



## SARS-CoV-2: A Systematic Review.

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**Received:** September 22, 2020; **Accepted:** September 23, 2020; **Published:** September 30, 2020

### Abstract

**Introduction:** SARS-CoV-2 outbreak in China has spread its roots to almost all the countries around the world and infected lakhs of individuals. To summarize the demographical, clinical, laboratory, radiographic features, comorbidities, and treatment strategies of confirmed SARS-CoV-2 infection, the systematic review was designed.

**Sources:** PubMed and Google Scholar articles were searched for English-language articles published between January and April 2020.

**Data:** A total of 156 articles were identified by the literature search from which 53 full text articles met the inclusion criteria. After quality assessment using various checklists, 15 articles were included.

**Study selection:** Articles included in the review presented studies from four continents of world with majority from China. Mean age of patients with corona infection was 49.3 years, with 56% males and 44% females. Along with this 8% of the individuals were reported with smoking. Major clinical symptoms were fever, dry cough, shortness of breath, fatigue and around 27.5% patients presented with comorbidities. Choice of treatment was antiviral therapy along with symptomatic therapy.

**Conclusion:** It can help clinician to diagnose and plan treatment for SARS-CoV-2 patient which appears to be highly communicable from the existing epidemiological data with varying fatality rate. More rapidly the cases are detected, isolated, and traced; the more efficacious will be the prevention strategies

for any country to evade community transmission.

**Keywords:** Corona, Pandemic, Antiviral, Fever, Cough, Virus

### Introduction

Since the dawn of severe acute respiratory syndrome Coronavirus (SARS-CoV) in 2002 with its spread through 32 countries, the world has experienced the wave of Middle East respiratory syndrome Coronavirus (MERS-CoV) and now, the unnerving novel Coronavirus (2019-nCoV) [1]. Corona viruses, the largest known RNA virus genomes are basically the enveloped, non-segmented, positive-sense single-stranded known to root diseases in mammals as well as humans. Among the four genera of coronavirus subfamily  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$ ,  $\alpha$ - and  $\beta$ -CoVs cause human infections. CoVs are supposed to be common human pathogens, and 30% to 60% of the Chinese population was already known to be positive for anti-CoV antibodies [1].  $\beta$ -CoV group umbrella both the SARS-CoV and MERS-CoV [2,3]. Moreover, the phylogenetic analysis showed that 2019-nCoV viral genome that scouted in Wuhan also belonged to the  $\beta$ -CoV [4]. Being 79% similar nucleotide sequence to SARS-CoV and 50% similar to MERS-CoV, 2019-nCoV can equally cause the disastrous infection and with a much faster spread than the two other corona viruses [5,6].

An outbreak of viral pneumonia cases of unknown cause was attested by health authorities in Wuhan, the capital of Hubei province, China during the end of 2019 and the beginning of 2020. Huanan Seafood Wholesale Market which vended live

animals, seemed to be one of the source as many of the infected cases were found to have recent visit; consequently making the origin of this unknown virus as zoonotic [1,7]. The pneumonia infection has rapidly spread from Wuhan to other provinces of china and crossing borders to other 114 countries. Over this global pneumonia outbreak, World Health Organization has declared a public health emergency of international concern on 30th January 2020 [5].

On 11th February 2020, WHO named the novel viral pneumonia as “Corona Virus Disease (COVID19)”, while the International Committee on Taxonomy of Viruses (ICTV) suggested this novel Coronavirus name as “SARS-CoV- 2” [8]. Since December 2019, SARS-CoV-2 has caused over 84,180 cases of COVID-19 in China, including 4,642 deaths, as of 18 April 2020. The epidemic has been spreading to almost all the countries around the world, with more than 23 lakh confirmed cases and more than 1.6 lakh deaths as reported by World Health Organization (WHO) on 20 April.

Transmission occurs chiefly via respiratory droplets from cough, sneeze and contact transmission. Carriers of SARS-CoV-2 include infected COVID-19 patients, asymptomatic patients and patients in their incubation period. The incubation period has been gauged to 5 to 6 days on average, but may extend to 14 days [9,10]. Researches stanch that this novel epidemic doubled in about every seven days, while the basic reproduction number ( $R_0$  -  $R$  naught) is 2.2. To a layman this means that on an average single patient transmits this infection further to superfluous 2.2 individuals. However, the estimations of the  $R_0$  of the SARS-CoV epidemic in 2002-2003 were made approximately as 3[11].

Since the appearance of SARS-CoV-2, few studies related to Coronavirus including case reports, retrospective studies have been published in past four months [12-15]. Most of these articles have reported clinical outcomes, investigations, treatment/response and complications. But a comprehensive systematic review with amalgamation of all the details has not been done till date. Hence the systemic review is planned with following objectives to understand COVID-19 and consider how to flatten the curve.

#### Objectives

- To summarize the clinical, laboratory, and

radiographic features of SARS-CoV-2 reported in available literature.

- To examine the various treatment regime followed for SARS-CoV-2 and to assess their effectiveness.
- To assess the outcome of SARS-CoV-2 cases, including risk factors, the proportion of patients requiring ICU and the fatality rate.
- To assess the prevalence of comorbidities among SARS-CoV-2 confirmed cases.

#### Methodology

##### Data sources and search strategy

A systematic literature search was conducted to identify English-language published peer-reviewed articles with demographical, clinical features, comorbidities, laboratory investigations, radiographic features and treatment strategies of confirmed SARS-CoV-2 infection. Studies published from January 1, 2020 until April 10, 2020 was searched on research portals like Google Scholar and MEDLINE (through PubMed). Following search terms relating to “COVID-19”, “coronavirus 2019”, “Novel Coronavirus”, “COVID-19 clinical and radiographic features”, “COVID-19 lab investigation”, “COVID-19 prevention and treatment”, “COVID-19 complications”. All records electronically identified were scanned by title, abstract and/ or the keywords by both authors and the full text of all the reports considered potentially relevant was obtained. The reference lists from the studies retrieved by this search were reviewed and any relevant references followed up.

##### Study selection

###### Studies were included

- 1) If details of at least one patient with corona infection given,
- 2) If clinical features, laboratory, radiographic investigations of SARS-CoV-2 were given,
- 3) All hospital based studies were included, providing treatment to cure the patient from COVID-19.

##### Study review and data extraction

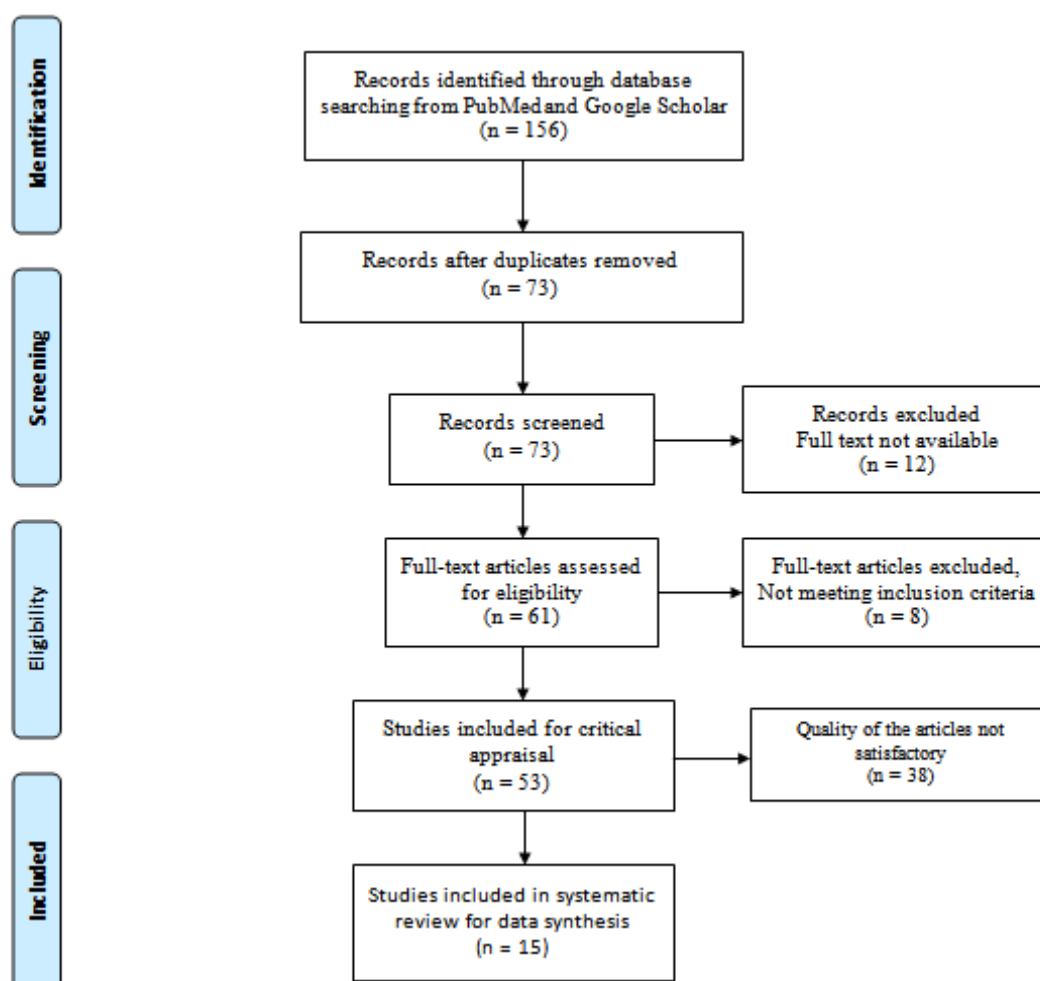
The baseline searches were carried out by all the authors. The selection of studies on the basis of title, keywords and abstract and decisions about eligibility were carried out independently by the

review authors. Studies not following inclusion criteria (according to study design, subjects) were discarded. The full text of all the studies considered potentially relevant for inclusion was obtained. If relevant information according to inclusion criteria was not available in the abstract or if the title was relevant but the abstract was not available, the full text of the report was obtained. Each study was reviewed and critically appraised for quality according to a set of validity criteria as per STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [16] and CARE (CASE REPORT) guidelines [17]. If all criteria were met, a maximum score of 22 was assigned. Studies scored 12 or more according to validity criteria were included in the study as good quality articles. All information and data was recorded independently by all the authors and no disagreements were there. Total 156 publications were retrieved, of which 73 publications were identified based on the title and abstract. From these 12 were excluded because full text was not available, 8 publications didn't meet inclusion criteria and 38 were of poor quality as per

STROBE or CARE guidelines (Figure 1). Finally 15 studies fulfilled our criteria, and from each article all the information pertaining to patient's demographic details, comorbidities, clinical, laboratory, and radiographic features and provided treatment were extracted and recorded in Microsoft Excel 2010 software.

## Results

In this review, 15 studies are included published between January and April, 2020 with representation from four continents of world with majority from China (Table 1). Publications from European region were also selected but due to stringent inclusion criteria it was excluded. Characteristics of 7770 participants were studied in these 15 publications. Mean age of patients with corona infection was 49.3 years, with 56% males and 44% females. Along with this 16.5% of the individuals were reported with smoking habit (Table 2). Around 27.5% patients presented with comorbidities like hypertension (13.7%), diabetes (9.8%) and cardiovascular issues (11.5%) as the substantial ones (Table 3).



**Figure 1:** Schematic flow for article selection.

Most common symptoms reported are fever (78.3%), cough (55.3%), dyspnea (49.3%), fatigue (48.4%), sore throat (27%) followed by headache (24.3%), nasal congestion (15.9%) and few more as shown in table 2. Laboratory investigations revealed decreased albumin (61.7%), lymphopenia (39.8%), High C-reactive protein (50.2%), increased LDH (48.4%) and increased AST (24.1%) as the major findings (Table 4) with bilateral pneumonia (64.5%), ground glass opacity (62.3%) and unilateral

pneumonia (47.1%) as major radiographic findings (Table 4).

Nine studies reported that 14.4% patients were admitted to intensive care unit (ICU) due to complications like acute respiratory distress syndrome (ARDS) in 28.4%, ventilator-associated pneumonia in 11.1%, acute cardiac injury in 9.4%, acute hepatic injury in 6.4% and few more listed in table 5. Around 54% were discharged and 7.8% had fatal outcomes.

Sl. No	Author	Journal	Country	Study Type	N	Ref:
1	Dawei Wang et al.	JAMA	China	Case series	138	12
2	Nanshan Chen et al.	Lancet	China	Retrospective	99	24
3	Matt Arentz et al.	JAMA	Washington	Case series	21	13
4	Jian Wu et al.	Clinical Infectious Diseases	China	Retrospective	80	18
5	Fei Zhou et al.	Lancet	China	Retrospective cohort	191	26
6	Xiao-Wei Xu et al.	BMJ	China	Retrospective	62	31
7	Kui Liu et al.	Chinese Medical Journal	China	Case series	137	25
8	Wei-jie Guan et al.	medRxiv	China	Retrospective	1099	22
9	Michael Chung et al.	Radiology	China	Case series	21	32
10	Yueying Pan et al.	European Radiology	China	Retrospective	63	33
11	De Chang et al.	JAMA	China	Retrospective	13	34
12	COVID-19 Australia Team	Epidemiology Report	Australia	Retrospective	5805	35
13	Moran Ki et al.	Epidemiology and Health	Korea	Case series	28	36
14	Juan Pablo Escalera-Antezana et al.	Formosan Medical Association	Bolivia	Retrospective	12	37
15	Eu Suk Kim et al.	Journal of Korean Med Science	Korea	Retrospective	28	15

**Table 1:** Details of articles related to Coronavirus included for review.

Variable	Mean/ percentage	No. of studies
Age	49.3	15
Gender	Males -56%, Females-44%	15
Smoking	16.5%	2
ICU	14.4%	9
Clinical symptoms		
Fever	78.3	14
Cough	55.3	14
Dyspnea	49.3	8
Sore throat	27	7
Myalgia	24.7	12
Fatigue	48.4	9
Sputum production	26.5	7

Headache	24.3	11
Nasal congestion	15.9	3
Haemoptosis	0.3	3
Diarrhoea	1	9
Anorexia	0.7	1
Pharyngalgia	0.6	2
Nausea	1	6
Dizziness	0.2	1
Vomiting	0.9	6
Abdominal pain	0.1	4
Confusion	0.1	1
Rhinorrhoea	1.2	5
Eye congestion	0.1	2

**Table 2:** Demographic details and clinical features summary.

In most of the studies (73%), choice of treatment was antiviral therapy including oseltamivir, ritonavir, lopinavir and ganciclovir along with antibiotics in 53% and antifungal in 13% of studies. Along with this intravenous immunoglobulin, corticosteroids, continuous kidney replacement therapy, extracorporeal membrane oxygenation and mechanical ventilation (both invasive and non-invasive) were also used as per the need of the patients (Table 5). One of the studies even tried Chinese medicine too [18].

#### Discussion

SARS-CoV-2 outbreak has been established as a public health emergency with more than 200 countries snowed under this pandemic. Within last

Variable	Percentage	No. of studies
Comorbidities	27.5	11
Hypertension	13.7	7
CVS	11.5	8
Diabetes	9.8	10
Cancer	1.4	7
COPD	4.4	8
Asthma	0.1	3
Chronic liver diseases	5.6	7
Chronic kidney diseases	4.5	7
HIV	0.03	1
Digestive system disease	0.2	2
CNS	0.2	4
Obstructive sleep apnea	0.1	1
Immunosuppression	0.1	2
Rheumatologic disease	0.01	1
Hypothyroidism	0.01	1
Community Acquired pneumonia	0.01	1
Radiographic Features		
Chest Ray Unilateral Pneumonia	47.1	7
Chest Ray Bilateral Pneumonia	64.5	11
Ground-glass opacity	62.3	11
Pleural effusion	0.2	1
Peribronchial thickening	0.2	2
Focal consolidation	2.1	5
Pulmonary edema	0.02	1
Intestinal abnormalities	2	1

**Table 3:** Comorbidities and radiographic features summary.

Variable	Percentage	No. of studies
Leucocytosis	2.4	8
Leucopenia	16.5	9
Lymphopenia	39.8	11
Thrombocytopenia	5.8	5
Low Hb	11.8	4
High AST	24.1	7
High ALT	23.7	7
High creatinine	7.8	6
High creatine kinase	11.1	7
High LDH	48.4	8
Decreased albumin	61.7	3
High bilirubin	11.3	3
High interleukin-6	8.3	3
High procalcitonin	9.1	7
High C reactive protein	50.2	6
Elevated ESR	33.9	3

**Table 4:** Laboratory features summary.

Variable	Percentage	No. of studies
Treatment provided		
Antiviral	48.7	11
Antibiotics	42.3	8
Antifungal	4.8	2
Vasopressor	6.4	2
Oxygen	26.5	5
Intravenous immunoglobulin therapy	23.6	5
Glucocorticoid therapy	35.3	7
Continuous kidney replacement therapy	12.4	4
Extracorporeal membrane oxygenation	15.2	4
Invasive mechanical ventilation	12.7	8
Noninvasive ventilation	13.4	8
Traditional chinese medicine	0.2	1
Complications		
Shock	5.1	4
Acute cardiac injury	9.4	3
ARDS	28.4	8
Arrhythmia	2.1	1
Acute renal injury	5.8	5
Acute hepatic injury	6.5	2
Acute respiratory injury	3.9	4
Heart failure	0.8	1
Sepsis	2.1	1
Seizures	0.5	1

Ventilator-associated pneumonia.....	11.1	2
DIC - Disseminated intravascular coagulation	0.1	1
Secondary infection	5.4	4
Outcome		
Hospitalization	38	15
Discharge	54.2	14
Death	7.8	8

**Table 5:** Summary of the treatment provided and the complications among the selected articles.

four months it has made around 6 lakh in USA, 1.7 lakh in Spain, 1.6 lakh in Italy, 1.25 lakh in Germany and around ten thousand in India as disease-ridden. Even the number of confirmed death increased to thousands in USA, UK, Spain, Italy, Germany, and France whereas in India there were 395 reported deaths [19]. To get a global outline of this desolation, studies from all over the world with presentation from each continent were included. And through this review it has been tried to calculate the fatality rate. Rendering to contemporary statistics, the fatality rate (cumulative deaths divided by cumulative cases) of COVID-19 was found to be 0.09% to 9.84%, contingent on diverse regions of world (USA 1.8%, Italy 9.84%, China 4.1%, India 2.4%, South Africa 0.09%), which appears to be lower than that of SARS ≈10% and MERS ≈39% and higher than that of seasonal influenza (0.01% to 0.17%) [10,20]. High case-fatality risks is comprehended at the peak of local epidemics, which may be appropriate in high-income countries with limited surge capacity in hospital services [21].

The majority of COVID-19 patients exist as mild asymptomatic cases. According to current researches, the section of severe COVID-19 cases in China fall upto 15% to 25% [10,22]. Representative clinical symptoms are fever and dry cough, with shortness of breath, fatigue, with some unusual symptoms, such as sore throat, muscle pain, pharyngalgia, confusion, anorexia, headache, eye congestion, diarrhea, nausea and vomiting. In presence of comorbidities like hypertension, nervous system, diabetes, cardiovascular system and digestive system it is challenging to diagnose the coronavirus disease as various initial symptoms gets encased. The median interval from the onset of initial symptoms to dyspnea or significant symptom aggravation was seven days, ranging between day

one (ie, appearance of acute respiratory distress syndrome) up to 20 days, which was consistent with previous reports. Day one involves fever, fatigue, muscle pain, dry cough leading to difficulty breathing on day five. On 10<sup>th</sup> day patients may experience abdominal pain. The complete recovery and hospital discharge usually takes two and half weeks [23-25]. Some of the patients subsequently developed ARDS, ventilator-associated pneumonia, acute cardiac or hepatic injury and required care in the intensive care unit [13,26]. Smoking is associated with the negative progression and adverse outcomes of COVID-19 [27]. In review 16.5% of the individuals were reported with smoking habit [15,22].

The early stage symptoms are nonspecific. Differential diagnosis should include the likelihood of a comprehensive array of common respiratory disorders counting both infectious like Adenovirus, Influenza, Human metapneumovirus (HmPV), Parainfluenza, Respiratory syncytial virus (RSV), Rhinovirus (common cold) and non-infectious like e.g., vasculitis, dermatomyositis. For alleged cases, rapid antigen detection, and other investigations should be espoused for gaging the prevalent respiratory condition [11].

Since emergence of SARS-CoV-2, scientists around the world are conducting studies to find the most effective drug for its treatment. Several drugs such as chloroquine, lovinavir, ritonavir, arbidol, remdesivir, oseltamivir and favipiravir are currently undergoing evaluation to test their effectiveness in the coronavirus treatment. Being a broad-spectrum antiviral, IFN-α is used to treat hepatitis, and has also been reported to inhibit SARS-CoV in-vitro replication. Lopinavir/ritonavir in combination with other drugs is known to treat adults and children over 14 days of age who are infected with HIV-1. Chloroquine, besides acting as antimalarial drug, was also found to be a prospective broad-spectrum antiviral in 2006. It was found to block SARS-CoV-2 infection at particularly at low micromolar concentration. Arbidol, another antiviral can be used to treat influenza virus [28]. And even in the review, almost half of the patients received some kind of antiviral therapy as a part of treatment in 73% of the studies along with supportive symptomatic treatment [12,18,24-26]. Chloroquine/hydroxychloroquine are advised as a prophylactic drug for SARS-CoV-2 infection especially for high risk population (asymptomatic health care workers involved in the care of suspected or confirmed cases

of COVID-19 and asymptomatic household contacts of laboratory confirmed cases) [29].

Results obtained from this systematic review may help clinicians in diagnosing patients using clinical, laboratory and radiographic findings among SARS-CoV-2 suspected patients visiting hospital for checkups. Along with these characteristics, vigilant medical history to be recorded along with recent international travel and contact with any confirmed case. Review results can also help the clinician to plan the treatment depending upon the patient symptoms and assessing its effectiveness. Further clinical trials are required to narrow down to the most effective drug for Coronavirus treatment.

#### Limitations

Bias could have been introduced due to restriction of studies to English language, relevant data included in other journals would have been missed because of limited access (high registration amount) and also MEDLINE, EBSCO and Google Scholar database do not contain all research reports. Furthermore, most of the studies included were from china which may not depict true geographic representation and may lack generalizability.

This systematic review is written as per the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [30-37].

#### Conclusion

SARS-CoV-2 appears to be highly communicable from the existing epidemiological data with varying fatality rate. Due to lack of drug trials, Coronavirus outbreak by a novel virus has limited the treatment options. In this baffling time, public health measures like social distancing, home quarantine, proper hygiene measures like hand washing along with mandatory vigorous community testing needs to be followed. More rapidly the cases are detected, isolated, and traced; the more efficacious will be the prevention strategies for any country to evade community transmission.

Conflict of Interest: Nil

Source of Funding: Nil

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