[Review Article]
Transmission, Pathological Mechanism and Pathogenesis of SARS-1 and SARS-2

Shahbaa Khalil A-Taee, Enas Sheet Mostafa and Ahmed M. Al-Saidya
Department of Pathology and Poultry Diseases, Collage of Veterinary Medicine, University of Mosul, Mosul, Iraq.

The coronavirus is an etiological agent of affects both animals and humans. Sever acute respiratory syndrome (SARS-2) and (SARS-1) are caused by two viruses belonging to subgenus beta-coronavirus. SARS-1 and SARS-2 are considered zoonotic diseases transmitted from animals to human causing epidemic SARS-1 and pandemic SARS-2. In animals and humans both viruses have a tropism binding receptors the ACE2 which is the entry site for host cells. In animal virus affected all aged and cause disturbances in all organs but main clinical signs are respiratory disorder with development some complications and organs failure functions in advance cases. Similarity of both SARS-1 and SARS-2 resulted in thrombus formation accompanied with elevated d-dimer, increase fibrin formation and long time for prothrombin. In addition neurological disorder and olfactory dysfunction was detected in SARS-2. This review focused on the coronavirus transmission, host defense mechanisms, pathophysiology and pathogenesis. There was similarity and different points between SARS-1 and SARS-2, but in general SARS2 is less pathogenic and more rapidly transmissible than SARS-1.

Key words: Pathological aspect, SARS-1, SARS-2, Complication, organs dysfunction.

Introduction
Coronaviruses pathogens that affects humans and animals, specially wild life species [1]. Coronaviruses are single stranded RNA, positive sense, enveloped and have spherical shape with finger spike projection giving them roughly crown appearance [2]. The genome is one part, linear composed of with 30kb, terminal cap structure”5 with 3 poly- A tails that represent the site for virus infection cycle, template site for virus replication and transcription also it is the units for packaging a new progeny virus [3,4]. The Nidovirales order includes Coronaviridae family which is divided into subfamily Letovirinae and Orthocoronavirinae, [5] last subfamily include four genus (Alpha coronavirus, Beta coronavirus, Gamma coronavirus and Delta coronavirus), the firsts two genera affected human and mammals while the other two genera affected birds [6]. According to phylogenetic analysis figure 1, Beta coronavirus divided into subgroup: Embecovirus, Merbocorvirus, Nobecorvirus and Sarbecorvirus (including SARS-CoV) [7].

Coronavirus was firstly isolated and identified in 1930s as causative agent of infectious bronchitis in chickens [9] and in 1940s it was detected in porcine and murine [10]. Also, it has been known in human from 1965 to 1967 as the pathogenic agent of common cold (229E, NL, OC43 and HKUI) Alpha coronaviruses are responsible for endemic diseases affecting the upper respiratory tract.

In 2002-2003, a new human disease was recognized by World Health Organization (WHO) in China as epidemic severe respiratory syndrome which is associated with coronavirus [11,12], another disease caused by coronavirus called Middle East Respiratory Syndrome (MERS) was found in Saudi Arabia in 2012 and also causes respiratory disorder and renal failure, [13]

Recently in December of 2019 a new version of coronavirus causing pandemic disease detected in Seafood Market in Wuhan, China and then spread to all world, WHO named this disease as COVID-2019 [14] and later as COVID-19, International Committee on Taxonomy of Virus (ICTV) named it severe acute respiratory syndrome (SARS-2) [15-17]
Zoonotic aspect and animal susceptibility

SARS-1 and SARS-2 is zoonotic disease that is transmitted from animals to human, SARS-1 disease investigated in Hong Kong in China and detected as respiratory disease (atypical pneumonia) that is transmitted from bats and civet which are natural reservoir [18,7]. Beta coronavirus are closely related to horseshoe bat (*Rhinolophus ferrumequinum*) investigated in China [19].

According to phylogenetic analysis, there was similarity feature of SARS-2 about 90.55% to the horseshoe (*Rhinolophus affinis*) which is consider revising for SARS-2 [20,23] Some reports suggested that Malayan pangolin acts as intermediated host for SARS-2 due to some regions in the S protein enveloped in SARS-2 virus are closely related and similarity about 91.02% to pangolin [20,24,25], so the bats and pangolin act as the origin of the disease. In Netherlands two farms of minks have positive tests for SARS-2 and this lead to suggested that mink farms may be source of human infection [26,27].

Susceptible animals to both diseases are variable, primate old aged animals may infected with SARS-1 and causing fever, mild labored breathing [28], cats and ferrets are more susceptible to SARS-2 which has been poor replication in ducks, chickens, dogs and pigs and there was not cross species transmission [29]. The disease is transmitted between human being through direct contact or via droplet during sneezing and coughing, also there is limited study reported that women in third trimester may be infected which may be transmitted to child through vaginal tract [30].

Due to RNA's tremendous capacity for mutation and the ongoing generation of novel viral strains with high virulence and severity [31], which play critical roles in the spread of viruses between humans, as well as due to the previous phylogenetic analysis and genetic sequence similarity between the animals and the Beta coronavirus these are lead to question Does SARS-1 and SARS-2 transmitted from human to animals? [32] reported that 487 amino acids of cell receptors ACE2 in both human and animals interaction with virus spike, this studying give indicator for opposite transmitted diseases from human to animals.A study of [33] reported that SARS-1transmitted from humans to pigs.

The SARS-2 can be transmitted to pet animals from illness owners [34], figure 2 many cases of pet animals give a positive test for SARS-2 in many countries of Europa and Asia, a tiger Nadia was considered the first case in the zoo in New York infected with SARS-2 get the infection from illness keeper zoo with SARS-2, the severity of disease is
variable from non-symptoms to mild respiratory disorder [35] therefore, biosecurity is considered one of the most important ways to prevent disease and prevent its transmission between humans and animals [36].

**Pathogenesis and Pathophysiology:**

The genome sequence analysis of SARS-2 is similarity about 82% to human SARS-1 and about 89% to bat SARS-like-CoV2[38], so SARS-2 and SARS-1 use the same entry cell pathway [39].

Five important steps for the life cycle of the virus should occur for pathogenesis, first of all is the ability of the virus to bind to host cell receptors (attachment) then virus enter target cell by endocytosis or by penetration (membrane fusion) which is more efficient than endocytosis [40], then biosynthesis is occupied the third step for viral life cycle which is mean released of viral content to inside target cell for replication and viral mRNA is act to create viral protein, fourth and fifth steps represented by maturation and released new viruses [16], figure 3.

**Fig. 2. Coronaviruses origin and transmission between humans and animals [37]**

**Fig. 3. Life Cycle of Coronavirus [41]**

Protein membrane is the one of the structural components of the coronavirus which is involves: spike (S), membrane (M), envelop (E) and nucleocapsid (N) [42]. Spike membrane consists of two subunits S1, its function is binding to cell receptors while S2 is responsible for fusion.

Angiotensin converting enzyme (ACE2) is more important receptors for SARS-1 and SARS-2 pathogenesis [43,44].

ACE2 is enzyme related to carboxyptidase, It is composed of two structures N-terminal domain (extracellular) which represent the binding site of
SARS-CoV and c-terminal (intracellular, cytoplasmic tail). The membrane-bound (cellular) and soluble (circulating) are the main types of ACE2, [45].

The functional importance of ACE2 its role in renin – angiotensin aldosterone system (RAAS) which has effects on ionic-fluid balance and maintainance blood pressure. ACE2 also defense and protection role against inflammation and have ability to regulate intestinal function [46].

ACE2 is shed by two enzymes (i) metalloprotease ADAM17 which play a role in circulating ACE2 cleaved from full-length ACE2 and released to extracellular although these soluble form represent binding site for SARS-CoV but the virus can’t be duplicate ,while TMPRSS is important enzyme for cleavage and shedding ACE2 and represent the main mechanism for SARS-CoV cell entry [47-48], figure 4.

ACE2 is expressed mainly in epithelial cells of respiratory tract (pneumocystis and enterocyte), kidney, brain, heart and endothelial cells of the vascular system and is not expressed in thymus, lymph nodes and bone marrow [49-50]. So dysfunction of ACE2 may led to distribution and functional failure in many organs, some drug binding to this receptors which act to reduce the disease [51].

**Fig. 4. Hypothesis of ACE2 shedding and SARS-CoV-2 entry, [52].**

**Host Defense Mechanism**

The pathogenic agent for both SARS-1 and SARS-2 has high affinity to the epithelial cells of respiratory tract. After entering the epithelial cells, alveolar macrophage and dendritic cell (DC) act as Antigen Presenting Cells (APC) which is the first line of innate immunity, [52] until adaptive immunity would be stimulated and T cells mediated responses act against the viruses, alveolar macrophage occupy the apical part of the epithelium and DC located beneath epithelium.

The virus of the SARS-2 enter the APC in three way (i) through phagocytic ability of DCs and macrophage which are phagocytizing the apoptotic infected epithelium cells [53], (ii) through the high affinity of the virus to splenic dendritic cells and macrophage, also (iii) there is another protein dendritic cells-specific intercellular adhesion molecules-3-grabbing nonintegrin (DC-SIGN) which is high expression in dendritic cells and macrophage and representing SARS-1 binding site receptors [54].

The immune response may result from vaccination or virus infection and may cause tissue damage [55]. Viruses transmitted through APC to the lymph nodes and activated CD4+ T cells for stimulated B cells for production specific antibodies and activated CD8+ T cells for killing virus, these T cytotoxic cells may cause injury to the lung and tissue [56]. The granulocyte–macrophage colony stimulating factors (GM-CSF) is the host response against virus infection, so it was investigated at high levels in SARS-2 patients, [57].

Cytokines swarmer represent one of the main physiological pathways of SARS diseases which play as host responses and at the same time cause injury to tissue and play a significant role in promoting disease severity, cytokines are involve IL-6, IL-10, IL-9, IL-7, IL-1B, IL-1RA, IL-2 and pro-inflammatory factors as monocyte chemoattractant protein (MCP1), tumor necrosis factors (TNF-alpha), macrophage inflammatory protein (MIP-1 alpha), interferon (INF-gamma) and GMCSF[58] besides increase levels of fibrinogen and d-dimer [59]. The IL-8 was high expression at high level in blood of patients with SARS-1 in addition to IL-6.
(52) these will act as chemoattractant to neutrophils, that have biological function as antigen phagocyte, also cause tissue damage [60].

CD14 + CD16+ is circulating monocyte released by pathological T cells to respond to GM-CSF, this monocyte had high expression of IL-6 accelerated the progression of systemic inflammatory response.

### Respiratory disorders

SARS-2 like SARS-1 and MERS transmitted from bats to human and cause respiratory syndromes [61-63], but SARS-2 approximately third of the 41 patient exhibit acute respiratory distress syndromes (ARDS) and 6 patients were died, similarity of the clinical signs in both SARS-1 and SRAS-2 have been reported as fever, dry cough and ground glass opacities in lobes of lung on the CT chest and dyspnea [58], other symptoms have investigated in SARS-2 patients were suffering from fatigue, headache, sputum and diarrhea which are less common in SARS-1[64,65]. Researcher noted unique symptoms of SARS-2 that affected lower airway of respiratory tract and it distinguished by upper respiratory tract symptoms as sneezing, sore throat and rhinorrhea [66]. According to the symptoms the stages of SARS-2 are summarized in table 1.

<table>
<thead>
<tr>
<th>SARS-2 stages</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>Patient do not have any clinical signs with positive test for SARS-2 and normal CT chest image.</td>
</tr>
<tr>
<td>Mild</td>
<td>General diseased signs in both upper respiratory tract disorder signs (cough, sneezing, sore throat, fatigue and fever) and digestive system disorder (vomiting, diarrhea, nausea and abdominal pain).</td>
</tr>
<tr>
<td>Moderate</td>
<td>Signs of pneumonia, without hypoxemia and lung CT with lesions.</td>
</tr>
<tr>
<td>Severe</td>
<td>Hypoxemia SpO2 less than 92% with pneumonia.</td>
</tr>
<tr>
<td>Critical</td>
<td>ARDS with multiple organs failure (heart, brain and kidney) with coagulation disturbances.</td>
</tr>
</tbody>
</table>

Histopathological examination revealed infiltration of inflammatory cells (representing innate and adaptive immunity) [67] in the lower respiratory tract and damage of the lung tissue with fibrosis and desquamation of pneumocyte and opacity of the lung as a result of hyaline membrane formation, figure 5.

Pulmonary embolism has occurred because of disorder in respiratory vasculature. The small intestine was target organ for the SARS-2 infection that cause segmental dilation and stenosis [69] and gastro intestinal tract symptoms as diarrhea will be occur, in contrast to SARS-1 additional to it is infection to RT and cause exudative lesion and mild fibrosis it detected in kidney, sweat gland and...
with less percentage of gastrointestinal than SARS-
2 [70,71].

**Coagulative disorder and Thrombus formation**

Since the SARS-2 is detected in Wuhan as severe acute respiratory syndrome with mild or severe illness and death occurs in some cases as a result of ARDS other patient die with sepsis and complication, vascular endothelium cells damage and thrombotic complication, the endothelium cells occupied the one third of the lung cells component and have vital function in vasodilatation, anti-aggregation and fibrinolysis and thrombotic regulation [59]. Coronavirus have high atropism to ACE2 receptors on the endothelium [72].

So there was increase D-dimer and developing disseminated intravascular coagulation (DIC) , increase degradation of fibrin product and prolonged prothrombin time [73] all these factors lead to thrombus formation and pulmonary embolism which lead to hypoxia as a result of endothelium injury the capillary bed permeability considered cofactor for viral invasion and lead to platelet activation and changes in megakaryocyte and these will cause thrombocytopenia [74].

Like SARS-2, SARS-1 had been combine with fibrin thrombus formation in the branchial and pulmonary venioles in the lung cause histological alteration as pulmonary edematous, hyaline formation and fibrosis [75]

**Neurological disorder**

Coronaviruses are known as the pathogenic agent affected nervous system, in 2002-2003 outbreak disease (SARS) diseases affected many organs and cerebral spinal cord have been involved in the SRAS [76].Recently, pandemic SARS-2 characterize by mild to severe acute respiratory symptoms to death and some cases associated with extra pulmonary features these are include nervous system[77].Poyiadgi et al., 2020 [78] was reported an infected women with SARS-2 showing clinical finding of acute necrotizing encephalopathy and hyper intense lesion occurring in medial and right temporal lobes with clinical symptoms of (headache, (perdizziness and nausea) Efe et al., 2020[79] reported in old woman SARS-2 patient with encephalitis, figure 6, Moriguchi et al., 2020 [80] detected SARS-2 ribonucleic acid in cerebral spinal fluid in patient with unconsciousness and convulsion.

![Image](image_url)

**Fig. 6. Photograph examination of SARS-2 brain patient with infiltration of lymphocyte and inflammatory cells (perivascular cuffing) with congestion(A) vacuolation and ischemic infarction (B) [79]**

Neuroinvasion mechanisms: Both viruses (SARS-1 and SARS-2) related to genus beta-coronavirus and have high homologous genetic analysis and share with similar virus structure and same entry to host cells [81] these are include: (i) cerebral SARS-1 invasion across the cerebiform intracranial entry via the olfactory bulb [82]. The virus have tropism to ACE2 which have expression in the nasal epithelial cells and cause damage to olfactory neuroepithelium and lead to inflammation and impaired to olfactory neuron receptor, olfactory dysfunction, lost temporary of the smell and or taste sense or long period for neurogenesis [83] , (ii) or the virus invade brain via blood stream through affinity of SARS-2 to ACE2 which is expression on the endothelium of capillary blood vessels and may cause destruction to blood –brain barrier and enter CNS, as well as ACE2 expressed in the neuron [84].

**Clinical Signs and Pathological lesions**

Many cases of uncare SARS-2 patients revealed neurological signs after 2-4 weeks from beginning of respiratory syndrome as in table 2
### Table 2. Categories of neurological signs [85]

<table>
<thead>
<tr>
<th>Categories stage</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific</td>
<td>Headache, dizziness, myalgia is result from the myocities and muscle damage which lead to elevated muscle enzyme. Olfactory dysfunction led to hyposmia, hypoguesia, lost visual function and peripheral nervous defect may be involvement with paralysis and consciousness defect and multiorans failure. Intracerebral hemorrhage resulting from viruses binding to protective factors (ACE2) which led to hypertension and thrombocytopenia hemorrhage. Ischemic stroke, the pathophysiological virus on the circulating system (elevated D-dimer) Acute necrotizing encephalopathy: is rare a systemic inflammation result from defect the liver, seizures and electrolyte and mental disorientation characterized by multifococal symmetric lesions in the brain. meningitis and encephalitis Guillain-Barré syndrome Innervation weakness with demylation in the motor in the lower extremities.</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. General differentiated points between SARS-2 and SARS-1

<table>
<thead>
<tr>
<th>Features</th>
<th>SARS-2</th>
<th>SARS-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year discovery</td>
<td>2019</td>
<td>2002</td>
</tr>
<tr>
<td>Region in the world</td>
<td>Wuhan city /China</td>
<td>Hong Kong in China</td>
</tr>
<tr>
<td>Natural reservoir</td>
<td>Bats</td>
<td>Horseshoe bats</td>
</tr>
<tr>
<td>Intermediate host</td>
<td>Malayan pangolin</td>
<td>Civet</td>
</tr>
<tr>
<td>Mode of Transmission</td>
<td>Direct contact with patients, contaminated objects with aerosol and droplet</td>
<td>Direct contact with patients, contaminated objects with aerosol and droplet</td>
</tr>
<tr>
<td>Incubation period</td>
<td>Two – Fourteen day</td>
<td>Two – Seven day</td>
</tr>
<tr>
<td>Receptors</td>
<td>ACE2</td>
<td>ACE2</td>
</tr>
<tr>
<td>Disease</td>
<td>Pandemic sever respiratory syndrome (ongoing disease)</td>
<td>A typical epidemic pneumonia (controlled disease)</td>
</tr>
<tr>
<td>Disease in animals</td>
<td>In tiger and ferrets: cough and loss appetite, disease characterize by conjunctivitis, vomiting, respiratory disease in cat</td>
<td>In aged animals: mildly labored breathing, fever</td>
</tr>
</tbody>
</table>

### Conclusion

Both SARS-1 and SARS-2 have similarity in phylogenetic analysis for the causative agent, source of infection, mode of transmission to human, site of entry and pathogeneses but SARS-2 have less pathogenicity but rapidly transmitted rather than SARS-1 and affected vascular and nervous systems rather than respiratory tract. In general differentiated points summarized in table 3.

### Conflict of Interest

The authors declare that there is no conflict of interest.

### References


طريقة انتقال وألية حدوث المرض والتغيرات المرضية في السارس-1 والسارس-2

شهباء خليل إبراهيم، ايناس شيت مصطفى واحمد محمد علي السيدية
فرع الأمراض والمراض المعدية - كلية الطب البيطري - جامعة الموصل - الموصل - العراق.

فيروس كورونا هو عامل مسبب للمرض يؤثر على كل من الحيوانات والبشر. تنجم المتلازمة التنفسية الحادة الوخيمة (سارس-2) عن فيروس كورونا جنباً إلى جنب مع فيروس كورونا كنا الـ"سارس" - السارس-1. في الأنواع المنشأة التي تنتقل من الحيوانات إلى الإنسان، بالرغم من نقص فيروس كورونا، يحتوي كلا الفيروسين على مستقبلات ربط الانتحار، وهي2ACE، وهو موقع دخول الخلايا المضيفة. يصيب الفيروس جميع أعمار الحيوانات وسبب اضطرابات في جميع الأعضاء ولكن العلامات السريرية الرئيسية هي اضطراب الجهاز التنفسي مع تطور بعض المضاعفات وفشل وظائف الأعضاء في الحالات المتقدمة. أدى التشابه بين كل من السارس-1 والسارس-2 إلى تسخير خطرة متصاعدة بارتفاع ديمير، زيادة تكوين الـ"أي دي" ووقت طويل للبروثربين. تم اكتشاف اضطراب عصبي بالإضافة إلى ضعف حساسية التحم في اللسان، ركزت هذه المراجعة على انتقال فيروس كورونا، والثبات الدفاعي، والفيزيولوجيا المرضية، والسبب في المرض. كان هناك تشابه وتفاوت متفاوت بين السارس-1 والسارس-2، ولكن بشكل عام، السارس-2 أقل إمراضًا وأكثر سرعة في الانتشار من السارس-1.