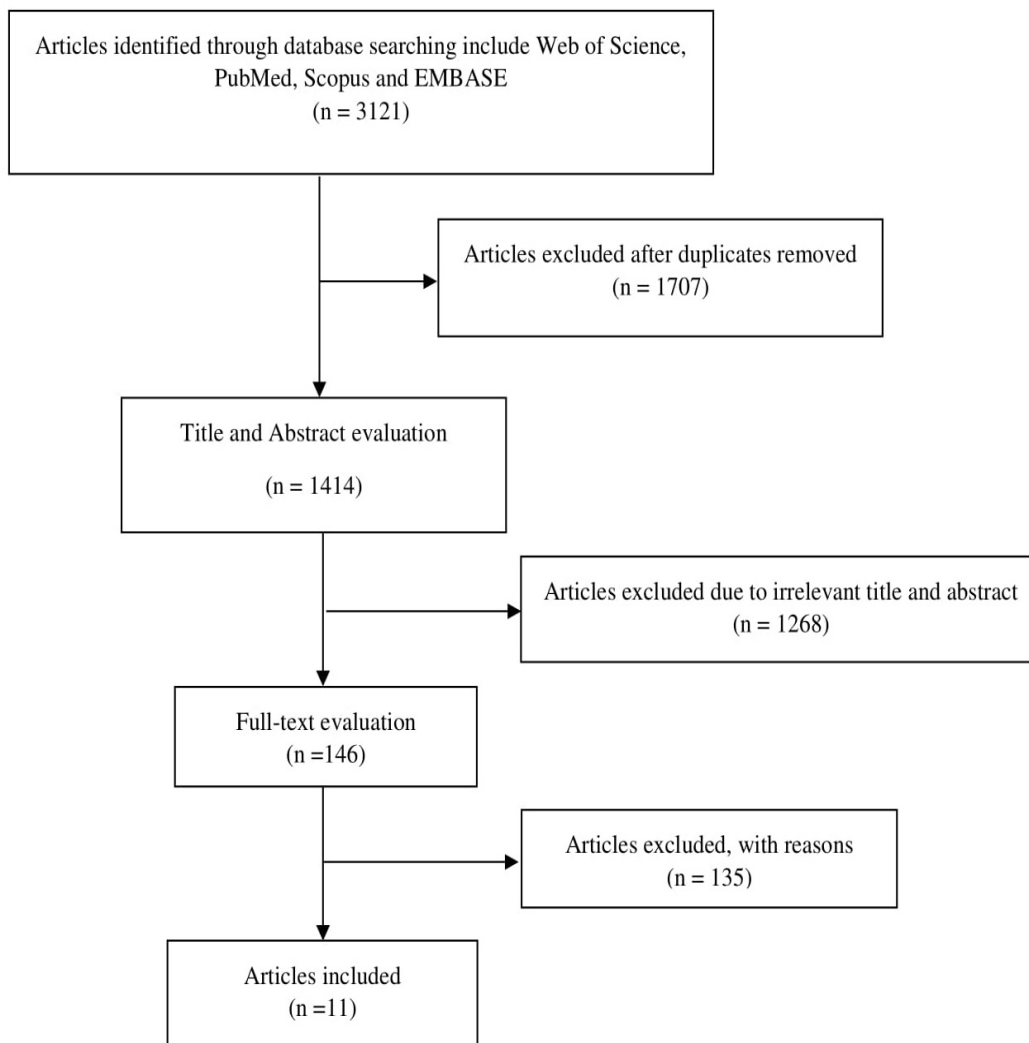

Fig. 1. Summary of the literature search and study selection

Table 1. Summary of therapeutic agents in the treatment of SARS-COV-2 patients

Author	location	Type of study	Number of cases Male	Female	Background medical condition	Mean age	Symptoms (Number of patients)	Intervention	Dose	Administration	Supportive care	Drug Outcome	Ref.
Han	China	Letter to editor	1		DBT(ll) HTN Smoker	47	Productive Cough, Fever, stuffy and runny noses, vertigo, and fatigue	Lopinavir/Ritonavir Methylprednisolone INF a2b Ambroxol hydrochloride Moxifloxacin hydrochloride	800/200 mg 40 mg 10 Million IU 60 mg 400mg	Daily Daily for 3 days then reduced to 20 mg for 2 more days Daily Daily Daily	-	Improves fever in 2 days, improved respiratory function in day 8, negative PCR of SARS-CoV-2 in days 6 and 7day, discharged in 10 day	[19]
Holshue	USA	Brief report	1		HTG	35	Mild cough, low-grade intermittent fever, dyspnea, nausea and vomiting, fatigue, abdominal discomfort, diarrhea	Remdesivir Vancomycin Cefepime	day8 day5-7 day5-7	- 1750-mg loading dose, 1g q8h -	Acetaminophen 650mg (q 4h), Ibuprofen 600mg (QID), Guaifenesin 600mg, N/S 6L in 6 days, O2 nasal 2L/min	After Remdesivir: Increase of O2 saturation, bilateral lower lobe rales fades, Fever improvement	[20]
Lim	Korea	Brief Communication	1	-	-	54	Myalgia, Chilling, intermittent fever, Dry cough, Diarrhea	Lopinavir Ritonavir	200 mg 50	Administrated on day 8of hospitalization BID for 10 days	-	Decrease of viral load and Symptom improvement	[21]
Zhang	China	Letter	1	1	-	38	Fever and Cough were common while dyspnea and vomiting seen in male and female patients, respectively	Methylprednisolone Gamma globulin Oseltamivir Arbidol hydrochloride Moxifloxacin Tanreqing	40 mg 10 mg - - - -	IV Single dose IV Daily for 5 days, then 5 mg - - - IV	-	Clinical improvement and both patients successfully treated and discharged	[22]
Wang	China	Case report		1	30 weeks pregnant woman		Intermittent fever for one week	Arbidol Lopinavir /Ritonavir Cefoperazone Sodium Sulbactam Sodium Human Serum Albumin	0.2 mg 400/100 mg 3 g - 20 g	PO, q8h PO, q8h IV, q 8h - IV, Daily	O2 mask at 5 L/min, Dexamethasone and magnesium sulphate as prophylaxis for the fetus, Emergency cesarean section	Clinical improvement of woman, Infant was unaffected by COVID-19	[23]
Wang	China	Brief report	3	1	-	44.2	Fever, Cough, Fatigue (all cases)	Lopinavir/Ritonavir Arbidol SFJDC	400/100 mg 0.2 mg 2.08 g	PO, q12h PO, q8h PO, q8h	O2 therapy	All patients had clinical improvement and discharged	[24]
Xu	China	Retrospective case series	35	27	liver disease (7), HTN (5), COPD (1), DBT (1)	41 median	Fever (48), Cough (50), Myalgia/Fatigue (32), Breath shortness (2)	INF alpha Lopinavir/Ritonavir Arbidol Corticosteroid Gamma globulin	50 micro g 400/100 mg 200mg 40-80mg 15-20 g/day	Inhalant, q12h PO, q12h PO, TDS Daily 3-5 days	-	One discharge, no death	[25]
Huang	China	Original research	30	11	DBT(7), HTN(6)	49	Fever (40), Cough (31), Dyspnea (22)	Oseltamivir Methylprednisolone antibiotics(not mentioned)	75mg 40-120mg -	PO, BID Daily -	O2 supplement (nasal)	clinical improvement and viral clearance, discharged 13 patients(32%) were admitted in ICU, 6	[26]

											patients died		
Cheng	Taiwan	Case report		1	HT		Fever, Dyspnea	Ceftriaxone Amoxicillin/Clavulanate	2mg Loading dose then daily 875/125 mg	IV, 2mg daily for one week and then replaced by Amoxicillin/Clavulanate PO, q12h, 7 days	O2 supplement (nasal)	Negative PCR and Rise of O2 Saturation	[27]
Chen	China	Original research	67	32	CVD (40), Endocrine (13), Malignancy (1)	55.5	Fever (82), Cough (81), Shortness of breath (31)	Oseltamivir Ganciclovir Lopinavir/Ritonavir Antibiotics(Carbapenems, tigecycline, linezolid)	75mg 0.25 g 500 mg -	PO, q12h (3-14d) IV, q12h (3-14d) PO, BID (3-14d) -	O2 supplement (75), Noninvasive mechanical ventilator (13), Invasive ventilator (4), ICU admission (23)	31 discharged, 11 died, 57 still in hospital	[28]
Yang	China	Original research	35	17	DBT(9), Malignancy (2), CVD (5)	59·7	Fever (51), Cough (40), Dyspnea (33), Myalgia (6)	Antiviral (23) include Oseltamivir, ganciclovir and Lopinavir, Antibacterial (49), Glucocorticoid (30), Immunoglobulin (28) and Vasoconstrictor (18)	-	-	High flow nasal cannula (33), Mechanical ventilation (37), ECMO(6)	After 28 days 32 patients died 32 patients Survived	[29]

DBT: Diabetes, HTN: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, BID: Bis in Die (2 Times a Day), TDS: Ter Die Sumendun (3 Times a Day), QID: Quarter in Die (4 Times a Day), q12h: each 12 hours, PO: Per Os, IV: Intravenous, ECMO: Extracorporeal Membrane Oxygenation, HTG: hypertriglyceridemia, HT: Hypothyroidism, CVD: Cardiovascular disease

SARS-CoV-1 and MERS-CoV may help to identify potentially effective available drugs, since it shares 79% and 50% sequence identity with his older cousins, SARS-CoV-1 and MERS-CoV, respectively [30]. SARS-CoV-1 infection process depends on spike proteins, two proteases (3CLpro, PLpro) and RNA-dependent RNA polymerase (RdRp) that each can be therapeutic targets [31,32].

Lopinavir, a proteinase inhibitor, is known for its antiviral activity and also blocks post-entry replication of MERS-CoV [33]. Analysis of molecular dynamics simulation has demonstrated the possible inhibition of SARS-CoV1's 3CLpro by Lopinavir/Ritonavir combination [34]. In this combination that had developed initially as HIV's protease inhibitor, Ritonavir increases Lopinavir blood concentration by decreasing its metabolism, and the main antiviral effect refers to Lopinavir [35,36-37]. The Lopinavir/Ritonavir and interferon-α combination has also been reported beneficial in MERS-CoV patients by viral clearance and recovered patients [38,39]. Some studies demonstrate the addition of Lopinavir/Ritonavir to Ribavirin was associated with reducing death rate, intubation and corticosteroid requirement [40,41]. Ribavirin a guanosine analogue and characteristic broad-spectrum antiviral agent [42,43], though its hemolysis side effect (in 76% of patients), and decrease in hemoglobin of 2 g/dL (in 49% of patients) reported between SARS patients [44]. Hsu et al. concluded that in several COVID-19 patients who received ribavirin did not observe any apparent reaction to this antiviral drug, and some patients become progressively worse [45].

Interferons are host cells-produced immunomodulatory in confronting pathogens which have been used for antiviral purposes while no antiviral drugs were available [46-50]. Some case reports mentioned that convalescent plasma obtained from recovered patients result in reducing hospital stay and mortality rate in patients in the early phase of SARS [51,52]. In a study published in February 2020, out of 140 patients who diagnosed as COVID-19, 90 cases (64.3%) had one or more underlying comorbidities. The most common ones were chronic diseases, including hypertension (30%), diabetes mellitus (12.1%) and cardiovascular diseases [53]. Other reported underlying comorbid situations in COVID-19 patients such as liver disease, renal failure, and cerebrovascular disease [25]; for 89% of patients antiviral drugs prescribed, while for 45% of

patients empirical antibiotic was prescribed, and 26% were received systematic corticosteroid and gamma globulin treatment; Finally, 2% of patients were discharged, and no COVID-19 patients had died [25)]. COVID-19 onset symptoms observed in hospitalized patients are mostly fever, cough and sputum, but there are other symptoms (e.g., headache and diarrhea) which are somewhat lower [54]. Currently, there are no FDA-approved treatments for any human coronavirus infection [55)]. This condition can be more dangerous for patients with underlying disease and lead to a higher mortality rate in this group of patients.

The concern for lack of reliable drugs or vaccines to cure COVID-19 is rising extensively. Also, Prior investigations have implemented and proposed diverse approaches for further research in order to overcome the complications that SARS-CoV-2 has made to this point. For instance, Remdesivir, a nucleotide analogue and antiviral agent, has recently been known for its antiviral action against SARS-CoV and MERS-CoV [56] and also its 100% protection against Ebola virus infection in nonhuman primates [57]. Remdesivir suggested for treating SARS patients and acts as an RNA- dependent RNA polymerase (RdRp) binding substrate, which takes over the position of ATP and puts an end to polymerization [16]. Chloroquine, an anti-malarial and autoimmune drug, has been identified as a broad-spectrum antiviral drug; it disrupts virus/cell fusion and entry by incrementing endosomal pH [15]. Recently reported for Chloroquine antiviral effect by decreasing endosomal pH and affecting entry and post-entry stage of SARS-CoV-2 infection in Vero E6 cells [58,59,60]. The study of Wang M. et al. suggests Remdesivir and Chloroquine be effective against SARS-CoV-2 infection *in vitro* [15]. Moreover, Teicoplanin, an antibiotic has proven to be an efficacious drug in inhibiting the cleavage of the viral spike protein, so it obstructs the first phase of the MERS-CoV viral cycle in humans [61]. Chen et al. compared Favipiravir versus Arbidol for COVID-19 in a randomized clinical trial [62]. Arbidol can inhibit hemagglutinin which will lead to the fusion prevention of host cell and some viruses; also, it induces body immune system by induction of cells to produce interferon and triggering NK cells [63]. Favipiravir, the antiviral agent that was used in influenza pandemics to inhibit RNA-dependent RNA polymerase(RdRp), has had significantly higher efficacy in clinical recovery rate in 7 days(1) cough relief and fever reduction in

SARS-COV-2 patients(with and without diabetes and hypertension) compared to Arbidol. However; some adverse effects such as gastrointestinal reaction and serum uric acid rise are reported that disappeared after treatment [62]. Thalidomide, an immunomodulatory and anti-inflammatory agent, known for disrupting the cell cycle, and it is currently used for patients diagnosed with cancer. Thalidomide Because of its efficacy on lung tissue and anti-fibrotic effects, it may be a great drug for treating COVID-19 patients. Recently Chen et al. reported that Thalidomide had a beneficial outcome in combination with low dose glucocorticoid by clinical improvement, increasing oxygen index, relieving cough and dyspnea and reducing fever in a case of SARS-COV-2 -related severe pneumonia [64]. As recent studies demonstrated, SARS-CoV-2 spike protein directly binds to ACE2, which expressed in alveolar epithelial cells (type 2) and some extrapulmonary tissues such as intestine, heart and kidney as well [65,66]. Dose-dependent administration of Human recombinant soluble ACE2 (hrsACE2) significantly reduced infection in Vero E6 cells by interfering attachment of SARS-CoV-2 to ACE2 [67]. Ivermectin, an FDA-approved anti-parasitic agent, has been known for its in vitro antiviral effect by inhibit importin α/β-mediated nuclear import result in blocking HIV-1 and dengue virus replication [68,69]. Caly et al. have demonstrated Ivermectin's antiviral activity against SARS-CoV-2 in infected Vero/hSLAM cells by reducing 93% of viral RNA in the supernatant at 24h and ~5000-fold reduction at 48h [18].

Despite the prescription of mentioned drugs in different studies, the drug side effects should also be considered. For example, the therapeutic and toxic dose border of Chloroquine is narrow and the Chloroquine intoxication associated with the cardiovascular side effect [70]. So Chloroquine as self-treatment is not recommended.

In a document published by WHO in March 2020, patients diagnosed with SARI and respiratory distress, hypoxemia or shock required to provide with supplemental oxygen therapy; Due to secondary infections, proper empiric antimicrobials should be given in less than one hour period after the patient with sepsis is initially assessed [71].

As mentioned earlier, the present literature review included 11 studies (3 original articles and

8 case presentations), 174 males, 91 females. Of 168 patients with subjective fever and cough whom Lopinavir/Ritonavir combination administrated for, 100 patients had clinical improvement, decrease in viral load and discharged with exceptional respiratory function and 11 deaths reported. However, in the study of Yang et al. on 52 COVID-19 patients with 20 survivors, only 23 patients given antiviral agents including Oseltamivir, Ganciclovir and Lopinavir (without Ritonavir) [29]. Although in some studies, administrating antiviral agents has resulted in 10 days of clinical improvement [19]. In the study of Cheng et al. patients turned afebrile on day 10 of illness, and SARS-CoV2 was not detected in sputum by day 17 without administrating any antiviral agents [27]. The data collected in this review revealed the dose of common prescribed Antiviral drug such as Lopinavir/Ritonavir, Arbidol and Oseltamivir, were 100-800 mg, 0.2-200 mg and 75 mg respectively, which showed different range.

In this review, fever as the most common reported symptom in 232 patients (of 265), and cough as the second most in 211 patients. However, the study of Zhang et al. [22] on a couple showed that COVID-19 infection might have different presentations; Although both patients presented with fever and cough, the male and the female presented shortness of breath and vomiting respectively [22]. The difference in the patient's response to a viral infection such as gastrointestinal symptoms may need symptomatic treatment. As shared genome sequence identity mentioned, it may justify the pathophysiology of COVID-19 resemblance to SARS-CoV and MERS-CoV, as they all have similar symptoms and use Proteinase enzyme for polyprotein processing. Therefore, the drugs that studied in vitro and animal models against MERS-CoV and SARS-CoV may have similar effects on SARS-CoV-2. Nevertheless, this topic needs further investigation.

Pregnant women seem to be more susceptible to viral infections, and their complications may worsen the pregnancy outcome. So this group of COVID-19 patients need to supportive care and specific treatment strategy to prevent the transmission COVID-19 through the birth canal. Wang et al. reported a case of COVID-19 in a 30-week pregnant woman with preterm delivery [23]. The pregnant woman went under treatment with Lopinavir/Ritonavir (tablets 400/100mg administered orally every 8 hours) and Arbidol

(Umifenovir) (0.2 g administered orally every 8 hours) as antiviral drugs; also dexamethasone and magnesium sulphate as prophylaxis for the fetus was given, and emergency cesarean section done which infant was unaffected by COVID-19 [23]. Amniotic fluid sample, placenta, umbilical cord blood, newborn's gastric juice and swabs were all negative for SARS-CoV 2 [23]. As abdominal cesarean section avoids newborn's oral and nasal airway exposure to vaginal canal seems superior to natural vaginal delivery. Providing the operating room with negative pressure and protecting the newborn's airway from aspiration during delivery can be useful. In addition, appropriate gears for personnel such as gown, facial masks and shields should be considered .However, vertical transmission of infected pregnant women to the fetus is yet to be fully understood.

Studies reported bilateral pneumonia in all COVID-19 patients regardless of the infection severity [26,72]. In the current review study, chest CT scan and X-ray abnormalities, as bilateral (more common) or unilateral patchy ground-glass opacities observed in 264 patients (of 265). This observation suggests the lower respiratory system as a vulnerable organ to SARS-CoV-2 replication. Although no definitive treatment has reported for COVID-19, supportive care including supplemental oxygen therapy (nasal or mask), supplemental IV fluids, antipyretics, antitussives, antiemetics, O_2 saturation cardiac and fluid intake/output chart monitoring, seems beneficial as in all 11 included studies improved patients' outcome.

Chen et al. reported that Smoking might be a severe risk factor, as of 11 deaths; first two victims (61 and 69 years old men) had a long smoking history which led them to fatal death by ARDS and respiratory failure on the ninth day of admission [28]. In addition to antiviral treatment for COVID-19, Some studies suggested antibiotics such as Moxifloxacin hydrochloride, Vancomycin, Cefepime, Cefoperazone sodium, Sulbactam sodium, Amoxicillin/Clavulanate, Carbapenems, Tigecycline and Linezolid) [25,27,29]. Although administration of antibiotics without proper indication may lead to resistance, in severe infections, it could be helpful as prophylaxis for secondary infection. Among the studies that announced antibiotics usage against COVID-19, the hypothesis is that this administration did to prevent secondary infection. Nevertheless, Teicoplanin function results in cleavage the viral spike protein.

5. CONCLUSION

In conclusion, Lopinavir/Ritonavir was the most improving administrated antiviral combination, which might be a good option for COVID19 due to its availability. Although the probability of insufficient health care facilities, supportive care such as O_2 supplementary and IV fluid therapy has improved outcomes. Although antibiotics administration in viral infections may increase the risk of bacterial resistance, considering antibiotics as prophylaxis for secondary infection in severe viral infections remains physicians' preference. There are not evidence for suggesting a new treatment or a new drug, which leads the researchers to the necessity of further investigations in drug fields. This study could suggest further investigations for drug research and clinical trial for a conclusion about the optimum treatment.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONENT

It is not applicable.

ETHICAL APPROVAL

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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