ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Review Article

# COVID 19: Gastrointestinal and Hepatic Perspective

**Balvir S Tomar[1]*, Deepak Nathiya[2], Pankaj Kumar Singh[3], Pratima Singh[2], Supriya Suman[2], Preeti Raj[2], Sandeep Tripathi[4] and Dushyant S Chauhan[5]**

*[1]Director - Institute of Gastroenterology, Hepatology and Transplant, Nims University Rajasthan and President - International Society of Gastroenterology, Hepatology, Transplant and Nutrition, India*

*[2]Department of Pharmacy Practice, Institute of Pharmacy, Nims University Rajasthan, Jaipur, India*

*[3]Department of Neurosurgery, National Institute of Medical Sciences and Research, Nims University Rajasthan, Jaipur, India*

*[4]Institute of Nutrition and Public Health, Nims University Rajasthan, Jaipur, India*

*[5]Institute of Advance Sciences, Nims University Rajasthan, Jaipur, India*

***Corresponding Author**: Balvir S Tomar, Professor, Director and Head, Institute of Gastroenterology and Hepatology, Nims University Rajasthan and President International Society of Gastroenterology, Hepatology, Transplant and Nutrition, India.

**Received:** April 24, 2020; **Published:** June 24, 2020

## Abstract

Since December 2019, nCOV becomes threat to world and due to this WHO declared this as Pandemic. As of today andgt;2.6 Million confirmed cases along with andgt;182,000 deaths has been reported so far. Clinical symptoms include varieties of Pulmonary and extra pulmonary viz Pneumonia, Cough, diarrohoea. COVID-19 cause large number of changes in biochemical profile of individual who is suffering from it includes lymphocytopenia, high creatinine levels, high blood urea and significant effect on various inflammatory factors. RT-PCR method of testing stands as Gold standard for testing of COVID-19. Liver and Gastrointestinal features are much prevalent in COVID-19. Further number of drugs are under investigation /or their efficacies are yet to establish in COVID-19. Hypoxia plays important role in worsening of COVID-19 which must be controlled by monitoring Silent Hypoxia by Pulse Oximeter so that morbidities leading to mortalities can be minimized. Elderly patients must be given special care for prevention of COVID-19 among them. Further in this review we will be summarizing various effect on Hepatic and Gastrointestinal involvement in COVID-19, and preventive measures to be taken against spread of COVID-19 Pandemic.

***Keywords:*** *SARS-CoV2; Liver; Gastrointestinal; AST; ALT; Hypoxia*

## Background

In December 2019, a large number of pneumonia cases, caused by a newly recognized β-coronavirus, which is enveloped non-segmented positive-sense RNA virus, occurred in Wuhan, China. This coronavirus name was given by World Health Organization (WHO) in 2019 and name of disease as COVID 19 (Corona Virus Disease) in 2020. [1].

By April 2020, total of > 2.6 Million cases of COVID including > 182,000 deaths has been identified globally [2]. Studies suggested the doubling rate ($R_0$) of SARS-CoV2 is around 2.2 [3] and ranges from 1.4 to 6.5 [4,5].

Coronaviruses (CoV) have four types of strains e.g. α/ β/γ/δ-CoV, out of which α and β-are prevalent for infection in humans, while γ and δ Corona virus strains are prevalent in birds [6]. Bat has been considered as inherited host of virus and transmitted by unspecified

hosts to humans. nCoV-2 could Use angiotensin-converting enzyme 2 (ACE2) as target for infection in humans, the same receptor which was used in SARS-CoV infection [7].

## Diagnostic criteria [8,9]

| Clinical Specimens used for COVID-19 Testing | Serological Tests used for COVID-19 Testing | Molecular Tests used for COVID-19 Testing |
|---|---|---|
| Nasal secretions (Snot) | Enzyme linked immunosorbent assay (ELISA) | Real Time-PCR (RT-PCR)<br><br>(Gold Standard) |
| Blood | Western blot (for detection of COVID-19 Proteins) | Northern blot hybridization targeting (for detection of COVID-19 genes) |
| Sputum (Saliva/Spit) | Direct immune fluorescent assay (IFA) (detection of Viral Antigen) | |
| Bronchoalveolar lavage (BAL) | | |

***Table 1:*** *Diagnostics used for COVID 19.*

## Clinical symptoms

A recent study of 1099 laboratory-confirmed cases, found that the common clinical manifestations included headache (13.6%), Sore throat (13.9%), Shortness of breath (18.6%), Sputum production (33.4%), fatigue (38.1%), cough (67.8%) and fever (88.7%). The geriatric people with comorbid cardiovascular, pulmonary, hormonal disorders undergo Septic Shock, ARDS and can lead to death [10]. Hyperthermia and Tussis were presiding signs while URTI and GI signs were less or not available, were indicative of differences in viral tropism as compared with SARS-CoV [11], MERSCoV [12] and influenza [13].

In Complete blood count test, majority of patients had low white blood cell counts, and lymphocytopenia [14]. But in the serious patients, the neutrophil, blood urea, and creatinine levels were higher, there was continue increase in lymphocyte counts. Additionally, in laboratory tests it was found that inflammatory factors (tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-10 increases, indicating the immune status of patients. Further data suggested higher plasma level of Interleukin-2, Interleukin-7, Interleukin-10, granulocyte colony-stimulating factor (GCSF), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α) and TNF-α [12]. Furthermore, the CT Scan on chest was ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%) [10,15].

## COVID-19: Liver involvement

Liver involvement has been reported in patients infected with SARS-CoV [16] and MERS-CoV [17]. Published case studies have suggested that Patient with SARS infection may develop different levels of liver abnormalities (summarized in table 2). In these studies, the incidence of liver injury ranged from 13% to 78%, mainly presenting with abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) accompanied by slightly elevated bilirubin levels [10,18-28].

| Name of Study | Number of Patients with COVID-19 | Patients with abnormal biochemical liver profile | Patients with pre-existing liver co-morbidities |
|---|---|---|---|
| Guan., *et al*. [10] | 1099 | • **Abnormal ALT, 158/741 (21.3%):**<br>  • 19.8% in non-severe COVID-19<br>  • 28.1% in severe COVID-19<br>• **Abnormal AST, 168/757 (22.2%):**<br>  • 18.2% in non-severe COVID-19<br>  • 39.4% in severe COVID-19<br>• **Abnormal total bilirubin 76/722 (10.5%):**<br>  • 9.9% in non-severe COVID-19<br>  • 13.3% in severe COVID-19 | 23 (2.1%) |
| Cai., *et al*. [18] | 298 | • **44 (14.8%):**<br>  • 9.6% in non-severe COVID-19<br>  • 36.2% in severe COVID-19 | 8 (2.7%) |

| | | | |
|---|---|---|---|
| Fan., *et al*. [19] | 148 | • **75 (50.7%):**<br>  • Abnormal ALT (18.2%)<br>  • Abnormal AST (21.6%)<br>  • Abnormal total bilirubin (6.1%) | 6 (8%) |
| Wang *et al* [20] | 138 | Mild elevation of ALT and AST | 4 (2.9%) |
| Chen *et al* [21] | 99 | **43 (43%)**<br>• Abnormal ALT 28%<br>• Abnormal AST 35%<br>• Abnormal total bilirubin 18%<br>• Abnormal albumin 98% | NA |
| Lu., *et al*. [22] | 85 | 33 (38.8%) | 6 (7%) |
| Shi., *et al*. [23] | 81 | 43 (53%) | 7 (9%) |
| Xu., *et al*. [24] | 62 | 10 (16%) | 7 (11%) |
| Yang., *et al*. [25] | 52 | 15 (29%) | NA |
| Huang., *et al*. [26] | 41 | 15 (31%) | 1(2%) |
| Zhang., *et al*. [27] | 82, deaths | • **64 (78%)**<br>  • Abnormal ALT 30.6%<br>  • Abnormal AST 61.1%<br>  • Abnormal total bilirubin 30.6% | 2(2.4%) |
| Huang., *et al*. [28] | 36, non survivors | • Abnormal ALT 13%<br>• Abnormal AST 58%<br>• Abnormal total bilirubin 12.9% | NA |

***Table 2:*** *Characteristics of liver biochemical profile in published COVID-19 case studies.*
*Abbreviations: SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2;*
*ALT: Alanine Transaminase; AST: Aspartate Aminotransferase.*

Currently, the primary reasons for hepatic injury in patients with COVID-19 are still unclear. Liver damage might be directly caused by virus-induced cytopathic effects. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter its target cells [29].

Recently its suggested that gamma-glutamyl transferase (GGT) was elevated in 54% of COVID-19 patients, whereas only 1.8% of patients (1/56) had elevated alkaline phosphatase level, Immune-mediated inflammation also may be the reason behind liver injury in severe ill patients [30,31].

Inflammatory cytokine over activity as seen in SARS-CoV and MERS-CoV [32,33], Continuously produces large amount of lymphocytes and macrophages which in turn releases large amount of Inflammatory Cytokines [34]. Lymphocytes plays crucial role during viral infection [35] and inhibit overactive natural immune response, thus lymphopenia during COVID-19 may increase IL-6, IL-10 and IFN-C levels leading to Pulmonary as well as other organ injury including Liver [36]. Drug induced liver injury must be taken care of as antiviral medications, Antipyretics, Antibiotics (Macrolides /Quinolones specially) or Steroids may increase chances of liver injury [37]. In USA, antiviral drug remdesivir reported to increase liver enzymes [38].

## COVID-19: Liver comorbidities

The agenda need to be investigated thoroughly, however as of now it suggests to have around 2 - 11% of patients with COVID-19 and pre-existing liver diseases [30].

In a study there were hepatitis B infection present in patient with COVID-19 [10]. Individuals at high risk for severe COVID-19 are typically of older age and/or present with comorbid conditions such as diabetes, cardiovascular disease, and hypertension, a similar profile to those at increased risk for nonalcoholic fatty liver disease, making them more susceptible to liver injury [39]. Liver transplantation could have risk of viral [40].

## COVID-19: Gastrointestinal tract

GIT involvement is well known because SARS-CoV-2 RNA was detected in a stool of COVID-19 patient [41,42]. Large number of studies have suggested that around 10.6% of patients with SARS and up to 30% of patients with MERS had diarrhea [43].

Similarly, in many studies of COVID-19, nausea, vomiting and diarrhoea are prevalent. In one study of COVID-19 large number of patient found with nausea or vomiting and diarrhoea [10].

In a recent study by Wei., *et al*. they noticed that COVID-19 patients with diarrhoea are more prone towards headache, myalgia or fatigue, cough, sputum production, nausea, and vomiting in comparison with patient patients without diarrhoea [45].

A comparison of gastrointestinal symptoms in COVID-19, SARS, MERS are summarized in table 3 [44].

| | Subject number | Diarrhoea | Nausea | Vomiting | Abdominal pain |
|---|---|---|---|---|---|
| **Covid-19** | | | | | |
| Guan W., *et al*. [49] | 1099 | 42 (3.8%) | 55 (5.0%) | 55 (5.0%) | NA |
| Chen N., *et al*. [50] | 99 | 2 (2.0%) | 1 (1%) | 1 (1%) | NA |
| Huang C., *et al*. [51] | 38 | 1 (2.6%) | NA | NA | NA |
| Liu K., *et al*. [52] | 137 | 11 (8%) | NA | NA | NA |
| Lu X., *et al*. [53] | 171 | 15 (8.8%) | NA | 11 (6.4%) | NA |
| Shi H., *et al*. [54] | 81 | 3 (3.7%) | NA | 4 (4.9%) | NA |
| Wang D., *et al*. [55] | 138 | 14 (10.1%) | 14 (10.1%) | 5 (3.6%) | 3 (2.2%) |
| Xu XW., *et al*. [56] | 62 | 3 (4.8%) | NA | NA | NA |
| Yang X., *et al*. [57] | 52 | NA | NA | 2 (3.8%) | NA |

| | | | | | |
|---|---|---|---|---|---|
| Zhou F., *et al*. [58] | 141 | 9 (4.7%) | 7 (3.7%) | 7 (3.7%) | NA |
| Zhang JJ., *et al*. [59] | 139 | 18 (12.9%) | 24 (17.3%) | 7 (5.0%) | 8 (5.8%) |
| Xiao F., *et al*. [60] | 73 | 26 (35.6%) | NA | NA | NA |
| **SARS** | | | | | |
| Booth CM., *et al*. [61] | 144 | 34 (23.6%) | 28 (19.4) | 28 (19.4) | 5 (5.0%) |
| Cheng VC., *et al*. [62] | 142 | 69 (48.6%) | NA | NA | NA |
| Choi KW., *et al*. [63] | 267 | 41 (15.4%) | NA | 19 (7.1%) | NA |
| Jang TN., *et al*. [64] | 29 | 4 (13.8%) | 5 (17.2%) | 5 (17.2%) | NA |
| Kwan AC., *et al*. [65] | 240 | 49 (20.4%) | NA | NA | NA |
| Lee N., *et al*. [66] | 138 | 27 (19.6%) | 27 (19.6%) | 27 (19.6%) | NA |
| Leung CW., *et al*. [67] | 44 | 9 (20.5%) | 13 (29.5%) | 13 (29.5%) | 4 (9.1%) |
| Leung WK., *et al*. [68] | 138 | 53 (38.4%) | NA | NA | NA |
| Liu CL., *et al*. [69] | 53 | 35 (66.0%) | 6 (11.3%) | 5 (9.4%) | 5 (9.4%) |
| Peiris JS., *et al*. [70] | 75 | 55 (73.3%) | NA | NA | NA |
| **MERS** | | | | | |
| Al Ghamdi M., *et al*. [71] | 51 | 13 (25.5%) | NA | 12 (23.5%) | NA |
| Almekhlafi GA., *et al*. [72] | 31 | 6 (19.4%) | NA | 4 (12.9%) | 9 (29.0%) |
| Arabi YM., *et al*. [73] | 330 | 38 (11.5%) | 58 (17.6%) | 58 (17.6%) | 47 (14.2%) |
| Assiri A., *et al*. [74] | 47 | 12 (25.5%) | 10 (21.2%) | 10 (21.2%) | 8 (17.0%) |
| Assiri A., *et al*. [75] | 23 | 5 (21.7%) | NA | 4 (17.4%) | NA |
| Choi WS., *et al*. [76] | 186 | 36 (19.4%) | 26 (14.0%) | 26 (14.0%) | 15 (8.1%) |

***Table 3:*** *Presentation of gastrointestinal symptoms in coronavirus infection: a comparison of Covid-19, SARS, MERS in major clinical cohorts. Case reports, series or cohorts with less than twenty subjects are not included.*

There are many hypotheses regarding why COVID-19 appears to cause digestive symptoms, but the exact molecular mechanism needs to be further investigated. First, interaction between SARS-CoV-2 and ACE2 might result in diarrhea [46]. Second, SARS-CoV-2 cause damage to digestive system via inflammatory response mediated pathway [44]. Another possible factor causing diarrhoea in COVID-19 patients might be antibiotic associated [45]. It may be due to changes in the composition and function of GI flora mutually affect the respiratory tract through immune regulation, the so-called ‘‘gut-lung axis” [47]. Autopsy studies are needed to understand the digestive system involvement of COVID-19 [48].

## COVID-19: Digestive comorbidities

In general, presence of co-morbidities is associated with poorer outcomes in patients with COVID-19 [77]. Cancer comorbid Patients are more prone to infection. Further patient with GI Cancer are more susceptible toward SARS-CoV-2 Infection [48]. In an analysis, around 18 (1%) of 1590 COVID-19 cases were having a history of cancer [78].

## COVID-19 and endoscopy

In whole world health-care workers are at highest risk from COVID-19. However, they are not directly involved in treatment of COVID 19. Workforce working in endoscopy units are still at increased risk from inhalation of air- borne droplets, conjunctival contact, and touch contamination [79].

All endoscopy department along with infection control department must develop standard operating measures to be taken for COVID-19 prevention and control with the help of prior experience of SARS and current understanding of epidemiological characteristics of COVID-19. The following steps should be implemented in endoscopy units:

- **Reduction of non-essential exposure to SARS-CoV-2:** It is recommended to limit endoscopy during the current COVID-19 outbreak to emergency procedures only e.g. acute gastrointestinal bleeding, acute cholangitis etc [80].
- **Risk assessment and stratification of patients prior to any endoscopic procedure:** Risk assessment and Screening of patients to prevent transmission of COVID-19, should be based on case definitions established by WHO and local health authorities [81]. E.g. history of fever, respiratory symptoms, history of contact with a suspected or confirmed case of COVID-19 etc [82].
- **Staff protection:** The minimal composition of personal protective equipment (PPE) for personnel in endoscopy units should include gloves, hairnet, protective eyewear (goggles or face shield), waterproof gowns, and respiratory protective equipment, modified on the basis of risk stratification [82]. The surgical facial mask is effective in blocking splashes and large-particle droplets, whereas, filtering face piece (FFP) respirator class 2 or 3 (FFP2/FFP3) achieves efficient filtration of air- borne particles (up to 0.3 mm) [83].
- **Reprocessing of endoscopes and endoscopic accessories:** Enveloped viruses such as SARS-CoV-2 can be inactivated by disinfectants having virucidal activity [84]. Whereas high- level disinfection is recommended for endoscopes, and other ''semi-critical'' instruments, sterilization is recommended for ''critical'' instruments, including biopsy forceps, polypectomy snares and papillotomes. Disposable accessories may be used [85].
- **Decontamination of endoscopy rooms:** Sanitization with 1% Sodium hypochlorite is recommended for floor cleaning every day [84].

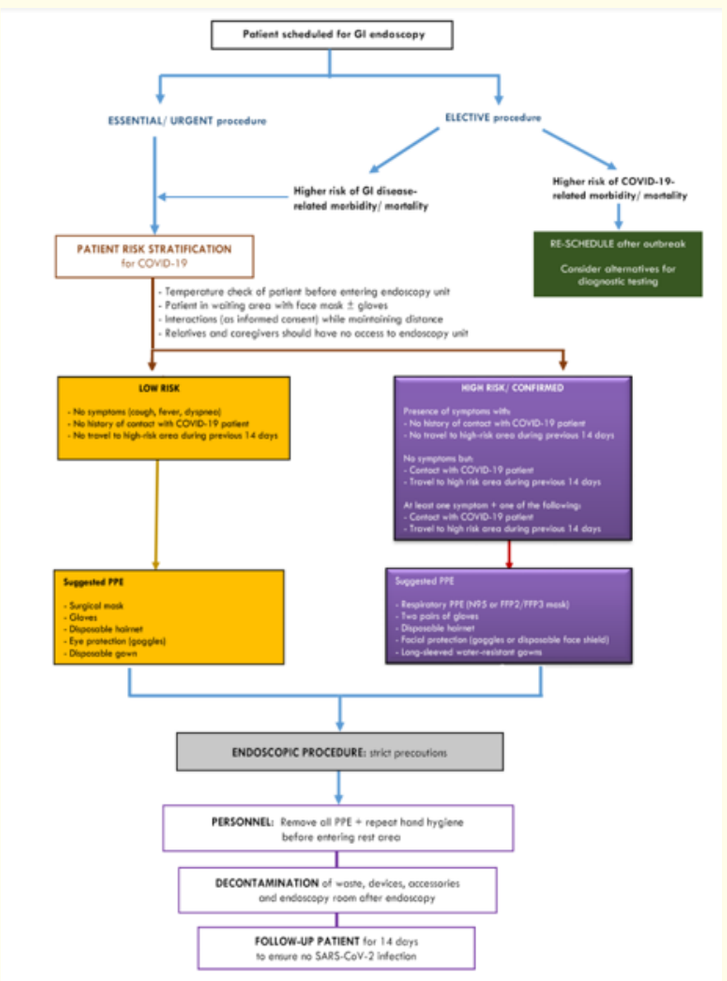


***Figure 1:*** *Suggested workflow in GI endoscopy units during SARS-CoV-2 outbreak [80-86].*

## Treatment of COVID-19

Therapies which are being used against COVID-19 have less specific antiviral effect and just provide only a symptomatic relief at some level along with pulmonary support and are according to guidelines issued by National Health Commission of the People's Republic of China [87]. Almost all patient with hypoxemia receives oxygen therapy and WHO recommended ECMO [88]. Treatment with plasma and IgG are also useful and being delivered according to condition of patient and found useful [89].

## Remdesivir

It have wide spectrum antiviral activity against large number of RNA viruses. Data suggested that it could interfere with the NSP (Non-structural protein)12 polymerase [90]. Remdesivir found useful in treatment of many cases in USA against COVID-19 successfully [91].

## Chloroquine

Chloroquine is widely used antimalarial drug [92]. Its antiviral mechanism is not much understood but it possibly inhibits pH-dependent steps of the replication of several viruses (Autophagy Inhibitor) [93], Several studies have found that chloroquine interfered with the glycosylation of cellular receptors of SARS-CoV [94]. Moreover, chloroquine suppresses the production of TNF-α and IL-6 [95].

## Lopinavir and ritonavir

These drugs are protease inhibitor and used in HIV Infection and found useful in treatment of MERS-CoV [96] and SARSCoV [97] patients. Viral load of COVID-19 significantly decreased in South Korea after treatment by these drugs [98].

Other antiviral drugs are in table 4 below.

| Status | Drugs | Action mode | Anti-infective mechanism | Target diseases | Ref. |
|---|---|---|---|---|---|
| Approved | Lopinavir/ Ritonavir | Protease inhibitors | Inhibiting HIV-1 protease for protein cleavage, resulting in non-infectious, immature viral particles | HIV/AIDS, SARS, MERS | [96-97,100] |
| Approved | Ribavirin | Synthetic guanosine nucleoside | Interfering with the synthesis of viral mRNA (a broad-spectrum activity against several RNA and DNA viruses) | HCV, SARS, MERS | [101-103] |
| Approved | Oseltamivir | Neuraminidase inhibitor | Inhibiting the activity of the viral neuraminidase enzyme, preventing budding from the host cell, viral replication, and infectivity | Influenza viruses A | [104,105] |
| Approved, Investigational | Ganciclovir | Nucleoside analog | Potent inhibitor of the Herpesvirus family including cytomegalovirus | AIDS-associated cytomegalovirus infections | [106] |
| Approved, Investigational, Vet approved | Nitazoxanide | Antiprotozoal agent | Modulating the survival, growth, and proliferation of a range of extracellular and intracellular protozoa, helminths, anaerobic and microaerophilic bacteria, viruses | A wide range of viruses | [107-109] |

| | | | | | |
|---|---|---|---|---|---|
| Approved, Investigational,<br><br>Vet approved | Chloroquine / Hydroxychloroquine | 9-aminoquinolin | Increasing endosomal pH, immunomodulating, autophagy inhibitors | Malaria, autoimmune disease | [93-95] |
| Experimental | Remdesivir (GS-5734) | Nucleotide analogue prodrug | Interfering with virus post-entry | Ebola, SARS, MERS<br><br>(A wide array of RNA viruses) | [90,110,111] |
| Investigational | Nafamostat | Synthetic serine protease inhibitor | Prevents membrane fusion by reducing the release of cathepsin B; anticoagulant activities | Influenza, MERS, Ebola | [112,113] |
| Investigational | Favipiravir (T-705) | Nucleoside analog: Viral RNA polymerase inhibitor | Acting on viral genetic copying to prevent its reproduction, without affecting host cellular RNA or DNA synthesis | Ebola, influenza A(H1N1) | [114-116] |

***Table 4:*** *Common and potent antiviral drugs.*

*HIV: Human Immunodeficiency Virus; AIDS: Acquired Immune Deficiency Syndrome; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; HCV: Hepatitis C Virus; VZV: Varicella-Zoster Virus.*

**Golden Opinion – "Silent hypoxia": It's Significant role in COVID-19 morbidity leading to Mortality and Use of Pulse Oximeter may reduce utilization of Ventilators for COVID-19 Patients by early detection of Hypoxia [118]**

Pneumonia is an infection of the lungs in which the air sacs fill with fluid or pus. Normally, patients develop chest congestion and breathing problems. But when Covid pneumonia first attacks, patients don't feel shortness of breath, even when oxygen levels low. And by the time they feel its, they have severe low oxygen levels which lead to pneumonia. Normal oxygen saturation level is 94 percent to 100 percent; in Covid pneumonia patients it goes as low as 50 percent.

**In spite of significant hypoxia, Patient looks like asymptomatic: Why?**

"The coronavirus attacks lung cells that make surfactant. This helps the air sacs in the lungs stay open between breaths and is important for normal lung functioning. As the COVID 19 pneumonia progresses, it causes the air sacs to collapse, and oxygen levels reduces. Yet the lungs initially remain "fine," not become stiff or heavy with fluid. This means patients can still expel carbon dioxide - and without a buildup of carbon dioxide, patients do not feel short of breath." Further in SARS-2 Corona. In the lungs, blood vessel constriction phenomenon also seen in pneumonia caused by COVID-19: Some patients have extremely low blood-oxygen levels and yet are fine for breath. It's possible that at some stages of disease, the virus alters the balance of hormones that helps in regulation of blood pressure and constricts blood vessels going to the lungs. So, oxygen uptake is impeded by constricted blood vessels, rather than by clogged alveoli.

Patients compensate for the reduced oxygen supply in their blood by breathing faster and deeper, and they do without realizing it. This silent hypoxia and the patient's physiological response to it, causes even more inflammation and more air sacs to collapse and the pneumonia worsens. In effect, patients are injuring their own lungs by breathing harder and harder by this Fluid builds up and the lungs become stiff, carbon dioxide rises, and patients develop acute respiratory failure.

"We can identify these positive patient bit early and can treat them in more better way. It just requires detection of silent hypoxia early through a common medical device know as "Pulse oximeter".

Pulse oximetry is as simple as thermometer in usage. These small devices turn on with one button and are placed on a fingertip. All COVID-19 positive patients should have pulse oximetry monitoring at least for two weeks, it's the time in which pneumonia typically develops. All persons with cough, fatigue and fevers should also have pulse oximeter monitoring.

## Conclusion

Scientists all over the world are continuously working to find vaccine and effective therapy against COVID-19. We had summarized COVID-19 review as:

1. Elderly and people with certain comorbidities are found to be most prone towards infection of COVID-19, which requires continuous attention and care.

2. Pneumonia cause by COVID-19 is strong in infectivity but less in virulence compared to SARS and MERS, in terms of mortality and morbidity.

3. So far till date, not specific treatment is available and antiviral drugs, such as remdesivir, or lopinavir/ritonavir, are being used which need solid data from more clinical trials to strengthen their efficacy towards COVID-19.

4. Large number multicentric studies required to be conducted to explore the transmission and pathogenicity mechanism of coronavirus, Molecular mechanism of viral replication for future development of treatment and vaccines.

5. Due to large number of patients, doctors are facing and bearing enormous pressure and severe challenge, including a high risk of infection and inadequate protection, as well as overwork, frustration and exhaustion [117].

6. Maintaining early hypoxia by pulse oximeter may reduce the requirement of ventilator and thus may reduce the morbidity and ultimately mortality [118].

## Bibliography

1. Lu R., *et al*. "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding". *Lancet* 395.10224 (2020): 565-564.

2. Worldometers. "COVID-19 Coronavirus Pandemic". Worldometers (2020).

3. Riou J and Althaus CL. "Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020". *Euro surveillance* 25.4 (2020): 2000058.

4. Liu Y., *et al*. "The reproductive number of COVID-19 is higher compared to SARS coronavirus". *Journal of Travel Medicine* 279.2 (2020): taaa021.

5. Chan JF., *et al*. "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster". *Lancet* 395.10223 (2020): 514-523.

6. Yin Y and Wunderink RG. "MERS, SARS and other coronaviruses as causes of pneumonia". *Respirology* 23.2 (2018): 130-137.

7. Zhou P., *et al*. "A pneumonia outbreak associated with a new coronavirus of probable bat origin". *Nature* 579.7798 (2020): 270-273.

8. Corman VM., *et al*. "Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR". *The European Surveillance* 25.3 (2020): 2000045.

9. Lu H., *et al*. "Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle". *Journal of Medical Virology* 92.4 (2020): 401-402.

10. Guan WJ., *et al*. "Clinical characteristics of coronavirus disease 2019 in China". *The New England Journal of Medicine* (2020).

11. Lee N., *et al*. "A major outbreak of severe acute respiratory syndrome in Hong Kong". *The New England Journal of Medicine* 348.20 (2003): 1986-1994.

12. Assiri A., *et al*. "Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study". *The Lancet Infectious Diseases* 13.9 (2013): 752-761.

13. Wang H., *et al*. "Factors associated with clinical outcome in 25 patients with avian influenza a (H7N9) infection in Guangzhou, China". *BMC Infectious Diseases* 16.1 (2016): 534.

14. Kui L., *et al*. "Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province". *Chinese Medical Journal* (2020).

15. Chung M., *et al*. "CT imaging features of 2019 novel coronavirus (2019-nCoV)". *Radiology* (2020): 200230.

16. Chau TN., *et al*. "SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases". *Hepatology* 39.2 (2004): 302-310.

17. Alsaad KO., *et al*. "Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection-clinicopathological and ultrastructural study". *Histopathology* 72 (2018): 516-524.

18. Cai Q., *et al*. "COVID-19 in a Designated Infectious Diseases Hospital Outside Hubei Province, China". *Journal Medicine Rxiv* (2020).

19. Fan Z., *et al*. "Clinical Features of COVID-19-Related Liver Damage". *Medicine Rxiv* (2020): 20026971.

20. Wang D., *et al*. "Clinical characteristics of 138 hospitalised patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China". *The Journal of the American Medical Association* (2020).

21. Chen N., *et al*. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395 (2020): 507-513.

22. Lu Li., *et al*. "Risk factors related to hepatic injury in patients with corona virus disease 2019". *Medicines Rxiv* (2020).

23. Shi Heshui., *et al*. "Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study". *The Lancet Infectious Diseases* 20 (2020): 425-434.

24. Xu X-W., *et al*. "Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series". *British Medical Journal* 368 (2020): m606.

25. Yang X., *et al*. "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study". *The Lancet Respiratory Medicine* (2020).

26. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395 (2020): 497-506.

27. Zhang B., *et al*. "Clinical characteristics of 82 death cases with COVID-19". *Journal Medicine Rxiv* (2020).

28. Huang Y., *et al*. "Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China". *Medicine Rxiv* (2020).

29. Hoffmann M., *et al*. "The novel coronavirus 2019 (2019-nCoV) uses the SARS-1 coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells". *Bio Rxiv* (2020).

30. Zhang Chao., *et al*. "Liver injury in COVID-19: management and challenges". *The Lancet Gastroenterology and Hepatology* (2020).

31. Zhe Xu., *et al*. "Pathological findings of COVID-19 associated with acute respiratory distress syndrome". *The Lancet Respiratory Medicine* (2020).

32. Chien JY., *et al*. "Temporal changes in cytokine/chemokine profiles and pulmonary involvement in severe acute respiratory syndrome". *Respirology* 11 (2006): 715-722.

33. Chu H., *et al*. "Middle east respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways". *The Journal of Infectious Diseases* 213 (2016): 904-914.

34. Tisoncik JR., *et al*. "Into the eye of the cytokine storm". *Microbiology and Molecular Biology Reviews* 76 (2012): 16-32.

35. Kim KD., *et al*. "Adaptive immune cells temper initial innate responses". *Nature Medicine* 13 (2007): 1248-1252.

36. Liu J., *et al*. "Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients". *Med Rxiv* (2020).

37. Fan Z., *et al*. "Clinical Features of COVID-19-Related Liver Damage". *Bio Rxiv* (2020).

38. The COVID-19 Investigation Team. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States". *Med Rxiv* (2020).

39. Bangash MN., *et al*. "COVID-19 and the liver: little cause for concern". *The Lancet Gastroenterology and Hepatology* 20 (2020): 30084-30084.

40. Kumar D., *et al*. "Severe acute respiratory syndrome (SARS) in a liver transplant recipient and guidelines for donor SARS screening". *American Journal of Transplantation* 3 (2003): 977-981.

41. Holshue Michelle L., *et al*. "First case of 2019 novel coronavirus in the United States". *The New England Journal of Medicine* 382.10 (2020): 929-936.

42. Leung WK., *et al*. "Enteric involvement of severe acute respiratory syndrome associated coronavirus infection". *Gastroenterology* 125 (2003): 1011-1017.

43. Chan JF-W., *et al*. "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster". *Lancet* 395 (2020): 514-523.

44. Pan L., *et al*. "Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study, The". *The American Journal of Gastroenterology* (2020).

45. Wei XS., *et al*. "Clinical characteristics of SARS-CoV-2 infected pneumonia with diarrhea". The Lancet Respiratory Medicine-Manuscript Draft (2020).

46. Zhang H., *et al*. "The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes". *Preprint Bio Rxiv* (2020): 927806.

47. Budden KF., *et al*. "Emerging pathogenic links between microbiota and the gut-lung axis". *Nature Reviews Microbiology* 15 (2017): 55-63.

48. Mao R., *et al*. "Implications of COVID-19 for patients with preexisting digestive diseases (2020): 30076-30075.

49. Guan WJ., *et al*. "Clinical Characteristics of Coronavirus Disease 2019 in China". *The New England Journal of Medicine* (2020).

50. Chen N., *et al*. "Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study". *Lancet* 395 (2020): 507-513.

51. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395 (2020): 497-506.

52. Liu K., *et al*. "Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province". *Chinese Medical Journal* (2020).

53. Lu X., *et al*. "SARS-CoV-2 Infection in Children". *The New England Journal of Medicine* (2020).

54. Shi H., *et al*. "Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study". *The Lancet Infectious Diseases* (2020).

55. Wang D., *et al*. "Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China". *The Journal of the American Medical Association* (2020).

56. Xu XW., *et al*. "Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series". *British Medical Journal* 368 (2020): m606.

57. Yang X., *et al*. "Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study". *The Lancet Respiratory Medicine* (2020).

58. Zhou F., *et al*. "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study". *Lancet* (2020).

59. Zhang JJ., *et al*. "Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China". *Allergy* (2020).

60. Xiao F., *et al*. "Evidence for gastrointestinal infection of SARS-CoV-2". *Gastroenterology* (2020).

61. Booth CM., *et al*. "Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area". *The Journal of the American Medical Association* 289 (2003): 2801-2809.

62. Cheng VC., *et al*. "Viral replication in the nasopharynx is associated with diarrhea in patients with severe acute respiratory syndrome". *Clinical Infectious Diseases* 38 (2004): 467-475.

63. Choi KW., *et al*. "Outcomes and prognostic factors in 267 patients with severe acute respiratory syndrome in Hong Kong". *Annals of Internal Medicine* 139 (2003): 715-723.

64. Jang TN., *et al*. "Severe acute respiratory syndrome in Taiwan: analysis of epidemiological characteristics in 29 cases". *Journal of Infection* 48 (2004): 23-31.

65. Kwan AC., *et al*. "Severe acute respiratory syndrome-related diarrhea". *Journal of Gastroenterology and Hepatology* 20 (2005): 606-610.

66. Lee N., *et al*. "A major outbreak of severe acute respiratory syndrome in Hong Kong". *Journal of Gastroenterology and Hepatology*348 (2003): 1986-1994.

67. Leung CW., *et al*. "Severe acute respiratory syndrome among children". *Pediatrics* 113 (2004): e535-e543.

68. Leung WK., *et al*. "Enteric involvement of severe acute respiratory syndrome-associated coronavirus infection". *Gastroenterology* 125 (2003): 1011-1017.

69. Liu CL., *et al*. "Clinical and laboratory features of severe acute respiratory syndrome vis-a-vis onset of fever". *Chest* 126 (2004): 509-517.

70. Peiris JS., *et al*. "Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study". *Lancet* 361 (2003): 1767-1772.

71. Al Ghamdi M., *et al*. "Treatment outcomes for patients with Middle Eastern Respiratory Syndrome Coronavirus (MERS CoV) infection at a coronavirus referral center in the Kingdom of Saudi Arabia". *BMC Infectious Diseases* 16 (2016): 174.

72. Almekhlafi GA., *et al*. "Presentation and outcome of Middle East respiratory syndrome in Saudi intensive care unit patients". *Critical Care* 20 (2016): 123.

73. Arabi YM., *et al*. "Critically Ill Patients With the Middle East Respiratory Syndrome: A Multicenter Retrospective Cohort Study". *Critical Care Medicine* 45 (2017): 1683-1695.

74. Assiri A., *et al*. "Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study". *The Lancet Infectious Diseases* 13 (2013): 752-761.

75. Assiri A., *et al*. "Hospital outbreak of Middle East respiratory syndrome coronavirus". *The New England Journal of Medicine* 369 (2013): 407-416.

76. Choi WS., *et al*. "Clinical Presentation and Outcomes of Middle East Respiratory Syndrome in the Republic of Korea". *The Journal of Infection and Chemotherapy* 48 (2016): 118-126.

77. Yang J., *et al*. "Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis". *International Journal of Infectious Diseases* (2020).

78. Liang W., *et al*. "Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China". *The Lancet Oncology* 21.3 (2020): 335-337.

79. Tang JW., *et al*. "Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises". *Journal of Hospital Infection* 64 (2006): 100-114.

80. Endoscopy activity and COVID-19: BSG and JAG guidance (2020).

81. Zhang Y., *et al*. "Suggestions of Infection Prevention and Control in Digestive Endoscopy During Current 2019-nCoV Pneumonia Outbreak in Wuhan". Hubei Province, China (2020).

82. Repici A., *et al*. "Coronavirus (COVID-19) outbreak: what the department of endoscopy should know". *Gastrointestinal Endoscopy* (2020).

83. European Centre for Disease Prevention and Control (ECDC). Personal protective equipment (PPE) needs in healthcare settings for the care of patients with suspected or confirmed novel coronavirus (2019-nCoV) 2020. Stockholm: ECDC (2020).

84. Geller C., *et al*. "Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies". *Viruses* 4.11 (2012): 3044-3068.

85. ASGE Quality Assurance in Endoscopy Committee, Calderwood AH., *et al.* "ASGE guideline for infection control during GI endoscopy". *Gastrointestinal Endoscopy* 87.5 (2018): 1167-1179.

86. S Musa. "Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now?" *Arab Journal of Gastroenterology* (2020).

87. National Health Commission of the People's Republic of China. Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (2020).

88. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected (2020).

89. Chen L., *et al*. "Convalescent plasma as a potential therapy for COVID-19". *The Lancet Infectious Diseases* (2020).

90. Agostini ML., *et al*. "Coronavirus susceptibility to the antiviral remdesivir (gs-5734) is mediated by the viral polymerase and the proofreading exoribonuclease". *mBio* 9.2 (2018): e00221-e002218.

91. Holshue ML., *et al*. "First case of 2019 novel coronavirus in the United States". *The New England Journal of Medicine* (2020).

92. Aguiar ACC., *et al*. "Chloroquine analogs as antimalarial candidates with potent in vitro and in vivo activity". *The International Journal for Parasitology – Drugs and Drug Resistance* 8.3 (2018): 459-464.

93. Savarino A., *et al*. "Effects of chloroquine on viral infections: an old drug against today's diseases?" *The Lancet Infectious Diseases* 3.11 (2003): 722-727.

94. Vincent MJ., *et al*. "Chloroquine is a potent inhibitor of SARS coronavirus infection and spread". *Virology Journal* 2 (2005): 69.

95. Golden EB., *et al*. "Quinoline-based antimalarial drugs: a novel class of autophagy inhibitors". *Neurosurgical Focus* 38.3 (2015): E12.

96. Arabi YM., *et al*. "Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-β1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial". *Trials* 21.1 (2020): 8.

97. Chu CM., *et al*. "Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings". *Thorax* 59.3 (2004): 252-256.

98. Lim J., *et al*. "Case of the index patient who caused tertiary transmission of COVID-19 infection in Korea: the application of lopinavir/ritonavir for the treatment of COVID-19 infected pneumonia monitored by quantitative RT-PCR". *Journal of Korean Medical Science* 35.6 (2020): e79.

99. Li H., *et al*. "Potential antiviral therapeutics for 2019 Novel Coronavirus". *Chinese Journal of Tuberculosis and Respiratory Diseases* 43 (2020): E002.

100. Cvetkovic RS and Goa KL. "Lopinavir/ritonavir: a review of its use in the management of HIV infection". *Drugs* 63.8 (2003): 769-802.

101. Paaasld-Idsa H Guidance and Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection". *Clinical Infectious Diseases* 67.10 (2018):1477-1492.

102. Tsang K and Zhong NS. "SARS: pharmacotherapy". *Respirology* 8.1 (2003): S25-S30.

103. Arabi YM., *et al*. "Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study". *Clinical Infectious Diseases* (2019).

104. McQuade B and Blair M. "Influenza treatment with oseltamivir outside of labeled recommendations". *American Journal of Public Health* 72.2 (2015): 112-116.

105. Jefferson T., *et al*. "Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments". *British Medical Journal* 348 (2014): g2545.

106. Al-Badr AA and Ajarim TDS. "Ganciclovir". *Purchase Profiles of Drug Substances, Excipients, and Related Methodology* 43 (2018): 1-208.

107. Rossignol JF. "Nitazoxanide: a first-in-class broad-spectrum antiviral agent". *Antiviral Research* 110 (2014): 94-103.

108. Cao J., *et al*. "A screen of the NIH clinical collection small molecule library identifies potential anti-coronavirus drugs". *Antiviral Research* 114 (2015): 1-10.

109. Rossignol JF. "Nitazoxanide: a first-in-class broad-spectrum antiviral agent". *Antiviral Research* 110 (2014): 94-103.

110. Tchesnokov EP., *et al*. "Mechanism of inhibition of ebola virus rna-dependent rna polymerase by remdesivir". *Viruses* 11.4 (2019): E326.

111. Lo MK., *et al*. "Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge". *Science Translational Medicine* 11.494 (2019): eaau9242.

112. Hsieh HP and Hsu JT. "Strategies of development of antiviral agents directed against influenza virus replication". *Current Pharmaceutical Design* 13.34 (2007): 3531-3542.

113. Nishimura H and Yamaya M. "A synthetic serine protease inhibitor, Nafamostat Mesilate, is a drug potentially applicable to the treatment of ebola virus disease". *The Tohoku Journal of Experimental Medicine* 237.1 (2015): 45-50.

114. Furuta Y., *et al*. "Favipiravir (T- 705), a novel viral RNA polymerase inhibitor". *Antiviral Research* 100.2 (2013): 446-454.

115. Goldhill DH., *et al*. "The mechanism of resistance to favipiravir in influenza". *Proceedings of the National Academy of Sciences of the United States of America* 115.45 (2018): 11613-11618.

116. Cardile AP., *et al*. "Will there be a cure for Ebola?" *The Annual Review of Pharmacology and Toxicology* 57 (2017): 329-348.

117. Kang L., *et al*. "The mental health of medical workers in Wuhan, China dealing with the 2019 novel coronavirus". *Lancet Psychiatry* 7.3 (2020): e14.

118. The New York Times. "The Infection That's Silently Killing Coronavirus Patients" (2020).

**Volume 7 Issue 7 July 2020**