Comparative pathology, molecular pathogenicity, immunological features, and genetic characterization of three highly pathogenic human coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2)


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Comparative review of three human coronaviruses

Abstract. – The last two decades have witnessed the emergence of three deadly coronaviruses (CoVs) in humans: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are still no reliable and efficient therapeutics to manage the devastating consequences of these CoVs. Of these, SARS-CoV-2, the cause of the currently ongoing coronavirus disease 2019 (COVID-19) pandemic, has posed great global health concerns. The COVID-19 pandemic has resulted in an unprecedented crisis with devastating socio-economic and health impacts worldwide. This highlights the fact that CoVs continue to evolve and have the genetic flexibility to become highly pathogenic in humans and other mammals. SARS-CoV-2 carries a high genetic homology to the previously identified CoV (SARS-CoV), and the immunological and pathogenic characteristics of SARS-CoV-2, SARS-CoV, and MERS contain key similarities and differences that can guide therapy and management. This review presents salient and updated information on comparative pathology, molecular pathogenicity, immunological features, and genetic characterization of SARS-CoV, MERS-CoV, and SARS-CoV-2; this can help in the design of more effective vaccines and therapeutics for countering these pathogenic CoVs.

Key Words: Pathology, Immunology, Genetic characterization, Coronaviruses, MERS-CoV, SARS-CoV, SARS-CoV-2, COVID-19.

Introduction

The devastating fact that zoonotic diseases attributed to coronavirus (CoV) strains can result in pandemics came to public attention in 2003 after a severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak. Since this realization, scientists and public health officials have raised concerns over health threats posed to the human population by the three coronaviruses (CoVs) SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)\(^1\). Among at least six strains of human-infecting CoVs that have been identified by studies, these three have proved to be highly pathogenic as they trigger severe pneumonia and systemic symptoms in humans\(^2\). CoVs are a complex and diverse family of enveloped, positive-sense, single-stranded RNA viruses and are divided into four genera: alpha, beta, gamma, and delta CoV\(^3,4,14,15\). Of these, beta CoVs have drawn the most attention due to their ability to cross animal-human barriers and act as significant global infectious agents\(^2,6,8,16\). SARS-CoV, SARS-CoV-2, and MERS-CoV have been identified as the most important and evolving beta CoVs, and their molecular biology and immunological features remain to be investigated in detail\(^1,4,5,8,17-19\). Seasonal variations have been observed in the pattern of these viruses: SARS-CoV-2 outbreak occurs in the winter, in contrast to MERS-CoV and SARS-CoV outbreaks and triggering severe pneumonia\(^18\). Moreover, these three viruses show similar genomic composition, clinical manifestations, and route of transmission\(^1,4,20\). The current pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has apparent similarities with SARS\(^9,10,21\), including disease progression, escape from the host immune system, and subsequent acute respiratory distress syndrome (ARDS). The International Committee on Taxonomy of Viruses (ICTV) designated the causal agent of COVID-19 as “SARS-CoV-2” due to its similarities with SARS-CoV\(^19,22,24\).

During the COVID-19 pandemic, the world has experienced unprecedented challenges, with over 4.9 million deaths and more than 243 million confirmed cases of SARS-CoV-2 infection in over 225 countries with a fatality rate ranging between 1.5% and 5% as of October 26, 2021\(^17,22,25\). A high case fatality rate of about 49%\(^9,36\) has been reported in patients with an acute disease requiring ventilator support and Intensive Care Unit (ICU) admission. There have been significant breakthroughs in vaccine development, with several vaccines administered globally for protection against SARS-CoV-2. In addition, many effective drugs and therapeutic candidates are being evaluated, such as antivirals, monoclonal antibodies, cytokine inhibitors, and immunosuppressants\(^27-32\).

SARS-CoV-2, when observed under an electron microscope, has a structure similar to a crown (corona). The mechanism of virus entry into the host is identical to that of SARS-CoV, which binds to the human angiotensin-converting enzyme 2 (ACE2) receptor via its protein receptor-binding domain (RBD)\(^33-35\). In contrast, MERS-CoV binds to the DPP4 receptor to enter host cells. Genomic analysis data has revealed that the genome sequence similarity of SARS-CoV-2 to SARS-CoV and MERS-CoV is 80% and 50%, respectively\(^21,36\). While exploring the evolutionary potential of SARS-CoV-2, studies have found that its genome exhibits 96%
similarity to that of bat-derived CoV isolated in 2013\textsuperscript{37,38}. SARS-CoV-2 and SARS-CoV have 380 amino acid (AA) substitution sites. It has been hypothesized that any substitution in the AA sequence could lead to a possible novel viral protein function with unclear pathogenesis\textsuperscript{39}. The spike (S) protein and the nucleocapsid protein are linked to higher transmission capability and lower pathogenicity in SARS-CoV-2. However, the mutations in the S protein are especially crucial because the S protein is key for the first step of viral transmission: entry into the cell by binding to the ACE2 receptor\textsuperscript{40-44}. SARS-CoV-2 steadily mutates during continuous transmission among humans, and naturally occurring S mutations can reduce or enhance cell entry via the ACE2 receptor\textsuperscript{45}. According to a recent study\textsuperscript{46}, six AA residues (D480, T487, Y442, N479, L472, and Y491) for SARS-CoV, and Q493, S494, L455, F486, Y505, and N501 for SARS-CoV-2) are essential for binding to the human ACE2 receptor. Among these six SARS-CoV-2 AA residues, the lack of similarity of five residues to those of SARS-CoV may be attributed to the deletions, insertions, or mutations in the S1 and S2 regions, which are responsible for evolutionary changes\textsuperscript{46,47}. The novel strain has an evolutionary path different from those of MERS-CoV and SARS-CoV, with lineage similarity to previously evaluated bat-derived CoV. However, there are proteomic and genomic differences between the bat and human CoVs, indicating a unique immune invasion mechanism and a distinct immunopathology associated with host response\textsuperscript{48}. The common clinical symptoms of COVID-19 are similar to those of SARS: dry cough (67.7%), fever (87.9%), myalgia (34.8%), fatigue (69.6%), hypoxia, and progressive dyspnea followed by damage to multiple organs. In contrast to SARS-CoV, SARS-CoV-2 is more transmissible, but the overall mortality rate is lower than that for SARS-CoV infection. Like MERS and SARS, COVID-19 is likely to be more severe in elderly people and those suffering underlying comorbidities, including many chronic health conditions. Here, we present salient and updated information on comparative pathology, molecular pathogenicity, immunological features, and genetic characterization of SARS-CoV, MERS-CoV, and SARS-CoV-2. As the current pandemic remains ongoing, this review can contribute to the design of more effective vaccines and therapeutics.

**Early Phase of Viral Infection**

In the early stages, SARS infection causes non-specific symptoms such as myalgia, fever, headache, and severe fatigue\textsuperscript{49}. These symptoms tend to diminish in seven days. Sequential nasopharyngeal aspirate samples from SARS patients indicate a direct relationship between clinical progression and viral load\textsuperscript{50}. After its peak, viral load usually decreases rapidly, with IgG seroconversion serving as an indicator of specific immunity development. However, some patients’ clinical conditions can worsen during this period, creating inconsistencies with viral clearance observations. Delay in viral peak can indicate absence or hindrance of host antiviral responses necessary to enhance viral clearance\textsuperscript{51}.

A retrospective study evaluating the cause of worsening clinical condition after viral load reduction highlighted the underlying association between viral clearance, immune dysregulation, and disease development\textsuperscript{52}. The host hyper-inflammatory response, not the cytopathic effect of the virus, may be responsible for this phenomenon\textsuperscript{53,54}. To some extent, rapid viral load elevation could be the contributing factor for disease pathology. Clinical features such as diarrhea, oxygen desaturation, hepatic dysfunction, and fatality indicate that high viral load may contribute to direct organ dysfunction\textsuperscript{55}. Clinical specimens of various anatomic sites of organ dysfunction have yielded virus. For instance, stool specimen was highly related to diarrhea, with viral particles detected in ileum and colon biopsies observed under an electron microscope\textsuperscript{54}. There is extensive evidence regarding the relationship between pathological effects, viremia, and viral loads from these findings. Strong evidence exists of high viral loads associated with massive infiltration of the inflammatory immune cells being significantly linked to worse clinical outcomes in patients\textsuperscript{54}. Patients with elevated viral load at an early stage were also likely to have higher mortality\textsuperscript{55,56}. Therefore, it is essential to address the molecular pathology, immunological characteristics, pathogenicity, and genetic sequence of MERS-CoV, SARS-CoV, SARS-CoV-2, and other CoVs. A few of the general characteristics of MERS-CoV, SARS-CoV and SARS-CoV-2 are presented in Table I.

**Genetic Similarities of MERS-CoV, SARS-CoV, and SARS-CoV-2**

Among the CoV subtypes, beta CoVs cause severe and fatal diseases in humans, while alpha CoVs cause mild infections. The genomic sequences of MERS-CoV, SARS-CoV, and SARS-CoV-2 are quite similar, but SARS-CoV-2 displays significant differences in genome com-
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A plethora of research evidence shows that pangolins may be the intermediate host—there is 99% homology between SARS-CoV-2 and the CoV strain originating from pangolins—but bats are the natural reservoir for the virus\(^62,63\). Bats are generally recognized as potential primary reservoirs for most of the RNA viruses\(^64\). The genome of SARS-CoV-2 showed 96.2% homology to that of the bat CoV (RaTG13) collected in the Yunnan province of China\(^43\). The SARS-CoV-2 genome is closely related (88%) to zoonotic bat viruses, bat-SL-CoVZXC45, and bat-SL-CoVZXC21\(^65\). The most commonly identified sequence similarity between these bat and human viruses is in the E gene, and the least commonly identified similarity is in the S gene. Multiple SARS-CoV-2 proteins have the same sequence as the bat-SL-CoVZXC45 and bat-SL-CoVZXC21, except for the S protein and protein 13\(^66\). A team of researchers concluded that pangolin-CoV is a highly associated descendant of SARS-CoV-2, suggesting that pangolins could be the natural reservoirs for SARS-CoV-2 and bat CoV\(^67\). The sequence similarity (89.2%) between SARS-CoV-2 and RaTG13, in terms of the RBD, is less than the sequence similarity (97.2%) between SARS-CoV-2 and pangolin-CoV. Additionally, the latter contains six complete identical RBD residues, whereas the former contains only one identical amino acid residue\(^43\). Notably, pangolins in China are categorized as endangered due to their decreasing numbers, which are close to the point of extinction; this reduces the likelihood of pangolins acting as an intermediate host of SARS-CoV-2. The selling of pangolins is against the law, and they have not been spotted in Wuhan’s wet markets in recent times\(^68\). Through the use of the optimized random forest model for human sequences of MERS-CoV and SARS-CoV, intermediate hosts (Camelids and Carnivores) were confirmed based on evolutionary signatures. With the same method, SARS-CoV-2 evolutionary signatures identified bats as hosts, further confirming bats as the suspected origin of the present pandemic\(^69\). Furthermore, a recent study\(^70\) based on genetic similarities proposed that snakes may be intermediate hosts, as there are similarities in codons among SARS-CoV-2, bat CoV, and a snake virus. However, this analysis was insufficient to reach a conclusive hypothesis, as several limita-

### Table I. Characteristics of MERS-CoV, SARS-CoV and SARS-CoV-2.

<table>
<thead>
<tr>
<th>Features</th>
<th>MERS-CoV</th>
<th>SARS-CoV</th>
<th>SARS-CoV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreak</td>
<td>2012, April</td>
<td>2002, November</td>
<td>2019, December</td>
</tr>
<tr>
<td>Location of the first case</td>
<td>Jeddah, Saudi Arabia</td>
<td>Guangdong, China</td>
<td>Wuhan, China</td>
</tr>
<tr>
<td>Key hosts</td>
<td>Bat, camel</td>
<td>Bat, palm civets,</td>
<td>Bat, pangolin</td>
</tr>
<tr>
<td>raccoon dogs</td>
<td>Bat, pangolin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active cases confirmed</td>
<td>2519 (from 2012 until January 31, 2020)</td>
<td>8096</td>
<td>Over 243 million (as of October 26, 2021)</td>
</tr>
<tr>
<td>Genome length (bp)</td>
<td>30,119</td>
<td>29,751</td>
<td>29,903</td>
</tr>
<tr>
<td>Mortality</td>
<td>34.40%</td>
<td>10% (6.8-16.1%)</td>
<td>2-5%</td>
</tr>
<tr>
<td>Days took to infect the first 1000 persons</td>
<td>903</td>
<td>130</td>
<td>48</td>
</tr>
<tr>
<td>Incubation period (day)</td>
<td>5 to 6</td>
<td>2 to 7</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Basic reproduction number (R0)</td>
<td>1</td>
<td>2-4</td>
<td>1.4-5.5</td>
</tr>
<tr>
<td>Receptor</td>
<td>DPP4</td>
<td>ACE2</td>
<td>ACE2</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>Touching or consumption of camel milk or meat. There is limited human-to-human transmission despite close physical contact</td>
<td>Believed to have spread from bats. There is evidence of human-to-human transmission.</td>
<td>Human-to-human on close contact (mainly through respiratory aerosols/droplets). The transmissions may be possible through fecal-oral route and contaminated objects/surfaces/fomites</td>
</tr>
</tbody>
</table>

Genomic analysis suggests that SARS-CoV-2 is closely related to pangolin CoV (86%-92%) and bat CoV (96%), which further suggests bats as the primary reservoir\(^57,58,60\). Furthermore, the outbreak of SARS-CoV-2 is thought to be linked to trading practices in Wuhan’s wet market, and due to the genetic identities between SARS-CoV-2 and BatCoV RaTG13 (a bat-CoV), it has been hypothesized that bats could be the natural source of SARS-CoV-2\(^28,43,61\). A plethora of research evidence shows that pangolins may be the intermediate host—there is 99% homology between SARS-CoV-2 and the CoV strain originating from pangolins—but bats are the natural reservoir for the virus\(^62,63\). Bats are generally recognized as potential primary reservoirs for most of the RNA viruses\(^64\). The genome of SARS-CoV-2 showed 96.2% homology to that of the bat CoV (RaTG13) collected in the Yunnan province of China\(^43\). The SARS-CoV-2 genome is closely related (88%) to zoonotic bat viruses, bat-SL-CoVZXC45, and bat-SL-CoVZXC21\(^65\). The most commonly identified sequence similarity between these bat and human viruses is in the E gene, and the least commonly identified similarity is in the S gene. Multiple SARS-CoV-2 proteins have the same sequence as the bat-SL-CoVZXC45 and bat-SL-CoVZXC21, except for the S protein and protein 13\(^66\). A team of researchers concluded that pangolin-CoV is a highly associated descendant of SARS-CoV-2, suggesting that pangolins could be the natural reservoirs for SARS-CoV-2 and bat CoV\(^67\). The sequence similarity (89.2%) between SARS-CoV-2 and RaTG13, in terms of the RBD, is less than the sequence similarity (97.2%) between SARS-CoV-2 and pangolin-CoV. Additionally, the latter contains six complete identical RBD residues, whereas the former contains only one identical amino acid residue\(^43\). Notably, pangolins in China are categorized as endangered due to their decreasing numbers, which are close to the point of extinction; this reduces the likelihood of pangolins acting as an intermediate host of SARS-CoV-2. The selling of pangolins is against the law, and they have not been spotted in Wuhan’s wet markets in recent times\(^68\). Through the use of the optimized random forest model for human sequences of MERS-CoV and SARS-CoV, intermediate hosts (Camelids and Carnivores) were confirmed based on evolutionary signatures. With the same method, SARS-CoV-2 evolutionary signatures identified bats as hosts, further confirming bats as the suspected origin of the present pandemic\(^69\). Furthermore, a recent study\(^70\) based on genetic similarities proposed that snakes may be intermediate hosts, as there are similarities in codons among SARS-CoV-2, bat CoV, and a snake virus. However, this analysis was insufficient to reach a conclusive hypothesis, as several limita-
tions were present in the study\textsuperscript{71}. In any case, beta CoVs are less likely to infect reptiles by crossing over through mammals\textsuperscript{72}. These findings made the natural reservoir of CoV a controversial topic, and a contingent of groups embrace the idea that different intermediate host species are yet to be discovered, other than bats\textsuperscript{73,75}. The disease outbreak related to SARS-CoV-2 demonstrates concealed virus reservoirs in animals that may spread into human populations occasionally\textsuperscript{76}. The lower effective number of codons and the extreme codon usage bias of SARS-CoV-2 in S, envelope, and matrix protein genes suggest higher gene expression efficiency than that of SARS, bat SARS, or MERS-CoV, which is similar to Pangolin beta CoV\textsuperscript{77}. In the human host, the SARS-CoV-2 dinucleotide pair, UpG and CpA dinucleotides, were highly preferred, and CpG dinucleotide was highly avoided. This strategy might imply evasion of the human immune system\textsuperscript{78}. Multiple sequence alignments of the ACE2 receptor proteins of humans with that of dogs, cats, tigers, minks, and other animals revealed a high homology and full conservation of the five AA residues, 353-KGD-FR-357, among the species, which may throw light on the possibility of transmission of SARS-CoV-2 from animals to humans\textsuperscript{78}.

MERS-CoV is closely related to two bat CoV (HKU4, HKU5); it has been suggested that it may be isolated from bats, and dromedary camels probably act as intermediate host, as evidenced from serological studies\textsuperscript{79,80}. In Qatar, the presence of MERS-CoV RNA was reported in swabs obtained from dromedary camels that shared a correlation with two human cases of MERS\textsuperscript{81}. A comprehensive evolutionary relationship analysis depicted the origin of MERS-CoV from bats due to the occurrence of recombination events within S and ORF1ab genes\textsuperscript{82,83}. Recombination events were also reported in SARS-CoV as regions for putative recombination were detected via computational genomic studies\textsuperscript{84}. The MERS-CoV strains isolated from humans and camels have been reported to share over 99% identity with variations located in the ORF3, ORF4b, and S genes\textsuperscript{85}. SARS-CoV-2 shows 80% similarity with SARS-CoV and 51% with the MERS-CoV\textsuperscript{86}. Most of the coding areas of SARS-CoV-2 indicate a similar genomic architecture to that of the bat-originating CoVs and SARS-CoV. The twelve coding regions predicted are; lab, 3, E, M, 7, 8, 9, 10B, N, S, 13, and 14. The proteins encoded by all the three CoVs are mostly similar in length\textsuperscript{87}. However, there is a significant variation in the S protein of SARS-CoV-2, which is longer in comparison to the protein encoded in the bat CoVs, SARS-CoV, and MERS-CoV\textsuperscript{88}.

SARS-CoV-2 shares many similarities in architecture and pathogenicity with SARS-CoV compared to MERS-CoV. Mathematical models such as decision-tree experiments have also shown remarkable characteristics of an AA sequence of SARS-CoV-2, which is different from MERS-CoV\textsuperscript{12}. The CoVs use a similar S protein for binding to their respective host cells and the same cellular protease enzyme for the activation of the S protein\textsuperscript{89}. The S protein in SARS-CoV-2 has a sequence similarity of about 77% with that of SARS-CoV, structural proteins are more than 90% similar to SARS-CoV, and 32.79% similar to MERS-CoV counterparts. The receptor-binding domain (S2) of SARS-CoV-2 has a sequence similarity of 74% with the S2 domain in SARS-CoV and an overall similarity of about 52% with that of SARS-CoV\textsuperscript{90}. The E protein of SARS-CoV-2 is 96.00% similar to that of SARS-CoV and 36.00% similar to that of MERS-CoV. The M protein of SARS-CoV-2 is 89.59% similar to that of SARS-CoV and 39.27% similar to that of MERS-CoV. The SARS-CoV-2 N protein is 85.41% similar to that of SARS-CoV and 48.47% similar to that of MERS-CoV\textsuperscript{91}.

Accessory proteins are regarded as essential for \textit{in vitro} replication of viral particles; however, some of these proteins are associated with viral pathogenesis\textsuperscript{92,93}. The 3CLpro (nsp5) and RdRp (nsp12) proteins of SARS-CoV-2 are prime mediators of replication and new virion production, and they share high sequence identity with SARS-CoV and MERS-CoV\textsuperscript{94}. Recent reports\textsuperscript{95,96} have demonstrated that ORF8b and ORF3a of SARS-CoV catalyze the induction of proinflammatory cytokines and thus play a role in regulating chemotaxis in macrophages. ORF8b of SARS-CoV and MERS-CoV is also involved in suppressing the induction of interferon (IFN-1)\textsuperscript{97,98}. Another study demonstrated that ORF8 of SARS-CoV-2 variant binds to major histocompatibility complex (MHC) and regulates its degradation in cell culture, indicating that immune evasion may be mediated by ORF8. However, SARS-CoV-2 ORF8 shows low homology to SARS-CoV ORF8\textsuperscript{99}. Generally, no homologous accessory proteins are found in CoV genera. However, some similar kinds of proteins might be present in closely associated CoVs. For instance, SARS-CoV-2 and SARS-CoV show over 80% similarities in ORF3a, 6, 7a, 7b, and 9b protein sequences.
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Comparative Molecular Pathology of MERS-CoV, SARS-CoV, and SARS-CoV-2 Infection

SARS-CoV is considered a zoonotic virus that was transmitted to humans from birds prior to human-to-human transmission\textsuperscript{100}. However, in humans, various risk factors including age, underlying metabolic disease like diabetes, and heart disease, lead to an increase in death risk\textsuperscript{101}. SARS starts with viral infection in the respiratory tract of people of all ages via droplet transmission of virus present in the mucus or saliva\textsuperscript{102}. It was reported that viral loads of SARS-CoV decreased with increased severity of the disease. On the contrary, a similar trend is still unclear for MERS-CoV\textsuperscript{103}. Clinical symptoms associated with SARS-CoV infection include fever, chills, diarrhea, myalgia, and fatigue\textsuperscript{94}. SARS-CoV enters into the human cell through the attachment of viral S glycoprotein (S protein) to the ACE2 receptor. ACE2 functions as a dominant host receptor, and the presence of two co-receptors, DC-SIGN (CD209) and L-SIGN (CD209L), are also reported\textsuperscript{105,106}. In dendritic cells, viral infection does not occur prior to DC-SIGN binding, but this binding may enhance SARS-CoV infection and dissemination substantially. On the other hand, L-SIGN is considered an alternative receptor that may bind with its spike protein and regulate cellular entry of SARS-CoV\textsuperscript{107}. Changes occur in the S glycoprotein in the endosomal environment via the serine protease cathepsins B and L to assist in the union process\textsuperscript{108}. The S glycoprotein is not just an essential structural protein of CoVs; it performs a vital role in the association of virus with the host cell. The S protein is made up of two subunits: S1 and S2\textsuperscript{109}. The S1 subunit contains the RBD, which is responsible for binding the virus to the host receptor, while the S2 subunit controls membrane fusion occurring during virus-host membrane interactions. These interactions lead to the penetration of the viral genome into the cytoplasm of the host cell\textsuperscript{110}. SARS-CoV-2 encodes a longer S protein compared to SARS-CoV and MERS-CoV, as identified by phylogenetic analysis\textsuperscript{20,70}. The RBD of SARS-CoV, MERS-CoV, and SARS-CoV-2 binds to functional receptors present on the cellular surface, allowing penetration of the virus into host cells\textsuperscript{111}. SARS-CoV and SARS-CoV-2 predominately utilize angiotensin-converting enzyme 2 (ACE2) as a host receptor\textsuperscript{105,110,111}. Additionally, viral entry by antibody-dependent enhancement (ADE) has been observed\textsuperscript{112}. Through ADE, the B cell producing antibodies may also expedite viral infection\textsuperscript{113}. Surprisingly, ACE2 exhibits stronger affinities for SARS-CoV-2 compared to SARS-CoV\textsuperscript{114}. For instance, the interaction between host ACE2 and SARS-CoV-2 spike ectodomain displayed 10- to 20-fold higher binding affinity than that for SARS-CoV in a recent study\textsuperscript{115}. Another study speculated that SARS-CoV-2 could use other cellular receptors and proteins to bind with host cell receptors such as integrins\textsuperscript{116}. However, there is to date insufficient evidence to corroborate this assumption. CD147-SP can be considered another entry portal of SARS-CoV-2\textsuperscript{117}. In addition to attachment of S proteins to functional host receptors, priming of S proteins is necessary for invading the cellular machinery of the host\textsuperscript{118}.

Apart from lung cells, the heart, kidney, liver, and tongue also express ACE2 receptors on their epithelial cells\textsuperscript{119,120}. In fact, cilia could be the entry gate of the virus\textsuperscript{21}. Surprisingly, after the S glycoprotein attaches to ACE2, there is a significant cilia loss, squamous cell metaplasia, and elevated macrophage migration into the alveoli, causing notable damage to alveoli in the lungs. Additionally, SARS-CoV generates 7a and 3a proteins that lead to substantial programmed death of cells in the lungs, liver, and kidney\textsuperscript{122}. Host translation elongation factor 1 (EF-1A) and serine protease 2 strongly bind to N protein of both SARS-CoV and MERS-CoV, and subsequently induce local or systemic inflammatory responses\textsuperscript{94}. TH1 activation also causes increased inflammation in the affected organs. MERS-CoV infection is more common in males than females\textsuperscript{23}, and SARS-CoV and SARS-CoV-2 infection follow the same order of gender prevalence\textsuperscript{8}. Clinical presentation of infection may range from being asymptomatic to massive organ damage. Notably, MERS is closely associated with metabolic syndromes such as diabetes mellitus, obesity, and cardiovascular morbidities\textsuperscript{24}. The developing metabolic syndrome in most cases alters the immunological function, exposing the infected person to further risk of more infections.

Many previous investigations reported that CoV infection leads to cytopathic effects, including cell lysis and apoptosis. Cellular fusion is caused by the virus and usually leads to syncytia formation. These processes are observed in the cell due to the mobilization of vesicles that form the replication complex and cause disruption of Golgi complexes at the time of viral replication\textsuperscript{94}. Unlike in SARS-CoV, DPP4 CD26 is the MERS-CoV attachment site to lung and respiratory tract...
epithelial cells. Notably, MERS-CoV carries a particular RBD in its S glycogen that binds DDP4 on the host cells. DPP4 plays a significant role in altering glucose metabolism, activating the T cells, modulating cytotoxicity, and regulating apoptosis. SARS-CoV-2 infects both the lower and upper respiratory systems and multiple other organs and systems, thus causing multiple pathological conditions, including neurological and gastrointestinal manifestations and kidney damage. ACE2 receptors are abundant in oral mucosa, nasal secretory and ciliated cells, lower airways, lungs, cornea, ileum, and colon. Hence, patients suffer from collapsed lung and symptoms of diarrhea. When spike D614 is replaced by mutant G614, S protein possesses greater stability and a potential to grow at a temperature of 37°C, compared to early SARS-CoV-2 isolates, which showed a preference for 33°C. While SARS-CoV-2 is less pathogenic than MERS-CoV or SARS-CoV, its human-to-human transmission is faster. Underlying illnesses (comorbidities) such as heart disease, diabetes, and hypertension have a close association with the severe pathogenesis of SARS-CoV-2 in affected patients. These disorders reduce the generation of IFN and interleukin that leads to the downregulation of the host’s innate immunity via blockage of lymphocyte and macrophage functions. In healthy people, ACE2 alters the renin-angiotensin system through angiotensin-II breakdown into angiotensin-17 to prevent the development of acute lung failure. Acute lung injury is directly related to a deficiency in ACE2 and an increase in Ang II. Postmortem analysis of SARS-CoV-2 patients has revealed pneumocyte hyperplasia and partial fibrosis leading to thickening and collapse of alveoli.

The sgRNAs are presumed to be translated into accessory and structural proteins of CoV in the cytoplasm. A recently concluded in vitro study indicated that the enzymatic function of the nsp14 exoribonuclease (ExoN) is crucial for replication of SARS-CoV-2 and MERS-CoV. By enhancing degradation and interfering with host mRNA translation, beta CoV nsp1 inhibits the expression of host genes and thus serves as a potent virulence factor. MERS-CoV nsp1 inhibits mRNA translation and induces mRNA degradation by selectively targeting nuclear mRNA translation and avoiding cytoplasmic viral mRNAs. Current structural analysis and related studies have unveiled that SARS-CoV-2 nsp1 inhibits ribosomal mRNA entrance. The delta CoVs and gamma CoVs cannot produce nsp1 due to lack of nsp1/nsp2 cleavage sites, though the same host shutoff is triggered by other mechanisms that have not been explored well.

Clinical and Immunological Features of MERS-CoV, SARS-CoV, and SARS-CoV-2 Infection

MERS is currently a common human coronavirus (hCoV) infection. MERS-CoV infection has lower transmissibility than the other two CoVs but causes severe symptoms, leading to a higher case fatality rate. Like SARS-CoV patients, patients with MERS-CoV usually show milder symptoms initially and later develop dyspnea and complications leading to respiratory failure, with most of the patients (63.4%) developing lethal pneumonia. Organ function later deteriorates, leading to fatality within two weeks after infection. Prominent comorbidities associated with mortality among MERS-CoV patients are diabetes and renal failure, which result in poor health outcomes. To better understand the pathogenesis and immunological features of MERS-CoV, it is essential to understand its comparative analysis with SARS-CoV infection.

Unlike the SARS-CoV abortive mechanism of infection, MERS-CoV multiplies in lymphocytes, dendritic cells, and macrophages. Viral genomes, nucleoprotein expression, and viral particles are detectable in virus-infected cells. Viral multiplication in macrophages and dendritic cells indicates that host cells are the source of viral reservoirs thwarting host immunorecognition of the virus. MERS-CoV has been reported to induce greater transcriptomic changes than those induced by SARS-CoV. Cells carrying the virus facilitate systemic dissemination of the infection to lymph nodes. Naïve T cells interact with the virus and trigger adaptive immune responses. This leads to the release of massive amounts of cytokines and chemokines. The diverse activation avenues that trigger production of cytokines during MERS-CoV infection cause a distinct cytokine profile compared to SARS-CoV infection.

The reason for productive replication is the high number of DDP4 receptors expressed in the dendritic and monocyte cells compared to the expression level of ACE2 receptors. This results in differential infection outcomes. MERS-CoV can infect cells from different human cell lines in ex vivo studies. DDP4 receptors are identifiable in endothelial and epithelial cells present in the prostate, liver, kidney, and intestines. Dis-
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Semination of the virus throughout the body was observed in patients with MERS-CoV infections, explaining the high incidence of systemic events like multi-organ failure and septic shock. Another important immunopathological feature is the antibody-dependent enhancement (ADE) confirmed in MERS-CoV[146]. The underlying mechanism is linked to the enhanced membrane fusion process. The interactions of antibodies and RBD of S protein tend to elevate proteolytic susceptibility, leading to conformational changes in the target host cells[15]. The binding Ab enhances virus entry via canonical receptor-dependent pathways.

Only three cytokines (IL-6, IP-10, and IFN-γ) display a marked increase in SARS-CoV, MERS-CoV, and SARS-CoV-2[144]. SARS-CoV shows significant IFN antagonism, while the MERS-CoV has minor antagonist characteristics that lead to enhanced sensitivity to IFN-I antiviral responses[147]. Furthermore, due to differences in the viral proteins among these human CoVs, SARS-CoV-2 is more sensitive to IFN-I-dependent antiviral response compared to other CoVs. In fact, the levels of IFN-I and IFN-III in patients with SARS-CoV-2 infections are reduced, unlike that in patients infected by SARS-CoV and other respiratory viruses[144]. MERS-CoV shares similar viral evasion strategies and IFN antagonism with SARS-CoV. As a result, MERS-CoV tends to decrease upregulation of antiviral interferon-stimulated gene (ISG) responses through a novel approach, resulting in the induction of repressive histone modifications in the host cells. Similar histone modifications, which mediate several biological events such as gene regulation, were identified in patients with H5N1 flu infection[121]. Inhibition of transcription factor binding is controlled by modifying the basal state of host chromatin, where genes are packed. This mechanism is linked to low ISG expression in IFN-administered MERS[40]. As in patients with SARS-CoV infection, levels of IFN-I in MERS-CoV infected patients are attenuated, and their rate of increase is slowed. The absence of IFN-I resulted in a lack of marked lung immunopathology in studies. It also improved the clinical outcomes compared to the delayed IFN-I group, suggesting an atypical IFN-I effect linked to SARS infection[146,147], but there were adverse outcomes linked to MERS-CoV infection. In this respect, early IFN administration improved the protection of mice from severe infection, irrespective of down-regulation of cytokine-related genes and ISG.

In seriously ill patients with MERS-CoV, the inability to activate Th1 cells reduces IFN-γ production, leading to activated natural killer (NK) cells and CD8+ T cells. This generates an uncontrolled immune response and attenuates viral clearance[148,149]. Extensive CD8+ T-cell responses were noted in critically ill patients during the acute phase, indicating no benefit associated with hyper-activated T-cell responses[150]. The acute-phase T-cell response for SARS-CoV shows positive effects relative to the observed against SARS-CoV infection[151].

Concentration of certain inflammatory cytokines and chemokines (CXCR3, SOCS5, IL-1β, IL-8, IL-15, IL-17, CCR2, IL-1α, IP-10, TNF-α, and IFN-γ) was reported to increase during MERS-CoV infection[144,152]. In terms of cytokines, MERS-CoV-associated IL-17 expression demonstrated significant upregulation compared to that associated with SARS-CoV. Secretion of IL-17 by CD4+ T cells can produce extensive pro-inflammatory effects on host cells[144,153]. IL-17 expression is known to aggravate respiratory syncytial virus (RSV). In MERS-CoV, IL-17 expression tends to induce immune-mediated pathology, resulting in an elevated mortality rate[142]. Patients with MERS-CoV infection exhibit higher and more prolonged production of cytokines compared to those with SARS-CoV infection[20].

The SARS-CoV-2 pandemic has resulted in devastating outcomes in the 21st century because of high transmissibility and viral-shedding properties[6,22]. COVID-19 patients show clinical symptoms that resemble flu during the onset of the disease, including myalgia, fever, and dry cough[128,134]. Symptoms such as rhinorrhea, pharyngalgia, alveolar edema, ambygeustia, shortness of breath, dry mouth, nausea, and vomiting have also been recorded in a small number of COVID-19 patients[4,155-157]. The laboratory findings obtained from patients infected by SARS-CoV, MERS-CoV, and SARS-CoV-2 are markedly similar; the most common abnormal findings include thrombocytopenia and lymphocytopenia. Additionally, significant elevation in serum levels of alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, and C-reactive protein have been recorded[156-160]. In severely affected pa-
tients, coagulation disorders, where D-dimer level is elevated and prothrombin time is prolonged, are commonly observed\textsuperscript{160}. Meanwhile, elevation in the creatine kinase and serum creatinine level were reported in some patients, largely those infected with MERS-CoV\textsuperscript{258-260}. Furthermore, a large number of COVID-19 cases with gastrointestinal symptoms such as extreme diarrhea have been recorded in numerous laboratories, implying that the virus is replicating in the digestive system and viral particles are shed via stool\textsuperscript{162,163}. In addition, the sheer volume of ACE2 receptors in the bile duct relative to the alveolar cells contributes to the hypothesis that infection with SARS-CoV or SARS-CoV-2 causes serious liver damage\textsuperscript{164-166}. SARS-CoV-2 infection has also been linked to neurological symptoms in several recent studies. Moreover, in some cases, SARS-CoV-2 RNA has been reported in cerebrospinal fluid\textsuperscript{167,168}. The involvement of ACE2 receptors in the central nervous system (CNS) has been connected to neurological symptoms such as stroke, polyneuropathy, acute encephalitis, anosmia, ageusia\textsuperscript{169,170}, and brain inflammation associated with COVID-19\textsuperscript{168,171}. In previous studies, patients with COVID-19 were evaluated for symptoms such as anosmia and dysgeusia, and a high percentage (approximately 75\%) revealed alteration in the senses of smell and taste\textsuperscript{172,173}.

Cerebral arteriopathies and ischemic vascular stroke have been attributed as the direct effects of SARS-CoV-2 on ACE2 receptors of endothelial cells and as indirect effects of misdirected host immune response\textsuperscript{174}. Neuro-opthalmic manifestations of COVID-19 syndrome are also increasingly recognized\textsuperscript{168,176}. SARS-CoV-2 has recently been shown to infect different cells of the renal system, including tubular epithelial cells and podocytes, through direct tropism and indirect action by induction of cytokine storm and other mechanisms, resulting in a variety of renal abnormalities, including acute kidney damage, and higher mortality\textsuperscript{177-180}. Several studies have linked COVID-19 to impaired kidney function during the course of COVID-19 progression. In seriously ill patients with COVID-19, numerous renal disorders such as proteinuria, hematuria, and acute kidney failure (AKF) have been identified\textsuperscript{181-184}. According to current observational evidence, AKF is one of the most important causes of illness and death in SARS-CoV-2 patients, second only to ARDS\textsuperscript{185}.

Secondary bacterial and fungal infections observed in patients infected with COVID-19 have been implicated to further complicate the severity of the disease, constituting an important factor, especially for high-risk patients\textsuperscript{186,187}. Even the microbiota, such as the bacterial microbiome, virome, and fungal microbiome, are found to affect the natural course of SARS-CoV-2 infection, along with comorbidities such as diabetes and hypertension\textsuperscript{188-190}. Additional manifestations undetermed during the COVID-19 epidemic, including psychological illnesses such as depression, anxiety, and sleep disorders\textsuperscript{191} and skin disorders such as urticaria, rashes, erythema, and acro-ischemic lesions, also should be considered\textsuperscript{192}. All the above COVID-19 manifestations are either the direct results of SARS-CoV-2 multiplication or of the indirect hyperinflammatory condition known as macrophage activation syndrome or cytokine storm. This syndrome leads to increased production of IL6, IL7, and TNF-alpha and inflammatory chemokines such as CCL2, CC13, and CXC10, as well as elevated amounts of serum ferritin, D-dimer, and chronic reactive protein; however, evidence for inflammasome activation is not present as IL1β production is not elevated\textsuperscript{193-195}.

Chronic cough is common in long COVID (post-COVID syndrome) after SARS-CoV-2 infection and may be associated with the vagal sensory neurons and/or neuroinflammatory response. Mechanisms of post-COVID-19 chronic cough and optimal management are still unclear. New anti-inflammatory drugs or neuromodulators (gabapentin or opioids) could be considered for treatment; however, randomized studies are highly recommended to analyze the safety and efficacy of these potential treatments\textsuperscript{196}. Gunst et al\textsuperscript{197} have performed a randomized trial to understand the safety and efficacy of TMPRSS2 inhibitors in COVID-19 patients and found that TMPRSS2 inhibitors or camostat mesylate may be effective in the early phase of the disease and lowers the risk of disease progression; however, this treatment is not effective for severely ill and hospitalized patients. According to another recent study, saliva and nasal swabs offered the best diagnostic performance and may be used as an alternative specimen collection method for diagnosing SARS-CoV-2 infection\textsuperscript{198,199}.

An overview of comparative clinical manifestations in patients with MERS, SARS, and COVID-19 is presented in Table II. Pathological studies on SARS-CoV-2 demonstrate increased infiltration into an infected person’s lung tissues\textsuperscript{154,206}. Viral particles/macrophages/inflammatory cells have been identified in...
the bronchoalveolar fluid (BALF) of COVID-19 patients. SARS-CoV-2 also targets both types of pneumocytes (I and II), similar to SARS-CoV. Monocyte-derived macrophages are present at high levels in the BALF, constituting 80% of the infiltrated cells observed in severely sick patients. Various forms of activation of monocyte-originating macrophages have been noted. ACE2 receptor expression on the surface revealed that entry-binding receptors for SARS-CoV-2 could be detected in alveolar macrophages, indicating the possibility of this path in the entry of SARS-CoV-2. From these findings, there is sufficient evidence that monocytes are essential in the cytokine storm and lung pathology. The pro-inflammatory classically activated phenotype (M1) identified in wound-healing can activate the phenotype (M2) that leads to inflammatory tissue injuries and the development of fibrotic lesions in ARDS patients. These results indicate features of SARS research findings that are common to those observed for SARS-CoV-2.

Studies evaluating chemokines and cytokines in SARS-CoV-2 infection would aid in clarifying the full cytokine profiles of patients with severe infection during the acute phase. This would help elucidate the pathogenic mechanisms that result in worse health outcomes. SARS-CoV-2 patients demonstrate increased concentration of pro-inflammatory cytokines, including IL1β, IL-2, IL-6, IL-8, IL-17, TNF-α, IP-10, MCP-1, GM-CSF, and G-CSF, which may be attributed to Th-1-cell responses. Significant cytokine elevation was identified in patients with severe symptoms, and Th-1-cell and Th-2-cell-related cytokines were detected simultaneously. Previous investigations confirmed that the increased level of certain pro-inflammatory cytokines (e.g., IFN-γ, IL1β, IL-6, IL-12) in serum positively correlated with severe lung damage and pulmonary inflammation in SARS-CoV patients. T cell-related CD molecules and lymphocyte levels showed a negative correlation with changes in cytokines in patients with SARS-CoV-2 infection. Therefore, there is a potential correlation between cytokine storms and adaptive immunity. In patients with mild symptoms, lymphocyte levels are usually normal during the convalescent phase and are undetectable later as the infection progresses. In acute stages in mild cases, lymphocyte elevation was not linked to elevation in cytokines. This could be due to cellular immune response initiation that tends to accelerate viral clearance during the early phases, inhibiting cytokine production through innate immune activation, thus alleviating disease severity. In severe cases, cytokine hyperactivation during the acute phase of SARS-CoV-2 resulted in dysregulated systemic disease inflammation and deterioration, as shown by CRP, ferritin, D-dimers, and procalcitonin elevation. Cytokine storms generate pathogenic effects instead of protective effects against SARS-CoV-2 infection of host cells. Excessive cytokine and chemokine activation by macrophages has similar outcomes, as reported in macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis. In particular, many proinflammatory cytokines, IL-1, IL-6, and TNF-α, are involved in COVID-19 pathogenesis. Single-cell RNA sequencing has revealed

<table>
<thead>
<tr>
<th>Clinical symptoms/manifestations</th>
<th>MERS-CoV 8,157,200</th>
<th>SARS-CoV 8,157,160</th>
<th>SARS-CoV-2 8,201–205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>63.5–83.5%</td>
<td>93–97.6%</td>
<td>67.7–90.8%</td>
</tr>
<tr>
<td>Cough</td>
<td>51–70%</td>
<td>49–59%</td>
<td>45.5–62.9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21–35%</td>
<td>31.2%</td>
<td>23.3–38.1%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5%</td>
<td>32%</td>
<td>21–40%</td>
</tr>
<tr>
<td>Sputum</td>
<td>22–43%</td>
<td>16–27%</td>
<td>21.2–37.2%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>≤ 25%</td>
<td>11–25%</td>
<td>14.6–31.0%</td>
</tr>
<tr>
<td>Headache</td>
<td>11–20%</td>
<td>30–46%</td>
<td>7.9–15.2%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms (like diarrhoea)</td>
<td>≤ 30%</td>
<td>≤ 32%</td>
<td>3–17%</td>
</tr>
<tr>
<td>Bilateral pneumonia</td>
<td>N.A.</td>
<td>N.A.</td>
<td>58.2–81.0%</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (ARDS)</td>
<td>20–30%</td>
<td>20%</td>
<td>18–30%</td>
</tr>
<tr>
<td>Neurological manifestations such as stroke</td>
<td>17.4 %</td>
<td>N.A.</td>
<td>17–30%</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>41–50%</td>
<td>7%</td>
<td>3–20%</td>
</tr>
</tbody>
</table>

N.A.* (Not Available).
potent interactions between immune and epithelial cells, with inflammatory macrophages that express multiple cytokines in samples with critical COVID-19 conditions. Amongst these, IL-8 and IL-6 are detected at elevated concentrations in individuals with critical or severe COVID-19. These high levels of both cytokines indicate lymphocytopenia that predicts disease progression.

During the initial stages of SARS-CoV-2 infection, the lymphocyte count decreases in patients with severe symptoms associated with a dramatic decrease in NK cells, B cells, CD4+, CD8+ T, and CD3+ cells. Mild cases of SARS-CoV-2 infection demonstrate a moderate increase in these lymphocytes. These findings further reveal that lymphocytes can reach comparable levels along with only slight variation in noticeable lymphocyte count. Changes in adaptive immunity occur due to imbalanced activation of Th1/Th2, and alteration of T lymphocyte function causes adverse effects on host cells, worsening the course of disease. Reduced function of CD8+ T cells serves as a predictor of the severity of SARS-CoV-2 infection. Moreover, the production of endogenous IFNβ in the nasal mucosa of critical patients can be considered a prognostic tool of IFN therapy for managing COVID-19, as it predicts clinical outcomes. The eosinophil level in COVID-19 patients was related to the reduced anticoagulant effect and therefore may be considered for determining the prophylactic anticoagulant administration strategy. The high eosino-
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Phil count is also associated with lower activity of anti-factor Xa. Liu and coworkers have also suggested the importance of familial cluster (FC) and non-familial (NF) patients during the treatment of COVID-19 patients.

An overview on pathology and pathobiology of SARS-CoV-2 is presented in Figure 1.

Immunocompetent infected individuals usually present mild manifestations or become asymptomatic. However, the immunocompromised, the elderly, and individuals with underlying conditions such as cardiovascular disease, diabetes, and cancer, develop severe symptoms and clinical disease. A recent study linked renal, cardiovascular, and respiratory diseases with greater ICU admission and fatality rate in COVID-19 patients. Cancer and diabetes conditions also showed a strong correlation with severe disease outcomes in SARS-CoV-2 infected patients. Male patients and older people showed higher ICU admission and mortality. The risk of COVID-19 was dramatically increased in older patients. In another report, hypertension, cardiovascular disease, and diabetes were closely associated with severe outcomes in COVID-19-infected individuals across all age groups. In contrast to elderly patients, young patients exhibited a varied prevalence of cardiovascular comorbidities.

The De Ritis ratio has been associated with poor survival in SARS-CoV-2 infected patients and is an important prognostic factor. Moreover, the De Ritis ratio on admission was significantly associated with hospital mortality in COVID-19 patients. However, since the sample size in the clinical study was considerably smaller, additional investigations are needed to validate the ability of this parameter to independently predict death in hospitalized patients. Obesity is strongly associated with immune cells, including MAIT and NK cells. Hence, it may be considered a factor for increased risk of severe COVID-19. Popkin et al. have recently conducted a meta-analysis and found 48% higher mortality in COVID-19 patients with obesity. In a recent cohort study, Gao et al. found a linear increase in the risk of severity in patients with COVID-19 leading to hospitalization and death with an increase in body mass index. This excess risk was observed particularly in younger people and also in black individuals. According to another cross-sectional study, Lega et al. found that COVID-19 patients with a severe psychiatric disorder (schizophrenia and others) died at a younger age compared to those without any psychiatric disorder. Additionally, the vulnerability of COVID-19 patients with psychiatric disorders may reduce the chance of recovery. Pregnant women were affected more by COVID-19, particularly in the second wave of infections, which may be associated with the emergence of increasing numbers of pathogenic strains. Moreover, people with physical disabilities are particularly at risk and need additional support from mental health services. In a similar report, authors have mentioned that older people with disabilities have been neglected during the COVID-19 pandemic.

Conclusions

Three highly pathogenic coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) have been reported in humans in the last two decades. Although these CoVs exhibit several similar features in their infection process, distinctive features and characteristics are observed in the immunopathology and clinical outcomes of each. Recurrent outbreaks of infectious and pathogenic strains of CoVs have posed a significant burden and danger to humankind, such as the current COVID-19 pandemic that has resulted in an unprecedented crisis with devastating social, health, and economic impacts worldwide. All three CoVs share immunological aspects that affect pathological characteristics. The viral agents undergo replication in the host immune cells and set off an innate immune response that leads to induction of pro-inflammatory cells and cytokines. This cytokine storm can be life-threatening. Finally, the body responds by producing protective antibodies that clear the viral infection and also confer immunity against future infection with the same virus. In vitro studies have been particularly helpful for understanding the immunological and pathological aspects of the viruses and in conducting drug trials against these agents. However, there is a need to advance clinical research since these viral agents can undergo further mutations and may give rise to viral species with enhanced pathogenicity in the future. Collaborative and intense efforts by scientists worldwide have resulted in advanced discoveries related to many aspects of SARS-CoV-2 and COVID-19. In addition, elucidating the immunopathology and clinical features of CoVs will help in developing better and more effective drugs, medicines, and vaccines to counter the emergence and re-emergence of pathogenic CoVs. Prospective outcomes from clinical inves-
tigations of different vaccines and antiviral candidates provide hope to end this pandemic soon. Continuous research efforts to better understand the pathogenesis, molecular biology, and immunological characteristics of SARS-CoV-2 and other CoVs will help to stem the tide of the ongoing COVID-19 pandemic and formulate prevention plans for future pandemics.

Conflicts of interest
All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

Author Contributions
All the authors substantially contributed to the conception, compilation of data, checking and approving the final version of the manuscript, and agree to be accountable for its contents.

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