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Corona Virus: SARS, MERS and SARS-CoV-2 a Real Three Threats of 21st Century

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ABSTRACT

Since the discovery to before the start of the 21st century, it was considered that coronaviruses (CoVs) are the pathogens of great relevance in veterinary medicine but with a reduced impact on human health. But with the beginning of 21st century CoVs emerged as the major global concern in human health with the epidemic of severe acute respiratory syndrome (SARS) in 2002-2003 and later after few years Middle East respiratory syndrome (MERS) in 2012. Moreover, one of the major outbreaks of 21st century of CoVs took place in China in the end of December 2019 which becomes the global concern in human public health within few months. CoVs are the viruses belong to Coronaviridae family with single stranded positive sense approximately 30 kb in size RNA enveloped viruses. Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus are the medically important four genera of CoVs and it was investigated that SARS-CoV and MERS-CoV belong to the genus Betacoronavirus. Furthermore, genome sequencing and phylogenetic analysis explored that novel SARS-CoV-2 previously known as 2019-nCoV or COVID-19 also belongs to the same genus. Currently coronaviruses attracted the attention of researchers, scientists and pharmaceutical industries worldwide due to major risk for global public health, so we compiled very recent data to summarize the historical aspects, epidemiological aspects as well as progress in the management of the three major coronaviruses related diseases in humans.

Keywords: Coronaviruses, RNA viruses, 21st century major viral threat, SARS-CoV-2, management

Introduction

Coronaviruses are positive, single-stranded RNA viruses that replicate in the cytoplasm and bud into cytoplasmic vesicles from the endoplasmic reticulum. Coronaviruses are divided into three groups: alpha, beta, and gamma [1,2]. Coronaviruses are a large family of viruses that usually cause mild to moderate upper-respiratory tract illnesses, like the common cold, in people. However, three times in the 21st century coronavirus outbreaks have emerged from animal

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reservoirs to cause severe disease and global transmission concerns [3,4]. More than 50% of all common colds are caused by coronaviruses with self-limited illness in healthy people but can be accompanied with complications in immunosuppressed individuals.

Human coronaviruses (hCoVs), termed hCoV-OC43 (1st hCOv), hCoV-229E (2nd hCov) have been known since the 1960s and cause chiefly mild respiratory disease [5,6]. In 2002–2003, an outbreak of severe acute respiratory syndrome (SARS) leading to ≈850 deaths was caused by a novel group 2b betacoronavirus, SARS-CoV (3rd hCoV) [7,8]. A fourth human coronavirus, hCoV-NL63 (4th hCoV), was identified in 2004 in the Netherlands. It was isolated from a 7-month-old child suffering from bronchiolitis and conjunctivitis, and was categorized to be a new group 1 coronavirus [9]. The fifth HCoV-HKU1 (5th hCoV), was discovered in Hong Kong in 2005. This group 2 coronavirus was detected in a 71-year-old man with pneumonia [10]. Middle East respiratory syndrome (MERS) were first documented in KSA in September 2012 and then attributed to the novel virus of betacoronavirus and named as MERS-Cov (6th hCoV) [11]. After seven years again at china in wuhan city in December 2019 novel coronavirus were emerged vigoursly causing severe respiratory infection called coronavirus disease 19 (COVID-19) which attributed to that virus who called SARS-CoV2 (7th hCoV) [12]. It is easy to allocate the seven human coronavirus (1st to 7th) in two sections (20th century hCoV and 21st century hCoV).

Classification

Coronaviruses (CoVs) were discovered in the 1960s and they were classified under family Coronaviridae, which is the largest family within the order Nidovirales (Figure 1) [13]. Family Coronaviridae encompasses two subfamilies: subfamily Orthocoronavirinae and subfamily Torovirinae. Subfamily Orthocoronavirinae includes four genera: alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus. CoVs are typically harbored in mammals and birds and are common in camels, cattle, cats, bats, and other animals. Alpha and betacoronaviruses circulate in mammals, including bats. Gammacoronaviruses mostly infect avian species Pathogens and a few mammalian species, whereas deltacoronaviruses infect birds and mammals [14]. Animal CoVs are known to cause important diseases in animals and could be responsible for economic losses in domestic animals or birds [15-17]. These animal CoVs include avian infectious bronchitis virus (IBV), transmissible gastroenteritis virus (TGEV), porcine epidemic diarrhea virus (PEDV), and more recently, swine acute diarrhea syndrome-CoV (SADS-CoV). Although rare, animal CoVs have the ability to infect humans and could further spread through human-to human transmission [16]. The first discovered CoVs were IBV that causes respiratory disease in chickens and the human CoVs, human CoV-229E (HCoV-229E) and human CoV-OC43 (HCoV-OC43), which cause the common cold in humans [18]. Since the emergence of HCoV-229E and HCoV-OC43, several other HCoVs were discovered, such as Severe Acute Respiratory Syndrome-CoV (SARS-CoV) in 2002, HCoV-NL63 in 2004, HCoV-HKU1 in 2005, Middle East Respiratory Syndrome-CoV (MERS-CoV) in 2012 [19]. Starting December 2019, there were reports of patients presenting with severe viral pneumonia in the city of Wuhan, China. Sequencing of the virus from these patients has identified a novel CoV as the causative agent of this respiratory disease [20,21].

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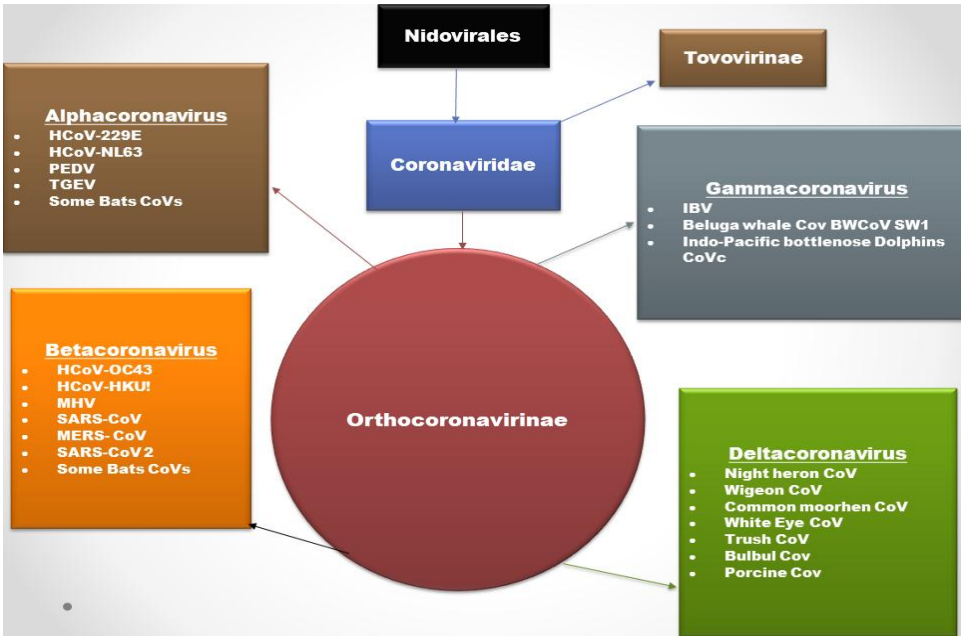

Figure 1. Classification of different types of coronaviruses within the family Coronaviridae, subfamily Orthocoronavirinae, and the respective genera: alpha-, beta-, gamma-, and deltacoronaviruses. The SARS-CoV-2 is classified as a betacoronavirus [18].

Human Coronavirus Infections during 20th Century

The 20th century has two bursting coronaviruses infection: hCoV-OC43 (1st hCoV)and hCoV-229E(2nd hCoV). The first two Human coronaviruses (HCoV) OC43, 229E were identified in the 1960s. These viruses are common causes of upper respiratory tract infections but also have association with lower respiratory tract disease especially in patients with underlying disease [5,6]. OC43 and 229E of human coronaviruses (HCoV) cause one-third of common colds and hospital-acquired upper respiratory tract HCoV infections have been reported in premature newborns. Virus survived in saline solution for as long as six days. After drying, HCoV-229E infectivity was still detectable after 3h on various surfaces (aluminum, sterile latex surgical gloves, and sterile sponges) but HCoV-OC43 survived 1h or less. Proviodine® reduced the virus infectious titer by at least 50% [22]. HCoV-NL63 and HCoV-OC43 infections occur frequently in early childhood, more often than HCoV-HKU1 or HCoV-229E infections. HCoV-OC43 and HCoV-NL63 may elicit immunity that protects from subsequent HCoV-HKU1 and HCoV-229E infection [23]. Children infections with HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1 are associated with acute respiratory tract illness, pneumonia and croup that eventually may leadto hospitalization [24].

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Table 1. Prevalence of different types of Coronaviruses infections worldwide during 21st century

Different types of hCoV	Case no./ total no.	Prevalence %	City/Country	Year	Ref.
hCoV-OC43	346/509	67.97	Guangzhou/China	2009-2016	[25]
hCoV-229E	65/509	12.77	Guangzhou/China	2009-2016	
hCoV-NL63	60/509	11.78	Guangzhou/China	2009-2016	
hCoV-HKU1	38/509	7.47	Guangzhou/China	2009-2016	
hCoV-OC43	25/47	53.2	Pavia/Italy	2003-2005	[26]
hCoV-229E	10/47	21.3	Pavia/Italy	2003-2005	
hCoV-NL63	9/47	19.1	Pavia/Italy	2003-2005	
hCoV-OC43	111/282	39.36	Edinburgh/UK	2006-2009	[27]
hCoV-229E	35/282	12.41	Edinburgh/UK	2006-2009	
hCoV-NL63	75/282	26.59	Edinburgh/UK	2006-2009	
hCoV-HKU1	61/282	21.63	Edinburgh/UK	2006-2009	
hCoV-OC43	19/66	28.78	Washington/USA	2003-2004	[28]
hCoV-229E	8/66	12.12	Washington/USA	2003-2004	
hCoV-NL63	11/66	16.66	Washington/USA	2003-2004	
hCoV-HKU1	28/66	42.42	Washington/USA	2003-2004	
hCoV-NL63	28/300	9.33	Caen/France	2002-2003	[29]
hCoV-OC43	53/87	60.91	Hong Kong	2004-2005	[30]
hCoV-229E	4/87	4.59	Hong Kong	2004-2005	
hCoV-NL63	17/87	19.54	Hong Kong	2004-2005	
hCoV-HKU1	13/87	14.94	Hong Kong	2004-2005	

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Table 2. Prevalence of different types of Coronaviruses infections among different age and sex groups during 21st century

Different types of hCoV	Male: Female	Age (year)	City/Country	Ref.
hCoV-OC43	(306:183)	≤14	Guangzhou/China	[25]
hCoV-229E	1.67:1			
hCoV-NL63				
hCoV-HKU1				
hCoV-OC43	NA	1-21	Pavia/Italy	[26]
hCoV-229E				
hCoV-NL63				
hCoV-OC43	(162:120)	1-65	Edinburgh/UK	[27]
hCoV-229E	1.35:1			
hCoV-NL63				
hCoV-HKU1				
hCoV-OC43	(36:30)	0-19	Washington/USA	[28]
hCoV-229E	1.2:1			
hCoV-NL63				
hCoV-HKU1				
hCoV-NL63	NA	<20	Caen/France	[29]
hCoV-OC43	(45:42)	0-89	Hong Kong	[30]
hCoV-229E	1.07:1			
hCoV-NL63				
hCoV-HKU1				

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Table 3. Prevalence of different types of Coronaviruses infections diagnosed using different modern techniques using selected specimens during 21st century

hCoV	Target Protein	Specimen	Technique	No. of detected/ total suspected (%)	Ref.
hCoV-OC43 **hCoV-229E**	M protein	Nasopharyngeal aspirates	PCR & hybridization	12/348 (3%)	[29]
hCoV-OC43 **hCoV-229E**	NA	Nasopharyngeal aspirates	Real time PCR	3/100 (3%)	[31]
hCoV-OC43 **hCoV-229E** **hCoV-NL63** **hCoV-HKU1**	NA	Nasopharyngeal aspirates	Real time PCR	509/11399 (4.5%)	[25]
hCoV-OC43 **hCoV-229E** **hCoV-NL63**	NA	Nasopharyngeal aspirates	Real time PCR+DFA	47/823 (5.7%)	[26]
hCoV-OC43 **hCoV-229E** **hCoV-NL63** **hCoV-HKU1**	NA	Bronchial Nasal Nasopharyngeal oral Tracheal	Real time PCR	282/11661 (2.41)	[27]
hCoV-OC43 **hCoV-229E** **hCoV-NL63**	NA	Nasal washes	Real time PCR	66/1043 (6.32)	[28]

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hCoV-HKU1					
hCoV-NL63	NA	Nasal aspirates	Real time PCR	28/1427 (1.96)	[29]
hCoV-OC43	NA	Nasopharyngeal aspirates	Real time PCR	87/4181 (2.08)	[31]
hCoV-229E					
hCoV-NL63					
hCoV-HKU1					

Human Coronavirus Infections during 21st Century

As of today, the known coronaviruses (HCoVs) are of 7 types, namely HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the novel coronavirus (2019-nCoV) [32]. In the mid-1960s, the HCoV-229E and HCoV-OC43 were first described for over 40 years, they were believed to be the only representatives of human coronaviruses. The infections were revealed to cause common cold symptoms and specifically Coryza for HCoV-229E infected patients and frequent sore throat for HCoV-OC43-positive patients [33]. Early in 2003, an initially uncharacterized virus was isolated from humans. The uncharacterized virus had been associated with the development of SARS, often progressing to severe lung disease with the patients often showing signs of atypical pneumonia with a potential of progressing to acute respiratory distress syndrome (ARDS) [34]. The virus was found to belong to zoonotic reservoirs from which it crossed to humas. It was identified to be of lineage B betacoronavirus and it was eventually named SARS-CoV [35]. It utilizes angiotensin-converting enzyme 2 (ACE2) as its receptor[36].

In 2004-2005, HCoV-NL63 and HCoV- HKU1, were discovered from clinical specimens and were found to be responsible for most human respiratory diseases exhibiting bronchiolitis and pneumonia in both infants, children and adults [34]. About ten years after the initial SARS cases occurred in 2003, new cases of a more lethal respiratory disease which became known as Middle East respiratory syndrome (MERS) raised a worldwide concern. Just like in the pathogenesis of SARS, the elderly are more affected post-MERS-CoV infection and in particular where and when comorbidities like renal diseas, cardiac disease, hypertension and diabetes are present [37]. MARS-CoV has been identified as a lineage C betacoronavirus which utilizes dipeptidyl peptidase 4 (DPP4) as its distinct receptor [38]. Recently, at the end of 2019, a new Chinese epidemic emerged to which a novel coronavirus (SARS-CoV-2) was identified as the etiologic agent and it was identified as COVID-19. Five epidemics of coronaviruses were emerged in 21st century including: hCoV-NL63, hCoV-HKU1, SARS-CoV, MERS, SARS-CoV2 as bellow:

SARS-CoV (Severe Acute Respiratory Syndrome (SARS) (2002-2003) (3rd hCoV)

Severe acute respiratory syndrome (SARS) pandemic in 2003–2004 [41,42]. SARS coronavirus has been detected in nasopharyngeal aspirates of up to 72% of SARS patients, being

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associated with increased mortality, and in the lungs of all autopsied patients [43,44]. According to the World Health Organization (WHO), viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded. Most recently, the Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia in 2012. In a timeline that reaches the present day, an epidemic of cases with unexplained low respiratory infections detected in Wuhan, the largest metropolitan area in China's Hubei province, was first reported to the WHO Country Office in China, on December 31, 2019. Published literature can trace the beginning of symptomatic individuals back to the beginning of December 2019. As they were unable to identify the causative agent, these first cases were classified as "pneumonia of unknown etiology." The Chinese Center for Disease Control and Prevention (CDC) and local CDCs organized an intensive outbreak investigation program. The etiology of this illness is now attributed to a novel virus belonging to the coronavirus (CoV) family [45]. A likely animal reservoir for SARS-CoV was identified in rhinolophid bats [46].

hCoV-NL63 (2004) (4th hCoV)

HCoV-NL63 was first isolated from the nasopharyngeal aspirate of a seven-month old child in Amsterdam in 2004; whose symptoms suggested respiratory tract infection (fever, conjunctivitis and coryza), and the chest X-ray depicted features typical of bronchiolitis. After cloning and amplification, the virus was identified as a member of Coronaviridae family [9]. On basis of sequence homology and genomic organization, three distinct groups of coronaviruses have been identified i.e Group I, Group II and Group III. Phylogenetic analysis showed that HCoV-NL63 is a new group 1 coronavirus, most closely related to HCoV-229E. Partial HCoV-NL63 sequences from Australia, Japan, and Canada have been submitted to the GenBank database, which indicates that this virus is distributed worldwide [29]. HCoV-NL63 then separated into two distinct HCoV-NL63 lineages which recombined during co-infection, resulting in the two currently observed genotypic subgroups and in a mixture of different virus variants [47]. New technique, VIDISCA, were used to to clone and amplify the HcoV-NL63 genome. VIDISCA is a novel approach that provides a fast and effective tool for amplification of unknown genomes based on cDNA-amplified fragment length polymorphism [9].

HCoV-NL63 uses angiotensin converting enzyme (ACE)-2 receptor, for entry into the host cell [48]. This is the same case with SARS-CoV however after entry, SARS-CoV induces severe respiratory distress, while HCoV-NL63 might cause a mild respiratory infection. This has been attributed to the weaker interaction by HCoV-NL63 S protein with ACE-2 as compared to the interaction by the SARS-CoV S protein. This varying levels of interaction equally partly explain the different varying pathological results of infection by SARS-CoV and HCoV-NL63 [49]. HCoV-NL63 patients have presented mild symptoms, indicating upper respiratory tract infection such as rhinorrhoea, cough and fever to more severe lower respiratory tract infections including bronchiolitis [50]. Of the rare findings, [51] has reported the association between HCoV-NL63 and Kawasaki disease presented as oropharyngeal erythema , polymorphic exanthema, fever and bilateral conjunctivitis. RT-PCR of nasopharyngeal samples is the method of choice and most popular method for detection of HCoV-NL63. Culture assays are used to confirm the infection. Enzyme-linked immunosorbent assays (ELISA) has also been used for screening antibodies in serum samples against HCoV-NL63 [52].

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hCoV-HKU1 (2005) (5th hCoV)

In 2005, a new human coronavirus, HCoV-HKU1, was identified in Hong Kong. Woo et al. (2005)[10] reported a novel group II CoV, designated HCoV-HKU1, from a 71-year-old man with pneumonia who had recently returned to Hong Kong from the Shenzhen, China. It presented with acute bronchiolitis, pneumonia and asthmatic exacerbation. However, upper respiratory infection is the most common presentation of CoV-HKU1 infections. It was shown to impose a higher incidence of febrile seizures (50%) as compared to those of respiratory syncytial virus (8%) infections, HCoV-OC43 (14%), human parainfluenza virus 1 (0%) and adenovirus (9%). However, compared to most other viral respiratory infections, there was no difference in maximum temperature in CoV-HKU1 infected children [30].

Genomic and phylogenetic analysis show that CoV-HKU1 is a novel member of group 2 coronavirus however is not very closely related to any member of group 2 coronaviruses. About 800bp have been deleted between replicase ORF 1b and the HE ORF in CoV-HKU1 as compared to other group 2 coronaviruses [10]. Phylogenetic analysis showed that this new group II CoV is most closely related to the mouse hepatitis virus and is distinct from HCoV-OC43, the only other known group II HCoV. Screening of 400 nasopharyngeal aspirates by reverse transcription–polymerase chain reaction (RT-PCR) with HCoV-HKU1–specific primers showed 1 other HCoV-HKU1 isolate from a 35-year-old woman with pneumonia. After the original report, HCoV-HKU1 was identified in 10 patients in northern Australia [53]. The genetic variability among HCoV-HKU1 isolates suggests that this virus was introduced into the human population some time ago. The sequences of HCoV-HKU1 isolates display marked genetic variability.

The Middle East respiratory syndrome (MERS) (2012) (6th hCoV)

On 20 September 2012, Dr. Ali Moh Zaki, a virologist at Dr. Fakeeh Hospital, Jeddah, Saudi Arabia, first reported on the Program for Monitoring Emerging Diseases (ProMED-mail) that a novel coronavirus (nCoV) had been isolated from the lungs of a 60-year-old male patient with acute pneumonia and acute renal failure [54]. In November 2012, the virus was identified as a novel betacoronavirus, the closest relative of the bat coronaviruses HKU4 and HKU5, by Dr. Ron Fouchier's group at the Erasmus Medical Center in Rotterdam, the Netherlands, and thus termed "hCoV-EMC". In May 2013, this virus was renamed as the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses , and the term was then adopted by WHO [12,13].Middle East respiratory syndrome (MERS)-CoV belongs to the genus Betacoronavirus (BCoV) in the family Coronaviridae. MERS-CoV is an enveloped, positive-sense, single-stranded RNA virus. The replication cycle is similar to other CoVs. The first case report of the novel Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) in Jeddah at September 2012 [55]. MERS also documented with low frequency in Jordan, Qatar, Tunisia, and the United Arab Emirates. It also confirmed in France, Germany, Italy, and the United Kingdom and linked by their direct or indirect contact through travel to middle east [56].

The host cell receptor for the MERS-CoV S protein is dipeptidyl peptidase-4 (DPP4) or CD26. This receptor is expressed on endothelial and epithelial cells of the kidney, lung, small intestine, liver, as well as on immune cells. This ability to infect many different organ cells may explain the extrapulmonary clinical characteristics in patients. MERS-CoV has been identified as the cause of pneumoniain patients in Saudi Arabia, Qatar, Jordan, the United Kingdom, Germany, France, Tunisia, and Italy [57]. The Middle East respiratory syndrome (MERS) is proposed to be a zoonotic disease caused by MERS-CoV virus in Middle East especially kingdom of Saudi Arabia

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(KSA). Dromedary camels have been implicated through reports that some victims have been exposed to camels, camels in areas where the disease has emerged have antibodies to the virus, and viral sequences have been recovered from camels in association with outbreaks of the disease among humans [58].There is a second attack of MERS in Korea May to July 2015 and it cause 36 death of the 185 confirmed [59].

Bats and camels were most proposed animal reservoir. Many scientific evidences can prove that: bat cell lines display the MERS-CoV receptor, dipeptidyl peptidase 4, and can be experimentally infected. A short sequence fragment consistent with MERS-CoV was reported in a bat in Bisha, KSA, collected in close proximity to the home and workplace of the 2012 index case patient from whom the initial virus isolate was obtained. In recent years molecular surveillance studies revealed the existence of at least 60 novel bat coronaviruses, including some closely related to SARS-CoV [47].

SARS-CoV2 (2019) (7th hCoV)

On December 31, 2019 a pneumonia outbreak caused by a new coronavirus (SARS-CoV-2) was detected in the city of Wuhan (China). Due to the high capacity of diffusion and human infection it has become a new zoonotic pandemic. The absence of a vaccine has determined the search for antiviral drugs [60]. The 2019 novel CoV virus (2019-nCoV) was recently named SARS-CoV-2 by the World Health Organization (WHO). The disease caused by SARS-CoV-2 has been named COVID-19. Prior to 2002, CoVs were treated as nuisances but never as serious viruses. Things changed after the emergence of SARS-CoV, which caused serious illnesses and deaths in 2002–2003 [21]. Unlike all human CoVs that cause mild respiratory symptoms, SARS-CoV, MERS-CoV, and SARS-CoV-2 are associated with serious respiratory diseases [18]. Since its emergence, the SARS-CoV-2 has drawn well-deserved attention from the world. Efforts are underway. SARS-CoV belongs to the family Coronaviridae within the order Nidovirales whose members cause respiratory or intestinal infections in animals and human. Phylogenetic analysis shows that SARS-CoV is considered as group 2b coronavirus [61].

Signs and symptoms typically kick in a week after onset of illness depicting as clinical deterioration often accompanied with diarrhea. The most common extrapulmonary manifestation is diarrhea, after which hepatic dysfunction occurs. Other manifestations include; dizziness, related to pulmonary arterial thrombosis and diastolic cardiac impairment; oxygen desaturation associated with higher nasopharyngeal and serum viral loads; myositis; petechiae; higher urine viral loads associated with abnormal urinalysis; epileptic fits; and neuromuscular abnormalities. Fever and respiratory symptoms may not be presented in the elderly patients. However, SARS infections in children are milder as compared to those in adults [62,63]. Etiological differentiation and diagnosis of SARS from other forms and causes of atypical pneumonia can only be achieved via laboratory confirmation since no pathogenic symptoms or signs are effective in the differentiation. Due to limited availability of sufficiently equipped laboratories, rapid detection using acid amplification or antigen detection are the alternative methods [64].

Corona virus Transmission:

There are hundreds of coronaviruses, most of which circulate among animals including pigs, camels, bats and cats. Sometimes those viruses jump to humans-called a spillover event and can cause disease. Human-to-human MERS-CoV transmission can occur [38]. The source of the severe acute respiratory syndrome (SARS) epidemic was traced to wildlife market civets and ultimately to bats [11]. The first pattern is the occurrence of sporadic cases in communities. The

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second pattern of transmission is transmission within families. The third transmission pattern is nosocomial transmission to health care worker [65].However, human-to-human transmissibility of MERS CoV appears to be low, as close monitoring of health-care workers and household contacts has not revealed large numbers of secondary infections [66].

Coronaviruses infect both birds and several species of mammals. HKU1 and HCoV-OC43 probably originated from rodents whereas SARS-CoV, MERS-CoV, HCoV-229E and HCoV-NL63 probably originated from bats [67]. Bats are considered the primordial hosts and can contain varying varieties of viral populations in a species which over time has facilitated the emergency of new coronaviruses variants with a capability of infecting intermediate hosts. In forms like SARS and MERS-CoV, recombination of genes and deletion of some genetic sequences has resulted in drastic changes which generally change the diseases' pattern [68]

Coronavirus receptor:

Angiotensin converting enzyme 2 (ACE2) act as a receptor for SARS-CoV. In addition, sialic acid may act as a receptor for some coronaviruses [69]. Alpha and Betacoronaviruses, two peptidases have been identified as receptors (aminopeptidase N (APN, CD13) [70]. Replication of this SARS coronavirus (SCV) occurs mainly in the lower respiratory tract, and causes diffuse alveolar damage [80].The cellular receptor for MERS-CoV has been identifi ed as dipeptidyl peptidase 4 (DPP4, CD26)5 and the structure of the receptor binding domain of the virus spike protein complexed with DPP4 has been established. The tissue distribution of this receptor within mammals is consistent with the lung and kidney pathology of the virus [71].

Epidemiology

Data provided by the WHO Health Emergency Dashboard (March 14, 06.00 am CET) report 142.320 confirmed cases worldwide since the beginning of the epidemic. 5.388 (3.78%) cases have been fatal. In china, 81.021 (57%) cases confirmed clinically and in the laboratory, and 3.173 deaths are reported. In addition to China, there are 61.299 confirmed cases in 129 other countries. The countries with most cases are Italy (17.660) and the Islamic Republic of Iran (11.364). The epidemiological scenario, therefore, has drastically changed, as on March 3 about 92% (79.968) of the confirmed cases were recorded in China, where almost all the deaths were also recorded (2,873, 96.5%). Of note, the "confirmed" cases reported between February 13, 2020, and February 19, 2020, include both laboratory-confirmed and clinically diagnosed patients from the Hubei province [72]. The most up-to-date source for the epidemiology of this emerging pandemic can be found at the following sources:

- The WHO Novel Coronavirus (COVID-19) Situation Board
- The Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

History and Physical characteristics

The authors of the Chinese CDC report divided the clinical manifestations of the disease by their severity:

- Mild disease: non-pneumonia and mild pneumonia; this occurred in 81% of cases.
- Severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial

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pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours; this occurred in 14% of cases.

- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); this occurred in 5% of cases [73].

Uncomplicated (mild) Illness

These patients usually present with symptoms of an upper respiratory tract viral infection, including mild fever, cough (dry), sore throat, nasal congestion, malaise, headache, muscle pain, or malaise. Signs and symptoms of a more serious disease, such as dyspnea, are not present. Compared to previous HCoV infections, non-respiratory symptoms such as diarrhea are challenging to find [74].

Moderate Pneumonia

Respiratory symptoms such as cough and shortness of breath (or tachypnea in children) are present without signs of severe pneumonia [75].

Severe Pneumonia

Fever is associated with severe dyspnea, respiratory distress, tachypnea (> 30 breaths/min), and hypoxia (SpO2 < 90% on room air). However, the fever symptom must be interpreted carefully as even in severe forms of the disease, it can be moderate or even absent. Cyanosis can occur in children. In this definition, the diagnosis is clinical, and radiologic imaging is used for excluding complications [76].

Acute Respiratory Distress Syndrome (ARDS)

The diagnosis requires clinical and ventilator criteria. This syndrome is suggestive of a serious new-onset respiratory failure or for worsening of an already identified respiratory picture. Different forms of ARDS are distinguished based on the degree of hypoxia. The reference parameter is the PaO2/FiO2:

- Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg. In not-ventilated patients or in those managed through non-invasive ventilation (NIV) by using positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cmH2O.
- Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg.
- Severe ARDS: PaO2/FiO2 ≤ 100 mmHg. When PaO2 is not available, a ratio SpO2/FiO2 ≤ 315 is suggestive of ARDS.
- Chest imaging utilized includes chest radiograph, CT scan, or lung ultrasound demonstrating bilateral opacities (lung infiltrates > 50%), not fully explained by effusions, lobar, or lung collapse. Although in some cases, the clinical scenario and ventilator data could be suggestive for pulmonary edema, the primary respiratory origin of the edema is proven after the exclusion of cardiac failure or other causes such as fluid overload. Echocardiography can be helpful for this purpose [77].

Sepsis

According to the International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis represents a life-threatening organ dysfunction caused by a dysregulated host response to

suspected or proven infection, with organ dysfunction. The clinical pictures of patients with COVID-19 and with sepsis are particularly serious, characterized by a wide range of signs and symptoms of multiorgan involvement. In this scenario, which is associated with increased mortality, circulatory, and cellular/metabolic abnormalities such as serum lactate level greater than 2 mmol/L (18 mg/dL) are present. Because patients usually suffer from persisting hypotension despite volume resuscitation, the administration of vasopressors is required to maintain a mean arterial pressure (MAP) ≥ 65 mmHg [78].

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