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RESEARCH PROGRESS ON THE PATHOGENESIS AND CLINICAL MANIFESTATIONS OF COVID -19

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Abstract: COVID-19 Since the outbreak in 2019, it has seriously affected global public health and is still epidemic in many countries. This review was approved by NCBI, CNKI, Web Search COVID-19 related literature in of Science, China National Knowledge Infrastructure and official reports to summarize and systematically explain the current COVID-19 genome characteristics. Research progress and existing deficiencies on the points, infection mechanism, and clinical characteristics, in order to provide new ideas and valuable reference materials for COVID -19 research and prevention and control.
Keywords: COVID-19; Genome; Mechanism of infection; Clinical manifestations

1 COVID-19 GENOME CHARACTERISTICS

Coronavirus disease(Coronavirus Disease 2019, COVID-19) 2019 An outbreak occurred in Wuhan City, Hubei Province at the end of 2020 January 30 day WHO (world health organization , WHO) Issue a statement declaring COVID-19 an emergency of global concern public health event. Imperial College London Medical Research Council (Medical Research Council,MR C) The epidemiological report of the Global Center for Infectious Disease Analysis points out that if adequate measures are not taken to mitigate the epidemic, COVID-19 may become a global pandemic in the coming months. Therefore, it is necessary to clarify the pathogenic mechanism, grasp and identify COVID-19 Clinical characteristics of COV- ID -19, develop vaccines and specific drugs as soon as possible to prevent and control The spread of the epidemic is inevitable. because COVID-19 is highly contagious, It has the characteristics of long incubation period and easy mutation [1], and has research conditions at home and abroad. There are fewer laboratories, which limits scientific researchers' ability to COVID-19 in Research at the molecular level. This article discusses the pathogenesis of COVID-19 and The progress of clinical manifestation research is reviewed.
COVID-19 genome size is approximately 29.9 kb, containing 14 open reading frames (Open Reading Frame, ORF), encoding at least 27 proteins, 4 structural protein in COVID-19 Zhongdu is relatively safe Shou. A special Furin- like cleavage site was discovered on the S protein Located between the S1 and S2 subunits, which are other members of the genus Coronavirus Not available, while in highly pathogenic avian influenza H5N1 of hemagglutinin (Hemagglutinin, HA) Similar insertion sites were also found on [2]. and SARSr-CoV compared to COVID-19 The orf1ab, spike glycoprotein, orf7a, and orf8 gene sequences include 17 There are non-synonymous mutations [3]. COVID-19 orf3b A new protein was discovered [4], which has the 4 indivual spiral, and known SARS-CoV and The SARS-r-CoV protein has no homology. COVID-19 The importance of the One-step verification and research. In SARS-CoV orf8b Found one in aggregation motif VLVVL(Amino acid 75-79), this motif can trigger Intracellular stress pathways and activation of NLRP 3 inflammasome, but not in CO - VID-19 orf 8 does not exist in [5]. in the right 11 share COVID-19 Patient-derived viral isolates were deeply sequenced and GI - SAID database A comparison of 1111 genome sequences found that CO- VID-19 has a total of 33 mutations, of which 19 new mutations discovered for the first time. COVID-19 A lot of mutations have appeared, and a considerable part of them are adaptation-related mutations. The mutations are enriched in the virus S egg. Albumin and angiotensin-converting enzyme II (Angiotensin converting enzyme 2,ACE2) The interface at the receptor binding site [5]. COVID-19 The two most important mutations D614G and S943P Need to focus on, The D614G mutant strain adapts to the local environment more quickly than the original strain territory. The researchers speculate that if the mutation also affects the virus's sensitivity to neutralizing antibodies, it may also mediate immune evasion, making it possible for healthy people to re-infected patient. S943P Mutation and HR 1 district integration related to a cluster of mutations at the core located at COVID -19 HR 1 spirochetes in the spike protein before fusion with the host cell membrane breakpoint, this cluster of Ser- and Thr-rich residues readily forms hydrogen bond, which can promote the formation of helices, S943P Mutations are near the fusion zone and can spread through recombination between different strains, suggesting that multiple strains circulate in the same area, which can enhance the fitness of multiple Mutations assemble in the same strain to make it more potent than a different original strain Pathogenic [6]. in the COVID-19 genome 198 sites have been Repeated independent mutations have occurred, and it is currently unclear whether the mutations change the transmissibility and toxicity of the virus [7]. In short, COVID -19 is a brand new coronavirus, similar to other members of the genus Coronavirus There are similarities and unique genomic characteristics to comprehensively analyze the disease To determine the characteristics of the toxic genome, the number and types of research samples need to be expanded.

2 COVID-19 INFECTION MECHANISM

COVID-19 enters cells in a cholesterol-dependent manner, COV- Significantly increased mortality in ID -19 patients may be related to tissue cholesterol levels associated with being too high, cholesterol is likely to be COVID-19 infection necessary Conditions [8], COVID-19 metabolome study also revealed lipid metabolism abnormal. COVID -19 Host cells can be invaded through different strategies cells, the most important of which is the receptor-mediated membrane fusion pathway. already Confirmed COVID-19 One of the receptors is ACE2 [9], ACE2 not only In II Highly expressed in alveolar cells, esophagus and stratified epithelial cells, Also highly expressed in absorptive enterocytes of the ileum and colon up, indicating that the respiratory and digestive systems are Potential for COVID-19 infection way. Shi Zhengli's team used genome sequence analysis and viral infection experiment correct Certainly exist surface reach ACE2 thin in the cell COVID-19 profit Use ACE 2 as a receptor to infect cells [10]. Analysis through computer modeling Discovered that COVID-19 and SARS-C oV Spike protein amino acids Sequence identity is only 76.47%, COVID-19 Spike proteinaceous receptor binding domain (receptor binding domain, RBD) with human resources ACE2 protein still has strong affinity, and COV ID-19 can pass through Spike-ACE2 binding pathway invades host cells [11]. Wrapp D et al. [12] used cryo-electron microscopy technology to analyze COVID-19 Spike protein The structure once again confirms that Spike protein binding to ACE2 is COVID- 19 Keys to Invading Cells. and SARS- CoV Compared to COVID - 19 Five key amino groups in Spike protein that bind to human ACE 2 4 of the acids have changed, and the changed amino acids maintain the overall SARS-CoV Spike protein and ACE2 The source of interaction structural conformation. Although COVID-19 and SARS-CoV and MERS -CoV is less virulent [13], but COVID-19 The higher affinity between Spike protein and ACE 2 suggests that the virus is more infectious, longer incubation period. In addition, research by Chen Zhinan's team found that COVID - 19 New ways to invade host cells, namely COVID-19 S protein and host receptors on chief cells CD147 binds, thereby mediating COVID-19 Invasion accommodation host thin cell [14]. CD147 again say Basigin or EMM- PRIN is a transmembrane glycoprotein belonging to the immunoglobulin superfamily. Participate in tumorigenesis and viral infection processes. Previous studies have confirmed the importance of CD 147 in viral invasion of host cells. Research passed use people source change anti- CD147 anti- body, surface noodle wait Leave son body common vibrate (Surface Plasmon Resonance, SPR), immunoelectron microscopy technology(Immuno-electron microscope), waived epidemic common sink precipitate (Co-Immunoprecipitation) Waiting for experimental methods, it was discovered that COVID - 19 can pass through receptors CD 147 binds a novel pathway to invade the host cell. CD147 antibody meplazumab can significantly improve COV- ID-19 Clinical symptoms [15]. Currently verified COVID-19 Invasion The host cell receptors are ACE 2 and CD 147. for respiratory diseases Disease wise, ACE 2 The loss will enhance vascular permeability and pulmonary edema, Causes severe lung damage to ACE 2 Targeted therapy may protect it negative impact on protective effects. CD 147 have been identified as extracellular cycline A (cyclophilin A, CypA) The main signaling receptor in Plays an important role in CyPA-mediated signaling processes. COV ID-19 Whether through CypA/The CD147 signaling pathway induces apoptosis, causing Tissue damage? The above theoretical speculations need to be further tested through experiments. certificate. The specific infection mechanism of COVID-19 is still unclear. As research progresses, With continued deepening, the pathogenic mechanism of COVID-19 will eventually be deciphered.

3 CLINICAL MANIFESTATIONS OF COVID-19 INFECTION

COVID-19 The main clinical symptoms are fever, dry cough and fatigue. In severe cases, it can lead to respiratory failure or even death. Most infected patients Male, median age 49.0 years old with underlying medical conditions, including diabetes, hypertension, and cardiovascular disease. Severely ill patients are significantly older ((median age 66 years), and they have more underlying diseases, mostly in Difficulty breathing and/or 1 or 2 weeks after onset of symptoms Or hypoxemia [16]. Most COVID-19 patients are mild and common, and a few are severe and Critically ill patients can rapidly develop acute respiratory distress syndrome (A- cute Respiratory Distress Syndrome, ARDS), and eventually die Death [17]. The main target organ damaged by COVID-19 is the lungs, but many Research results indicate that COVID-19 may also affect other organs.

3.1 Impact Of Covid-19 on the Respiratory System

chest CT scan Showing bilateral lung flakes/Dotted ground glass shadow (85. 7%) and Flaky parenchyma (19%), mainly distributed in the subpleura. As the disease progresses, the scope of ground-glass density plaques and parenchyma increases, and is distributed in the lungs. Ministry and outside [18]. COVID-19 The slices of the patient's lungs show that immune cells gather in the alveoli or air sacs. When the virus attacks, the cell walls will rupture, reducing the absorption of oxygen, causing the patient to cough, have a fever, and exhale. Difficulty breathing and other clinical symptoms. exist COVID -19 virus replication process , the main pathological change in the lungs is the terminal bronchioles within the pulmonary lobules Mucous membrane, alveolar duct epithelial cells, alveolar epithelial cells, alveolar peripheral capillary network, pulmonary lobules and septal interstitium, lymphatic vessels and other different tissues Congestion, edema, alveolar and alveolar wall edema, small vessel endothelial injury vasculitis, multiple small vessel fibrin embolism [19].

3.2 Covid-19 Effects on Cardiovascular System

Liu etc. [20] COVID-19 patient plasma Ang found II level is significantly higher than healthy healthy people, and is closely related to viral load and degree of lung damage, suggesting that COVID-19 infection is likely to cause RAS

System imbalance may induce Hypertension, arrhythmia, heart failure and other acute cardiovascular events occur, This has a more serious impact on patients with underlying cardiovascular diseases. Although there is insufficient pathological evidence to confirm that COVID-19 causes indirect myocardial injury, but Liu et al. [20] reported 1 example COVID-19 The infection was complicated by fulminant myocarditis. The patient's myocardial enzyme spectrum was significantly elevated, and his heart rate was A sharp decline in function was accompanied by a very high and persistent viral load. Continued More than 1 week, indicating that COVID-19 can directly attack myocardial cells, viral myocarditis. Huang Wait [21] to release the earliest confirmed information in Wuhan Among the 41 COVID-19 patients diagnosed, 5 were diagnosed with virus-related myocardial injury, mainly manifested by increased cTnI levels. Current research shows that COVID-19 is closely related to the occurrence and progression of cardiovascular disease close. COVID -19 invades the host by binding to cell surface receptors Chief cells cause blood clots and cardiovascular system diseases.

3.3 Covid -19 Impact on Vision

Clinical studies report that COVID -19 patients can develop eye infection symptoms mainly conjunctivitis, and it is proposed to use ocular nucleic acid testing as an auxiliary for early infection of the virus. diagnostic tools. Animal experiments on rhesus monkeys have shown that COV - ID -19 inoculated into the conjunctiva can induce a strong inflammatory response in conjunctival epithelial cells by infecting the conjunctiva [22]. COVID -19 Among patients with conjunctival congestion as the first symptom, most of the infected patients showed conjunctival congestion, photophobia, tearing, and Clinical symptoms include increased secretion and blurred vision [23]. Tears are spread One of the body fluids of the virus, Xia et al. [24] used real-time fluorescence quantitative PCR (Quantitative Real-time PCR, RT-P CR) suffering from conjunctivitis COVID -19 detected in patients' tears and conjunctival secretions. corner of eye membrane and conjunctiva ACE 2 Higher expression levels, ocular surface detection ACE 2 Positive expression may indicate the risk of COVID-19 infection [25].

3.4 COVID -19 Effects on the Genitourinary System

Clinically severe COVID -19 patients can rapidly develop metabolic acidosis that is difficult to correct, suggesting the existence of renal dysfunction. Confirmed COVID-19 suffer from kidney achievement can sick example research In the study, kidney damage hurt exist It is commonly found in COVID-19 patients [26]. COVID-19 deaths Autopsy case results also showed glomerular epithelial degeneration and shedding, interrenal A series of injuries such as mass congestion and. Due to the clinical needs of COVID-19 patients Treat with antiviral and antibacterial drugs, which can cause kidney Impairment of glomerular filtration function and tubular reabsorption causes renal function damaged. And COVID-19 Patients complicated by sepsis and hypoemia Oxygen deficiency can also cause kidney damage. Therefore, COVID-19 Is it straight? damaged kidney dirty have treat Enter one step by step research study certificate Reality. this Outside, Fan [27] have shown that ACE2 is highly expressed in renal tubular cells and interstitial cells. cell harmony testis pill born Refined thin cells, COVID-19 Can able Pass Pass Targeting ACE 2 affects kidney and testicular tissue and therefore fertility, but this There are currently few reports on this aspect.

3.5 Effects of COVID-19 on the Nervous System

based on Study of SARS - CoV-susceptible neuronal cells in confirmed Among severe COVID-19 patients, clinical manifestations include disturbance of consciousness, acute cardiovascular and cerebrovascular diseases, Among the 241 COVID-19 hospitalized patients, 78 had neurological symptoms. Symptoms suggestive of COVID-19 Possibly via retrograde neuronal pathways Entering the central nervous system, or harmful immunity mediated by viral infection The reaction causes damage to the nervous system [28]. exist COVID-19 In a retrospective study of confirmed patients, Zhong Nanshan's team found that 1,099 patients Currently about 13.6% There are headache symptoms [29]. The above research results are sufficient It shows that COVID-19 has an impact on the nervous system.

4. OUTLOOK

from SARS Popular till now COVID-19 outbreak, coronavirus Poison seems to have never been far away from human beings, but has a negative impact on human beings. more profound impact. COVID-19 Since the outbreak at the end of last year, it has caused a global pandemic, causing huge economic losses and affecting public health. health poses a huge threat to the medical system and government decision-making and execution etc. brought a severe test. Signed by more than 60 major research organizations around the world A joint statement from the two agencies proposed sharing research data to jointly fight the epidemic [30]. The world's top medical journals have also set up special modules to report on the latest epidemic Research progress. Judging from existing research, COVID-19 The genome is large quantity Can Change turn Translation, tool have Change different Fast, many Sample sex High special Zheng [31]. COVID-19 Multiple site mutations have occurred, but these sites Whether mutations in the virus alter the transmissibility and virulence of the virus remains unknown. Epidemiological data show that COVID-19 is generally susceptible to the population, and the disease It is positively correlated with age and underlying diseases such as hypertension, diabetes, and cardiovascular disease [32]. Affected by different countries' governance, economy, medical Affected by many factors such as the level of COVID -19 Global popularity degree remains to be further verified.

Although the epidemic has been basically controlled in many countries, there is still the possibility of another outbreak in the near future. Before it is released, no one can relax their vigilance and take it lightly. Heart, the vaccine is currently only in the animal testing stage, and it is unknown when it will be released on the market. COVID -19 Receptors that have been discovered include ACE 2 and CD147, COVID-19 Invasion of host cells via cell surface receptors. The clinical manifestations of COVID-19 patients are related to the distribution of ACE2 in the human body. Heart, colon, esophagus, kidneys, and male testicular tissue All have higher ACE 2 expression of which renal ACE 2 Expression ratio The lungs are 100 times higher [33], but the clinical manifestations are the most severe in the respiratory system. It is speculated that COVID-19 has other ways to invade cells and cause clinical manifestations, which needs further research to support. COVID -19 Infection in the plasma of infected patients IL-7, IL-8, IL- 10, IFN-γ, TNFα The levels of inflammatory factors are higher than those in healthy adults, and ICU patients than non- ICU patients, indicating that the cytokine storm is associated with the severity of the disease. degree correlation. Recent studies conducted systematic proteomic and metabolomic studies on serum samples from multiple COVID-19 patient groups and controls, revealing proteins with differential proteomic expression changes and Abnormal lipid metabolism in the metabolome deepens the understanding of Understanding the pathogenesis of COVID-19 [34]. COVID-19 Clinical symptoms vary depending on patient gender, There are great differences in age, blood type, and health status. males than females Sex on COVID-19 Susceptible, study shows male plasma ACE 2 concentrations Higher than women [35]. The elderly and those in poor health are often The target of COVID -19 infection, but there are also reports that obese young people may be more susceptible to COVID-19 infection, mainly because on the one hand Obese patients have difficulty breathing; on the other hand, fat itself has metabolic activity, it can produce considerable amounts of pro-inflammatory substances called cytokines molecules, thereby inducing low-level background inflammation in the body [36]. A blood Risk of COVID-19 infection and severe COVID-19 disease higher, while O blood type has a lower risk [37]. COVID-19 causes disease The mechanism is still unclear, but according to current research, COVID-19 has Most organs in the body will suffer varying degrees of damage. because COVID-19 RNA depends on RNA Polymerase (RNA depend- ent RNA polymerase, RdRp) Lacking varsity functionality, the COVID -19 genome has a high mutation rate, which poses challenges for our efforts to develop drugs and vaccines have brought new challenges, and the vaccines and drugs currently developed are yet to be aftermarket able no right sudden Change After COVID-19 Produce born effect Should? Follow SARS-CoV, MERS-CoV arrive COVID-1 9 outbreak, wild It has been concluded that animals serve as intermediate hosts. In the future, wildlife protection Questions worth pondering. from Since the COVID-19 outbreak, scientific researchers around the world have made outstanding achievements in COVID-19 research. Yes, but there are still many existing problems that we need to delve into. Comprehensive understand the pathogenic mechanism of COVID-19, grasp the epidemic trends and characteristics, and return to the Acceptance and identification of clinical manifestations and responses COVID-19 Only by adjusting research directions immediately when mutations occur can we effectively prevent and control the epidemic and develop specific drugs as soon as possible. drugs and vaccines.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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