Pathogenesis and Clinical Research Progress of COVID-19

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Abstract: The global pandemic caused by the novel coronavirus disease (COVID-19) in December 2019 has had an unprecedented impact on human society. Over the past three years, the medical and scientific communities have been working to study the mechanisms of infection and identify effective prevention and treatment measures. This article reviews the molecular characteristics, origin and host, transmission and evolution, pathogenesis, clinical characteristics, complications, examination methods, clinical treatment progress, etc. of COVID-19, providing a theoretical framework for in-depth understanding of COVID-19 and finding effective treatments. And explore the feasibility of traditional Chinese medicine therapy in the treatment of new coronavirus.

1. Introduction

A cluster of individuals with pneumonia of unknown origin who were epidemiologically connected to a seafood market in Wuhan, Hubei Province, China, was reported by certain local health authorities in late December 2019 [1]. On January 30, 2020, the World Health Organization (WHO) declared coronavirus disease (COVID-19) a public health emergency of major global significance. [2]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the agent that produced the COVID-19 virus, which spread to become a global pandemic in 2020. The COVID-19 virus has regularly sparked cycles of epidemics in different nations over the past few years, leading to a variety of difficulties and the appearance of new mutant strains, which has drawn the attention of medical professionals.

The coronaviridae family includes SARS-CoV-2. The coronavirus gets its name from a particular spike protein that has the appearance of a crown and can enter cells using a variety of strategies. Mice were used to find and successfully isolate the first coronaviruses. The six human coronaviruses (HCoVs) that have been identified so far (MERS-CoV) are the Middle East respiratory syndrome coronavirus, the severe acute respiratory syndrome coronavirus (SARS-CoV), HCoVs-NL63, HCoVs-229E, HCoVs-OC43, and HCoVs-HKU1. Due to coronaviruses' high prevalence and widespread dispersion, their genetic diversity and frequent genome recombination, as well as the rise in human-animal contact activities, new coronaviruses occasionally develop in humans. The cause of 5% to 30% of human patients' upper respiratory tract illnesses is a coronavirus, which can also cause lower respiratory tract infections and gastroenteritis in humans, and severe symptoms may also be life-threatening. The initial infection of coronaviruses to humans was limited to mild symptoms similar to colds, until the discovery of atypical pneumonia (SARS) in 2003 and SARS-CoV-2 in 2019, making people pay more attention to it.

2. Molecular structure of SARS-CoV-2

The SARS-CoV-2 virus is an enveloped, pathogenic, single-stranded RNA virus [3]. There are 11 protein-coding genes, 12 expressed proteins, and 38% GC in the SARS-CoV-2 genome. The recently sequenced SARS-CoV-2 genome, with a size of approximately 29.9 Kb, has been submitted to the NCBI genome database (NC 045512.2). SARS-open CoV-2's reading frame's genetic makeup is remarkably similar to that of SARS-CoV and MERS-CoV. SARS-genomic CoV-2's structure has a sequence identity with other CoVs of about 89%. Spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein are the four structural proteins found in SARS-CoV-2 (N). These four proteins play a great role in XXX invading the human body(figure 1). Perhaps we can study related targeted drugs based on the characteristics of these four proteins.

High sequence similarity exists between these proteins.

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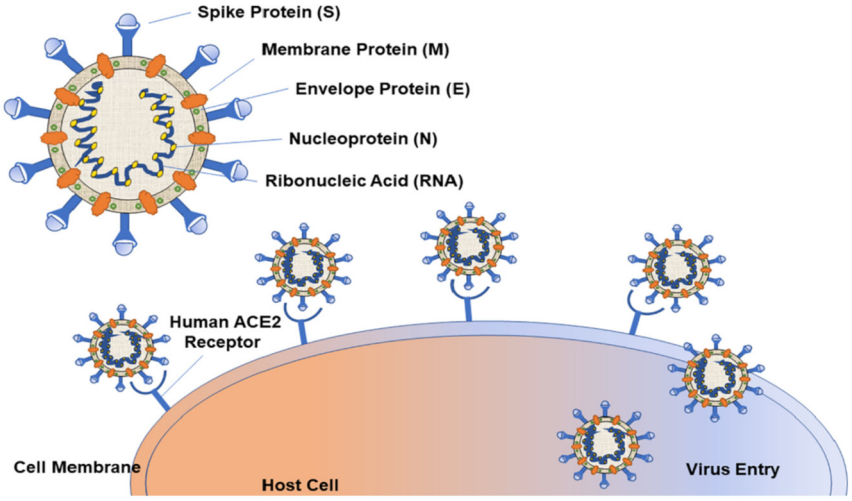

Figure 1 Schematic diagram of the structure of SARS-CoV-2 and its host entry method [8]

3. Origin and host of SARS-CoV-2

Most experts agree that SARS-CoV-2 is a naturally occurring RNA virus that is carried by bats and can infect people with 2019-nCoV. There are currently 1,420 species of bats, making up the second-largest order of mammals after the Rodentia, and they make up around 22% of all species of identified mammals [4]. Several human diseases have zoonotic origins, and deadly viruses like the Marburg, Hendra, and Ebola viruses are carried by bats. Aside from bats, other species that can serve as intermediate hosts for viruses include pigs, cows, deer, hedgehogs, and mice. These four proteins play a great role in SARS-CoV-2 invading the human body. Perhaps we can study related targeted drugs based on the characteristics of these four proteins.

Before the discovery of SARS-CoV-2, six human coronaviruses were known: HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS coronavirus (MERS-CoV) [5]. Four of them, including HCoV-229E, HCoV-NL63, SARS-CoV, and MERS-CoV, which have zoonotic origins, may be important reservoirs in bats. Several investigations have demonstrated that SARS-CoV-2-related coronaviruses are carried by bats across a significant portion of Asia. For instance, two novel beta-coronaviruses (STT182 and STT200) that are closely related to SARS-CoV-2 and the six important spike proteins found in SARS-CoV were identified in R. shali bats collected in Cambodia in 2010. 92.6% of the nucleotides at five body-binding domain (RBD) locations are identical [6]. While pangolin viruses from Guangdong shared six important receptor residues with human SARS-CoV-2 RBDs, viruses from Malaysian pangolin viruses, including two lineages, mirrored Chinese provinces (Guangdong and Guangxi) that were gathered by local customs authorities. These facts show that coronavirus is a complex virus with a long evolutionary history, the capacity to infect different animals, and numerous evolutionary routes. To sum up, the SARS-CoV-2 is most likely to have originated from animals and mutated to become a zoonotic infectious disease introduced through cold chain and other methods. The laboratory origin is basically ruled out. Transmission and mutation of SARS-CoV-2.

The World Health Organization (WHO) closely monitored the SARS-CoV-2 outbreak that started in December 2019, and on January 31, 2020, it declared it to be a public health emergency of worldwide concern. The key factor that has made SARS-CoV-2 a threat to the lives and health of the global public is its potent transmissioncapacity (figure 2).

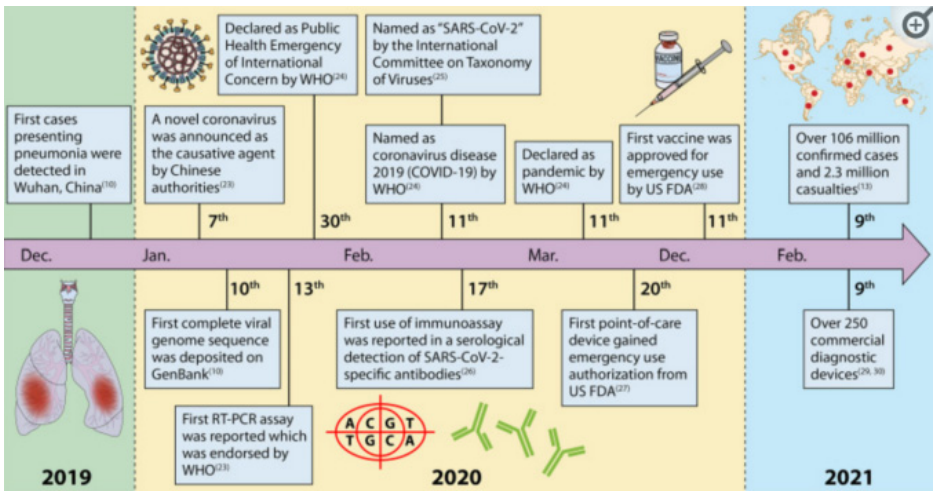

Figure 2 The evolution history of SARS-CoV-2 transmission

There have been cases of SARS-CoV-2 infection in household cats and pet hamsters, among other mammals. When a cat infected with SARS-CoV-2 in Belgium developed respiratory illness, nausea, and diarrhea, the cat's owner's SARS-CoV-2 infection was highly probable to have been the source of the cat's infection [7]. According to research, SARS-CoV-2 can also identify and infect host animals with ACE2 receptors, including cats, primates, and ferrets. (Figure 3).

There is genetic proof that animals were infected with SARS-CoV-2, according to some academics. Shi et al. claim that SARS-CoV-2 strains can experimentally infect cats and ferrets in various environments, and that infected cats can spread the virus to healthy cats residing nearby [8]. The research also discovered that in pigs, ferrets, cats, orangutans, monkeys, and humans, the SARS-CoV-2 spike RBD had comparable binding efficiency to ACE2. There are also studies that among all known bat coronaviruses, SARS-CoV-2 is highly lacking in dinucleotides, which may indicate changes in the evolutionary pathway and intermediate host of SARS-CoV-2.

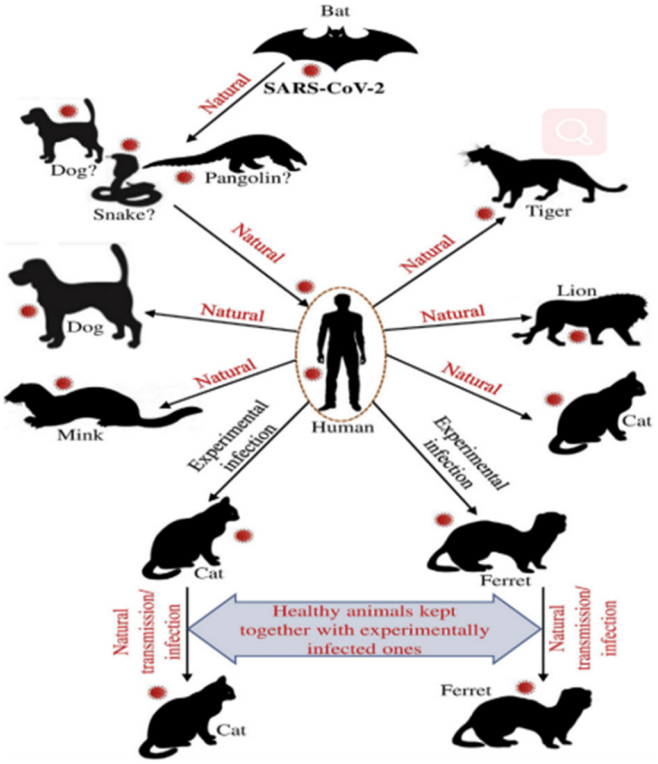

Figure 3 Host range of SARS-CoV-2 and animal susceptibility in natural or experimental situations[9]

The international community has been monitoring COVID-19's potential mutations ever since the disease became a worldwide pandemic. Some unique mutations can result in increased viral pathogenicity, transmission capacity, and even the capacity to evade vaccination. In order to develop protective interventions to stop the mutation and further spread of the virus, it is essential to understand the virus's current mutant strains and to constantly detect virus mutation. RNA viruses, like SARS-CoV-2, have a higher mutation rate than DNA viruses. Some mutations will be maintained over time through natural selection or unintentional events, leading to the emergence of a new epidemic strain. SARS-CoV-2 has so far developed a number of variants with greater frequency. The B1.1.7 variant was first identified in the UK in October 2020，called the "British variant" as well. This variant demonstrates resistance to monoclonal antibodies that target the spike protein's N-terminal region and a few RBDs. The B1.1.7 strain has a total of 23 mutations, which can significantly increase its capacity for transmission[10]. Additionally, it is 56% more infectious than other mutant strains, demonstrating its competitive edge[11]. The B.1.351 variety was discovered to have 21 mutations in South Africa in October 2020. Similar to B.1.1.7, B.1.351 demonstrated a number of alterations in the spike protein, including the N501Y site, which makes the virus more contagious[12]. The P.1 variant was first identified in the United States in January 2021, and it first emerged in Brazil in December 2020 as a branch of the B.1.1.28 lineage2021. This variant had undergone 17 mutations by the time it was identified in the human population. N501Y, E484K, and K417N, three of them, were comparable to those found in B.1.351 and therefore resistant to neutralizing antibodies. After modifications, other variants, such the A.23.1 variant that appeared in Uganda and the B.1.526 variant that appeared in New York, USA, also proliferated throughout the populace. Vaccine-induced immunological responses and antibodies. In Figure 4.

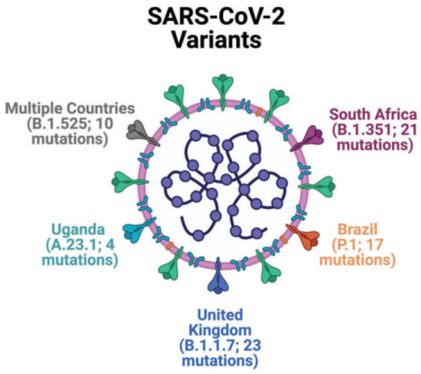

Figure 4 Five variants of SARS-CoV-2, with multiple mutations, originated from various countries, all have vaccine escape ability and higher infectivity

4. Infection mechanism of SARS-CoV-2

4.1. Virus replication mechanism

The SARS-CoV-2 copies its genome and carries out gene transcription using RNA-dependent RNA polymerase (RdRp). Numerous coronavirus polymerases have been demonstrated to be inhibited by the nucleoside analog inhibitor remdesivir. Viral replication likely occurs in the intima inside the cytoplasm of the replicating organelle. Thus, replication intermediates such as dsRNA can physically shield host innate immune defenses, such as pathogen recognition receptors present in the cytosol. The formation of replicating organelles allows the spatial coordination of the different steps required for viral replication and assembly. Thus, membrane remodeling plays a crucial role in the (+)RNA virus life cycle(figure 5).

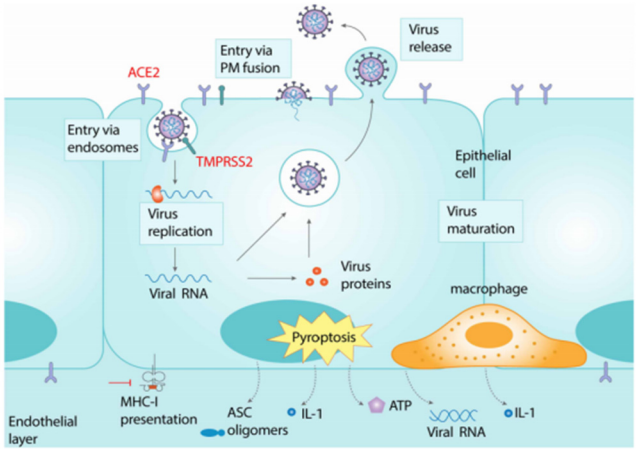

Figure 5 Schematic diagram of the complete life cycle of SARS-CoV-2 in cells and related immunopathology

4.2. Assembly and diffusion mechanism

SARS-assembly, CoV-2's release, and transmission mechanisms are still not completely known. In one experiment, the structural proteins S, E, M, and N of the SARS-CoV could assemble into virus-like particles (VLPs) and discharge them into the culture medium when expressed in Vero E6 cells. Viral RNA must be packaged into these VLPs using the viral N protein and packing cues present in the genomic RNA's 579-nucleotide length domain. According to the tropism and replication of SARS-CoV-2 in vitro cultures of human bronchi, lung, and conjunctiva, type 1 pneumocytes, which are rod-shaped, ciliated, and mucus-secreting cells of the bronchial epithelium, were able to infiltrate the bronchi. Lungs and conjunctival epithelium. The expression of two mucosa-specific serine proteases, TMPRSS2 and TMPRSS4, increased SARS-CoV-2 spike fusion activity and the spread of the virus in these cells, according to a previous study that showed efficient infection of SARS-CoV-2 in ACE2+ mature enterocytes in the human small intestine.

5. Clinical symptoms of COVID-19

5.1. General Symptoms

The clinical characteristics of COVID-19 patients demonstrate that SARS-CoV-2 infection in humans has significant pathological variations. The virus enters the respiratory tract through the mucous membranes of the nose and throat before moving on to the lungs. One of the earliest and most prevalent signs of illness is fever. while the median time from symptom onset to acute respiratory distress syndrome is approximately 8 days. According to recent research, B lymphopenia may also develop early in the illness and may have an impact on the host's ability to produce antibodies. Lymphocytes were dramatically reduced in severe instances. The exact cause of this sharp decline in lymphocytes is still unknown. Additionally, a

"cytokine storm" of pro-inflammatory substances like IL-6, IL-10, and TNF, which are frequently enhanced, contributed to the disease's worsening 7 to 14 days after it first appeared. Some researchers broadly divide the clinical course of SARS-CoV-2 into three stages: the viremia stage, the acute stage (pneumonia), and the severe or recovery stage. This is based on the characteristics of COVID-19 patients. An important factor in determining the course of a disease appears to be the immune system of the affected host. Even in the acute phase, the infection normally goes away if there are no underlying comorbidities. However, the condition often progresses to a severe or critical stage in older or immunocompromised people when paired with additional comorbidities including hypertension and diabetes mellitus.

5.2. Asymptomatic infection

After the COVID-19 epidemic, the disease has swiftly spread to other countries and provinces in China. Among COVID-19-infected individuals, a sizable percentage of asymptomatic infections have appeared. This unique group poses a threat to the containment of the pandemic because it is both disguised and somewhat transmissible. Consistent respiratory symptoms (cough, sore throat, runny nose, shortness of breath, etc.), systemic symptoms (fever, chills, fatigue, muscle aches, headache, etc.), circulatory symptoms (chest pain, chest tightness, palpitations, etc.), the primary clinical symptoms of COVID-19 patients (diarrhea, vomiting, anorexia, etc.) are digestive problems. If a patient does not display any of the relevant symptoms mentioned above once the pathogen is identified, they are considered to have an asymptomatic infection. There were 511 patients in the study with a diagnosis of SARS-CoV-2 infection, ranging in age from 1 month to 87 years. Of these, 100 had no symptoms and 411 had symptoms.

For those who experienced symptoms, the median incubation period was 6 days (the range was 2–15 days). Of the 62 patients in the asymptomatic group who received thorough prognostic information during hospitalization, 17 (27.3%) had prolonged symptom-related days (median: 7 days, range: 1-13 days) after the SARS-CoV-2 virus was identified. The presence of systemic and respiratory symptoms could indicate an infection. All of the presymptomatic patients' CT scans for pneumonia were positive when they were admitted. Solely respiratory symptoms were present in 28.9% of patients, solely systemic symptoms in 32.3%, and symptoms involving several systems were present in 33.1% of patients.

Table 1 Distribution of symptoms in the symptomatic COVID-19 group

System	Performance	Number of cases	Percentage(%)
Respiratory symptoms	Cough (mostly without phlegm)	102	24.8
	Sore throat or runny nose	17	4.1
Systemic symptoms	Fever	98	23.8
	Chills or fatigue	3	0.7
	Muscle aches or headaches	32	7.8
Circulatory symptoms	Chest pain, tightness, or palpitations	10	2.4
Digestive symptoms	Diarrhea, vomiting, or anorexia	13	3.2
Multisystem symptoms	cough and fever	76	18.5
	Cough and other non-fever symptoms	27	6.6
	Fever and other non-fever symptoms	33	8.0
All		411	100.0

6. Complications of COVID-19 (mainly neurological symptoms)

From a nomenclature perspective, COVID-19 is known as new coronary pneumonia, which indicates its major influence on the respiratory system. COVID-19 is a new type of coronavirus pneumonia. By ongoing research, experts have also learned that it also has an impact on various human body tissues and organs to differing degrees through the various difficulties of patients.

It has been repeatedly highlighted in previous papers that ACE2 is crucial to the infection of the human body by the new crown. ACE2 is expressed not just in alveolar cells but also in numerous other organs. SARS-CoV-2 is therefore expected to infiltrate tissues and organs through ACE2 binding and cause harm to various organs, including brain injury, liver dysfunction, kidney injury, and heart disease.

It has also been shown that SARS-CoV-2 can enter the central and peripheral nervous systems (CNS) through retrograde axonal transport or infection of astrocytes and pericytes, the two cells that make up the blood brain barrier (BBB) and cause neurological issues. It's possible that COVID-19 directly or indirectly invaded the central nervous system (CNS), which is the location of its neurologic effects. According to epidemiological studies, the 1-week incubation period between the first infection and severe infection in COVID-19 patients provides enough time for potential viral entrance into the central nervous system. Besides altering the blood-brain barrier's (BBB) functionality, the spike protein of SARS-CoV-2 aids in the virus's entry into the central nervous system. According to a study of 214 COVID-19 patients from

Wuhan, China, 41.1% (88/214) had a severe SARS-CoV-2 infection, while the remaining patients (58.9%; 126/214) did not have a severe infection. Due to damage to sensory neurons, 36.4% (78/214) of these patients experienced overt neurological symptoms, which included sensory abnormalities in taste and smell as well as neuropathic pain, seizures, and stroke. Patients with COVID-19 in various nations throughout the world can also see these symptoms.

The neurological manifestations of COVID-19 are separated into CNS indicators and markers of skeletal and muscle injury based on symptoms. Acute cerebrovascular disease, headache, dizziness, ataxia, disruption of consciousness, and seizures were listed as the most serious symptoms among these neurologic manifestations. Infection with SARS-CoV-2 alters the PNS, resulting in neuropathic pain, loss of taste, smell, or vision. According to the study's findings, 36.5% (78/214) of the patients had neurologic abnormalities, including signs of PNS functional deficit, skeletal muscle injury, and CNS dysfunction. The majority of elderly individuals (60 years or older) with concomitant conditions, such as hypertension, diabetes mellitus, chronic malignancy, and cerebrovascular disease, exhibit all of these neurologic symptoms.

7. Advances in TCM clinical treatment of COVID-19

Regarding COVID-19 treatment options, WHO has launched a clinical trial called "Solidarity" to evaluate the effects of drugs such as remdesivir, chloroquine or hydroxychloroquine, and lopinavir/ritonavir. After many experiments, it was concluded that all 19 candidate drugs, including remdesivir, were ineffective or had little impact on the newly mutated COVID virus. Compared with such biological drug prevention methods, while facing lower adaptability to viral mutations, traditional Chinese medicine also provides different treatment methods.

A treatment plan with a permanent curative effect can be provided by traditional Chinese medicine, which has amassed a wealth of relevant knowledge in the prevention and treatment of "epidemic diseases" over thousands of years of transmission. The "Diagnosis and Treatment Program for Pneumonia Infection by Novel Coronavirus (Trial Version 5)" emphasizes the critical part traditional Chinese medicine plays in the treatment of novel coronavirus pneumonia. Different from traditional antiviral drugs such as Naimatevir Tablets/Ritonavir Tablets and other drugs, Qingfei Paidu Decoction can more effectively prevent complications in addition to its inhibitory effect on viruses.

7.1. Antiviral effect of Qingfei Paidu Decoction

The national Chinese medicine treatment plan was initially presented in the "Diagnosis and Treatment Plan for New Coronavirus Pneumonia (Third Edition)" on February 22, 2020. "Qingfei Paidu Decoction" was clinically recommended by the Administration of Traditional Chinese Medicine because it has a total effective rate that can exceed 90% based on the clinical treatment and curative effect observation of traditional Chinese and Western medicine. Maxing Shigan Decoction, Shegan Mahuang Decoction, Wuling Powder, and Xiaochaihu Decoction are the four primary prescriptions that make up Qingfei Paidu Decoction, which has good medicinal efficacy. It is now known that it has good antiviral action in vitro and can inhibit coronavirus at the RNA and protein levels as well as prevent coronavirus from adhering to human cells and enhancing the expression of intracellular interferon and other associated genes. Research have shown that the serum of COVID-19 patients has higher concentrations of pro-inflammatory substances like IL-1, IFN-, and MCP-1. Qingfei Paidu Decoction can reduce the "cytokine storm" in response to this occurrence, which in turn will inhibit the new coronavirus. Pneumonia resulting from. The administration of this substance can improve the treatment and prognosis of older individuals with COVID-19, according to a retrospective investigation of the clinical efficacy, and it also has a certain improvement effect on severe patients.

7.2. The effectiveness of TCM therapy in clinical application

Retrospective analysis was done on the medical records of 40 patients, including 27 men and 27 women, who underwent non-critical new coronary pneumonia treatment at Taiyuan Fourth People's Hospital, Jinzhong Infectious Disease Hospital, and Xinzhou People's Hospital between January and March 2020. Among the 13 instances, 12 had underlying conditions, including 7 cases of hypertension, 2 cases of diabetes, 2 cases of coronary heart disease, and 1 case of chronic bronchitis. The average age of the cases was 34.88.27 years. The syndrome of damp-heat buildup in the lung was found in 11 cases and 29 cases, respectively, at the time of admittance. The patients' median incubation period was 6.55 4.39 days, with an average hospitalization time of 13.03 5.19 days. The lowest hospitalization time was 5 days (for an infection without symptoms), and the longest was 31 days (for a recurring illness). Qingfei Paidu Decoction was administered orally. The Shanxi Health and Health Commission assembled a team of renowned and experienced Chinese medicine experts to add and subtract the patients based on the initial prescription. Following therapy, fever, sweating, coughing, expectoration, The conditions of 40 patients' pulse, tongue coating, wheezing, chest tightness, abdominal pain, diarrhea, constipation, headache, and other symptoms were better than they were before therapy (P 0.05). The cold-damp stagnation in the lung group and the damp-heat accumulation in the lung group did not significantly vary in TCM syndrome scores prior to treatment (P>0.05). The TCM syndrome ratings of the two groups were lower following treatment than they were prior to it (P 0.01). The disparity between the groups, however, was not statistically significant (P>0.05). Look at Tables 1, 2, 3 and 4.

Table 2 Comparison of TCM symptoms before and after treatment in 40 non-critical patients with novel coronavirus pneumonia [case (%)] [14]

Time	Degree	Fever	Sweat	Cough	Expectoration	Gasp
Before treatment	Not have	7 (17.5)	23 (57.5)	21 (52.5)	20 (50.0)	21 (52.5)
	Mild	18 (45.0)	10 (25.0)	10 (25.0)	11 (27.5)	11 (27.5)
	Moderate	13 (32.5)	5 (12.5)	6 (15.0)	6 (15.0)	5 (12.5)
	Aevere	2 (5.0)	2 (5.0)	3 (7.5)	3 (7.5)	3 (7.5)
	Not have	40 (100.0)	37 (92.5)	35 (87.5)	35 (87.5)	38 (95.0)
After treatment	Mild	0 (0)	3 (7.5)	5 (12.5)	5 (12.5)	2 (5.0)
	Moderate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Aevere	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 3 Comparison of tongue coating before and after treatment in 40 non-critical patients with novel coronavirus pneumonia [case (%)] [13]

Time	White thick	White thick greasy	Yellow greasy	Yellow thick greasy
Before treatment	15 (37.5)	14 (35.0)	8 (20.0)	3 (7.5)
After treatment	38 (95.0)	2 (5.0)	0 (0)	0 (0)
P	<0.01	<0.01	<0.01	<0.01

Table 4 Comparison of pulse conditions before and after treatment in 40 non-critical patients with novel coronavirus pneumonia [case (%)] [13]

Time	Ease	Pulse count	sinking pulse	Huamai
Before treatment	2 (5.0)	34 (85.0)	2 (5.0)	2 (5.0)
After treatment	29 (72.5)	0 (0)	9 (22.5)	2 (5.0)
P	<0.01	<0.01	<0.01	<0.01

As a new type of therapy with Chinese characteristics, traditional Chinese medicine therapy for COVID-19 has achieved outstanding results in the "battle" against the COVID-19 epidemic. This is primarily reflected in the ability to treat non-severe patients with non-significant negative side effects. Chinese medicine therapy is expected to gain a reputation for its potent curative effect by further refining the prescription and course of treatment. I also look forward to the day when traditional Chinese medicine and Western medicine can work together to treat more complex and diverse illnesses that conventional medicines are unable to treat.

8. Research Outlook

The COVID-19 epidemic has ended on a worldwide scale. COVID-19 has transformed from "a brand-new, highly pathogenic and contagious Systemic disease" to "low specificity disease requiring certain monitoring, prevention, and treatment" as a result of study on the disease itself and its vaccine in numerous nations and areas. In this new situation, people should draw lessons from the pandemic's experience and lessons in order to prepare for the next time a different pathogen with similar traits spreads widely and to lessen the loss of life and property across all nations.

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