Review Article

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TANAFFOS

Coronavirus in Recent Years: Characteristics, Outbreaks, and Treatments

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Background: Coronaviruses cause acute respiratory syndromes, e.g., SARS, MERS, and COVID-19, whose treatment depends on several factors, specifically the age of patients, adopted treatments, time of hospitalization, and timely diagnosis. The present study was conducted to investigate the interaction between the mentioned factors and treatment.

Materials and Methods: Relevant full-text publications were indicated by searching in the five online databases MEDLINE, EMBASE, WOS, Science Direct, and Cochrane Library using MeSH terms during 2010-2024. Only original case reports (n=55) that worked on signs and treatments were selected and analysed according to age, gender, medical history, diagnostic methods, treatments, kind of respiratory syndrome, and transmission ways. Articles that met the inclusion criteria were evaluated by each of the reviewers independently, and non-agreements were solved by consulting with a fourth reviewer.

Results: According to the results, the severe respiratory syndromes occurred more in the elderly than younger people and in males than females (58% and 42%, respectively). Medical history of diabetes and heart disease showed the maximum effect on the person to get involved with the severe respiratory syndrome. Clinical methods were used more for the diagnosis of the diseases because of easy access and less time consumption. Combination therapy was better than single therapy. The most common route of transmission was human to human and nosocomial.

Conclusion: It can be concluded that these types of fatal respiratory illnesses can be controlled if the health care workers become familiar with the type of illness and apply the early and effective treatments.

Keywords: Coronaviruses; Acute Respiratory Syndrome; SARS; MERS; COVID-19

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-I) first spread from China in November 2002 (1). This disease proved to be highly infectious with respiratory droplets (2). Infected cases also played an important role in some cluster outbreak cases (3). Observations showed that the SARS virus cannot infect a healthy person during the patients' incubation period (4). In 2012, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), as the sixth human coronavirus, was first identified in Saudi Arabia (5). MERS was reported to have a higher case fatality rate than SARS (6). It caused large nosocomial outbreaks in Jeddah, Saudi Arabia, and Korea during 2014-2015 (7). In December 2019, an unknown pneumonia spread rapidly in Wuhan, China, and most initial cases were related to source infection from a seafood wholesale market by SARS-CoV-II (8). Therefore, the main aim of this review was to conduct a systematic

review of case reports to gain a more precise estimate of the effectiveness of different strategies in managing respiratory syndrome coronavirus.

Coronavirus family

Coronaviruses are classified into α-coronavirus, ß-coronavirus, γ-coronavirus, and δ-coronavirus genera. α - and ß-coronaviruses infect mammals, γ-coronaviruses infect avian, and δ-coronaviruses infect mammalian and avian (9).

Human coronavirus NL63 (HCoV-NL63), porcine transmissible gastroenteritis coronavirus (TGEV), PEDV, and porcine respiratory coronavirus (PRCV) are classified in α-coronavirus. On the other hand, SARS-CoV, MERS-CoV, bat coronavirus HKU4, mouse hepatitis coronavirus (MHV), bovine coronavirus (BCoV), and human coronavirus OC43 are entered in ß-coronavirus class. Avian infectious bronchitis coronavirus (IBV) is in γ-coronaviruses and porcine δ-coronavirus (PdCV) is in δ-coronaviruses class (10). They are a spherically enveloped virus with a diameter of 120–160 nm and positive-stranded RNA that typically ranges from 27 to 32 kb (11). Coronaviruses are capable of adapting to new hosts with relative ease through mutations and recombination because of their large enveloped RNA by the nucleocapsid protein (N) (12). Membrane protein (M), envelope protein (E), and spike protein (S) are structural proteins that are associated with viral mechanism (13) and the spike forms the crown appearance on the surface of the virus (14).

In addition, hemagglutinin-esterase protein (HE) that was found in some kind of viruses has a role in the release of the virus from infected cells. The metallopeptidase angiotensin-converting enzyme 2 (ACE2) (15), which is abundantly expressed on polarized epithelium in the lung and gastrointestinal (GI) tract (16), is the primary receptor for SARS-CoV and NL63-CoV. Serine protease dipeptidyl peptidase-4 expressed on the cells is a receptor for MERS-CoV. Also, aminopeptidase N on the lung and enteric epithelium are receptors for HCoV-229E, TGEV, and feline and canine CoVs (17). In addition, Sialic acid moieties act as a receptor for a couple of Coronaviruses (18). Previous studies confirmed that HIV, Ebola virus, and Dengue virus could uptake into the cells through the CD209 and CD209L cell-surface Ca-dependent lectins, then enhance the infection (19). Fusion peptides (highly hydrophobic peptides) have a critical role in initiating membrane fusion in enveloped viruses to target cell membranes that are protected by being buried deep within the glycoproteins. Environmental stimuli, acidic pH for example, could act as a receptor for fusion peptide to insert the viral into cells membrane. This is still unclear whether the proteolysis of the virus spike is enough for fusion and insertion (20).

Treatment of Coronavirus infection depends on several factors, specifically the age of patients, adopted treatments, time of hospitalization, and timely diagnosis. The present study aimed to investigate the interaction between the mentioned factors and treatment.

MATERIALS AND METHODS

The early detection and diagnosis of coronaviruses (MERS, SARS, and COVID-19) is an essential issue for the effective treatment of novel coronavirus (CoV) infection. The diagnosis methods contain molecular techniques and serological assays. RT-PCR, RT-LAMP, and RT-RTPA techniques were used as the initial diagnosis methods in coronavirus infection (21, 22). Serology tests are blood-based tests that can be used to diagnose people who have been exposed to a coronavirus virus. Several types of serological assays like neutralization tests which can show functional antibodies to the target pathogen, the immunofluorescence assay (IFA), protein microarrays [enzyme-linked immunosorbent assay (ELISA)], spike pseudo particle neutralization and micro neutralization assay, recombinant spike immunofluorescent assay, and western blot experiments have been used for CoV detection. However, these tests are just for surveillance or research purposes, not for diagnostic purposes. They are tools developed in response to the COVID-19 outbreak. A recent study indicated that the real-time PCR method was superior to culture identification, which is a fast and easy assay.

Chest radiographs (X-ray) and computed tomography of the chest (CT) scan are also used to detect coronavirus diseases. Chest imaging plays a vital role in both the assessment of disease extent and follow-up. Unlike SARS and MERS which primary chest imaging abnormalities are more frequently unilateral, COVID-19 is more likely to involve both lungs on primary CT imaging. Moreover, some CT studies showed that COVID-19 has a diversity of manifestations (23, 24).

Treatments

Despite the high incidence and mortality rate of different types of coronavirus diseases, no effective and certain drug or treatment has been reported so far. Most of the studies on MERS disease have shown that *in vitro* repurposed drugs on MERS-CoV could not be readily available.

Antivirals

Effective antivirals are crucial in order to improve the clinical outcome of MERS disease. Scientists assessed three *in vitro* anti-MERS-CoV repurposed drugs: Mycophenolate mofetil [MMF], Lopinavir/Ritonavir, and interferon-β1b in humans. Their results showed that Lopinavir/Ritonavir and interferon-β1b alone or in combination could be effective, although MMF may worsen the outcome of the disease and should not be used (25). The combination of Ribavirin and interferon-alpha is the most used therapeutic regimen, and some investigations showed that it may be effective in MERS-CoV infections (26). However, there are some conflicting ideas that show this treatment could not reduce the 90-day mortality of the disease or clear the MERS-CoV RNA when initiated in 2 days (27). A case report study reported that combination therapy of Lopinavir /Ritonavir, Ribavirin, and Interferon-alpha could be effective in some cases of MERS infections despite the late introduction (48 h) with 7-day treatment duration (28). Ribavirin and Lopinavir/Ritonavir were used as post-exposure prophylaxis (PEP) strategy for individuals who were exposed to MERS-CoV patients. This strategy limited the spread and the risk of infection (40%) (29). Another study introduced Lopinavir/Ritonavir and interferon-β1b as the "MIRACLE trial" for MERS (30). Nitazoxanide is another introduced antiviral against viral respiratory infections, especially MERS-CoV, although many investigations need to be done before its clinical trial (31).

INTERCEPT™ Blood System

Blood banks receive large amounts of blood from donors who may be infected with some viruses, including the coronavirus. Serological screening and nucleic acid testing are the most common techniques to recognize the infections. It has been described recently that HBV and HIV could be transmitted *via* blood. The effect of amotosalen/ultraviolet A (UVA) light on the human platelet showed that the MERS-CoV was completely inactivated in spiked platelet units even after cell culture. Therefore, this may be one of the suggested treatments (32).

Convalescent plasma (CP) therapy

Another suggested potential therapy is the use of convalescent plasma (CP). The feasibility, safety, and clinical/laboratory effects of CP therapy were evaluated, and the method was presented as a protocol (33). In another study, the effect of CP therapy for MERS-CoV has been evaluated. Results showed that there is a limitation of the plaque reduction neutralization test (PRNT). In addition, they claimed that in resource-limited situations, ELISA IgG could be used (34).

Extracorporeal membrane oxygenation (ECMO)

The other study that evaluated rescue therapy in severely hypoxemic patients of MERS-CoV infection supports the use of ECMO (35).

Antibodies

One of the treatments of viral infections is the use of human IgG antibodies against the virus. Trying to produce this antibody in trans chromosomic (Tc) bovines after MERS-CoV vaccination showed that Tc bovines could produce Tc hIgG quickly and develop *in vitro* assays and animal models, so they can offer a platform to produce a therapeutic protocol (36).

Macrolides

Macrolides, which have been reported to be useful in the treatment of some viral pneumonia diseases related to influenza and other viruses, indicated that they could not

reduce the three months mortality or improve the clearance of virus' RNA (27).

Research Question

What are the important factors in the transmission, outbreak, and disease recovery of coronaviruses?

Study Objectives

1) Introducing coronaviruses, their transmission, outbreaks, and disease treatments.

2) Comparing the treatments of respiratory syndrome coronavirus and introducing the best one in recent years.

3) Conducting a systematic review of case reports to gain a more precise estimate of the effectiveness of different strategies in managing respiratory syndrome coronavirus.

4) Critically appraising existing evidence and identifying the gaps in the literature to provide future research directions.

The protocol for this systematic review was developed and reported with guidance from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (37).

Eligibility Criteria

The excluded studies included conference abstracts, letters, and other studies without detailed data. English studies published between the years 2010 to 2024 investigating respiratory syndrome coronaviruses, including SARS, MERS, and COVID-19, were eligible. Reviews and basic experiment studies were also excluded.

The interventions included in the study are

1) Different kinds of coronaviruses, their disease signs, and treatment methods

2) All kinds of studies, e.g., case reports and clinical studies.

3) Comparing treatment methods

Data Sources

Full publications were identified by electronic searching of five online databases: MEDLINE, EMBASE, WOS, Science Direct, and the COCHRANE Library (from their inception of two months before submission).

Search Strategy

Searches were conducted using both text words and exploded Medical Subject Heading (MeSH) terms: (coronavirus) AND (respiratory) AND (syndrome). The search strategy was specified for each dataset based on its rules. For the PubMed dataset, it was ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) AND (respiratory [All Fields] AND ("syndrome"[MeSH Terms] OR "syndrome"[All Fields])). For the EMBASE dataset, it was 'coronavirus' in all fields AND 'respiratory' AND 'syndrome' as Emtree-exploded. For the COCHRANE Library, it was Coronavirus AND respiratory syndrome in all text. For the Web of Science library, Coronavirus AND respiratory syndrome in the title/keyword/abstract were used. For the Science Direct dataset, the following strategy was used in Expert search: "Coronavirus" AND "respiratory syndrome" in all sources. References were managed in EndNote (version X7), and duplicates were removed and then exported to a Microsoft Excel (version 2010) spreadsheet in order to complete the search process.

Study selection and data Collection

Four independent reviewers selected the included citations based on the title and abstract of the papers. Each of the three reviewers assessed full-text papers that met the inclusion criteria independently, and disagreements were solved by consulting with a fourth reviewer. The minimum follow-up time of the included studies was 2 months.

Data were collected from full-text papers based on the method mentioned in the Cochrane Consumers Handbook (38). The following information was recorded for each study: basic characteristics (author, title, year of publication, study design), intervention data (the method, dose, time of treatment), and outcome data (follow-up time).

Data Extraction and Management

A data extraction form was developed, and the relevant data were extracted from the included studies. The method of the treatment (case reports), gold standard, and outcome variables (safety and survival probability) were extracted as detailed information in the results.

RESULTS

Included trials in systematic review

The search was conducted in June 2024. A total of 117 records were obtained through PubMed, 70 records through EMBASE, 17 records through Cochrane Library, 69 records through Web of Science Library, and 54 records through Science Direct (Figure 1).

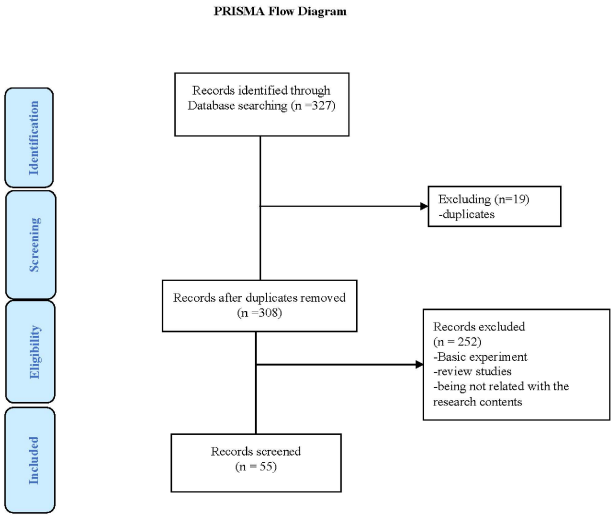

Figure 1. Literature search and inclusion process

Methodological quality

Studies were categorized according to subject, type, methodology, and results parameters that were summarized in Table 1. Subjects were grouped in SARS, MERS, and COVID-19 diseases. Generally, there were 308 papers, of which 37 were in SARS, 207 in MERS, and 58 in COVID-19, and the other 6 papers in HCoV OC43, HCoV 229E, OC43, and H1N1. According to Table 1, from 308 full-text papers, 100 were reviews, and 208 were original papers.

Review papers and basic experiment papers were excluded, and only case report papers were screened for later analysis (Table 2).

Included trials

Review papers were omitted from quantitative synthesis, and only original case reports papers (n=55) that worked on signs and treatments were selected and analysed according to age, gender, medical history and diagnostic methods, treatments, kind of respiratory syndrome and transmission ways (Table 3). According to the results, the minimum percentage (8%) of the patients had an age range of 0- 20 years old, while the age range of 40-80 years old showed the maximum percentage (70%). 58% of the patients were men, and 42% of them were female. Medical history of diabetes and heart disease showed the maximum effect on the person to get the severe respiratory syndrome. Clinical methods were used more for the diagnosis of the diseases because of easy access and less time consumption (67%). Combination therapy had a better treatment effect compared to single therapy (51%). The most common route of transmission was human to human and nosocomial (38%) (Table 3).

Table 1. Grouping studies by subject, type, methodology, and parameters (gold standards)

Subject	Type		Methodology	Parameters (gold standards)
	Review	Original		
SARS	14	23	Basic experimental	Safety and Survival Probability
MERS	67	140	Case reports	
COVID-19	19	39	Clinical studies	
HCoV OC43		1		
HCoV-229E		2		
HCoV 229E and OC43		1		
H1N1		2		

Table 2. Evaluating studies based on their results considering the relevant parameters of this research

Ref.	Case characterization	Signs	Treatment	Main finding	Conclusion
(39)	1. A 4-month-old male infant with no notable pathological history 2. A five-year-old male child with no particular pathological history 3. A 5-year-old female child	Upper respiratory infection high fever, dry cough, asthenia, diarrhea, and dyspnea Fever and asthenia, dry cough, dyspnea	Oxygen therapy by mask, Noradrenaline Oxygen therapy Antibiotics, Dexamethasone, Tinzaparin.	Died Discharged Died	Mortality in children with COVID-19 is linked both to the severity of the pulmonary involvement and to the length of care in pediatric intensive care.
(40)	1. A 22-month-old, full-term boy 2. A thirteen-year-old girl	Dyspnea, cough, anorexia, and Chronic granulomatous disease fever and cough and Chronic granulomatous disease	Vancomycin 150 mg every six hours, Piperacillin/Tazobactam 1g every six hours, and Voriconazole 50mg every 12 Vancomycin 500 mg every six hours, Piperacillin/Tazobactam 3 g every six hours, Voriconazole 300 mg every twelve hours, and Meropenem 340 mg every eight hours	Discharged Discharged	It is hypothesized that diseases with impairment of phagocytes, such as CGD, would not be prone the patients to viral infections such as COVID-19.
(41)	A 78-year-old man	Black stool and constipation	Hydroxychloroquine tablets with 200 mg dose per 12 hours, Pantoprazole tablet 40 mg twice a day, and Lactulose syrup 10 cc three times a day	Discharged	The emergence of breathing symptoms along with digestive symptoms led to the decision to perform radiography and chest CT scan and final diagnosis of COVID-19 disease
(42)	A 70-year-old woman An 88-year-old woman A 63-year-old woman	Dry cough, dyspnea, and fever	Intravenous levofloxacin 500 mg and ceftriaxone 2 g, methylprednisolone 250 mg, and infusion of tocilizumab at a dose of 8 mg/kg	Discharged	Pulmonary fibrosis can develop early in patients with COVID-19 pneumonia after hospital discharge. The role of early antifibrotic therapy in high-risk patients needs to be investigated
(43)	A 7-year-old boy	Fever, abdominal pain, and non-bloody vomiting and diarrhea	Hydroxychloroquine, azithromycin, Kaletra (lopinavir/ritonavir), and one dose of intravenous immunoglobulin, meropenem, and vancomycin	Discharged	Gastrointestinal symptoms can be the primary manifestations of COVID- 19 infection and may present before respiratory Symptoms in children
(44)	A 77-year-old man	Cough and shortness of breath	Vancomycin with Meropenem, hydroxychloroquine, lopinavir/ritonavir	Died	Although most of the reported symptoms of COVID-19 are related to the respiratory system, there is concern that the occurrence of serious manifestations, such as mesenteric ischemia in the gastrointestinal tract, may be overlooked
(45)	A 46-year-old male	Fever, dry cough, and shortness of breath	Dexamethasone, Heparin, ceftriaxone	Discharged	Successful management of severe hypoxic COVID-19 disease includes oxygen titrated to SpO2, self-proning to improve lung perfusion, dexamethasone access to heparin, and effective multidisciplinary teamwork
(46)	A 56-year- old male	Cough, fatigue, dyspnea and myalgia, lymphoma	atazanavir/ritonavir and Dexamethasone, Remdesivir cyclophosphamide, doxorubicin, and vincristine	Died	a disturbance in viral clearance, especially in immunologically suppressed conditions such as lymphoma, inevitably leads to viral replication
(47)	A 56-year-old Caucasian male	Myalgia, fever, anorexia, fatigue, dysgeusia, constant colic-type periumbilical pain, nausea, and diarrhea	Chloroquine, Azithromycin, heparin	Discharged	supportive treatment with hospitalization and intensive care for severe cases are the only reliable options
(48)	A 38-year-old male	Fever, cough, shortness of breath, and chest tightness	Tocilizumab, Immunoglobulin, hydroxychloroquine, oseltamivir, piperacillin & tazobactam	Discharged	IVIG of higher dose has been a choice of immunomodulatory therapy for autoimmune or inflammatory disease and for prophylaxis and treatment of severe infections, especially in immunocompromised patients.
[49]	A 73-year-old woman	Cough, expectoration, shortness of breath, and general weakness	Lopinavir and ritonavir, interferon alpha-2b, methylprednisolone sodium succinate, moxifloxacin hydrochloride and sodium chloride, human immunoglobulin	Discharged	Cirrhotic patients with confirmed SARS-CoV-2 infection needed hospitalization or prolonged an ongoing one

(50)	A 39-year-old woman, poorly controlled diabetes mellitus	Fevers, dyspnea, cough, hypoxemic respiratory failure, elevated C-reactive protein and mild anemia, positive HCoV OC43 PCR	Lung protective ventilation for 2 days, successfully extubating, functional recovery	Discharged	HCoV OC43 has been known to cause lower respiratory tract infections in transplant patients, HIV patients, and patients with hematologic malignancies.
(51)	A 40-year-old female nurse, wearing a surgical mask and gloves and without other protective equipment, nursing a 24-year-old male MERS-CoV–positive patient			Discharged	General measures of limiting the virus spreading via droplets are not efficient, and more monitoring is needed to be done to avoid outbreaks of such diseases without clear transmission chains.
(52)	A 68-year-old man returned to Korea from Bahrain and Saudi Arabia.	Cough, myalgia, dyspnea, nausea-vomiting, shortness of breath, and general weakness, well-controlled hypertension, ground glass opacity in chest of right upper lobe showed, positive MERS-CoV PCR	Pegylated Interferon-alpha, Ribavirin, Vancomycin, Tigecycline, Colistimethate	Discharged	
(53)	1- A 51-year-old male with Obesity, type II diabetes mellitus, 2-month progressive back pain, lower limb weakness, and urinary incontinence 2- Brother of Patient 1; 39-year-old, with no medical history 3- Brother of Patient 1 and 2; 40-year-old, overweight but no pre-existing chronic medical illness	1- 4th lumbar vertebral Para spinal mass in MRI, multiple myeloma, high fever, cough, shortness of breath after 14 days after of admission 2- Cough, fever, fatigue, progressive shortness of breath, hypoxia and bilateral pulmonary infiltrates, positive MERS-CoV 3- Cough, fever, and productive of clear sputum; unremarkable chest x-ray	1- Meropenem, Vancomycin, Voriconazole, Oseltamivir, Colistin, Tigecycline 2- Cefuroxime, Vancomycin, Piperacillin-Tazobactam, Azithromycin, Oseltamivir, Hydrocortisone, Linezolid, Imipenem 3- Ceftriaxone, Azithromycin, Oseltamivir	1- Died 2- Died 7 days after the onset of symptoms 3- Discharged	
(54)	A 45-year-old male with ARDS and renal failure	Shortness of breath, tachypnea and tachycardia, High-grade fever, Cough, malaise, fatigue, Positive novel-HCoV PVR	Ceftriaxone, Oseltamivir, Piperacillin/Tazobactam, Azithromycin, Colistin, Clarithrimycin, Imipenem/Cilastatin, Vancomycin, Voriconazole, Prednisolone	Discharged	1- Corticosteroids or interferon could be effective in the treatment of virus-induced ARDS 2- Appropriate infection control measures must be taken in MERS-CoV-infection probability. 3- MERS-CoV should be considered as a differential diagnosis in patients with severe ARDS of unknown origin.
(55)	A 45-year-old female	Dry cough, high-grade fever, headache, positive HCoV-229E PCR	Ceftriaxone, Azithromycin, Levofloxacin, Corticosteroids, Bronchodilators, Linezolid	Discharged	The process by which HCoV-229E could evade immune defence and cause illness is not clear.
(56)	A 3-year-old girl	Shortness of breath, inability to walk, fever, rhinorrhea, cough, weakness, positive for HCoV 229E, OC43, and HCoV co-infection	Intravenous immunoglobulin (IVIG)	Discharged	1- Coronavirus family can cause respiratory, intestinal, hepatic and neurological diseases of various severities in humans and animals. 2-In particular, HCoV OC43 is a neurotrophic, neuro-invasive and neuroinflammatory virus. 3-Experimental animal studies reported that HCoV OC43 causes flaccid paralysis and demyelination. 4- HCoVs can cause neurological symptoms such as seizures and meningoencephalitis in children but AFP has not been reported until now. 5- HCoVs may cause more serious respiratory disease in case of immune suppression and with various respiratory agents rather than single infection. 6- In addition, HCoV, 229 and OC43 co-infection causing more severe respiratory disease.
(57)	A 60-year-old man, healthy	Cough, 4-day history of fever, shortness of breath, chest pain, which was worsened by inspiration, positive MERS-CoV PCR	Piperacillin/Tazobactam, Furosemide	Discharged	MERS-CoV could cause acute myocarditis and acute heart failure.

(58)	A 61-year-old man with hypertension and diabetes mellitus who visited Kuwait frequently	Watery diarrhea 3 to 4 times a day, lower abdominal pain, general weakness, cough, sputum, dyspnea, mild leukopenia and thrombocytopenia, fever, bilateral interstitial infiltrations, positive MERS-CoV PCR	Ceftriaxone, Azithromycin	Discharged	
(59)	1- A 42-year-old female with anemia, thrombocytopenia, and lymphopenia. Exposed to the MERS patient at a 223.9 m^2 -sized room of ED for 23 h 2- A 49-year-old female received autologous peripheral blood stem cell transplantation (auto-PBSCT) two months prior for recurred diffuse large B-cell lymphoma 3- A 34-year-old male, received an auto-PBSCT six months prior due to peripheral T cell lymphoma (PTCL), shared the same radiology room at the same period (30 min before and 2 h after) with the MERS patient on the next day, recurrence of PTCL at the time of evaluation, based on his contact history with the MERS patient, he was tested for MERS-CoV rRT-PCR	1- Myalgia, fever, diarrhea, cough, menorrhagia, abdominal pain, pneumonic infiltration in left upper lobe, positive MERS-CoV PCR 2- Fever and dry cough, *M. tuberculosis in* Mycobacterial culture 3- Cough, sputum, and mild fever, mild infiltration of both lower lobes in chest CT, positive MERS-CoV PCR	1-Ribavirin, Lopinavir/Ritonavir, Interferon alpha 2a 2- Piperacillin/Tazobactam, Anti-Tuberculosis, Ribavirin, Lopinavir/Ritonavir, Interferon alpha 2a 3- Methylprednisolone, Prednisone, Ribavirin, Lopinavir/Ritonavir, Interferon alpha 2a	1- Discharged after two consecutive negative MERS-CoV rRT-PCR tests 2- Died 3- Discharged	
(60)	1- A 65-year-old physician, working in a hospital in the Kingdom of Saudi Arabia (KSA) where MERS-CoV patients were treated, with prolonged nonspecific prodromal illness, hypertension and coronary artery disease, benign prostatic hypertrophy and had prostatitis, flew to the United States on day of illness His medications include valsartan, atenolol, atorvastatin, and clopidogrel	Myalgias, malaise, low-grade fever, a dry cough, dyspnea, first respiratory symptom, hypoxia, infiltrate on the right lower lobe, positive MERS-CoV PCR	Vancomycin, Piperacillin/ Tazobactam, Levofloxacin, Ceftriaxone, Furosemide, Linezolid, Immunoglobulin	Discharged	People who travel to the Arabian Peninsula, especially healthcare workers, must be vigilant for MERS-CoV.
(61)	1- A 64-year-old man with hypertension and diabetes, renal transplantation, visited Dubai, and his existing treatments were mycophenolate mofetil, ciclosporin 2- A 51-year-old man with myocardial infarction, arterial hypertension, dyslipidemia, and histamine-induced angioedema, several episodes of deep venous thrombosis, treatments were corticosteroids and vitamin K antagonist, hospitalized because of left arm deep venous thrombosis and shared patient 1's room	1- Fever, chills, myalgia, diarrhea, dyspnea, cough, positive MERS-CoV PCR 2- Asthenia, myalgia, and cough. complete consolidation of the right lung and involvement of the lower left lobe in CT, positive MERS-CoV PCR	1- Ceftriaxone, Levofloxacin, Co-Trimoxazole Piperacillin + Tazobactam, Linezolid, Noradrenaline, Norepinephrine. 2- Linezolid, Dobutamine, Norepinephrine Nor dobutamine	1- Died due to refractory multiple organ failure 2- Discharged	Isolating patients with respiratory symptoms returning from the Middle East or exposed to a confirmed case and investigations for MERS-CoV is essential. The incubation period is 12 days. Immunosuppression may be a risk factor.
(62)	A 73-year-old man from Abu Dhabi, with multiple myeloma and high-dose chemotherapy with autologous stem-cell transplantation, lenalidomide plus dexamethasone, owned and took care of diseased camels, thrombocytopenia, renal insufficiency on day 14	Fever and non-productive cough, pneumonia, positive MERS-CoV and herpes simplex PCR	Meropenem, Levofloxacin, Vancomycin, Caspofungin, Acyclovir, Oseltamivir	Died on day 18 due to septic shock, with hemolysis and acute coagulation disorder	MERS-CoV might have different patterns from severe acute respiratory syndrome, so might need alternative diagnostic approaches.
(63)	A healthy, non-smoking 45-year-old Filipino man, no contact with sick people or animals, no recent travel, shared department with five paramedic roommates	Rhinorrhoea, fever, cough, shortness of breath, renal failure and dialysis, positive MERS-CoV PCR	Prednisolone, Paracetamol, Levofloxacin, Oseltamivir, Ceftriaxone, Azithromycin, Hydrocortisone	Died	

(64)	1- A 52-year-old woman with hypertension had close contact with a woman who travelled to Saudi Arabia and had an influenza-like illness 2- A 50-year-old sister of patient 1 with hypertension 3- A 35-year-old female nurse assistant who had contact with patient 1 stayed home with infection control precautions 4- A 44-year-old male physician with chronic heart disease, contact with patient 1 5- A 67-year-old woman hospitalized because of chronic obstructive pulmonary disease, discharged after 8 days, then severe acute respiratory infection (SARI) developed, close contact with another patient with SARI but negative MERS-CoV test in hospital.	1- High fever, diarrhea, cough, nausea, dyspnea, hemoptysis, anorexia, and vomiting 2- Negative PCR results 3- Co-infection with influenza A(H1N1)		1- Died with progressive respiratory failure 2- Discharged after 19 days 3- Stayed at home until her respiratory samples tested negative 4- Discharged 5- Died	All 5 patients were in Kerman Province with no recent travel or contact with animals. The samples from patients 1, 2, and 4 were positive for MERS-CoV. A cluster of MERS-CoV infections in Iran was identified, had unclear person-to-person transmission. In this cluster, patient 1 was in close contact with a suspected person. Patient 2 seems to have acquired the infection from patient 1. The source of infection for patients 3 and 4 was patient 1 or 2, but patient 5's infection source remains unknown.
(65)	A 64-old year man, diabetes mellitus, pancreatic neoplasm	Fever, weakness, aggressive cough	Lopinavir/Ritonavir	Discharged	Triple antiviral therapy can be used for some cases of MERS-COVIR despite the 7-day delay in introduction.
(66)	3 MERS-CoV cases in 1 family in Tunisia 1- The index case-patient, a 66-year-old Tunisian man with untreated diabetes Mellitus 2- His daughter, 30-year-old 3- His son, a 34-year-old nurse	1- Chills, arthralgia, dry cough, fever, multiple organ failure 2- Sore throat, cough, and fever	Acetaminophen, Aspirin, Dexamethasone, Amoxicillin-Clavulanate, Noradrenalin, Amoxicillin-Clavulanate, Ciprofloxacin, Rifampin, Oseltamivir	All discharged	The index case-patient's respiratory tract samples were negative for MERS-CoV by PCR, but diagnosis was confirmed by PCR of serum.
(67)	1- A 15-month-old child with severe combined immunodeficiency, coronavirus HKU1-related pneumonia, and fatal respiratory distress syndrome Mother with human papillomavirus (HPV)	Lymphopenia, anemia, and thrombocytosis	BCG Vaccine, Tetanus, Diphtheria, Haemophilus Influenzae B vaccines, Aspirin, Immunoglobulins, Antibiotics, Trimethoprim/Sulfamethoxazole, Acyclovir, Antifungal	Discharged	A novel insight into the epidemiology of coronavirus was achieved by the identification of HCoV-HKU1. Further, epidemiological studies are needed to define the impact of HCoV on lung disease in children with immunodeficiencies.
(68)	A 61-year-old male, hypertension and diabetes without smoking, coronary bypass surgery	Febrile with mild hypoxia, a few bilateral infiltrates, kidney injury		Discharged	Infection control measures and protocols of hospitals should be upgraded at the time of handling suspected or confirmed cases to prevent outbreaks. Transmission mode and risk factors are not clear.
(69)	A 43-year-old male healthcare provider	productive cough, dyspnea, myalgia, pleuritic chest pain, fever, bilateral ground glass opacities in CT, positive MERS-coronavirus PCR	Vancomycin, Meropenem, Ciprofloxacin, Oseltamivir	Discharged	MERS outbreaks were prevalent in the healthcare facilities, healthcare setting infection is a risk factor for person-to-person transmission. disease recognition at early stages is based on clinical presentations alone. Thus, infection control practices in medical facilities should be enhanced to protect those at risk of MERS. The development of an effective vaccine and treatment should be the priority.
(70)	A 33-year-old female, working as a critical care nurse pregnant	Fever, dry cough, shortness of breath	Imipenem, Vancomycin, Azithromycin, Oseltamivir, Dexamethasone	Discharged	Age, stage of pregnancy, and possible differences in immune response are the various factors that must be considered for a successful outcome.

(71)	A 30-year-old male	Fever, abdominal pain and diarrhea, patchy increased opacity in the left lower lung zone in CT, retrocardiac area, multifocal patchy areas of nodular consolidations with ground-glass opacity (GGO) halo and nodular GGO lesions in both upper lobes	Ribavirin, Kaletra, [Ritonavir + Lopinavir], Interferon-alpha) Tabaxin [Piperacillin + Tazobactam], Cravit [Levofloxacin])	Discharged	The extent of previously detected lesions was decreased with remaining fibrotic changes.
(72)	A 34-year-old female with diabetes mellitus	Fever, bone pain, fatigue	Tazocin, Azithromycin, Mannitol, Dexamethasone	Died after two months	MERS-CoV has caused many confirmed cases and deaths with no treatment, so it has created anxiety in the health sector.
(73)	A 32-year-old woman in Abu-Dhabi, United Arab Emirates, a school teacher, 32 weeks pregnant	Fever, back pain, respiratory failure, hypotension	Ceftriaxone, Azithromycin, Oseltamivir, Vancomycin, Ribavirin, Peginterferon-A, Meropenem	Died	MERS-CoV infection and pregnancy were a fatal combination in this case. Death occurred despite treatment with Ribavirin/Interferon regimen and although the virus shedding was cleared and radiography showed improvement at death.
(74)	1- A 62-year-old woman with diabetes, hypertension, and end-stage renal disease (ESRD) on hemodialysis 2- A 58-year-old man with diabetes, hypertension, and ESRD on hemodialysis 3- A 63-year-old woman with severe bronchial asthma and obstructive sleep apnea, coronary artery disease, diabetes, hypertension, and chronic kidney disease 4- An 81-year-old man with atrial fibrillation, diabetes mellitus, hypertension, progressive respiratory distress, and hypoxemia 5- A 24-year-old man with ESRD on hemodialysis	1- Fever, cough, and respiratory failure of 3-day duration, positive MERS-CoV PCR 2-Cough, fever, and hypoxemic respiratory failure of 2-day duration, positive MERS-CoV PCR 3- Fever, cough, dyspnea, and pneumonia. Positive MERS-CoV PCR 4- Fever, positive MERS-CoV PCR 5- Febrile illness, cough, and respiratory failure, positive MERS-CoV PCR	Oseltamivir, Levofloxacin, Imipenem, Ribavirin, Interferon-a2b- a2b, Methylprednisolone	1- Died after 34 days with respiratory and multi-organ failure 2- Died after 35 days with multigrain failure 3- Died after 45 days with multi-organ failure 4- Died after 52 days with multi-organ failure 5- Died after 32 days with multi-organ failure	Adverse effects from combination Ribavirin and Interferon therapy were observed in three cases.
(75)	1- A 52-year-old man 2- A 42-year-old woman	1 & 2- Upper respiratory tract infection, progressive shortness of breath, fever, small bilateral infiltrates in CT, Positive for MERS	Azithromycin, Ceftriaxone, Rvf/ina2b, Methylprednisolone	The patients were discharged home on day 18 after complete recovery.	Combination therapy was successful in two cases of MERS infection.
(76)	1- A 74-year-old Saudi male patient with diabetes, hypertension, and dyslipidemia 2- A 57-year-old man diabetic, hypertensive 3- A 45-year-old man, diabetic, hypertensive	1-Ataxia, vomiting, confusion, fever, infiltrate in the mid right lung zone, multiple chronic lacunar strokes in brain CT 2- peripheral vascular disease, flu-like illness, gangrenous toe, fever, acute myocardial ischemia with pulmonary edema, coronary angiography, wo subtle hypo densities in brain CT 3- Chronic kidney disease, ischemic heart disease, cough, dyspnea, rigors, fever, and diarrhea with no significant travel or animal exposure, infiltrate in the lower and mid right zones, Positive for MERS	Oseltamivir, Bronchodilators, Methylprednisolone, Peginterferon alpha-2b, Ribavirin	1- Died on day 34 2- Discharged 3- Discharged	MERS-CoV infection is associated with multiple organ damage, including pulmonary, cardiovascular, renal, coagulation, gastrointestinal tract, and muscular damage. Another target may be CNS, and this should be considered in patients.
(77)	A 42-year-old health care female	High-grade fever, shortness of breath, cough, bony pains, positive history of contact with a patient of similar complaints, bilateral infiltrates in chest x-ray, MESR was positive	Antibiotics, Oseltamivir, Peg Interferon Alpha-2a, Ribavirin, Methylprednisolone	Died due to Cardiac arrest	Multiorgan failure, severe ARDS, encephalopathy, and septic shock are some of the signs of MERS-CoV infection. Multiorgan failure and septic shock pathophysiology is not clear. CNS may also be involved functionally or structurally.

(78)	A 54-year-old man with hypertension, diabetes, hepatitis B infection, and liver cirrhosis		Cefotaxime, Levofloxacin, Corticosteroid, Methylprednisolone	Discharged	Corticosteroid treatment may be beneficial for organizing pneumonia in MERS-CoV infection.
(79)	1- A 56-year-old male with rheumatoid arthritis 2- A 52-year-old male with diabetes mellitus, dyslipidemia 3- A 53-year-old male, with chronic HBV carrier, diabetes mellitus	All patients had generalized tiredness, dizziness, weakness, nausea, and a positive MERS-CoV test.	Interferon-α2b, Ribavirin	Discharged	Three-phase illness patients with initial phase of fever and clinical stability of probable viral replication. The second phase was the immunologic phase with clinical and radiographic deterioration and further stabilization.
(80)	A 68-year-old man	Diffuse ground-glass opacity and consolidation in CT in the central portion of the right upper lobe of the lung, positive MERS-CoV PCR	Ceftriaxone, Amikacin, Azithromycin, Oseltamivir	Discharged	Proper infection control measures are acquired for preventing MERS-CoV transmission in the healthcare setting in Korean hospitals.
(81)	1- A 39-year-old female 2- A 61-year-old female with diabetes mellitus and dyslipidemia 3- A 29-year-old female 4- A 73-year-old female with hypothyroidism, heart failure, lymphoma, and lung fibrosis	All patients had Fever, cough, sore throat, and positive MERS-CoV test.	Azithromycin, Ceftriaxone, Oseltamivir, Piperacillin Tazobactam, Erythromycin	All discharged	The co-infection of MERS-CoV and influenza was observed in these patients. The influenza test was negative, and it may be for the reason that MERS-CoV inhibits the PCR reaction for the influenza virus.
(82)	A 10-month-old male	Left lower lobe opacity in chest radiography with atelectasis or pneumonia	Heliox		In airway disease with severe acute airflow obstruction, heliox is not effective, while it could be used as a bridge treatment for reducing Raw and respiratory muscle work. Before starting definitive therapies, usually within 24–48 h.
(83)	1- A 52-year-old woman with type 2 diabetes 2- The patient's 50-year-old husband	1- Fever and myalgia, Cough, rhinorrhea, and sore throat 2- Diffuse interstitial opacities and consolidation in chest radiography	Oseltamivir, Levofloxacin	Both discharged	Suggests short transmission in families
(84)	A 41-year-old man, a local indoor seafood market worker **Notably,** fish, shellfish, a variety of live wild animals like hedgehogs, snakes, badgers, and birds (turtledoves), and animal carcasses and animal meat were available in the market before the outbreak	Fever, chest pain, tightness, weakness, unproductive cough, mild lymphopoenia, elevated levels of aspartate aminotransferase, C-reactive protein, dehydrogenase, lactic and creatine kinase, ground glass opacities and consolidation in chest radiographs of both lungs	Combination of antibiotic, antiviral, and glucocorticoid therapy	Discharged	Indicating the ability of viral spill-over from animals to humans that cause acute diseases. A new detected virus strain from the Coronaviridae family (2019-nCoV).
(85)	A 54-year-old Korean man living in Wuhan	Chills, fever, dry cough and muscle pain, small consolidation in right upper lobe, ground-glass opacities in both lower lobe	Lopinavir/ritonavir	Discharged	The natural course of the healing process of SARS-CoV-2 is more effective than the administration of lopinavir/ritonavir, or both in decreasing the load of virus.
(86)	1- A 32-year-old male 2- A 19-year-old male 3- A 63-year-old male 4- A 63-year-old female	All had fever, dizziness, cough, nasal congestion, fatigue, rhinorrhea, constipation, lung auscultation, respiratory rate, and pneumonia in CT	Antibiotic, Lopinavir/ritonavir/arbidol/SFJDC, Intravenous immunoglobulin	All discharged	
(87)	1- A 10-month-old boy, his parents, and his sister have positive COVID-19 tests 2 days before 2- A 36-year-old man	1- Fever, increased, differential count of lymphocytes, normal WBC count, elevated C-reactive protein level, diffuse ground glass opacities in both lungs in CT 2- Diarrhea, decreased differential count of lymphocytes, elevated C-reactive protein level, emphysema in both upper lungs, diffuse ground glass opacities in the right lower lobe in CT, suggestive of viral pneumonia		Both discharged	
(88)	A 35-year-old man visited family in Wuhan, China, and returned to Washington State	Cough, fever, persistent dry cough, nausea, and vomiting	Acetaminophen, Ibuprofen, Guaifenesin, Vancomycin, Remdesivir	Discharged	

(89)	A 55-year-old woman	Sore throat, dry cough, fatigue, low-grade fever	Antibiotic, Ceftriaxone, Amoxicillin/Clavulanate	Discharged on day 28	A good example of the natural course of NCP with self-recovery rather than medical treatments.
(90)	A 10-year-old girl	Low-grade fever, a small amount of sputum, mild pneumonia in CT	Antiviral therapy was not required	Discharged	Low-grad infection or illness of children is not understood. It had been shown also in SARS and MERS epidemics.
(91)	1- A 65-year-old man, hypertension, type 2 diabetes, coronary heart disease, and lung cancer 2- Wife of patient 1 3- Their 27-year-old son Flown to Hanoi from the Wuchang district in Wuhan (after the outbreak of COVID-19)	All had fever, dyspnea, and hypoxemia	Antiviral, antibiotics	All discharged	This family cluster of 2019-nCoV infection showed human-to-human transmission and became a concern.
(92)(	A 51-year-old male, taxi driver	Fever, cough, and myalgia		Discharged	His wife, son, and nephew, all of whom lived in the same house as the patient, were asymptomatic and tested negative for SARS-CoV-2 on RT-PCR assay.
(93)	1- A 33-year-old healthy German businessman 2-The business partner, a Shanghai resident, had visited Germany between January 19 and 22 with no signs or symptoms of infection 3- Three additional employees at the company with positive 2019-nCoV test	Sore throat, chills, myalgia, fever, and productive cough.		All discharged	Diagnosis of 2019-nCoV infection in Germany and outside Asia. Transmission can occur during the incubation period with no signs.

Table 3. Analysis of the effective parameters on severe respiratory syndromes

Parameters		Total patients (71)
Age (years)	**0-20**	8%
	20-40	23%
	40-60	42%
	60-80	27%
Gender	**Male**	58%
	Female	42%
Medical history	**Diabetic**	28%
	Cardiovascular	25%
	Nephrology	10%
	Overweight	3%
	Cancers	8%
	Transplant	4%
Diagnostic methods	**Molecular methods**	56%
	Clinical methods	67%
Treatments	**Single therapy**	3%
	Combination therapy	51%
Kind of respiratory syndrome	**MERS**	37%
	SARS	1%
	COVID-19	33%
Transmission ways	**Human & Nosocomial**	38%
	Animal	10%
	Travel & unknown exposure	16%

DISCUSSION

According to the reviewed studies, there are many effective factors in treatment and controlling the acute respiratory syndromes caused by Coronaviruses, including SARS, MERS, and COVID-19. Some of these factors including age, gender and profile of patients, adopted diagnosis and treatment methods, time of hospitalization, timely diagnosis, the way of transmission, and the infectious dose of the virus that enters the body at the time of exposure to a causative agent as it has been reported that the viral load kinetics of CoV-19 might be different from the other coronaviruses (94).

Reviewing the results of different studies indicated that age has a profound effect on the severity of the disease and the main reason for this may be the immune system disorders caused by aging as approximately 70% of patients were in the age range of 40-80 years however the severity of the disease and the extent of lung involvement in children are decisive factors (39). On the other hand, the risk of cardiovascular disease, diabetes, and pulmonary disease also increases with aging, which increases the cellular receptors required for these viruses on the cell surface. Males exhibited increased rates (58%) because of a higher proportion with underlying comorbidities and various socio-cultural behaviours. For example, they do

not adopt hygienic measures and health-seeking behaviors as much as females. In addition, their immunity system is weaker than women's against new diseases. The results of the present study showed that people with a history of cardiovascular disease, diabetic diseases, lymphoma, hepatic cirrhosis, and renal failure were more susceptible to acute respiratory disease (46, 49). For example, about 25% of patients with a history of heart disease and approximately 28% of diabetics have been reported to likely activate specific receptors for these viruses as described above.

Since the findings of the present study indicate that coronaviruses have become prevalent almost every ten years and have become more virulent each time, specific diagnosis and treatment protocols for acute respiratory diseases need to be designed. Molecular and clinical methods are the most important diagnostic methods. In clinical methods that are based on the number of white blood cells and lungs CT scan, the infection would be detectable rapidly. The likelihood of assessing disease progression improves with chest CT scans; however, the challenge lies in the physician's inability to identify the causative agent of the infection. As a result, they can only prescribe medication to eliminate the infection while also considering the potential side effects of various treatments and the patient's profile (47). As a result, the patient is not isolated, and the safety of health care workers would not be met. In the molecular method, it is possible to identify the main causative agent of the infection; thus, the physician is aware of the disease and can choose the effective treatment for the patient and prevent the spread of the disease. Our results indicated that drug administration specifically for coronavirus was more effective (51%). Reported antiviral drugs, in many cases, have had a significant impact on the treatment process. However, further studies are needed to finally confirm a favourable drug. In addition, as the virus is likely to recur every few years, vaccination against it is urgently needed.

Studies have suggested that the spread of the virus is fueled by its asymptomatic nature and the delayed onset of symptoms caused by a prolonged incubation period. A prolonged incubation period offers valuable opportunities to prepare and take prompt action against COVID-19 (95). It allows for the possible diagnosis of asymptomatic cases at the disease's onset and the identification of early symptoms, enabling earlier diagnosis than usual (96). Early detection depends on evaluating signs and symptoms from various studies, which provide important clinical features for suspected COVID-19 cases. Early diagnosis and using solutions to break the chain of disease transmission and providing appropriate guidelines will be very helpful (41). On the other hand, since there is a possibility of long-term and late damage in affected people, follow-up of patients is very important (42). Most of the time, because of the late diagnosis of the disease, patients were not isolated; so, emerging viruses were easily transmitted to other patients and health care workers that were in contact. The best way to solve this problem is to have a proper treatment protocol for patients with unknown symptoms. Isolating these patients until a complete diagnosis of the disease could prevent the transmission to others.

According to studies, COVID-19 can have a different pathogenesis than other viruses. Accordingly, in the study of Esmaeilzadeh and colleagues, it was stated that patients with chronic granulomatous disease (CGD) who have normal immunity to many viruses may have different symptoms when confronted with COVID-19 (40). It has been reported that the most important way of transmitting acute respiratory diseases was human to human and nosocomial (38%) that was related to cluster transmissions in patients' family and health care workers. Other ways of transmitting the disease have been domestic animals, which are in the form of people who have contact with them, but the transfer rate was very low due to the inaccuracy of hospital reporting. Another way, that is often overlooked, is the travel and unknown exposure of these types of epidemics (97). A review of studies of acute respiratory syndrome over recent years has shown that most studies have reported MERS disease. The prevalence of MERS is very high, probably because of its second

hosts (domestic animal disease), especially camels, and humans have been in close contact with camels in the Middle East (98).

Based on the findings of this systematic review, it is essential to carefully consider each of the factors mentioned in order to effectively respond to similar pandemics in the future. Evidence indicates that healthcare systems with experience in managing such events, along with timely diagnosis and appropriate treatment for hospitalized patients, could significantly reduce the mortality rate.

CONCLUSION

It can be concluded that these types of fatal respiratory illnesses can be controlled if the health care workers become familiar with the type of illness and begin early and effective treatments considering different aspects of the pandemic. On the other hand, the WHO's prognosis about the prevalence of this type of emerging diseases has an important role in preventing people from being surprised. Like influenza-like illnesses that occur every year during the cold season, communities should raise awareness to prevent sudden outbreaks that can significantly affect society.

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