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POTENTIAL ZOONOTIC TRANSMISSION OF HKU5-COV-2: A COMPREHENSIVE REVIEW OF HOST SUSCEPTIBILITY, VIRAL PATHOGENESIS, AND PUBLIC HEALTH IMPLICATIONS

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ABSTRACT
HKU5-CoV-2, a bat-derived betacoronavirus from the Merbecovirus subgenus, has received attention because to its genetic resemblance to coronaviruses that infect humans, such as MERS-CoV and SARS-CoV-2. This study summarizes current findings about its genetic structure, receptor utilization, host susceptibility, and potential for cross-species transmission. Notably, HKU5-CoV-2 uses ACE2 receptors in some animals, suggesting a potential danger of human infection despite the lack of proven cases. Its spike protein adaptations and recombination events increase its evolutionary adaptability, raising concerns regarding zoonotic spillover. Furthermore, similarities in immune evasion and inflammatory responses to SARS-CoV-2 indicate that it could cause systemic disease if transferred to humans. The review emphasizes the significance of proactive surveillance, particularly in areas with dense bat populations and human-wildlife interfaces, and calls for a One Health strategy that combines human, animal, and environmental health. This analysis is crucial because it gives timely information about a potentially emergent pathogen, driving early detection measures and global preparedness initiatives. Future research should seek to experimentally examine host-pathogen interactions and identify intermediary hosts in order to better understand HKU5-CoV-2 transmission potential.

KEYWORDS: HKU5-CoV-2, zoonotic potential, ACE2 receptor, bat coronaviruses, viral pathogenesis.

INTRODUCTION

Coronaviruses, CoVs are enveloped, positive-sense RNA viruses characterized by a club-like surface spike, unique replication methods, and large genomes. They belong to the nidovirales order and coronaviridae family. These are further classified into alpha, beta, gamma, and delta coronaviruses. CoVs infect various animal species causing diverse diseases ranging from enteritis in livestock to respiratory infections in humans and even in birds. Notable human coronaviruses include ARS-CoV, MERS-CoV, and the recent SARS-CoV-2, responsible for the COVID-19 pandemic. Core research on CoVs focuses on their pathogenicity, replication, host specificity, and receptor interaction.[1–3]

Among the several betacoronaviruses, the HKU5-CoV lineage, discovered in Rousettus bats, has received interest due to its strong genetic affinity to known human-infecting CoVs. While no direct human instances have been identified, its genetic traits indicate the possibility of interspecies transmission. Understanding the host range, molecular adaptations, and evolutionary dynamics of HKU5-CoV-2 is critical for determining its hazard to public health.[4–9]

The HKU5-CoV lineage is a betacoronavirus from the Merbecovirus subgenus that was discovered in Hong Kong's Rousettus bats. This lineage is of virological interest since it shares genetic similarities with MERS-CoV and other dangerous human coronaviruses, raising worries about its zoonotic potential. HKU5-CoV has important genetic characteristics that allow receptor engagement, immunological evasion, and recombination, potentially facilitating cross-species transmission.[7,10–13]

This review aims to provide a comprehensive and the latest overview and clinical perspective of HKU5-CoV-2, focusing on its host susceptibility, viral pathogenesis, and public health implications. By synthesizing current research, this work seeks to enhance understanding of its zoonotic potential and contribute to proactive strategies for monitoring and mitigating emerging outbreak threats.

Genomic and Structural Characteristics of HKU5-CoV-2

Its genome is a positive-sense single-stranded RNA around 30 kilobases long, divided into many open reading frames (ORFs) that encode structural and non-structural proteins. The replicase complex (ORF1a and ORF1b) is normally included in the genome structure, followed by genes that encode structural proteins such as spike (S), envelope (E), membrane (M), and nucleocapsid. HKU5-CoV-2 also contains accessory proteins whose activities are unknown, but they are thought to play a role in viral replication and host interaction.HKU5-CoV-2 belongs to the Merbecovirus subgenus of the Betacoronavirus genus and shares a lineage with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[8,13]

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The spike (S) glycoprotein of HKU5-CoV-2 is an important characteristic that allows the virus to enter host cells more easily. The S protein has two subunits: S1, which is responsible for receptor binding, and S2, which is involved in membrane fusion. The receptor-binding domain (RBD) is located within the S1 subunit and is responsible for determining host specificity through interactions with cell receptors. MERS-CoV primarily employs dipeptidyl peptidase 4 (DPP4) as an entrance receptor. Notably, investigations have demonstrated that HKU5-CoV-2 can enter cells via the angiotensin-converting enzyme 2 (ACE2) receptor found in certain bat species and other animals, such as artiodactyls. This receptor utilization differs from MERS-CoV, which primarily uses dipeptidyl peptidase 4 (DPP4) as its entrance receptor.[16–18]

HKU5-CoV-2 shares similarities with coronaviruses while also differing from them. HKU5-CoV-2, like Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-CoV-2, can use ACE2, implying that it may be transmitted between species. However, the specific amino acid residues implicated in ACE2 binding vary, implying a distinct evolutionary process. Despite being in a separate subgenus, HKU5-CoV-2 is more closely related to SARS-associated coronaviruses because it employs ACE2, as opposed to MERS-CoV, which requires DPP4. This emphasizes the different evolutionary mechanisms used by coronaviruses to adapt to host receptors. When compared to other coronaviruses, HKU5-CoV-2 shares similarities and distinctions. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-CoV-2, HKU5-CoV-2's capacity to use ACE2 raises the possibility of cross-species transmission. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-CoV-2, HKU5-CoV-2's capacity to use ACE2 raises the possibility of cross-species transmission. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-CoV-2, HKU5-CoV-2's capacity to use ACE2 raises the possibility of cross-species transmission. The capacity of HKU5-CoV-2 to use ACE2 supports the possibility of cross-species transmission.[19,20]

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Evolutionary investigations indicate that HKU5-CoV-2 has undergone recombination events, a frequent feature in coronaviruses that allows for fast genetic diversification. Such recombination can result in the generation of new viruses with different host ranges and virulence. Coronavirus evolution and their ability to adapt to new hosts. Coronavirus evolution and their ability to adapt to new hosts. The separate evolution of ACE2 usage among merbecoviruses, including HKU5-CoV-2, demonstrates the dynamic nature of coronavirus evolution and the viruses' ability to adapt to new hosts. Zoonotic spillovers. Understanding these evolutionary pathways is critical for predicting and preventing future zoonotic outbreaks. Its ability to use ACE2 receptors, combined with indications of recombination events, emphasizes the need for ongoing surveillance and study to determine its zoonotic potential and improve public health interventions. HKU5-CoV-2 stands out from other coronaviruses due to its unique spike protein and receptor-binding domain, as well as its genomic structure. Its ability to use ACE2 receptors, combined with indications of recombination events, emphasizes the need for ongoing surveillance and study to determine its zoonotic potential.[22,23] Table 1 provides an overview

about the genomic and structural characteristics of HKU5-CoV-2, kindly refer for better understanding.

Table 1: Genomic and Structural Characteristics of HKU5-CoV-2.

Feature	***Description***
Genome Type	Positive-sense single-stranded RNA (~30 kb)
Genomic Structure	Contains multiple ORFs encoding: - Non-structural proteins (Replicase complex: ORF1a & ORF1b) - Structural proteins (Spike [S], Envelope [E], Membrane [M], Nucleocapsid [N]) - Accessory proteins (functions unknown)
Genus & Subgenus	Betacoronavirus → Merbecovirus
Relation to Other Coronaviruses	Shares lineage with MERS-CoV; uses ACE2 receptor like SARS-CoV and SARS-CoV-2MERS-CoV;
Spike (S) Protein Structure	Two subunits: - S1: Receptor Binding Domain (RBD) - S2: Involved in membrane fusion
Host Receptor Usage	Primarily uses ACE2 (in bats, artiodactyls); MERS-CoV uses DPP4
Evolutionary Notes	- Undergoes recombination events - ACE2 binding residues differ from SARS-CoV/SARS-CoV-2 SARS-CoV/S Suggests distinct evolutionary pathway and cross-species potential
Zoonotic Potential	High; due to ACE2 receptor use and genetic recombination capacity
Need for Surveillance	Continuous monitoring required to assess zoonotic risk and inform public health responses

[Abbreviations: ACE2 – Angiotensin-Converting Enzyme 2, DPP4 – Dipeptidyl Peptidase 4, E – Envelope Protein, kb – Kilobase (1,000 base pairs), M – Membrane Protein, MERS-CoV – Middle East Respiratory Syndrome Coronavirus, N – Nucleocapsid Protein, ORF – Open Reading Frame, RBD – Receptor-Binding Domain, RNA – Ribonucleic Acid, S – Spike Protein, SARS-CoV – Severe Acute Respiratory Syndrome Coronavirus, SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2.]

Clinical features of HKU5-CoV-2 infection

The most common symptoms of HKU5-CoV-2 infection, now known as SARS-CoV-2, are fever, cough, and exhaustion. The infection usually manifests as a minor upper respiratory tract infection, but some patients may need supplementary oxygen or critical care. Patients who are older or have underlying comorbidities are more likely to experience severe outcomes. The virus can be detected in nasopharyngeal swabs, stool, and, on rare occasions, blood for an extended period of time. While these studies focus on SARS-CoV-2, other coronaviruses, such as HKU1, can cause respiratory illnesses in people, especially during the winter months. However, clinical characteristics alone cannot distinguish coronavirus infections from other types of community-acquired pneumonia.[7,24–26]

Currently, there are no documented human infections caused by HKU5-CoV-2, hence particular clinical aspects of this virus in humans have not been detected or published. SARS-CoV-2, the virus that causes COVID-19. SARS-CoV-2, the virus that causes COVID-19. However, the current study reveals that HKU5-CoV-2 can enter human cells via the same ACE2 receptor route as SARS-CoV-2, the virus that causes COVID-19. SARS-CoV-2.SARS-CoV-2. This shows a possibility of human infection, however the virus does not infect human cells as well as SARS-CoV-2. Given this possibility, it is critical to study the clinical presentations of related coronaviruses to predict prospective symptoms.SARS-CoV-2 infection causes a wide range of clinical symptoms, from asymptomatic individuals to severe respiratory distress. Common symptoms include fever, coughing, and exhaustion. Patients may also have shortness of breath, nasal congestion, and rhinorrhea. There have been reports of gastrointestinal problems such as diarrhea, nausea, and vomiting. Neurological symptoms such as headaches and loss of taste or smell are noticeable. Musculoskeletal issues, such as muscle aches, are often reported. Some patients may experience sore throats and chest pain. A fraction of people have developed cutaneous symptoms, such as rashes. The severity of symptoms varies, with older persons and those with underlying health issues being more likely to develop severe disease, which can progress to acute respiratory distress syndrome (ARDS) and multi-organ failure.[18,25,27–32]

While these clinical traits are connected with SARS-CoV-2, they help to understand probable symptoms if HKU5-CoV-2 infects people. Continuous surveillance and research are critical for detecting new infections and understanding the clinical implications of HKU5-CoV-2.

Public Health Relevance and Pandemic Potential

The development of HKU5-CoV-2 underscores the risks of zoonotic spillover. While no proven human instances have been recorded, its ability to use human ACE2 receptors raises worries about its potential to infect humans. Previous experiences with SARS-CoV, MERS-CoV, and SARS-CoV-2 highlight the unpredictability of coronavirus spillover outbreaks, demanding ongoing observation.[9,33]

SARS-CoV and SARS-CoV-2, both originating in bats, caused large outbreaks with global consequences. MERS-CoV, another merbecovirus, produced severe disease with a high case fatality rate, although having little human-to-human transmission. These outbreaks highlight the importance of monitoring bat coronaviruses with zoonotic potential, as mutations and recombination events can boost their ability to spread in human populations.[10,29,34]

Effective pandemic preparedness methods are crucial for reducing the hazards posed by developing coronaviruses. The One Health approach, which considers human, animal, and environmental health, is critical for early detection and intervention. Strengthening monitoring systems in areas with high wildlife biodiversity can aid in the detection of new viruses before they become a substantial problem.[35,36]

Investments in research are critical for understanding HKU5-CoV-2 transmission pathways and pathogenicity. Developing broad-spectrum antivirals and vaccines against numerous coronaviruses can help improve preparation. To limit the likelihood of spillover occurrences, public health education and biosecurity measures must be implemented, including avoiding human-wildlife encounters. Although HKU5-CoV-2 has not yet caused human infections, its potential necessitates preventative actions. Improving surveillance, encouraging interdisciplinary collaboration, and investing in research will be critical in limiting the pandemic potential of new coronaviruses.[13,37,38]

Discovery and Classification

HKU5-related bat coronaviruses were initially discovered in Hong Kong bats. Pi-BatCoV HKU5 was found to be 25% prevalent in Pipistrellus abramus, while Ty-BatCoV HKU4 was found to be 29% prevalent in Tylonycteris pachypus, according to Lau and his colleagues.[38] While various studies discovered MERS-related CoVs in a variety of bat species at 8.4%, several more studies later reported rates of 12% in Hong Kong and 9.8% in northern Germany.[7,12]

According to recent research, bats have an incredibly diverse range of coronaviruses, especially those relating to the Betacoronavirus genus. Numerous bat species have been shown to harbor novel lineage C betacoronaviruses, such as Pipistrellus pipistrellus coronavirus HKU5 and Tylonycteris pachypus coronavirus HKU4, which are closely linked to MERS-CoV.[12] HKU5 shares the normal 27–30 kb genome as well as significant open reading frames, including those for spike and nucleocapsid proteins, with closely related strains, according to several animal studies of bat and human coronaviruses **(2)**. The genetic characteristics of HKU5's spike protein genes, such as two deletions in the loop sections of the S1 subunit, distinguish it from strains like SARS-CoV-2, which have special insertions that easily facilitate human ACE2 binding. Comparative data analysis also revealed notable variations in the spike protein, where Zhu and his team discovered a furin-like S1/S2 cleavage site in a novel bat CoV, a characteristic suggestive of SARS-CoV-2, and Lau and his colleagues observed notable variation in HKU5's S protein**.** Furthermore, research indicates that HKU5's receptor binding domain does not bind to human CD26, although HKU4's receptor binding domain does. Instead, one study demonstrates a distinct ACE2 recognition mechanism that extends to other non-bat mammalian receptors.[39,40]

Host Range and Zoonotic Potential

Over the last two decades, bat-borne coronaviruses have posed a significant zoonotic threat, resulting in three major human outbreaks: SARS-CoV in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and the ongoing coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2.[41] The exact mode of transmission to humans is unknown, but infected bats shed the virus through blood, feces, nasal secretions, and saliva, and viruses are transmitted between bats via the urine-oronasal mode, while other mammals may be infected by food or fomites contaminated with the aforementioned bodily fluids, most likely from infected bats roosting above or feeding on the same foods. Ultrasonic waves produced in the larynx and emitted through the mouth or nose may also transmit viruses by aerosolizing them. Furthermore, livestock raising and agriculture in arboreal settings near bat habitats not only harm native wildlife and plant species but also raises the danger of contact with domesticated animals or even people, increasing the potential of zoonotic spillover.[42–46]

Additionally, betaCoVs, including HKU5, have the potential to recombine and cause interspecies transmission. All HKU5 coronaviruses have been proven to infect their hosts with ACE2 from their native host species, Pipistrellus abramus. Furthermore, appropriate intermediate hosts include creatures that interact with reservoir hosts, bats, and humans. Domestic animals such as pigs, horses, and dromedary camels play a major role in zoonotic transmission. Wild animals such as Himalayan palm civets and raccoon dogs, which are farmed as exotic food by humans in Vietnam, Cambodia, Myanmar, other Southeast Asian nations, and southern China, are intermediate hosts for SARS-CoV.[47,48] Comparative genomic investigations have shown that SARS-CoV-2 has a significant degree of sequence similarity with bat coronaviruses, particularly those found in Rhinolophus bats, with pangolins, camels, snakes, and turtles being proposed as potential intermediate hosts. Bat coronaviruses' zoonotic potential is strengthened by their large genomes, which allow for adaptation to different hosts, as well as the usage of conserved mammalian cell entrance mechanisms. Sarbecoviruses, a subgenus that includes SARS-CoV and SARS-CoV-2, are especially concerning because of their genetic variety in horseshoe bat hosts.[15,49–52]

Pathogenesis and Immunological Insights

Structural analyses have demonstrated that the spike (S) protein of HKU5-CoV-2 has a strong binding affinity for the human angiotensin-converting enzyme 2 (ACE2) receptor, which serves as the primary entry point for the virus into host cells.[39] ACE2 is widely expressed across various tissues, including the endothelial cells of arteries and veins, cerebral neurons, immune cells, tubular epithelial cells of the kidneys, mucosal cells of the intestines, and epithelial cells of renal tubules. This broad distribution of ACE2 presents multiple susceptible targets for viral invasion, potentially contributing to the virus's ability to infect diverse organ systems and leading to systemic disease manifestations. The mechanism by which HKU5-CoV-2 engages with ACE2 is structurally distinct from that of other known ACE2-utilizing coronaviruses, such as SARS-CoV-1 and SARS-CoV-2. The receptor-binding domain (RBD) of HKU5-CoV-2 exhibits unique structural adaptations, while also sharing notable similarities with ACE2-using arboviruses and the human coronavirus HCoV-NL63, which is associated with mild respiratory infections. These similarities suggest a possible evolutionary convergence in ACE2 binding strategies among different coronaviruses, underscoring the adaptability of these viruses in utilizing ACE2 for host cell entry.[53–56]

The potential immune evasion strategies of HKU5-CoV-2 can be inferred from related coronaviruses. For instance, SARS-CoV-2 has been shown to exploit the spike–ACE2 interaction to impair cytotoxic T lymphocyte (CTL)-mediated killing by suppressing immunological synapse assembly. Additionally, human coronaviruses can subvert the induction of innate immune responses and interferon signaling through multiple mechanisms, allowing them to evade host defenses. While specific studies on HKU5-CoV-2's immune evasion tactics are limited, its structural similarities to these viruses suggest it may employ comparable strategies.[57–59]

The role of immune responses in disease progression has been widely investigated in the context of SARS-CoV-2 infections, revealing crucial insights into host-pathogen interactions. Upon viral entry, the innate immune response is triggered when pathogen-associated molecular patterns (PAMPs) of the virus, such as viral RNA, are recognized by pattern recognition receptors (PRRs) on immune cells, including toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors. This recognition activates intracellular signaling pathways that lead to the production of interferons (IFNs), pro-inflammatory cytokines, and chemokines, which coordinate the recruitment of immune cells to the site of infection and establish an antiviral state. However, an imbalance in this immune response can have detrimental consequences. In some cases, dysregulated signaling results in excessive production of cytokines, a phenomenon known as the cytokine storm. This hyperinflammatory state leads to widespread tissue damage, endothelial dysfunction, and multi-organ failure, significantly contributing to disease severity and poor clinical outcomes in COVID-19 patients. Although direct studies on HKU5-CoV-2—a bat-derived coronavirus—are currently lacking, its structural and functional similarities to SARS-CoV-2 suggest that it may trigger comparable immune response mechanisms.[60,61]

Over time, the mechanisms of viral invasion and immune dysregulation can contribute to severe systemic complications. One of the most critical consequences is the development of acute respiratory distress syndrome (ARDS), characterized by widespread inflammation, alveolar damage, and impaired gas exchange, leading to severe hypoxia and respiratory failure. In severe cases, this can necessitate mechanical ventilation and intensive care management. Beyond the respiratory system, prolonged immune activation and direct viral effects can contribute to multi-organ failure, affecting vital systems such as the cardiovascular, renal, hepatic, and nervous systems. Neurological complications, including cognitive impairments, brain fog, and even encephalopathy, have been reported, potentially due to neuroinflammation, microvascular damage, or direct viral invasion of the central nervous system. Similarly, pancreatic involvement has been observed, with cases of pancreatic complications such as acute pancreatitis or worsening glycemic control in diabetic patients, possibly linked to direct viral attack on pancreatic beta cells or systemic inflammation. In addition to these severe systemic effects, the gastrointestinal (GI) system is also frequently affected. Patients may experience gastrointestinal distress, manifesting as nausea, vomiting, diarrhea, and abdominal pain. Persistent inflammation and disruptions in gut microbiota may contribute to the development of ulcers, irritable bowel syndrome (IBS), and gastroesophageal reflux disease (GERD or acid reflux). Chronic GI symptoms can significantly impact quality of life, and in some cases, prolonged inflammation may increase susceptibility to further gastrointestinal complications.[62–64] Refer Table 2 for a summarized version of this section.

Table 2: Pathogenesis and Immunological Insights of HKU5-CoV-2.

Aspect	***Details***
Viral entry	Spike (S) protein binds strongly to ACE2 receptor, allowing host cell entry.
ACE2 Expression Sites	Endothelial cells (arteries, veins), neurons, immune cells, kidney tubules, intestinal mucosa, renal epithelium.
Structural Insights	RBD of HKU5-CoV-2 shows unique features; shares similarities with HCoV-NL63 and arboviruses.

Immune Evasion (Inferred)	- Potential suppression of CTL synapse assembly - Subversion of interferon signaling and innate immune responses
Innate Immune Response	- Recognition of viral PAMPs by TLRs, RIG-I - IFN and cytokine production - Recruitment of immune cells
Immune Dysregulation	Cytokine storm causing tissue damage, endothelial dysfunction, multi-organ failure.
Systemic Complications	- **ARDS:** Alveolar damage, hypoxia - **Neurological:** Brain fog, encephalopathy - **Pancreatic:** Pancreatitis, altered glycemic control - **Gastrointestinal:** Diarrhea, nausea, GERD, IBS, gut microbiota disturbance
Similarities to SARS-CoV-2	Structural binding to ACE2, potential immune evasion mechanisms, triggering of cytokine storm.

[Abbreviations: ARDS, Acute Respiratory Distress Syndrome; ACE2, Angiotensin-Converting Enzyme 2; CTL, Cytotoxic T Lymphocyte; GERD, Gastroesophageal Reflux Disease; HCoV-NL63, Human Coronavirus NL63; HKU5-CoV-2, Hong Kong University 5 Coronavirus-2; IFN, Interferon; IBS, Irritable Bowel Syndrome; PAMPs, Pathogen-Associated Molecular Patterns; PRRs, Pattern Recognition Receptors; RBD, Receptor-Binding Domain; RIG-I, Retinoic Acid-Inducible Gene I; SARS-CoV-1, Severe Acute Respiratory Syndrome Coronavirus 1; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TLRs, Toll-Like Receptors]

Surveillance and Detection Methods

Surveillance of HKU5-CoV-2 in different bat species and geographically different locations implies that this coronavirus is an old, unrecognized reservoir rather than an emergent novel coronavirus.[65] Its wider circulation increases the possibility of recombination among coronaviruses, leading either to more pathogenic viral variants or greater transmissibility among species.[66] Hence, it is important to place high priority on viral recombination events and human spillover occurrences through extensive surveillance campaigns, such as genome sequencing, serological surveys, as well as environmental sampling. Though surveillance is mostly focused on the reservoir in bats, end surveillance should be carried out in monitoring the target animals as well as human beings in areas where the virus is already known to circulate to enable detection of initial occurrences of spillover. New tools like CRISPR-based detection assays, wastewater epidemiology, as well as AI-driven predictive models for viral tracing, may be u, used significantly for surveillance. For diagnostic reagents, the use of RT-PCR combined with Next Generation Sequencing (NGS) shows high sensitivity as well as specificity for the detection of viral mutants as well as allows for in-depth genomic characterization; however, challenges persist in terms of geographic as well as taxonomic coverage in surveillance planning. Shortcomings in serological detection, such as cross-reactivity among coronavirus species, emphasize the need for improved testing reagents as well as meticulous sampling in wildlife groups. One Health global coordination in conjunction with international vaccination campaigns may be the key to controlling the looming threat posed due to HKU5-CoV-2 as well as other zoonotic diseases.[7,9–11,21,55,67–71]

CONCLUSION

A betacoronavirus known as the HKU5-CoV2 which belongs to the merbecovirus subgenus that is found in bat populations is not very well studied in terms of it being a potential zoonotic risk. The genetic features of the virus, such as the structure of its spike glycoprotein, receptor attachment adaptations, and recombination tendency, overall propose greater evolutionary plasticity facilitating its acclimatization in novel hosts. Studies have revealed HKU5-CoV-2 shares genomic and structural homologies with other coronaviruses infecting people and thus can potentially take a similar pathogenic route in cases of cross-species transmission. Additionally, the possibility of immune evasion along with the induction of hyperinflammation, which is most commonly seen with SARS-CoV-2, highlights why surveillance is required. Although clinical data related to this information is limited, hypotheses derived from closely related coronaviruses suggest HKU5-CoV-2 can cause both respiratory and systemic diseases. Given that human expansion into wildlife habitats as well as frequent exposures to possible intermediary hosts remain unchecked, the risk for spillover events is significantly high. Therefore, proactive measures—ranging from One Health surveillance as well as intensified genomic research to public health preparedness—must be taken for the risk posed by HKU5-CoV-2 to be curbed. An in-depth understanding of its transmission patterns as well as its patterns of evolution is essential for the prevention of future outbreaks as well as global health protection.

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Ethical Statement

Ethical approval is not required for this type of study.

Conflict of interest

The authors declare no conflict of interest.

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