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COVID-19: From bench to bed side

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ABSTRACT

Background and aims: The last two decades have experienced the outbreaks of three different coronaviruses in the different parts of the world namely; Severe acute respiratory syndrome cornonavirus-1 (SARS-CoV-1), Middle East respiratory syndrome (MERS-CoV) and Severe acute respiratory syndrome cornonavirus-2 (SARS-CoV-2). We aimed to delineate the differences in viral dynamics and clinical features between them and tried to focus on every basic details of SARS-COV-2 (COVID-19) that every health care provider must know.
Methods: We systematically searched the PubMed database up till April 2, 2020 and retrieved all the articles published on SARS-CoV-2, SARS-CoV-1, MERS-CoV that dealt with viral dynamics.
Results: Ample data is available to suggest the differences in etiology, transmission cycle, diagnosis, genetics, hosts, reproductive rates, clinical features, laboratory diagnosis and radiological features between SARS-CoV-1, MERS-CoV and SARS-CoV-2.
Conclusion: Although SARS-CoV-2 (COVID-19) is more infectious than SARS-CoV-1 and MERS-CoV, most infections are generally mild and self-limiting. However, case-fatality rates are very high in patients with COVID-19 with comorbidities, compared to SARS-CoV-1 and MERS-CoV.

1. Introduction

Viral diseases continue to pose a serious threat to public health. The world has witnessed several viral epidemics in past twenty years that include severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2003, H1N1 influenza in 2009 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.

Recently, an outbreak of pneumonia of unknown etiology was detected in Wuhan City, Hubei Province of China and reported to China Country Office of The World Health Organization (WHO) on December 31, 2019. The National Health Commission of China reported that the outbreak is associated with exposures in one seafood market in Wuhan City. The etiological agent of the atypical pneumonia was isolated on January 7, 2020 by the Chinese authorities as novel coronavirus (2019-nCoV). The genetic sequence of the novel coronavirus identified was shared to other countries to develop specific diagnostic kits on January 12, 2020. Subsequently, the Ministry of Public Health Thailand, the Ministry of Health, Labour and Welfare, Japan and Republic of Korea reported their first imported case of lab-confirmed 2019-nCoV on 13 January 13, January 15 and January 20, 2020 respectively. Subsequently, International Committee on Taxonomy of Viruses termed it SARS-Cov-2, due to similarity of its symptoms to those induced by the SARS. On February 11, 2020, the WHO announced that the disease caused by this new virus as a "COVID-19," which is the acronym of "coronavirus disease 2019". On March 11, 2020, WHO declared this disease as pandemic. As of March 30, 2020, WHO has reported 693,224 case and 33,104 death, that has occurred worldwide [1].

2. Etiology

Coronavirus (CoV) belongs to Coronaviridae family of order Nidovirale. CoV are single-stranded RNA viruses (+ssRNA) having a spike glycoprotein on the envelope, giving it a crown-like appearance, when seen on electron microscope. The subfamily Orthocoronavirinae has four genera of CoVs: Alpha-coronavirus, Beta-coronavirus, Delta-coronavirus and Gamma-coronavirus. Furthermore, the genus Beta-coronavirus divides into five sub-genera or lineages. While bats and rodents are considered to be the genetic sources of alpha and beta-coronavirus, avian species represents the genetic sources of delta and gamma-coronavirus [2].

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To date, seven human coronaviruses (HCov) have been identified. The A lineage of beta-coronavirus (such as HCoV-OC43 and HCoV-HKU1) as well as alpha-coronavirus (such as HCoV-229E and HCoV-NL63), causes common colds and self-limiting respiratory infections. In contrast, B lineage of beta-corona virus causes SARS-CoV-1, SARS-CoV-2 (COVID-19), while C lineage of beta-corona virus causes MERS-CoV; both responsible for recent epidemics with a variable clinical severity of pulmonary and extra-pulmonary involvement and associated significant increase in mortality [3].

COVID-19 is a single-stranded, positive sense RNA virus, having a diameter of 60–140 nm with a round or elliptic shape, however, it often exists in pleomorphic form. Its RNA genome contains 29891 nucleotides, encoding for 9860 amino acids and shares 99.9% sequence identity, suggesting a very recent host shift into humans [4,5]. Like other CoVs, it is sensitive to ultraviolet rays and heat. Besides, these viruses can be effectively inactivated by lipid solvents including chloroform, ether (75%), ethanol, peroxyacetic acid and chlorine-containing disinfectant. Chlorhexidine does not inactivate this virus [4,5].

3. Transmission cycle

Coronaviruses are naturally hosted by bats and it is believed that most human coronaviruses are derived from the bat reservoir [5,6]. Genomic sequence studies of COVID-19 have identified nearly 50%, 79% and 96% similarity to MERS-CoV, SARS-CoV-1 and bat SARS-related coronavirus, respectively [7–9]. The specific route of transmission to human from natural reservoirs is still yet to be known, however, some of the studies suggests pangolin could be the intermediate mammalian hosts. Since spike protein of SAR-CoV-2 are nearly identical to one virus isolated from pangolin, it is believed that pangolins could have provided a partial spike gene to SARS-CoV-2, to infect mammals [10,11]. A recent study has also shown a development of new variations at the functional sites in the receptor-binding domain of the spike of SARS-CoV-2 and viruses from pangolin, likely caused due to either a natural selection or mutations or recombination or both [12].

Nevertheless, once human is infected, virus could also be transmitted from human-to-human through the respiratory droplets and aerosols from coughing and sneezing, like other respiratory pathogens, including SARS-CoV-2. SARS-CoV-2 also uses the angiotensin converting enzyme II (ACE2) receptors like the SARS-CoV [13].

The incubation period of COVID-19 could vary from 3 days to 14 days, based on the data from Chinese CDC. The longest time from infection to symptoms was 12.5 days (95% CI, 9.2–18 days). The Chinese epidemic also doubled about every seven days and on average, each patient transmits the infection to an additional 2.2 individuals, suggesting the basic reproduction number (R0 or R naught) to be 2.2, which is a bit lesser compared to R0 of the SARS-CoV-1 epidemic of nearly 3.0, in 2002–2003 [14,15]. An epidemiological and transmission difference in characteristics between SARS-CoV1, MERS and Covid-19 has been summarized in Table 1.

A recent study from a genetic analysis of SARS-CoV-2 genomes ($n = 103$) found this virus to be evolving into two major types (designated as L and S) with two different SNPs. While the L type is more prevalent (~70%), aggressive and spread more quickly, as seen in the early stages of the outbreak in Wuhan, the S type (~30%) is an ancestral version, evolutionarily older, and less aggressive. It appears that the frequency of the L type has decreased after early January 2020, and it is hypothesized that the change in selective pressure might change the behavior of this virus. It is thought that coercive human interventions may have placed a more severe selective pressure on the L type to mutate to S type. Conversely, the S type might have been increased also due to a relatively weaker selective pressure [13].

These ultra-rapid development in viral epidemics strongly suggest an urgent need of understanding about these viral dynamics to cope up with this public health emergency of COVID-19.

4. Clinical features of COVID-19

There may be a variety of symptoms that a patient with COVID-19 may present with. The usual triad to suspect is fever, dry cough and dyspnea. It may be classified as asymptomatic or symptomatic, carrier or infective state, from mild prodrome to profusely symptomatic; depending upon immunity status of patients. There are reports of conjunctivitis, gastrointestinal symptoms like diarrhea, vomiting, nausea, abdominal pain. Some critically ill may present without fever but with abdominal pain, anorexia and dyspnea. Less common symptoms were gastrointestinal, anosmia, dysgeusia [13]. Overall, the case fatality rate was varied between 2.3% and 5% with an average of 3%. Poor prognostic epidemiological risk factors include older age, male sex, smokers and associated comorbidities including obesity, hypertension, diabetes, chronic pulmonary diseases, cardiovascular disease and chronic kidney disease. More the number of risk factors, more is the severity at presentation [18].

Depending on the clinical features of COVID-19, patients are generally divided as mild, moderate, severe and critical [18].

a. *Mild COVID-19*: low grade fever, cough, malaise, rhinorrhea, sore throat with or without hemoptysis, nausea, vomiting, diarrhea, but without any radiological features of pneumonia and absence of mental changes.
b. *Moderate COVID-19*: fever, respiratory symptoms including dry cough and shortness of breath that may emerge along with the radiological features [15].
c. *Severe COVID-19*: dyspnea, respiratory frequency $\geq$30/minute, blood oxygen saturation $\leq$93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24–48 h.
d. *Critical COVID-19*: usually develops after 7 days in patients with mild/moderate/severe COVID-19 with features of Acute respiratory distress syndrome (ARDS) requiring mechanical ventilation along with presence of multiorgan dysfunction failure, metabolic acidosis and coagulation dysfunction.

The differences in clinical features of SARS-CoV-2, SARS-Co-V1, MERS-CoV have been summarized in Table 2 [16–23].

5. Laboratory findings

Hemogram: leukopenia especially lymphopenia (in 80% of cases), mild thrombocytopenia. However, leukocytosis has also been reported [13,17]. Some researchers suggested neutrophil-to-lymphocyte ratio (NLR) as an independent risk factor for severe illness and NLR $\geq$ 3.13 was considered as threshold for progression to severe illness in COVID-19 patients.

Inflammatory Markers: serum procalcitonin is normal initially, may increase with severity. Increase in C-Reactive Protein (CRP), lactate dehydrogenase (LDH), SGOT, troponin (rule out non coronary false positive; refer Table 3), D-dimer, ferritin, Creatine kinase and ESR [24]. CRP may be used to track the severity of disease. Severe and critically ill patients may have very high levels of other inflammatory markers, interleukin (IL)-6, IL-4, IL-10, and tumor necrosis factor (TNF)-α. Poor laboratory prognostic factors include high D-Dimer, lymphopenia, thrombocytopenia, CRP [13]. However, these findings may not always concur with the contact/travel history/clinical symptoms. Table 3 summarizes the important investigations and prognostic factors [16,24].

Serology: Blood sampling is much easier than swab sampling

Table 1
Differences in epidemiological characteristics between SARS-CoV-2, SARS-CoV-1 and MERS-CoV [15,18,23,24,31].

Feature	SARS-CoV-2	SARS-CoV-1	MERS-CoV
Origin	Wuhan, China	Guangdong, China	Jeddah, Saudi Arab
Asymptomatic viral load	High	Less	Less
Long period of infectivity	Yes	No	No
Estimated R0	2.2–3.28	2.0–5.0	<1
Median Incubation (days)	6.4 (0–24)	4.6 (3.8–5.8)	5.2(1.9–14.7)
Serial interval (days)	2.6–7.5	8.4	12.6
Case-fatality rate (%)	3–3.5	9.6	35.5
Case-fatality rate with comorbidities (%)	73.3	46.0	60.0
Host			
Natural Host	Bats	Chinese horseshoe bats	Bats
Intermediate Host	Pangolin	Civet	Camel
Terminal Host	Humans	Humans	Humans
Transmission			
Respiratory droplets	Yes	Yes	Yes
Fomites, Contact	Yes	No	No
Zoonotic	Yes	Sporadic	Sporadic
Aerosol	High Possibility	Yes	Yes
Feco-Oral	High Possibility	Yes	No
Human to human	Yes	Yes	Limited
Nosocomial	Yes	Yes	Yes
Cell entry receptor	ACE2	ACE2	DPP-4/CD26

Table 2
Differences in clinical features between SARS-CoV-2, SARS-CoV-1 and MERS-CoV [17–24].

FEATURE	SARS-CoV-2	SARS-CoV-1	MERS-CoV
Mild	80%	61%	21%
Severe/Critical	14–15%/4–5%	11%	46%
Fever	Yes, Mild	Yes	Yes
Chills	No	Yes	Yes
Dry Cough	Yes	Yes	Yes
Rhinorrhea	May be	Yes	May not
Sputum	Rare	Yes	May be
Diarrhea	Less	Yes	Yes
MOF	Renal, Liver, Testes	Liver	Liver
Critical	ARDS	ARDS	ARDS, ARF

MOF – multi-organ failure, ARDS: Acute Respiratory Distress Syndrome, ARF-Acute Renal Failure.

from oropharynx or nasopharynx. Two kinds of serological test can detect COVID-19 - a. Enzyme linked immune-sorbent assay (ELISA) and b. Immunochromatography (Card test). ELISA is considered better compared to card test due to higher sensitivity. While ELISA has sensitivity of 87.3%, Card test has a sensitivity of 82.4%, and both have specificity of 100%. However, card test is convenient, cheaper and offers a rapid turnover [25]. ELISA is based on Rp3 nucleoprotein to detect IgM and IgG against SARS-CoV-2. Although ELISA has quick turn over time, however it may have a false positive results due to N (Nucleocapsid) proteins of SARS-CoV-2 [16,26]. Cross reactivity is expected with SARS-CoV-1 infection since there is 90% homology in genetic sequence with SARS-CoV-2. Hence, S protein (Transmembrane Glycoprotein Spike) ELISA should be developed specific to SARS-CoV-2.

Reverse-transcriptase polymerase-chain-reaction (RT-PCR): RT-PCR, and genomic sequencing (wherever available) is the gold standard and confirmatory test for COVID-19. Overall, the sensitivity of RT-PCR is nearly 70% with a 30% false negative rate, and its sensitivity decreases from >90% on day 1- to 3 post-symptoms, to nearly 80% on day 6 and < 50% by day 14 [27]. For RT-PCR, specimen collection from the upper/lower respiratory tract or sputum or bronchoalveolar lavage samples to be performed under strict precautions, and should be taken as early as symptom onset, to obtain high virus concentrations [28]. It should be noted that RT-PCR may take few hours to 2 days for reporting and second sample with different viral gene may be needed if initial test is negative. Moreover, RT-PCR may be false negative at a times e.g. low viral load in very early phase or in late phase of disease, mutation of COVID-19 virus or other technical difficulties in collection of samples. Similarly, result may be false-positive in influenza or other respiratory pathogens. In either case it is important to remain vigilant. Other issues with RT-PCR is incorrect sample collection and processing, potential risk to health care workers due to aerosol transmission, beside delayed report delivery, requirement of expertise, setup of laboratory and the cost [27].

Although both serology and RT-PCR are complimentary to each other, however since antibodies can appear as early as 1-day post-symptoms, it is estimated that IgM-ELISA can detect more cases than RT-PCR on day 5.5 of illness [27]. While another study reported a higher sensitivity (66.7%) of RT-PCR in first week, compared to the serological test (38.0%). However, during second week, the serological test had higher sensitivity than RT-PCR. Collectively, this suggest ideally to combine both the modalities of test to increase the sensitivity for early detection and diagnosis of COVID-19 [27,28]. Indeed, the combined IgM-ELISA plus RT-PCR has been shown to detect 98.6% of cases versus 51.9% with a single RT-PCR [26–28].

From the available evidence [16,25–28] and to put the things in to perspective, it is logical as well as advisable (but not superseding any recommendation, if any) that – a. for the rapid screening of

Table 3
Summary of important investigations and prognostic factors [17,25].

Important investigations	Hemogram, CRP, Troponin, ferritin, D-dimer, creatinine, Liver function tests
Inflammatory Markers	CRP, Interleukins:IL-6, IL-4, IL-10, and tumor necrosis factor (TNF)-α.
Poor laboratory prognostic factors	High D-Dimer, ferritin and CRP; neutrophil-to-lymphocyte ratio ≥3.13, lymphopenia, thrombocytopenia
Non-ischemic causes of troponin positivity	VT, SVT, AF, myocarditis, pericarditis, fibrin in specimen, heterophile antibodies.

AF-Atrial fibrillation, VT-ventricular tachycardia, SVT- Supra ventricular tachycardia, CRP- C-reactive protein, AF- Atrial fibrillation.

Table 4
Specimen positivity for SARS-CoV-2 in descending order [29].

Specimen type	Positivity (%)
Broncho-alveolar lavage	93
Sputum	72
Nasal swab	63
Fibro-bronchoscope brush biopsy	46
Pharyngeal swabs	32
Feces	29
Blood	1
Urine	0

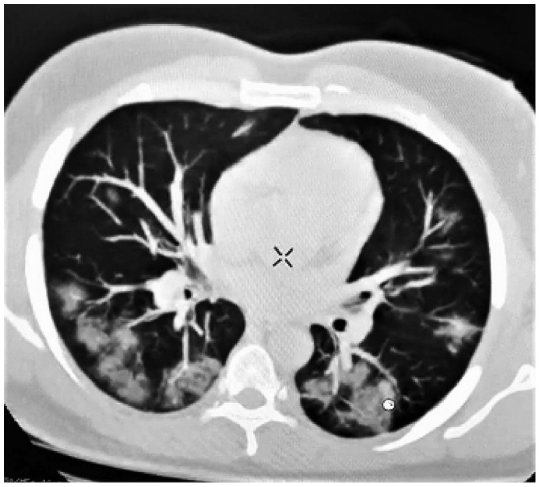

Fig. 1. High-resolution CT thorax of a 42-year-old male, doctor by profession without any comorbidities, showing progressive stage of GGO.

SARS-CoV-2 carriers (symptomatic or asymptomatic), combined IgM- IgG-ELISA may offer a better utility and sensitivity, compared to a either a IgM- or IgG-ELISA test alone. b. all symptomatic subjects or contacts should be assessed with rapid antibody testing first, if positive then RT-PCR should be done as the confirmatory test. c. all highly suspicious cases should undergo RT-PCR first, even if the rapid antibody tests are negative. d. If antibody test is negative initially, it should be re-tested after 7–10 days.

Bronchoscopy: Bronchoalveolar lavage (BAL) may be done when sputum sample cannot be obtained to rule out alternative diagnosis such as tuberculosis and other bacterial or fungal pneumonias and to remove bronchial mucous plugs. Strict precautions are to be taken while doing BAL to avoid aerosol infections. The sensitivity (positivity rates) of RT-PCR in patients with SARS-CoV-2 in different specimen in was lowest for urine 0% and highest for BAL 93%, as summarized in Table 4 [29].

6. Radiology

Radiological examination includes Chest X-ray (CXR), Computed tomography (CT) and point-of-care lung sonography, done on a case to case basis. Avoid pulmonary function test as chances of droplet infection may be high. CXR findings are non-specific, normal in initial phases to patchy unilateral or bilateral involvement to lobar/multi-lobar/bilateral consolidation [30].

The CT changes are of four stages: a. *Early stage* of ground glass opacities (GGO) in sub-pleural distribution involving mainly lower lobes. b. *Progressive stage* of multi-lobe distribution with GGO, bilateral consolidation of airspaces (Fig. 1). c. *Peak stage* of dense consolidation in almost all cases (Fig. 2). d. *Absorption stage* denotes GGO without crazy paving pattern.

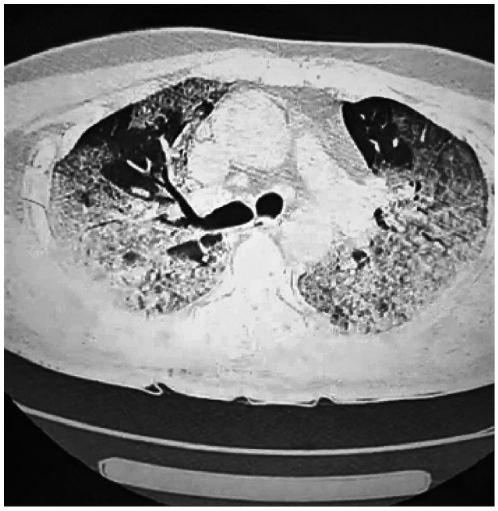

Fig. 2. High-resolution CT thorax of a 65-year-old male and a known diabetic, showing dense consolidation.

Table 5
Radiographic characteristics of SARS-CoV-2, SARS-CoV-1, MERS-CoV [17,23,24].

Feature	SARS-CoV-2	SARS-CoV-1	MERS-CoV
Area	B/L Patchy	Basal/Peripheral	U/L, B/L Hilar
GGO	Yes	Yes	Yes
Effusion	No, Rare	No	Yes, Small

GGO: Ground Glass Opacity, U/L –unilateral, B/L-bilateral.

Sonography of the lungs may be helpful as it can be done at bedside to reduces the movement of patient to different department. There can be irregular pleural lines, consolidation of subpleural areas, areas of white lung and thick B lines [31].

Table 5 shows summarizes the differences in radiological findings of SARS-CoV-2, SARS-CoV-1, MERS-CoV [16,22,23,31].

7. Prevention and treatment

Isolation is the main stay of prevention. Vaccine for COVID-19 is currently under phase 1 trial. Recently a mRNA-1273 vaccine that targets the Spike (S) protein of the coronavirus has been manufactured by Vaccine Research Center, Moderna (a unit of the National Institute of Allergy and Infectious Diseases) in USA. The trial began on 16 March at the Kaiser Permanente Washington Health Research Institute in Seattle, Washington in total of 45 males and females aged between 18 and 45 where the participants will be divided into three cohorts and will be administered 25 μg (mcg), 100mcg or 250mcg dose 28 days apart.

Presently, treatment of COVID-19 is only supportive, and prevention is the only way to reduce the community transmission. Convalescent sera from COVID-19 positive patients has been approved by FDA in severe and critical patients only [27]. Although no anti-viral therapy or other drugs till the time of writing is proven to work substantially against the COVID-19 in humans, few small-scale studies have claimed some benefit with chloroquine and hydroxychloroquine in less severely ill patients. Other drugs which are also being tried include Lopinavir/Ritonavir, Remdesivir, Favipiravir, Oseltamivir, Ribavirin, Interferon beta, Tocilizumab and Abidol [32]. Multiple RCTs are currently undergoing with these agents and results are eagerly awaited.

8. Conclusions

SARS-CoV-2 is more infectious than SARS-CoV-1 and MERS-CoV. Most infections with COVID-19 are generally mild and self-limiting. However, even asymptomatic carriers may spread infection. Newer possibilities of feco-oral transmission are also speculated. Rapid diagnostic tests will be helpful for screening and diagnosing COVID-19 patients. Trials for specific anti-viral drugs and vaccine are currently underway to curb the pandemic, meanwhile isolation and containment is only way of prevention from contracting COVID-19.

Declaration of competing interest

We hereby declare that we have no conflict of interest related to this article.

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