Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period

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SUMMARY

The novel coronavirus SARS-CoV-2 (Covid-19), spreading from Wuhan, China, is one of the causes of respiratory infections that can spread to other people through respiratory particles, and can cause symptoms such as fever, dry cough, shortness of breath, anorexia, fatigue and sore throat in infected patients. This review summarizes current strategies on the diagnosis. Additionally, treatments, infection prevention and control of the SARS-CoV-2 are addressed. In addition to the respiratory system, this virus can infect the digestive system, the urinary system and the hematological system, which causes to observe the virus in the stool, urine and blood samples in addition to throat sample. The SARS-CoV-2 causes changes in blood cells and factors and makes lung abnormalities in patients, which can be detected by serological, molecular, and radiological techniques by detecting these changes and injuries. Radiological and serological methods are the most preferred among the other methods and the radiological method is the most preferred one which can diagnose the infection quickly and accurately with fewer false-negatives, that can be effective in protecting the patient's life by initiating treatment and preventing the transmission of infection to other people.

Keywords: COVID-19, diagnosis, serological, molecular, radiological.

INTRODUCTION

In December 2019, a new infection by the coronavirus, named SARS-CoV-2 began in Wuhan, Hubei Province, China, and quickly spread around the world and was declared as a global concern by the World Health Organization (WHO) [1]. Coronaviruses are non-segmented positive-sense RNA genome viruses surrounded by an envelope that cause respiratory and gastrointestinal infections in humans and animals [2]. Considering the severity of SARS-CoV-2 (COVID-19) outbreak all over the world, it is urgent to seek solutions to control the spread of the disease to susceptible groups and to identify effective treatments.

Six coronaviruses have been identified as human pathogenic viruses [3]. The two important strains,

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Abbreviations: COVID-19, Coronavirus disease 2019; WHO, World Health Organization; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; LDH, lactate dehydrogenase; CRP, C-reactive protein; ALT, alanine aminotransferase, AST, aspartate aminotransferase; LAMP, Loop-mediated isothermal amplification; PFU, plaque-forming units; SNP, single nucleotide polymorphism; SARS, severe acute respiratory syndrome; IB, infectious bronchitis; NGS, next-generation sequencing; IBV, infectious bronchitis virus; CT, computerized tomography; GGO, ground-glass opacities.

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) that can infect human, camel, bat, cow, and civet, and cause acute and fatal respiratory infections in humans, which their zoonosis and high genetic diversity and recombination in their genomes, have caused the global outbreak of these viruses [4-6]. NL63, OC43, 229E, and HKU1 are other coronaviruses that cause nonfatal and cold-like diseases in people with a weak immunity system [7-9]. The rapid and accurate detection of coronavirus is, therefore, becoming increasingly important.

The novel coronavirus (2019-nCoV) that emerged from China and then spread throughout the world is a zoonotic virus and is the seventh coronavirus that infects the human and causes a respiratory disease with some near symptoms to the common cold [10]. This virus first transmitted from animal to human at the wet store of the sale of seafood and can transmit from humans to humans [11]. Coronaviruses, like influenza viruses, circulate in nature in various animal species. Alpha-coronaviruses and beta-coronaviruses can infect mammals and gamma-coronaviruses and delta-coronaviruses tend to infect birds, but some of them can also be transmitted to mammals. Although still preliminary, current data suggest that bats are the most probable initial source of the current 2019 novel SARS-CoV-2 (COVID-2019) outbreak, that begun on December 2019 in Wuhan, China, apparently spreading from a "wet market" to multiple cities and provinces in China [12].

The virus can cause symptoms such as sore throat, tremor, confusion, high fever, shortness of breath, dry cough, headache, nausea, vomiting, and diarrhoea in the patients [13, 14]. Because of the incubation period of 2-14 days of the SARS-CoV-2, its high transmission power and the similarity of its symptoms to the common cold, most people neglect the infection, which causes its increased transmission and more outbreaks among people [15-17]. So, the rapid diagnosis of the infection is very important that prevents the spreading of infection and helps the patients to start the remedy faster In this study, we look at the methods of fast diagnosis of SARS-CoV-2 and blood factors changes to show the best ways of diagnosis to help the medical staff in fast and accurate diagnosis of infection, and surviving patients' life and preventing the spreading of infection.

DIAGNOSIS OF SARS-CoV-2 POSITIVE PATIENTS

Clinical signs and symptoms

Patients with suspected infection usually go to health centers with symptoms such as fever over 38.5°C, dry cough, shortness of breath and diarrhoea, which should be examined for respiratory symptoms [18-20]. In the study of Nanshan Chen et al., on patients of Wuhan Jinyintan Hospital, Wuhan, China, from the 99 patients with SARS-CoV-2 infection, 51% had chronic diseases and they had symptoms of fever (83%), cough (82%) shortness of breath (31%), muscle ache (11%), fatigue (9%), headache (8%), sore throat (5%), rhinorrhoea (4%), chest pain (2%), diarrhoea (2%), and nausea and vomiting (1%) [14]. In another study of Huijun Chen et al. on nine pregnant women of Zhongnan Hospital of Wuhan University, Wuhan, China, patients with COVID-19 infection showed fever (in seven of nine patients), cough (in four of nine patients), myalgia (in three of nine patients), sore throat (in two of nine patients), Malaysia (in two of nine patients), diarrhoea (in one of nine patients) and dyspnoea (in one of nine patients) that by sampling and examining of their newborn babies, there were no signs of coronavirus in their neonates, which has shown that there is no evidence for vertical transmission of COVID-19 infection (Figure 1) [21].

Another study which is done by Huang et al. on 41 patients of a hospital in Wuhan with confirmed SARS-CoV-2 infection showed that 32% of patients had an underlying disease such as diabetes, hypertension, and cardiovascular disease and had clinical symptoms such as fever (98%), cough

(76%), fatigue (44%), sputum production (28%), headache (8%), haemoptysis (5%), and diarrhoea (3%) [22]. Moreover, the symptoms of four patients that their SARS-CoV-2 confirmed by Shanghai Public Health Clinical Center, Shanghai, China, showed that most of them had fever, fatigue, and dry cough and some of them had nasal congestion, runny nose, and diarrhoea [23]. Another study done by Wang et al. on 138 Hospitalized Patients with confirmed SARS-CoV-2 admitted by Zhongnan Hospital of Wuhan University in Wuhan, China, shows that most common symptoms

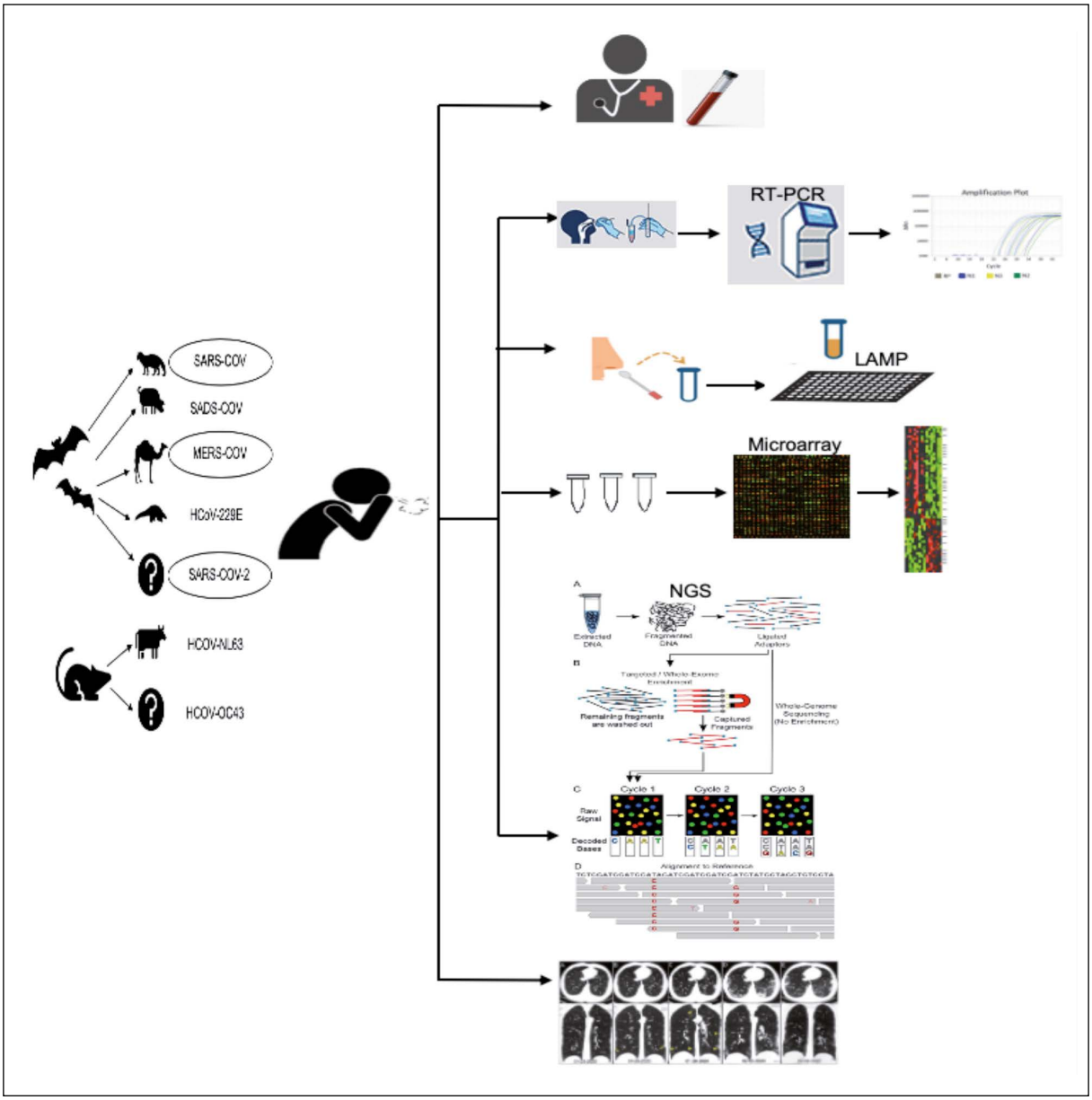

Figure 1 - Animal origins of human coronaviruses. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were transmitted to humans from bats by civet cats and dromedary camels, respectively. The 2019 SARS-CoV-2 was likely transmitted to humans through pangolins that are illegally sold in Chinese markets. An overview of symptoms, diagnosis and sources

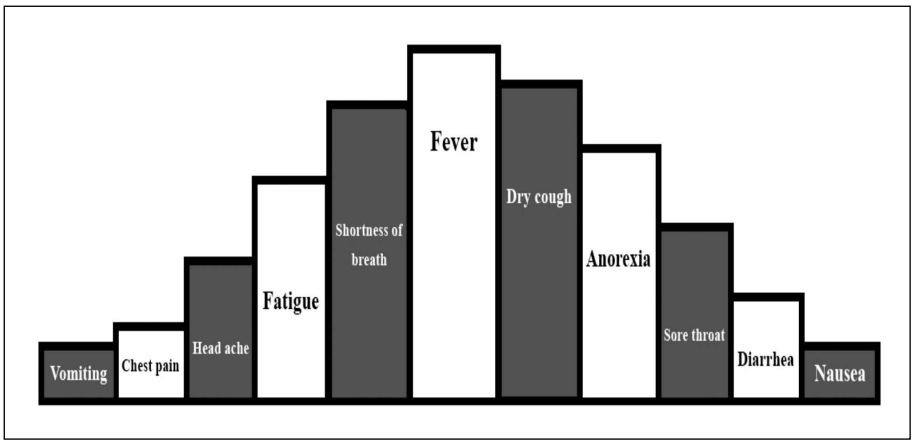

Figure 2 - The most common signs and symptoms of patients with confirmed SARS-CoV-2.

of infected patients are fever, fatigue dry cough, anorexia, myalgia, dyspnoea, expectoration, pharyngalgia, diarrhoea, nausea, dizziness, headache, vomiting, and abdominal pain respectively (Figure 2) [24].

Serological study

Serological techniques of diagnosis compared with other methods are the most widely used for the diagnosis of infections [25]. The number of different blood cells, including leukocytes, lymphocytes, neutrophils, platelets, and haemoglobins, undergo changes that can be evidence for the type and severity of the disease. SARS-CoV-2 also causes changes in the levels of different blood cells in patients [19]. For instance, in the study of Chen et al., on 99 patients with admitted SARS-CoV-2 infection, the rate of leucocytes was lower than the normal range in 9% of patients and the rate was higher than the normal in 24% of patients [14]; 38% of patients had a higher rate of neutrophils than the normal range; 12% of patients had a decreased rate of platelets and 4% of them had a higher rate of platelets, and the rate of haemoglobin and lymphocytes was decreased in most of the patients. The amount of albumin was decreased in 98% of patients and the amount of glucose and lactate dehydrogenase (LDH) was increased in more than half of the patients. There was also a significant increase in patients' infection-related biomarkers such as interleukin-6, serum ferritin, C-reactive protein (CRP) and erythrocyte sedimentation rate.

Another study by Guan et al., on the blood samples of 1099 infected patients with SARS-CoV-2 from the different provinces of China, showed that the rate of lymphocytes was below the normal range in 83.2% of patients, the platelet was below the normal range in 36.2% of patients, and the rate of leucocytes was lower than the normal range in 33.7% of infected patients [26]. The rate of CRP was very high in most of the patients and also alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase and D-dimer had increased rate in patients. The study by Zhang et al. on clinical serological factors of 140 infected patients of Wuhan with 2019-nCoV, showed that 68.1% of the patients had normal leukocytes rate, the rate of lymphocytes was below the normal range in 75.4% of the patients and 52.9% of patients had decreased rate of eosinophils [27]. Also, in the study of blood factors, the rate of CRP and serum amyloid was high in more than 90% of the patients, the D-dimer was high in 43.2% of them and the serum procalcitonin and creatine kinase had increased amount in patients. In a study by Wang et al. on serological parameters of 138 patients with confirmed SARS-CoV-2 in Wuhan, the results showed an increased rate of white blood cells and neutrophil and decreased rate of lymphocytes and platelets [24]. There was also an increased rate of D-dimer, creatine kinase, creatine, and LDH in the patient's blood factors. The study of Hu et al. on blood samples of 24 asymptomatic carriers with confirmed 2019-CoV from a hospital of Nanjing, China, showed that 16.7% of patients had decreased lymphocyte rate and most of the patients had increased rate of ALT, AST, CPR, D-dimer, and creatine kinase [28]. The study of Huang et al., on 41 patients declare

Table 1 - The main blood abnormalities in patients with SARS-CoV-2 (Covid-19).

Increased	*Decreased*
Neutrophil	Lymphocyte
D-dimer	Platelet
CRP	Albumin
LDH	
ALT	
AST	
Creatinine	
Creatine kinase	
IgG & IgM	

that 63% of them had lymphocyte below the normal, and ALT, AST, D-dimer, bilirubin, creatinine, and LDH of them were increased [22].
For serological analysis of the 2019-nCoV, ELISA kits containing viral nucleoproteins can also be used to detect immunoglobulins such as IgM and IgG [29]. In the study by Zhang et al. on infected patients with 2019-nCoV, the rate of antibodies was low or undetectable at the first days of diagnosis but there was an increased rate of IgG and IgM antibodies in the later days of infection which can be useful in the diagnosis of the infection (Table 1) [30].

Molecular study of 2019-nCoV

PCR-based method

PCR is an enzymatic method to produce numerous copies of a gene by separating the two strands of the DNA containing the gene segment, marking its location with a primer, and using a DNA polymerase to assemble a copy alongside each segment and continuously copy the copies [31]. It is widely used to amplify minute quantities of biologic materials so as to provide adequate specimens for laboratory study [32]. Owing to its large range of applications, high sensitivity and high sequence specificity, the PCR-based method has become a routine and reliable technique for detecting coronavirus. Generally, coronavirus RNA is transferred into cDNA by reverse transcription [33]. Afterwards, the PCR is performed and followed by the detection of PCR product through specific detection methods or instruments. Among these, gel visualization and sequencing after PCR are the conventional methods for the detection of coronaviruses [34]. However, due to its time-consuming process and high cost, these methods are not commonly used in clinical samples.
Real-time reverse transcriptase-PCR (RT-PCR) detection is currently favoured for the detection of coronavirus because of its advantages as a specific, and simple quantitative assay [35]. Moreover, real-time RT-PCR is more sensitive than the conventional RT-PCR assay, which helps much for the diagnosis in early infection [36]. Some patients show unusual symptoms of SARS-CoV-2 infection or the disease is in its first levels [37]. For these reasons and to confirm of the beliefs about the respiratory and oral-faecal transmission of the virus, molecular studies are needed to identify the causative agent. For the molecular study of 2019-nCoV, various specimens such as throat swab and rectal swabs are tested using real-time reverse transcriptase-polymerase chain reaction testing (RT-PCR) [30]. In the study by Zhang et al. on patients with confirmed 2019-nCoV, the results of testing of throat swabs and rectal swabs of patients show that the virus can be detected in both samples. In this study, 50% of throat swabs and 25% of rectal swabs were positive in the first sampling for the diagnosis [30]. During the later days, the rate of positive rectal swab (75%) was higher compared to positive throat swabs (50%), showing that, compared to rectal swabs, throat swabs are more likely to be positive in the first days of infection and by contrast, rectal swabs are more likely to be positive in the latter period of infection. In the study of Qian et al. on 91 patients with confirmed 2019-nCoV, to ensure finding the virus in asymptomatic patients, they used an anal swab and oropharyngeal swab, whose results showed that the anal swab was positive even in patients whose oral swab were negative after numerous experiments which showed the importance of anal swab in the effective detection of infection [37].
The study of Peng et al. on different samples of patients including blood, urine, anal and throat swabs tested by RT-PCR and screening of virus in all samples showed that this virus can infect all respiratory, digestive, urinary and haematological system, which indicates that clinical signs in all parts of the body should be taken into account when diagnosing the disease and sampling from different parts of the body is recommended (Figure 3) [38].

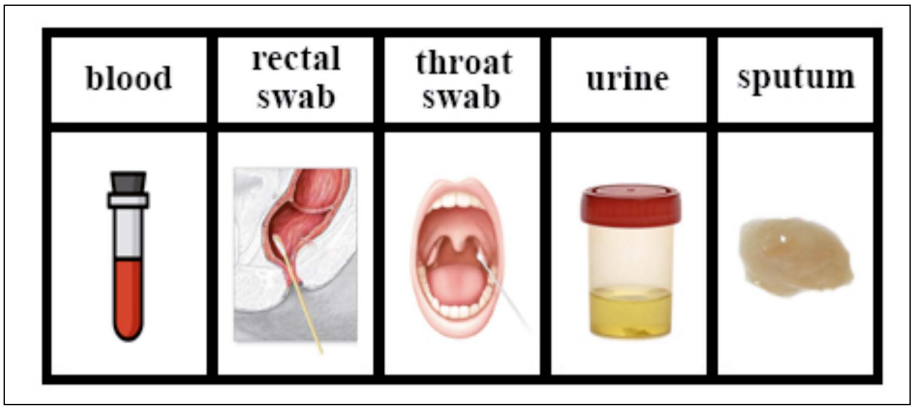

Figure 3 - The most important samples for diagnosis of SARS-CoV-2 (COVID-19).

In the study by Chu et al. on sputum and throat swab samples of 2 suspected patients, both specimens were diagnosed positive which showed that the virus can be transmitted through the sputum in addition to respiratory droplets, that showed the importance of sputum in the diagnosis of SARS-CoV-2 in addition to other samples [39].

LAMP-based method

The Loop-mediated isothermal amplification (LAMP) is a unique isothermal nucleic acid amplification technique with high performance. It's used for the amplification of DNAs and RNAs, showing great sensitivity and high specificity due to its exponential amplification function and 6 special goal sequences diagnosed by 4 unique primers simultaneously, respectively [40]. The LAMP assay is fast and does not require highly-priced reagents or devices. Consequently, the application of the LAMP test might assist to reduce the cost for the detection of coronavirus [41]. Herein, some LAMP-based total coronavirus detection strategies will be described that have been advanced and implemented in clinical prognosis. Gel electrophoresis was generally used to investigate the amplified products for endpoint detection. Poon et al. reported a simple LAMP assay for SARS analysis and tested the feasibility of the use of this technology for the detection of SARS-CoV. The ORF1b place of SARS-CoV was chosen for SARS diagnosis and amplified through LAMP response inside the presence of 6 primers, then the amplified products had been analysed by gel electrophoresis [42]. The detection costs and the sensitivity for SARS-CoV inside the LAMP assay are similar to those of traditional PCR-based methods. Pyrc et al. efficiently implemented LAMP to the detection of HCoV-NL63 which performed through agarose gel electrophoresis with favourable sensitivity and specificity in mobile cultures and medical specimens. Significantly, the detection restriction changed into found to be 1 replica of RNA template in keeping with a response [43]. Amplification can be detected as the precipitation of magnesium pyrophosphate or fluorescence dye. These strategies can be accomplished in actual time through tracking the turbidity of the pyrophosphate or fluorescence, which correctly solved the limitations of the endpoint detection [44].

A beneficial RT-LAMP assay for the diagnosis and epidemiologic surveillance of human MERS-CoV became developed in this way with the aid of Shirato et al., which turned into capability of detecting as few as 3.4 copies of MERS-CoV RNA, and became tremendously precise, and not using a pass-response with different breathing viruses [45]. Thai et al. evolved a one-step unmarried-tube extended real-time quantitative RT-LAMP assay monitored by the real-time dimension of turbidity in a photometer for the early and speedy diagnosis of SARS-CoV [46]. In medical samples, the assay turned to be one hundredfold more sensitive than conventional RT-PCR with a detection restrict of 0.01 plaque-forming units (PFU). However, if the methods depended on nonspecific sign transduction schemes, including the fluorescence dyes intercalation into any double-stranded DNA amplicons, or solution turbidity due to the release of pyrophosphates at some stage in polymerization, the opportunity of unexpected indicators derived from primer-dimer or non-primer reactions

cannot be excluded [47]. A sequence-particular and strong approach for tracking LAMP and different isothermal amplification reactions that can quite simply separate actual signal from nonspecific noise could deal with this problem. Shirato et al. improved the RT-LAMP assay by using a quenching probe (QProbe) to reveal sign, which has the identical performance as the standard real-time RT-PCR assay in the detection of MERS-CoV [45].

Microarray-based methods

The microarray is a detection technique with fast and excessive throughput. For this approach, the coronavirus RNA will first produce cDNA categorized with particular probes through reverse transcription [48]. Then those labelled cDNAs might be loaded into each properly and hybridized with solid-phase oligonucleotides fixed on the microarray accompanied through a series of washing steps to remove unfastened DNAs. Finally, the coronavirus RNA can be detected through the detection of particular probes. Due to its superiority, the microarray assay has been broadly used inside the detection of coronavirus [49]. Shi et al. designed a 60mer oligonucleotide microarray according to the sequence of TOR2 and effectively applied it to the detection of SARS coronavirus in medical samples but, thinking about the fast mutation of SARS-CoV, Guo et al. advanced a microarray to discover 24 single nucleotide polymorphism (SNP) mutations a few of the spike (S) gene of SARS-CoV with 100% accuracy in pattern detection [50,51]. Since coronavirus might also result in an unexpected outbreak, it's far of remarkable significance that diagnostic assays are capable of locating a huge range of coronavirus and be deployable at or near the factor of care (p.c). Consequently, Luna et al. designed a no fluorescent low-value, low-density oligonucleotide array for detecting the whole coronavirus genus with sensitivity equal to that of individual real-time RT-PCR, and Hardick et al. evaluated a novel, portable, and near-percent diagnostic platform primarily based at the microarray chip, the cell evaluation Platform (MAP), which has an awesome performance in identifying the virus and desirable detection restrict [52, 53].

However, if the techniques relied on nonspecific signal transduction schemes, which include the fluorescence dyes intercalation into any double-stranded DNA amplicons, or answer turbidity due to the release of pyrophosphates at some stage in polymerization, the possibility of sudden indicators derived from primer-dimer or non-primer reactions cannot be excluded [47]. A sequence-precise and strong approach for monitoring LAMP and other isothermal amplification reactions which could readily separate genuine signs from nonspecific noise could cope with this problem. Shirato et al. advanced the RT-LAMP assay through the use of a quenching probe (QProbe) to reveal sign, which has the identical overall performance as the standard real-time RT-PCR assay in the detection of MERS-CoV [45].

NGS-based methods

RNA viruses are of great diversity, and they are the etiological agents of many important human and animal infectious diseases, including influenza, rabies, several types of infectious hepatitis, severe acute respiratory syndrome (SARS), classical swine fever, rinderpest and avian infectious bronchitis (IB) [54, 55]. The next-generation sequencing (NGS) and electron microscope technology play a role in the early diagnosis. However, their diagnostic values have been weakened through the discovery of specific nucleic acid detection technology [56]. Further, NGS detection can inform whether or not the pathogen has mutated or now. The rapid discovery of novel viruses using NGS technologies including DNA-Seq and RNA-Seq expanded the understanding of viral diversity [57]. The timely identification of novel viruses using NGS technologies is also important for us to control emerging infectious diseases caused by novel viruses.

The development of the NGS technologies in recent years has helped us make great progress in the rapid identification of novel RNA viruses via RNA-Seq [58]. RNA-Seq can simultaneously sequence millions of DNA fragments reversely transcribed from RNA using random primers. Usually, most RNA-Seq reads are from cellular RNA, but some may be from RNA virus genomes, if the sequenced samples have been properly processed to minimize the quantity of cellular RNA before reverse transcription, and thus RNA-Seq could be used to identify RNA viruses [59].

Chen et al. identified a novel duck coronavirus (CoV), distinct from that of chicken infectious

bronchitis virus (IBV), using RNA-Seq. The novel duck-specific CoV was a potential novel species within the genus Gammacoronavirus, as indicated by sequences of three regions in the viral 1b gene [57]. They also performed a survey of CoVs in domestic fowls in China using reverse-transcription polymerase chain reaction (RT-PCR), targeting the viral nucleocapsid (N) gene. A total of 102 CoV positives were identified in the survey. Phylogenetic analysis of the viral N sequences suggested that CoVs in domestic fowls have diverged into several region-specific or host-specific clades or subclades in the world, and IBVs can infect ducks, geese, and pigeons, although they mainly circulate in chickens. Moreover, this study provided novel data supporting the notion that some host-specific CoVs other than IBVs circulate in ducks, geese, and pigeons, and indicated that the novel duck-specific CoV identified through RNA-Seq in this study is genetically closer to some CoVs circulating in wild waterfowls.

Timely identification of RNA viruses is of great significance in the diagnosis, treatment, control, and prevention of human and animal infectious diseases [60]. Regarding molecular surveys of pathogenic viruses, it is important to select a proper region in the viral genomes as the detection target. If the target region in the viral genome is too conserved, the sequences of the region may be of little use in phylogenetic analysis, due to limited mutations in the conserved sequence. On the other side, if the region in the viral genome is highly variable, the detection may be insensitive in identifying the target virus, although the sequences of the region may be useful in the phylogenetic analysis.

Coronaviruses (CoVs) of bat origin have caused two pandemics in this century. (SARS)-CoV and (MERS)-CoV both originated from bats [61]. Active surveillance is both urgent and essential to predict and mitigate the emergence of bat-origin CoV in humans and livestock [62]. However, great genetic diversity increases the chance of homologous recombination among CoVs. Per-forming targeted PCR, a common practice for many surveillance studies, would not reflect this diversity [63].

NGS is currently the preferred methodology for virus discovery to ensure unbiased sequencing of bat CoVs, considering their high genetic diversity [64]. However, unbiased NGS is an expensive methodology and is prone to missing low-abundance CoV sequences due to the high background level of non-viral sequences present in surveillance field samples [59]. Li et al. employed a capture-based NGS approach using baits targeting most of the CoV species. Using this technology, authors effectively reduced sequencing costs by increasing the sensitivity of detection [62]. This finding demonstrated that targeted, cost-effective, large-scale, genome-level surveillance of bat CoVs is now highly feasible.

Radiological study of SARS-CoV-2diagnosis

Molecular methods of detecting the SARS-CoV-2 are slow and the probability of false-negative is high, which can endanger the health of the patient by delaying the diagnosis [1]. Therefore, we need faster and more effective methods of diagnosis. The radiologic technique, chest computerized tomography (CT) scan, is one of the effective ways of detecting viral infection in suspected individuals, which can be especially helpful in those without clinical symptoms and in the diagnosis of infection, it can act as a complementary method to molecular methods and make the diagnosis more effective [66].

Radiological images of the lungs of patients with confirmed SARS-CoV-2 can provide comprehensive information about the severity of the infection. Images taken from the lungs of various patients show different abnormalities in the lungs of patients including ground-glass opacities (GGO), consolidation, centrilobular nodules, architectural distortion, bronchial wall thickening, vascular enlargement, traction bronchiectasis, reticulation, crazy paving pattern, intrathoracic lymph node enlargement and subpleural bands, that cause pulmonary discomfort and require rapid diagnosis and treatment [67-78].

The study by Bernheim et al. on thoracic CTs of 121 patients with confirmed SARS-CoV-2 showed that 60% of patients had bilateral lung disease and 10.7% of patients had only right lung involvement and 5.7% of patients had only left lung involvement. The most common abnormalities of these patients include GGO, consolidation, bronchial wall thickening and peripheral distribution [79]. Also in the study by Pan et al., on CT images of 63 infected patients with 2019-nCoV, the results showed that the most common abnormalities of lungs include GGO, consolidation, fibrous stripes

and irregular solid nodules [80]. Another study by the same author on 21 patients with admitted SARS-CoV-2 showed that the most pulmonary involvement and injury occurred 10 days from the appearance of symptoms, and the most lung injuries included consolidation in 91% of patients, GGO in 75% of patients and crazy-paving patterns in 53% of patients, which threaten the lives of patients [81].

The SARS-CoV-2 can infect various lung lobes depending on its severity. For example, the study by Chung et al. on 21 patients infected with 2019-nCoV, showed that 5% of patients had one involved lobe, 10% had two involved lobes, 14% had three involved lobes, 19% had four involved lobes and 38% had all five involved lobes [75]. In this study, the right superior lobe was affected in 67% of patients, the right middle lobe was affected in 57%, the right inferior lobe was affected in 76%, the left superior lobe was affected in 67% and the left inferior lobe was affected in 67% of the patients and the rate of bilateral lung disease was more than unilateral. In the study by Song et al., the involvement rate of lobes of the lung in 51 patients with confirmed SARS-CoV-2 was 84% in superior lobes, 59% in the middle lobe and 90% in inferior lobes and the 86% of patients had bilateral lung disease and 14% had unilateral lung disease and the most common abnormalities of the lung were GGO, consolidation, air bronchogram, and reticulation, which be aware of these abnormalities can be helpful in the diagnosis [70].

FALSE-NEGATIVE AND FALSE-POSITIVE IN DIAGNOSIS

It should be declared that sometimes the virus can be detected in blood and rectal swabs but not found in the throat swab, with the result that these patients can act as carriers and transmit the infection to other people, which shows the importance of testing samples from different sources to confirm the infection [30].

Failure of diagnostic methods in assessing the absence of a virus in the body although its presence and viceversa, causing false-negatives and false-positives, can be due to different causes. Among these, the following can be cited: an improper collection of sputum samples, inhomogeneous sputum, contamination of the sample from the contaminated environment when sampling, that shows the requirement of special sampling rooms, sampling by inexperienced and unskilled staff, improper laboratory equipment, not paying attention to secondary infection of patients which can induce SARS-CoV-2, sampling from inappropriate site of the throat in the throat swab sampling, inadequate and undetectable viral load due to the early stages of the infection, improper storage of samples, inappropriate diagnostic kits, incorrect diagnostic methods and failure to ask patient history, that help the health centers to diagnose and treat patients quickly [82-85].

PREVENTION OF THE SARS-CoV-2

People with close contacts and suspicious exposure need to be advised to have a 14-day health observation duration, which starts from the last day of contact with the SARS-CoV-2 infected patients or suspicious environmental publicity[85]. When displaying any sign and symptom, mainly fever, respiration signs like coughing, shortness of breath, or diarrhoea, they must reach out for medical attention right now [19]. Contact surveillance has to be allotted for people who had been exposed to accidental contact, low-level exposure to suspected or confirmed sufferers, *i.e.* checking any symptoms whilst concluding everyday activities [86].

Patients with a suspected infection should be isolated, monitored, and diagnosed in the hospital as quickly as possible. Doctors ought to make suggestions supported the affected person's situation. Patients with mild signs and suspected infection may additionally remember in-home isolation and domestic care [19]. Suspected infected with severe symptoms and those who have to stay in the health facility for remark through physician's judgment have to observe the isolation guidelines for suspected patients [87].

International site visitors should take ordinary precautions while getting into and leaving the affected regions, which includes avoiding near contacts with human beings with acute breathing infection, washing hands frequently, mainly after contacting with the ill or their surrounding environment; following appropriate coughing etiquette; and warding off close touch with live or lifeless farming animals or bats or other wild animals [87, 88]. Passengers ought to avoid a needless tour as possible.

TREATMENT AND CONTROL OF 2019-nCoV

Respiratory support has to be given to patients with hypoxic respiration failure and acute respiratory distress syndrome [22]. HFNO or NIV may be decided on whilst nasal cannula or masks oxygen therapy was ineffective, or the affected person had hypoxic respiration failure. However, when patients had hypercapnia, hemodynamic instability, a couple of organ failure, and strange intellectual reputation HFNO oxygen is not the robotically followed degree [89]. If respiration failure cannot be improved or worsens continuously within a short time after using HFNO or NIV, intubation has to be carried out at once.

Low-level evidence covered retrospective cohort, traditionally managed studies, case reviews, and case collection revealed that lopinavir/ritonavir alone or in combination with antivirals produced certain advantages in the treatment of SARS and MERS, which include decreasing the incidence or mortality of ARDS [90-92]. A lately systematic assessment confirmed that lopinavir/ritonavir's anti-coronavirus effect was particularly seen in its early application, for reducing affected person mortality and reduced glucocorticoid consumption. However, if the early treatment window is neglected, there can be no significant effect of their late application [93]. Real-world study stills need to further explore the scientific effects of its early use in SARS-CoV-2 inflamed pneumonia. The effectiveness of the combined use of antivirals remains controversial [94-96].

The usage of corticosteroids for severe ARDS is controversial; therefore, it's desirable that systemic use of glucocorticoids to be cautious [97]. Methylprednisolone can be used as appropriate for patients with fast disease progression or severe infection. Consistently with the severity of the disease, 40 to 80 mg of methylprednisolone per day can be considered, and the total each day dose should not exceed 2 mg/kg [89]. SARS management related researches showed that well-timed use of non-invasive continuous effective airway stress and corticosteroids is an effective method for increased lung shadows and increased dyspnea [98]. Suitable use of glucocorticoids can deeply enhance the clinical signs and symptoms of patients with SARS, reduce the degree of disorder development, and accelerate the absorption of lung lesions; however, it cannot shorten the duration of hospital stay [99]. Caution should be taken with hormonal remedy due to some incidence of damaging reactions [88].

CONCLUSION

The various diagnosis methods such as serological, molecular, and radiological can help the health centers in the detection of SARS-CoV-2; radiological and serological techniques are the best methods among the others and the radiological method is the most preferred one, able to diagnose the infection quickly and accurately with fewer false-negatives. The use of effective methods in the diagnosis of the infections is very important, which is vital in saving lives of patients and preventing transmission of infection to other people.

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Transparency declaration
None to declare.

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REFERENCES

[1] Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *New Eng J Med*. 2020; 382, 1199-207.
[2] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses: Springer; 2015, 1-23.
[3] Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microb*. 2016; 24, 490-502.
[4] de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microb*. 2016; 14, 523.
[5] Hilgenfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. *Antivir Res*. 2013; 100, 286-95.
[6] Wong G, Liu W, Liu Y, Zhou B, Bi Y, Gao GF. MERS, SARS, and Ebola: the role of super-spreaders in infectious disease. *Cell Host Microb*. 2015; 18, 398-401.

[7] Gaunt ER, Hardie A, Claas EC, Simmonds P, Templeton KE. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. *J Clin Microb*. 2010; 48, 2940-7.
[8] Dijkman R, Jebbink MF, Gaunt E, et al. The dominance of human coronavirus OC43 and NL63 infections in infants. *J Clin Virol*. 2012; 53, 135-9.
[9] Matoba Y, Abiko C, Ikeda T, et al. Detection of the human coronavirus 229E, HKU1, NL63, and OC43 between 2010 and 2013 in Yamagata, Japan. *Japan J Infect Dis*. 2015; 68, 138-41.
[10] Bassetti M, Vena A, Roberto Giacobbe D. The Novel Chinese Coronavirus (2019-nCoV) Infections: challenges for fighting the storm. *Europ J Clin Invest*. 2020; e13209.
[11] Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019-nCoV. *bioRxiv*. 2020.
[12] Rodriguez-Morales AJ, Bonilla-Aldana DK, Balbin-Ramon GJ, et al. History is repeating itself: probable zoonotic spillover as the cause of the 2019 novel Coronavirus Epidemic. *Infez Med*. 2020; 28, 3-5.
[13] Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health-The latest 2019 novel coronavirus outbreak in Wuhan, China. *Intern J Infect Dis*. 2020; 91, 264-6.
[14] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020; 395, 507-13.
[15] Organization WH. Novel Coronavirus (2019-nCoV): situation report. 2020; 3.
[16] Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019. Novel coronavirus (2019-nCoV), December 2019 to January 2020. *Eurosurveillance*. 2020; 25.
[17] Tang B, Wang X, Li Q, et al. Estimation of the transmission risk of the 2019-nCoV and its implication for public health interventions. *J Clin Med*. 2020; 9, 462.
[18] Cao M, Zhang D, Wang Y, et al. Clinical Features of Patients Infected with the 2019 Novel Coronavirus (COVID-19) in Shanghai, China. *medRxiv*. 2020.
[19] Yuen K-S, Ye Z-W, Fung S-Y, Chan C-P, Jin D-Y. SARS-CoV-2 and COVID-19: The most important research questions. *Cell Biosci*. 2020; 10, 40.
[20] Organization WH. Home care for patients with suspected novel infection presenting with mild symptoms, and management of their contacts: interim guidance, 04 February 2020. *World Health Organization*. 2020.
[21] Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet*. 2020; 395 (10226), 809-15.
[22] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020; 395, 497-506.
[23] Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *BioSci Trends*. 2020; 14 (1), 64-8.
[24] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *J Am Med Assoc*. 2020.
[25] Zhang J, Liu J, Li N, et al. Serological detection of 2019-nCoV respond to the epidemic: A useful complement to nucleic acid testing. *medRxiv*. 2020.
[26] Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *New Eng J Med*. 2020; Feb 28 [Online ahead of print].
[27] Zhang Jj, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. *Allergy*. 2020; Feb 19 [Online ahead of print].
[28] Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Science China Life Sci*. 2020; 1-6.
[29] Zhou P, Yang X-L, Wang X-G, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. *BioRxiv*. 2020.
[30] Zhang W, Du R-H, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microb Infect*. 2020; 9, 386-9.
[31] Balboni A, Gallina L, Palladini A, Prosperi S, Battilani M. A real-time PCR assay for bat SARS-like coronavirus detection and its application to Italian greater horseshoe bat faecal sample surveys. *Scientific World J*. 2012; 989514.
[32] Uhlenhaut C, Cohen JI, Pavletic S, et al. Use of a novel virus detection assay to identify coronavirus HKU1 in the lungs of a hematopoietic stem cell transplant recipient with fatal pneumonia. *Transp Infect Dis*. 2012; 14, 79-85.
[33] Adachi D, Johnson G, Draker R, et al. Comprehensive detection and identification of human coronaviruses, including the SARS-associated coronavirus, with a single RT-PCR assay. *J Virol Method*. 2004; 122, 29-36.
[34] Setianingsih TY, Wiyatno A, Hartono TS, et al. Detection of multiple viral sequences in the respiratory tract samples of suspected Middle East respiratory syndrome coronavirus patients in Jakarta, Indonesia 2015–2016. *Intern J Infect Dis*. 2019; 86, 102-7.
[35] Wan Z, Zhang Yn, He Z, et al. A Melting Curve-Based Multiplex RT-qPCR Assay for Simultaneous Detection of Four Human Coronaviruses. *Intern J Mol Sci*. 2016; 17, 1880.
[36] Noh JY, Yoon S-W, Kim D-J, et al. Simultaneous detection of severe acute respiratory syndrome, Middle East respiratory syndrome, and related bat coronavi-

ruses by real-time reverse transcription PCR. *Arch virol*. 2017; 162, 1617-23.
[37] Qian G-Q, Yang N-B, Ding F, et al. Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series. *medRxiv*. 2020.
[38] Peng L, Liu J, Xu W, et al. 2019 Novel Coronavirus can be detected in urine, blood, anal swabs and oropharyngeal swabs samples. *medRxiv*. 2020.
[39] Chu DK, Pan Y, Cheng S, et al. Molecular diagnosis of a novel coronavirus (2019-nCoV) causing an outbreak of pneumonia. *Clin Chem*. 2020; Jan 31 [Online ahead of print]. tomi T, Okayama H, Masubuchi H, al. Loop-mediated isothermal amplification of DNA. *Nucl Acid Res*. 2000; 28, e63-e.
[41] Enosawa M, Kageyama S, Sawai K, et al. Use of loop-mediated isothermal amplification of the IS900 sequence for rapid detection of cultured Mycobacterium avium subsp. paratuberculosis. *J Clin Microbiol*. 2003; 41, 4359-65.
[42] Poon LL, Leung CS, Tashiro M, et al. Rapid detection of the severe acute respiratory syndrome (SARS) coronavirus by a loop-mediated isothermal amplification assay. *Clin Chem*. 2004; 50, 1050-2.
[43] Pyrc K, Milewska A, Potempa J. Development of loop-mediated isothermal amplification assay for detection of human coronavirus-NL63. *J Virol Method*. 2011; 175, 133-6.
[44] Mori Y, Nagamine K, Tomita N, Notomi T. Detection of loop-mediated isothermal amplification reaction by turbidity derived from magnesium pyrophosphate formation. *Biochem Biophys Res Commun*. 2001; 289, 150-4.
[45] Shirato K, Semba S, El-Kafrawy SA, et al. Development of fluorescent reverse transcription loop-mediated isothermal amplification (RT-LAMP) using quenching probes for the detection of the Middle East respiratory syndrome coronavirus. *J Virol Method*. 2018; 258, 41-8.
[46] Thai HTC, Le MQ, Vuong CD, et al. Development and evaluation of a novel loop-mediated isothermal amplification method for rapid detection of severe acute respiratory syndrome coronavirus. *J Clin Microbiol*. 2004; 42, 1956-61.
[47] Njiru ZK. Loop-mediated isothermal amplification technology: towards point of care diagnostics. *PLoS Negl Trop Dis*. 2012; 6.
[48] Shen M, Zhou Y, Ye J, et al. Recent advances and perspectives of nucleic acid detection for coronavirus. *J Pharm Anal*. 2020.
[49] Chen Q, Li J, Deng Z, Xiong W, Wang Q, Hu Y-q. Comprehensive detection and identification of seven animal coronaviruses and human respiratory coronavirus 229E with a microarray hybridization assay. *Intervirol*. 2010; 53, 95-104.
[50] Shi R, Ma W, Wu Q, et al. Design and application of 60mer oligonucleotide microarray in SARS coronavirus detection. *Chin Sci Bull*. 2003; 48, 1165-9.
[51] Guo X, Geng P, Wang Q, Cao B, Liu B. Development of a Single Nucleotide Polymorphism DNA Microarray for the Detection and Genotyping of the SARS Coronavirus. *J Microbiol Biotechnol*. 2014; 24, 1445-54.
[52] de Souza Luna LK, Heiser V, Regamey N, et al. Generic detection of coronaviruses and differentiation at the prototype strain level by reverse transcription-PCR and nonfluorescent low-density microarray. *J Clin Microbiol*. 2007; 45, 1049-52.
[53] Hardick J, Metzgar D, Risen L, et al. Initial performance evaluation of a spotted array Mobile Analysis Platform (MAP) for the detection of influenza A/B, RSV, and MERS coronavirus. *Diagn Microbiol Infect Dis*. 2018; 91, 245-7.
[54] Orílio AF, Lucinda N, Dusi AN, Nagata T, Inoue-Nagata AK. Complete genome sequence of arracacha mottle virus. *Arch Virol*. 2013; 158, 291-5.
[55] Bordería AV, Stapleford KA, Vignuzzi M. RNA virus population diversity: implications for inter-species transmission. *Curr Opin Virol*. 2011; 1, 643-8.
[56] Gaudin M, Desnues C. Hybrid capture-based next generation sequencing and its application to human infectious diseases. *Front Microbiol*. 2018; 9, 2924.
[57] Chen G-Q, Zhuang Q-Y, Wang K-C, et al. Identification and survey of a novel avian coronavirus in ducks. *PLoS One*. 2013; 8.
[58] Wang K-C, Chen G-Q, Jiang W-M, et al. Complete genome sequence of a hemagglutination-negative avian paramyxovirus type 4 isolated from China. *Gen Ann*. 2013; 1, e00045-13.
[59] Dillies M-A, Rau A, Aubert J, et al. A comprehensive evaluation of normalization methods for Illumina high-throughput RNA sequencing data analysis. *Briefing Bioinform*. 2013; 14, 671-83.
[60] Zhou P, Fan H, Lan T, et al. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. *Nature*. 2018; 556, 255-8.
[61] Lau SK, Woo PC, Li KS, et al. Complete genome sequence of bat coronavirus HKU2 from Chinese horseshoe bats revealed a much smaller spike gene with a different evolutionary lineage from the rest of the genome. *Virol*. 2007; 367, 428-39.
[62] Li B, Si H-R, Zhu Y, Yang X-L, Anderson DE, Shi Z-L, et al. Discovery of Bat Coronaviruses through Surveillance and Probe Capture-Based Next-Generation Sequencing. *M Sphere*. 2020, 5.
[63] Noyes NR, Weinroth ME, Parker JK, et al. Enrichment allows identification of diverse, rare elements in metagenomic resistome-virulome sequencing. *Microbiom*. 2017; 5, 142.
[64] Wylie TN, Wylie KM, Herter BN, Storch GA. Enhanced virome sequencing through solution-based capture enrichment. *Genome Res*. 2015; gr. 191049.115.
[65] Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. *Am J Roentgenol*. 2020; 1-7.

[66] Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. *Radiol*. 2020; 200642.
[67] Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. *Radiol*. 2020; 200343.
[68] Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Ped*. 2020; 9, 51.
[69] Wei J, Xu H, Xiong J, et al. 2019 Novel Coronavirus (COVID-19) Pneumonia: Serial Computed Tomography Findings. *Korean J Radiol*. 2020; 21.
[70] Song F, Shi N, Shan F, et al. Emerging 2019 Novel Coronavirus (2019-nCoV) Pneumonia. *Radiol*. 2020; 200274.
[71] Lee KS. Pneumonia Associated with 2019 Novel Coronavirus: Can Computed Tomographic Findings Help Predict the Prognosis of the Disease? *Korean J Radiol*. 2020; 21, 257-8.
[72] Vaseghi G, Mansourian M, Karimi R, et al. Clinical characterization and chest CT findings in laboratory-confirmed COVID-19: a systematic review and meta-analysis. *med Rxiv*. 2020.
[73] Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. *American J Roentgenol*. 2020; 1-6.
[74] Diao K, Han P, Pang T, Li Y, Yang Z. HRCT imaging features in representative imported cases of 2019 novel coronavirus pneumonia. *Prec Clin Med*. 2020.
[75] Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiol*. 2020; 200230.
[76] Fang Y, Zhang H, Xu Y, Xie J, Pang P, Ji W. CT manifestations of two cases of 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiol*. 2020; 200280.
[77] Xie Y, Yang L, Dong H, Peng H, Yu Y, Tu G, et al. CT scores predict mortality in 2019-nCoV pneumonia. Clinical Trial registered. NCT04284046.
[78] Kong W, Agarwal PP. Chest imaging appearance of COVID-19 infection. *Radiol Cardiothor Imaging*. 2020; 2, e200028.
[79] Bernheim A, Mei X, Huang M, et al. Chest CT findings in coronavirus disease-19 (COVID-19): Relationship to duration of infection. *Radiol*. 2020; 200463.
[80] Pan Y, Guan H, Zhou S, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Europ Radiol*. 2020; 1-4.
[81] Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiol*. 2020; 200370.
[82] Wang M, Wu Q, Xu W, et al. Clinical diagnosis of 8274 samples with 2019-novel coronavirus in Wuhan. *medRxiv*. 2020.
[83] Xiao SY, Wu Y, Liu H. Evolving status of the 2019 novel coronavirus Infection: proposal of conventional serologic assays for disease diagnosis and infection monitoring [Commentary/Review]. *J Med Virol*. 2020.
[84] Yang L. Clinical Reports on Early Diagnosis of Novel Coronavirus (2019-nCoV) Pneumonia in Stealth Infected Patients. *ScienceOpen Res Preprint*. 2020.
[85] Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Intern J Surg* 2020; 76, 71-76, Feb 26 [Online ahead of print].
[86] Kim JY, Song JY, Yoon YK, et al. Middle East respiratory syndrome infection control and prevention guideline for healthcare facilities. *Infect Chemother*. 2015; 47, 278-302.
[87] Organization WH. Infection prevention and control during health care when infection is suspected: interim guidance, January 2020. *World Health Organization*. 2020.
[89] Jin Y-H, Cai L, Cheng Z-S, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Milit Med Res*. 2020; 7, 4.
[90] Meyer B, Basra A, Aberle S, et al. 1225: MERS-COV disease associated ARDS - a case report. *Critical care medicine*. 2015; 43, 308.
[91] Lai S. Treatment of severe acute respiratory syndrome. *Europ J Clin Microbiol Infect Dis*. 2005; 24, 583-91.
[92] Que T, Wong V, Yuen K. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J*. 2003; 9, 399-406.
[93] Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *The Lancet Infect Dis*. 2014; 14, 1090-5.
[94] Guo Y-R, Cao Q-D, Hong Z-S, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. *Milit Med Res*. 2020; 7, 1-10.
[95] Qin X, Qiu S, Yuan Y, et al. Clinical characteristics and treatment of patients infected with COVID-19 in Shishou, China. China (February 18, 2020). 2020.
[96] Chan JF-W, Yao Y, Yeung M-L, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis*. 2015; 212, 1904-13.
[97] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020; 102433.
[98] Khan PA, Nousheen B, Maryam N, Sultana K. Middle east respiratory syndrome (mers): a systematic review. *Intern J Pharm Sci Res.* 2018; 9, 2616-25.
[99] Zhao Z, Zhang F, Xu M. Clinical analysis of 190 cases of outbreak with atypical pneumonia in Guangzhou in spring, 2003. *Guangdong Med J*. 2003; 24, 73-6.