

Clinical features and management of COVID-19: A systematic review

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Abstract. Novel coronavirus disease, the latest world pandemic is one of the most contagious viral infections to date. There has been a lack of uniformity on recognizing this condition clinically because of poorly understood pathophysiology and clinical nature. Also due to ongoing clinical trials, its management is also varied. This is a systematic review from evidence-based studies until March 1st, 2020, covering an update on its clinical features and management. This study shows the multisystem involvement of COVID-19 with dominant respiratory features followed by the musculoskeletal, gastrointestinal system and others. The clinical features varied from asymptomatic to severe forms. Major causes of fatality were acute respiratory distress syndrome, shock, acute cardiac injury, acute kidney injury, rhabdomyolysis, and arrhythmia. Major modalities of management included supportive, antiviral and antibiotic therapy. There was no direct relationship between the specific treatment and the outcome.

INTRODUCTION

The years 2019 and 2020 have been a period of the pandemic of the novel coronavirus, a disease of zoonotic origin (Ahmad *et al.*, 2020). The virus named as Novel Corona Virus (2019-nCoV), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or Wuhan-virus causes Coronavirus Disease 2019 (COVID-19) and comes from the same family of viruses that caused Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) in the preceding years (Lai *et al.*, 2020; Xu *et al.*, 2020). The discovery was made in December 2019 in the series of cases identified as pneumonia of unknown etiology that occurred in Wuhan, Hubei Province of China (She *et al.*, 2020; Yee *et al.*, 2020). It is one of the most contagious viral diseases to date

(Guan *et al.*, 2020; Phan, 2020). In the short span of two months, it has appeared in almost all the countries covering six continents which validates its highly contagious nature. The disease has become the prime issue for almost all countries regarding its impact on health, economy, trade, travel, and tourism, and socio-ethnocultural aspects (Z. Wu & McGoogan, 2020).

This novel coronavirus is an enveloped positive-sense double-stranded RNA virus belonging to the beta-coronavirus cluster and subgenus botulinum of Coronaviridae (Wang *et al.*, 2020; Xu *et al.*, 2020). The source of transmission and pathophysiology are indeterminate. However, the source of interspecies transmission is suggested to be from bats as recent findings have shown that SARS-CoV-2 is 96% identical to a bat coronavirus (Ahmad *et al.*, 2020; Rodriguez-

Morales *et al.*, 2020). From the series of studies reported worldwide, it is well known that it affects multi-system (Chen *et al.*, 2020; Huang *et al.*, 2020; Sun *et al.*, 2020). The presentation and severity range from asymptomatic to mortality-causing disease (Chan *et al.*, 2020; C Huang *et al.*, 2020a; Huang *et al.*, 2020; Mizumoto *et al.*, 2020; Jian *et al.*, 2020). The complex nature of this disease has created difficulties in its identification and management. There are a series of protocols and guidelines released for the local prevention and management of this pandemic. However, there is no uniformity for effective protocols describing clinical features and management of COVID-19 and the practice varies among countries and centers (Sun *et al.*, 2020). The existing protocols including those provided by WHO have changed frequently over a short period. This has brought significant misunderstandings among health care providers and the general public to recognize this momentous pandemic.

Because of emerging concerns of this pandemic, updated medical knowledge is sought, which brought the need for this systematic review. Thus, to summarize the evidence-based updates on identification, prevention, and management we conducted a systematic review of published studies with similar objectives including all the final and pre-print articles till March 1st, 2020. Here, we aim to provide a scientific summary of clinical features to address the hurdles on daily clinical practice and overcome the myths surrounding COVID-19 in public. We have also managed to summarize the outcomes of different interventions tried all over the world.

METHODOLOGY

This is a systematic review of various studies published for an update of clinical features and management of COVID-19 until March 1st, 2020. The updated PRISMA guidelines for systematic reviews were followed for this review. We conducted our search in two major medical databases PubMed and Google Scholar. The search included all publications in the English language till the start of the study i.e. March 1st, 2020. The Keywords for the systematic search were “COVID-19” or “Nobel coronavirus” or “COVID-19” AND “Clinical presentations”/ AND “Treatment”. We included case reports, case series, case-control studies, cross-sectional studies, cohort studies and randomized control trials (RCTs). We have excluded expert opinion, news articles, meta-analysis, review articles or other forms of non-scientific information published.

RESULT

Search strategy

An initial search identified a total of 8724 results from PubMed and Google Scholar (Table 1). Out of them, 72 articles were related to clinical features of COVID-19 while 198 articles were related to the management of COVID-19. After the application of inclusion and exclusion criteria 40 studies were included for this review (Figure 1).

Out of the 40 studies, most of them were case series (26) followed by case reports (12). There were one cohort and one cross-sectional study each. Most studies were reported from China (30) followed by South

Table 1. Keywords and search results

Keywords	PubMed	Google Scholar	Total
COVID-19	854	4210	5064
Novel Coronavirus	2190	1200	3390
COVID-19 AND Clinical features	46	26	72
COVID-19 AND Management	190	8	198
Total	3280	5444	8724

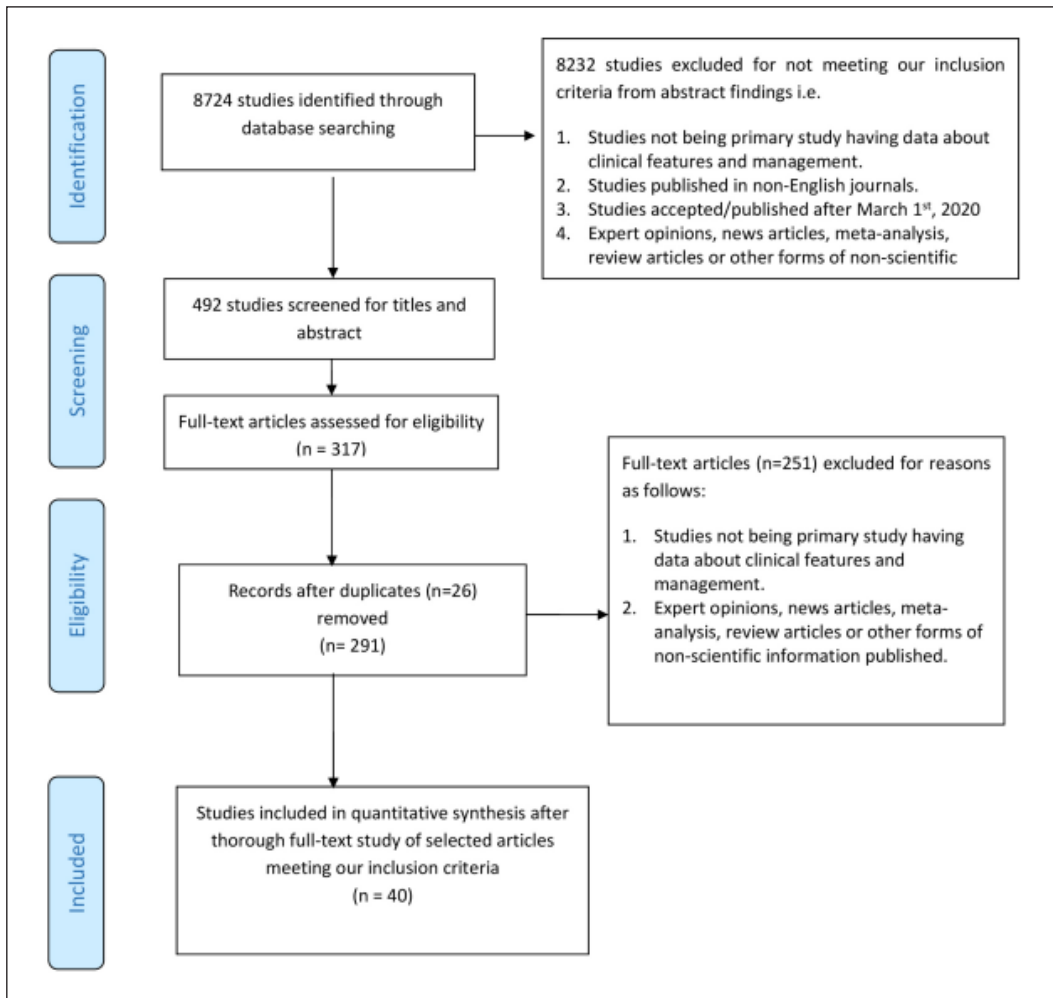


Figure 1. PRISMA 2009 Flow Diagram.

Korea (3). Nepal, Singapore, Taiwan, UK, USA, and Vietnam had one study each.

Out of 2735 total confirmed COVID-19 cases, 1499 (54.8%) were male with a sex ratio of 1.2:1 (Male: Female). Table 2 and Table 3 outlines the profile among a total of 2735 confirmed cases of 2019-nCoV infection. It is apparent that COVID-19 is a multisystem disease with predominant respiratory features. The most common presenting clinical feature is found to be fever (84.3%) followed by cough (62.4%) being the predominant respiratory feature. A case series of nine 2019-nCoV confirmed cases has shown that patients initially could present with only gastrointestinal symptoms such as anorexia, nausea, and vomiting but no fever

or respiratory symptoms (An *et al.* 2019). In contrast, studies have shown that 2019-nCoV infected patients may also present asymptotically (1%).

Table 4 elucidates complications seen in 242 cases of COVID-19. More than half of the patients developed respiratory complication i.e. acute respiratory distress syndrome (54.96%). Other complications included rhabdomyolysis (14.46%), shock (11.57%), arrhythmia (9.51%), and acute cardiac injury (6.20%). Other uncommon complications were acute kidney injury (AKI; 1.65%), and secondary infection (1.65%). The multi system involvement was seen in these cases as well.

Table 2. List of included studies

Name of Study	Country	Study Design	Sample size	Sample character	Study Placement	Mean Age group (yrs)	Male	Female
Silverstein <i>et al.</i> , 2019	Canada	Case report	1	General	Single-centered	56	1	0
Song <i>et al.</i> , 2019	China	Case series	51	General	Single-centered	15-76	25	26
Xu <i>et al.</i> , 2020	China	Case series	62	General	Multicentric	41	-	-
Liu <i>et al.</i> , 2020	China	Case series	137	General	Single-centered	57 (20-83)	61	76
Wang <i>et al.</i> , 2020	China	Case series	4	General	Single-centered	19-63	3	1
Liu <i>et al.</i> , 2020	China	Cross-section	24	General	Single-centered	43 (12-84)	8	16
Cai <i>et al.</i> , 2020	China	Case series	10	Children	Single-centered	2.43 (1-4)	4	6
Huang <i>et al.</i> , 2020	China	Case series	2	Elderly	Single-centered	71	0	2
Zhu <i>et al.</i> , 2020	China	Case report	1	General	Single-centered	44	1	0
Cheng <i>et al.</i> , 2020	Taiwan	Case report	1	General	Single-centered	55	0	1
Wang <i>et al.</i> , 2020	China	Case series	138	General	Single-centered	56 (22-92)	75	63
Kim <i>et al.</i> , 2020	South Korea	Case report	1	General	Single-centered	35	0	1
Tian <i>et al.</i> , 2020	China	Case series	262	General	Single-centered	47 (1-94)	127	135
Yang <i>et al.</i> , 2020	China	Cohort study	149	General	Multicentric	45.11 (+/- 13.35)	81	68
Ji <i>et al.</i> , 2020	China	Case series	49	General	Single-centered	43.6 (+/- 17.1)	31	18
Shrestha <i>et al.</i> , 2020	Nepal	Case report	1	General	Single-centered	32	1	0
Chen <i>et al.</i> , 2020	China	Case series	99	General	Single-centered	55.5 (+/- 13.1)	67	32
Ren <i>et al.</i> , 2020	China	Case series	5	General	Single-centered	52 (41-65)	3	2
Huang C <i>et al.</i> , 2020	China	Case series	41	General	Single-centered	49	30	11
Chan <i>et al.</i> , 2020	China	Case series	6	General	Single-centered	37 (10-66)	3	3
Wu <i>et al.</i> , 2020	China	Case series	80	General	Multicentric	46.1	39	41
Guan <i>et al.</i> , 2020	China	Case series	1099	General	Multicentric	47	639	460
Li <i>et al.</i> , 2020	China	Case series	83	General	Single-centered	45	44	39
Xu <i>et al.</i> , 2020	China	Case series	90	General	Single-centered	50 (18-86)	39	51
Xu <i>et al.</i> , 2020	China	Case series	50	General	Single-centered	29	29	21
Shi <i>et al.</i> , 2020	China	Case series	81	General	Single-centered	49 (+/- 11.0)	42	39
Kong <i>et al.</i> , 2020	South Korea	Case series	28	General	Multicentric	20-79	15	13
Lim <i>et al.</i> , 2020	South Korea	Case report	1	General	Single-centered	54	1	0
Giang <i>et al.</i> , 2020	Vietnam	Case report	1	General	Single-centered	24	0	1
Holsbue <i>et al.</i> , 2020	USA	Case report	1	General	Single-centered	35	1	0
Han <i>et al.</i> , 2020	China	Case report	1	General	Single-centered	47	1	0
Chang <i>et al.</i> , 2020	China	Case series	13	General	Multicentric	34 (34-48)	10	3
Lille <i>et al.</i> , 2019	UK	Case series	2	General	Single-centered	23	1	1
Wang X <i>et al.</i> , 2020	China	Case report	1	Pregnant (30 WOG)	Single-centered	28	0	1
Hao W, 2020	China	Case report	1	General	Single-centered	58	1	0
Yang Z <i>et al.</i> , 2020	China	Case series	4	General	Single-centered	-	1	3
Liu Y <i>et al.</i> , 2020	China	Case series	109	General	Multicentric	55 (22-94)	59	50
Fu <i>et al.</i> , 2020	China	Case series	36	General	Single-centered	45 (3-79)	16	20
An P <i>et al.</i> , 2019	China	Case series	9	General	Single-centered	35.8	4	5
Kam <i>et al.</i> , 2020	Singapore	Case report	1	Infant	Single-centered	0.5	1	0

Table 3. Clinical features of COVID-19

Clinical Features	Number	Percentage (%)
Total COVID-19 Confirmed cases	2735	100
Fever	2305	84.3
Cough	1706	62.4
Myalgia	895	32.7
Dyspnea	436	15.9
Sore throat	271	9.9
Headache	141	5.2
Loss of Appetite	75	2.7
Diarrhea	72	2.6
Nausea and Vomiting	33	1.2
Asymptomatic	26	1.0
Nasal Congestion and rhinorrhea	20	0.7
Chest tightness	18	0.7
Dizziness	7	0.3
Hemoptysis	13	0.5
Chest pain	2	0.1
Palpitation	10	0.4

Table 4. Complications of COVID-19

Complications	Number	Percentage
Total	242	100.00
ARDS	133	54.96
Rhabdomyolysis	35	14.46
Shock	28	11.57
Arrhythmia	23	9.51
Acute cardiac injury	15	6.20
AKI	4	1.65
Secondary infection	4	1.65

Table 5 illustrates different management modalities that have been used for the management of COVID-19 and their respective outcomes. Supportive care and symptomatic management are shown to be the mainstay of the treatment of the disease. Commonly used antivirals included Lopinavir, Ritonavir, and Ribavirin. Also, antibiotics like Levofloxacin, Clarithromycin, Cefepime, and Ceftriaxone have been used. Fu *et al.*, in a case series of 36 patients have shown the use of interferon in all patients; while 14 of them received immunoglobulins and hormone therapy, and 28 of them received Chinese medicinal broth treatment. Although most of the patients appeared to be stable or improved, there is no direct evidence

supporting that the benefit is due to the management modalities that have been used.

DISCUSSION

Studies have shown that patients presenting with typical clinical features of 2019-nCoV infection have been tested negative on RT-PCR. In resource-poor countries the only confirmatory tool for detecting 2019-nCoV infection is RT-PCR. Recognizing the cases from the clinical features alone would add great value to the early diagnosis and management of COVID-19. The results conclude multisystem manifestation of novel coronavirus. The possible pathogenesis behind the multisystem involvement with prominent respiratory features is possibly explained by the involvement of Angiotensin converting enzyme 2 (ACE2) receptors by novel coronavirus (Ahmad *et al.*, 2020; Donoghue *et al.*, 2000; He *et al.*, 2020; Kruse, 2020; 2020; Pang *et al.*, 2020; Shanmugaraj *et al.*, 2020). The entry of the virus is mediated by ACE2 receptors which are predominantly found in the respiratory tract. Besides that, these receptors are also present at various sites of the body including vascular endothelia, kidney cells, and small intestine

Table 5. List of studies for management modalities

SN	Study	Country	Study Design	Sample size	Management modalities used	Outcome
1	Silverstein <i>et al.</i> , 2019	Canada	Case report	1	Supportive	Fever resolved after 5 days
2	Liu <i>et al.</i> , 2020	China	Case series	137	Symptomatic and respiratory support, Antiviral, Antibacterial	Apart from 16 mortalities, remaining patients improved
3	Huang <i>et al.</i> , 2020	China	Case series	2	Supportive, Levofloxacin, Clarithromycin, Cefepime	Improved
4	Cheng <i>et al.</i> , 2020	Taiwan	Case report	1	Antitussive, O ₂ supplementation, Saline infusion, Antipyretics, empirical Ceftriaxone	Improved after 25 days
5	Kim <i>et al.</i> , 2020	South Korea	Case report	1	Lopinavir/Ritonavir	Improved after 14 days
6	Chan <i>et al.</i> , 2020	China	Case series	6	Supportive	Stable
7	Giang <i>et al.</i> , 2020	Vietnam	Case report	1	Supportive	Improved
8	Holshue <i>et al.</i> , 2020	USA	Case report	1	Supportive	Resolved
9	Fu <i>et al.</i> , 2020	China	Case series	36	Supportive, Lopinavir/Ritonavir, Ribavirin, IFN, IG, hormone therapy, Chinese medicinal broth	Stable

cells (Ahmad *et al.*, 2020; Donoghue *et al.*, 2000; He *et al.*, 2020; Kruse, 2020; Y.-C. Li *et al.*, 2020; Pang *et al.*, 2020; Ren *et al.*, 2020; Shanmugaraj *et al.*, 2020). So it is possible to manifest extra-pulmonary symptoms with extensive complications (Ahmad *et al.*, 2020; Donoghue *et al.*, 2000; He *et al.*, 2020; Kruse, 2020; Y.-C. Li *et al.*, 2020; Pang *et al.*, 2020; Ren *et al.*, 2020; Shanmugaraj *et al.*, 2020). Additionally, experimental studies on mice have confirmed the neuro-invasive potential of SARS-CoV and MERS-CoV, which suggests similar property in 2019-nCoV. This fact highlights the possible depression of the respiratory center in the brainstem due to CNS penetrating property of the virus (Li *et al.*, 2020). A study that explored the contrast between SARS-CoV-2 of the present and SARS-CoV of the preceding years showed that

SARSCoV2 infected patients rarely showed prominent upper respiratory tract signs and symptoms, indicating that the target cells of SARSCoV2 may be located in the lower airway (Dong *et al.*, 2015; Li *et al.*, 2020).

Antiviral agents such as Lopinavir used during the SARS-CoV that share 79.5% sequence identity with COVID-19, can be a potential drug (Ahmad *et al.*, 2020; Yao *et al.*, 2020). Studies in our review reveal that there is a significant role of protease inhibitor Lopinavir in decreasing the viral load in COVID-19. Currently, there are ongoing clinical trials regarding the efficacy of this drug in COVID-19. A retrospective matched cohort study among SARS patients has shown an association between treatment with Lopinavir and Ritonavir combination and reduced death rate. It has shown that

combining Lopinavir and Ritonavir produces a synergistic effect for the treatment of SARS (Peiris *et al.*, 2003). Other antivirals such as approved nucleoside analogues (Favipiravir and Ribavirin) and experimental nucleoside analogues (Remdesivir and Galidesivir) have been proposed to have potential against 2019-nCoV based on the therapeutic experience with two other infections caused by SARS and MERS. As the 2019-nCoV and SARS-CoV share a very high sequence identity on their RNA dependent RNA polymerase (RdRp) and 3'-chymotrypsin-like protease (3CLpro) proteins, Remdesivir and 3CLpro-1 could be used to treat the 2019-nCoV infection (G. Li & De Clercq, 2020). Adding to this, a case report on first COVID-19 patient in the United States (US) reported that Remdesivir inhibited 2019-nCoV and the patient recovered after receiving intravenous Remdesivir (Morse *et al.*, 2020).

Furthermore, we came across various *in-vitro* studies that showed the efficacy of Chloroquine, an immunomodulatory drug in reducing viral replication in other infections like the SARS-CoV and MERS-CoV (Colson *et al.*, 2020; Cortegiani *et al.*, 2020; Ge *et al.*, 2013). A systematic review of the efficacy and safety of Chloroquine revealed that it is highly effective in reducing viral replication due to its favorable penetration in tissues including the lung (Cortegiani *et al.*, 2020). It has been postulated that it increases the endosomal pH and interferes with the glycosylation of ACE2 receptor used by the SARS-CoV and the same receptor is used by 2019-nCoV during cell entry (Cortegiani *et al.*, 2020; Pang *et al.*, 2020; Vincent *et al.*, 2005). In an *in vitro* study done in Vero E6 cells, it has been shown that Remdesivir and Chloroquine to be highly effective in the control of 2019-nCoV infection (Wang *et al.*, 2020). Following the findings of the *in vitro* study, clinical trials conducted in China to test the efficacy and safety of Chloroquine or Hydroxychloroquine have shown significant improvement in COVID-19 patients with exacerbated pneumonia, promotion of a virus-negative conversion and shortening the course of the disease (Gao *et al.*, 2020).

A meta-analysis covering the use of corticosteroids, commonly used in severely

ill SARS patients has predicted data from four studies, all of which indicate potentially harmful effects in COVID-19 patients. Findings included psychosis, viremia, diabetes and avascular necrosis as complications following steroid therapy. Another noteworthy outcome included an increased length of stay in the Intensive Care Unit (ICU) (Russell *et al.*, 2020). However, another study favors the use of low-dose corticosteroids in severely ill patients with 2019-nCoV, though the benefits have not been proven or studied (Zhou *et al.*, 2020). Additionally, another study has also shown that the use of corticosteroids may have no therapeutic benefit in patients infected with the 2019-nCoV, but rather would accentuate the viral replication process within the neurons (Li *et al.*, 2020).

CONCLUSION

This systematic review concludes multisystem association of COVID-19. The majority of patients present with fever (84.3%), respiratory features like cough (62.4%), dyspnea (15.9%), chest tightness (0.7%), and hemoptysis (0.5%) and other symptoms like myalgia (32.7%), sore throat (9.9%), headache (5.2%), loss of appetite (2.7%), nasal congestion (0.7%) etc. The reviews shows 1% people were asymptomatic, this should be seen with caution as the studies are taken from hospital setting not community. In community more asymptomatic cases might be present than in hospital. Major modalities of management included supportive, antiviral and antibiotic therapy having no direct relationship between the specific treatment and the outcome. The need for further study for specific treatment and timely evidence-based updates on existing guidelines is required.

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