Combination of Chinese and Western Medicine: Molnupiravir and Lianhua Qingwen in the Treatment of Novel Coronavirus Pneumonia (COVID-19)

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Research Article

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Abstract

Objective: This study aimed to assess the effectiveness of Molnupiravir and Lianhua Qingwen in treating patients with novel coronavirus pneumonia (COVID-19).

Methods: We conducted a study involving 14 cases of COVID-19 infection within a unit group in Laos. During the treatment regimen, these patients received the antiviral drugs Molnupiravir and Lianhua Qingwen as prescribed. We utilized laboratory results of viral nucleic acid tests as observational parameters and statistically analyzed the data using SPSS 26.0 software (t-test). Our data analysis aimed to determine if there were significant differences in the Ct values of the N gene and ORF1ab gene of SARS-CoV-2 before and after treatment.

Results: The results indicated statistically significant differences in the N gene ($t = -7.014, P < 0.001$) and ORF1ab gene ($t = -7.398, P < 0.001$). Post-treatment, the values of the N gene and ORF1ab gene were significantly higher than their pre-treatment values, signifying that the combined utilization of Molnupiravir and Lianhua Qingwen had a substantial impact on the treatment of COVID-19.

Conclusion: Molnupiravir and Lianhua Qingwen effectively inhibited the replication of SARS-CoV-2, resulting in a marked improvement in the clinical symptoms of the patients. Laboratory test results also indicated a significant reduction in viral load. These findings provide substantial evidence supporting the efficacy of the combination of Molnupiravir and Lianhua Qingwen in the treatment of COVID-19.

Introduction

Since December 2019, the world has been grappling with an outbreak of novel coronavirus pneumonia, known as Coronavirus Disease 2019 (COVID-19), originating in Wuhan, Hubei Province, China. This outbreak soon spread to numerous countries worldwide\(^1\). The gravity of the situation prompted the World Health Organization (WHO) to declare the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC) on January 30, 2020. Subsequently, on March 11, 2020, WHO escalated its classification to declare COVID-19 a global pandemic\(^2\).

Consequently, in addition to the extensive efforts directed toward the development and promotion of antiviral vaccines, nations have been actively engaged in the development of various antiviral drugs. In November 2021, the United Kingdom’s Medicines, and Healthcare Products Regulatory Agency (MHRA) granted approval for the marketing of Merck Sharp & Dohme (MSD)’s antiviral drug, Molnupiravir. During the same period, Laos swiftly approved the utilization of Molnupiravir, a potent drug for the treatment of neo-coronavirus infections produced by MSD.

Lianhua Qingwen is an innovative patented traditional Chinese medicine with potential efficacy against respiratory system diseases\(^3\). It can alleviate symptoms such as fever, cough, fatigue, muscle pain, and shortness of breath. This traditional Chinese medicine is used to prevent severe acute respiratory syndrome (SARS) and can inhibit and kill coronaviruses associated with SARS and Middle East
respiratory syndrome. Over the past decade, it has become a representative traditional Chinese medicine for treating respiratory infectious diseases\[{4}\].

Our research reveals a higher incidence of COVID-19 infection among a group of employees in a specific organization in Laos, including both Chinese and Laotian nationals. These individuals, upon contracting the virus, received treatment with the COVID-19 antiviral drug Molnupiravir and the traditional Chinese medicine Lianhua Qingwen. We conducted a two-course treatment for selected infected individuals and closely monitored their viral nucleic acid levels through PCR technology. The study findings indicate that the combination therapy of Molnupiravir and Lianhua Qingwen effectively suppresses the replication of the SARS-CoV-2 virus in the early stages of infection. This combined treatment significantly improved inflammatory symptoms such as fever, cough, fatigue, muscle pain, and shortness of breath, consequently reducing hospitalization and mortality rates.

Using laboratory PCR techniques, we monitored the viral nucleic acid levels in infected individuals before and after receiving the combination of traditional Chinese and Western medicine for COVID-19. This process provides robust evidence supporting the use of combination therapy in early-stage COVID-19 infections to suppress viral replication. Furthermore, our research offers valuable insights for laboratories conducting SARS-CoV-2 nucleic acid testing analysis. The primary objective of this study is to investigate the efficacy of combining Molnupiravir and Lianhua Qingwen in treating COVID-19, aiming to provide a more reliable foundation and guidance for further research and clinical applications.

Our research constitutes a retrospective analysis, comprehensively examining and analyzing past data to reveal potential trends and correlations between early infection and the combination of traditional Chinese and Western antiviral treatments. Through this method, we extract valuable insights from the data, potentially offering valuable perspectives for future endeavors. By synthesizing existing data and employing a systematic review approach, we aim to extract critical insights and contribute to the foundational knowledge for the ongoing research into antiviral treatments for COVID-19.

**Methods**

1 Information and Methodology

1.1 Subjects We enrolled a total of 14 COVID-19-infected patients from a specific unit group in April 2022 for this study. Among these participants, there were 12 male patients and 2 female patients, ranging in age from 27 to 57 years. It is essential to clarify that this was not an intentional choice in the study design but rather a result of employing a randomized sampling method at the beginning of our research to ensure a representative sample of cases. Throughout the actual data collection process, we strictly adhered to the principles of random sampling without deliberate intervention or adjustment of the gender ratio of cases. We understand the reliability and generalizability of the study results depend on the representativeness of the sample; thus, we committed to maintaining randomness in both the design and execution of the study. Although the gender ratio in our study was not a pre-established target, we believe
that the use of random sampling methods contributes to minimizing potential biases and enhances the
generizability and comparability of the study results. The diagnosis of COVID-19 in these patients
adhered to the criteria outlined in the "Diagnostic and Treatment Program for Novel Coronavirus
Pneumonia (Trial Ninth Edition)." It is worth noting that these patients did not have any specific records or
events related to a history of infection-like illnesses. Consequently, our study focused on a relatively
healthy cohort of individuals.

1.2 Methods The patients received a prescribed course of medication following the instructions for
Molnupiravir and the guidance provided in the "Diagnostic and Treatment Program for Novel Coronavirus
Pneumonia (Trial Ninth Edition)." During the study, we conducted SARS-CoV-2 nucleic acid testing on the
infected patients, encompassing the detection of ORF1ab and N genes. We performed these tests using
PCR technology at two key stages: the initial stage of infection (before commencing treatment) and
during the treatment period (The completion of the first course of medication). We recorded the
corresponding Ct values during both stages. This approach was designed to provide a comprehensive
understanding of the virus's spread and the effectiveness of drug treatment in suppressing its
transmission.

1.3 Reagents and Instruments

1.3.1 Sample Collection: For sample collection, single-use virus sampling tubes containing guanidinium
salts were employed. Both nasal and pharyngeal areas were simultaneously sampled in this study.

1.3.2 Nucleic Acid Extraction Apparatus: The nucleic acid extraction apparatus used was the Xi'an
Tianlong Science and Technology Co., Ltd. Automatic Nucleic Acid Extractor (GeneRotex 96), bearing
Serial Number: TL39LH21100083.

1.3.3 Nucleic Acid Extractor Reagent: The reagent used for nucleic acid extraction was the Xi'an Tianlong
Science & Technology Co., Ltd. Nucleic Acid Extractor Kit. The Lot Number was 22020820T014H, and it
was valid until February 7, 2023.

1.3.4 Nucleic Acid Amplification Instrument: The nucleic acid amplification instrument employed was the
fully automated medical PCR analysis system (Gentier 96E), produced by Xi'an Tianlong Science and
Technology Company Limited. It had been granted the Serial Number: GuoMeZhuZi20173401384.

1.3.5 Nucleic Acid Amplification Reagent: The nucleic acid amplification reagent used was the New
Coronavirus 2019-nCoV Nucleic Acid Detection Kit (Fluorescence PCR Method), manufactured by
Shanghai Bojie Medical Technology Company. It had been granted the Serial Number: GuoMeZhiQuan
20203400065. The Batch Number was 20220122C, and the expiration date was October 21, 2022.

1.3.6 Procedure: Begin by retrieving the nucleic acid amplification reaction solution, enzyme mixture, and
ORF1ab/N reaction solution from the kit, allowing them to reach room temperature. Next, briefly
centrifuge them with full shaking and prepare the reaction system with a total volume of 20 μL. Take 200
μL of the sample and nucleic acid extraction reagent and employ the nucleic acid amplification
instrument for purification and nucleic acid extraction. Add 5 μL of the purified sample to the reaction system, and then briefly centrifuge them with tightly fitted caps. For each batch of experiments, include 3 negative controls and 1 positive control. Also, ensure that you add 3 negative controls and 1 positive control for every batch of experiments. Perform reverse transcription at 50°C for 10 minutes, pre-denaturation at 95°C for 5 minutes, denaturation at 95°C for 10 seconds, and annealing/extension/detection of fluorescence at 55°C for 40 seconds for a total of 45 cycles.

1.3.7 Methodology: In this study, real-time fluorescence PCR was employed, with specially designed primers for the ORF1ab and N genes of SARS-CoV-2, along with TaqMan probes. These were amplified using a fluorescence quantitative PCR instrument. We used the ROC curve method to determine the CT values for the ORF1ab and N genes. To ensure experiment accuracy, we incorporated endogenous ribonuclease P (RNase P) as an internal reference control. This was done to monitor the experiment throughout the process and prevent false-negative results resulting from misclassification.

1.3.8 Quality Control: Each batch of experiments must adhere to the requirements outlined in Table 1 for both negative and positive controls. Additionally, the Ct value of the RNase P assay for human samples should be less than 45, ensuring the quality of the experiment.

Table 1 Negative/positive control Ct value

<table>
<thead>
<tr>
<th>target of detection</th>
<th>negative control</th>
<th>positive control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORF1ab</td>
<td>No Ct value</td>
<td>Ct ≤ 30</td>
</tr>
<tr>
<td>N</td>
<td>No Ct value</td>
<td>Ct ≤ 30</td>
</tr>
<tr>
<td>internal reference (within the same publication)</td>
<td>—</td>
<td>Ct ≤ 30</td>
</tr>
</tbody>
</table>

The instructions for the new coronavirus nucleic acid test specify that any sample with a Ct (Cycle Threshold) value of 40 or lower is reported as a positive result. In this study, we considered samples with a Ct value of 41 as negative results and included them in our statistical analysis.

1.4 Statistical processing

Statistical analysis of the data was conducted using SPSS 26.0 software. Paired-sample t-tests were employed to compare the Ct values of the N gene and ORF1ab gene before treatment with those after treatment. The statistical results are provided in Table 2. The significance of the difference between the Ct values of the N gene and ORF1ab gene before and after treatment was determined based on the data analysis. A significance level of $p < 0.05$ was used to indicate that the observed differences were statistically significant.

Table 2 Case data statistics
<table>
<thead>
<tr>
<th>serial number</th>
<th>gender</th>
<th>age</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>ORF1ab</td>
</tr>
<tr>
<td>1</td>
<td>male</td>
<td>33</td>
<td>18.285</td>
<td>34.371</td>
</tr>
<tr>
<td>2</td>
<td>female</td>
<td>32</td>
<td>28.246</td>
<td>41.000</td>
</tr>
<tr>
<td>3</td>
<td>male</td>
<td>40</td>
<td>26.887</td>
<td>41.000</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>27</td>
<td>23.457</td>
<td>31.973</td>
</tr>
<tr>
<td>5</td>
<td>male</td>
<td>38</td>
<td>22.238</td>
<td>41.000</td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>32</td>
<td>28.629</td>
<td>37.543</td>
</tr>
<tr>
<td>7</td>
<td>Man</td>
<td>39</td>
<td>22.137</td>
<td>37.988</td>
</tr>
<tr>
<td>8</td>
<td>Man</td>
<td>48</td>
<td>37.098</td>
<td>41.000</td>
</tr>
<tr>
<td>9</td>
<td>Man</td>
<td>38</td>
<td>31.902</td>
<td>36.887</td>
</tr>
<tr>
<td>10</td>
<td>Man</td>
<td>42</td>
<td>26.410</td>
<td>34.316</td>
</tr>
<tr>
<td>11</td>
<td>male</td>
<td>45</td>
<td>20.801</td>
<td>41.000</td>
</tr>
<tr>
<td>12</td>
<td>male</td>
<td>45</td>
<td>18.348</td>
<td>41.000</td>
</tr>
<tr>
<td>13</td>
<td>male</td>
<td>57</td>
<td>14.980</td>
<td>25.234</td>
</tr>
<tr>
<td>14</td>
<td>male</td>
<td>50</td>
<td>19.035</td>
<td>41.000</td>
</tr>
</tbody>
</table>

**Results**

The statistical results presented in Table 3 reveal significant differences in the N gene ($t = -7.014, P < 0.001$) and ORF1ab gene ($t = -7.398, P < 0.001$). Moreover, the post-treatment values of the N gene and ORF1ab gene were notably higher than their respective pre-treatment values. This indicates that the combined treatment of Molnupiravir and Lianhua Qingwen was effective in the management of COVID-19.

**Table 3**  
Differential comparison of treatment effects before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>$t$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
<td>SD</td>
</tr>
<tr>
<td>N</td>
<td>24.175</td>
<td>6.044</td>
<td>37.138</td>
<td>4.614</td>
</tr>
<tr>
<td>ORF1ab</td>
<td>24.526</td>
<td>6.393</td>
<td>37.921</td>
<td>4.881</td>
</tr>
</tbody>
</table>
Discussion

Currently, the Omicron strain has replaced the Delta strain as the predominantly endemic strain. Although the Omicron strain is more transmissible than the Delta strain, its pathogenicity has diminished. In our study, we observed that many cases infected with the Omicron strain did not exhibit significant clinical symptoms. Patients only displayed mild to moderate respiratory and systemic symptoms and did not develop hypoxia, shortness of breath, or other complications necessitating hospitalization. In our clinical laboratory, we employ PCR to detect SARS-CoV-2 viral load. Studies, such as the work of E. Pujadas and others, have established a correlation between SARS-CoV-2 viral load and mortality\[^5\]. Our research primarily focused on patients in the early stages of the disease when the virus was actively replicating, and our findings indicated that outpatient antiviral therapy could effectively halt disease progression, reducing hospitalization and mortality rates\[^6\].

Molnupiravir, an oral antiviral drug developed by MDS in collaboration with Ridgeback, has demonstrated efficacy in treating patients with early-stage, mild cases of COVID-19\[^7\]. It recently completed Phase III clinical trials in late 2021 and was approved for use in late 2022. The UK was the first country to authorize the use of Molnupiravir\[^8\]. Some researchers, like F. Kabinger et al., have noted that Molnupiravir's mechanism of action includes increasing the frequency of viral RNA mutations and impairing SARS-CoV-2 replication in both animal models and humans\[^9\]. This aligns with our findings, as we observed a decline in Ct values of SARS-CoV-2 nucleic acid assay results after two courses of the drug, suggesting a reduction in viral load. Our findings supported the discontinuation of centralized isolation, as per the newly released "Diagnostic and Treatment Protocol for Novel Coronavirus Pneumonia (Trial 10th Edition)."

Lianhua Qingwen is an innovative and patented herbal medicine with potential efficacy in treating respiratory diseases\[^3\]. In COVID-19 treatment, Lianhua Qingwen has demonstrated favorable therapeutic effects with minimal adverse reactions\[^10\]. It was included in the "New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Ninth Edition)" issued by the National Health Commission in March 2022 as a therapeutic drug for patients with medically observed, mild, and common forms of the disease. Recent studies, such as those by Chen Chaowu\[^11\], Tan Duxun\[^12\], and Li Ya\[^13\], have confirmed its effectiveness in improving clinical symptoms and reducing inflammation in patients. Additionally, research by Liu M and others\[^14\] suggests that combining Chinese and Western medicine is more effective in treating COVID-19 without increasing adverse effects.

Molnupiravir, as a ribonucleoside analog, can inhibit the replication of the coronavirus. When combined with Lianhua Qingwen in our study, it effectively reduced viral load in patients, as evidenced by declining Ct values. However, as a drug that recently completed clinical phase III trials, its efficacy and potential side effects in treating COVID-19 require further scientific investigation. Scholars, such as R. Dal-Ré, emphasize the importance of assessing the safety and efficacy of antiviral medications against the Omicron variant\[^15\]. Furthermore, the active metabolite of Molnupiravir, β-d-n4-hydroxy cytidine, has been
reported to be cytotoxic and mutagenic in mammalian cells\textsuperscript{[9,16]}. The use of Molnupiravir has drawn significant attention, and more research is needed to comprehensively assess its efficacy and safety in combination therapy.

The potential of Molnupiravir has garnered considerable interest in the treatment of COVID-19. While some positive research outcomes have been achieved, additional in-depth scientific exploration is required to assess its efficacy and safety, especially in combination therapy. Our study supports the promising performance of Molnupiravir in the treatment of COVID-19 patients. It aligns with previous studies and provides valuable insights for reducing viral load and aiding patient recovery, as well as improving the drug's clinical application. Lianhua Qingwen, as an innovative traditional Chinese medicine, has also emerged as a promising tool in the fight against COVID-19. Its ability to improve symptoms and modulate the body's response underscores its potential for early treatment. The importance of combining Chinese and Western medicine is increasingly recognized by scholars, and our study offers a new perspective, particularly for early-stage infection. The combination of Molnupiravir and Lianhua Qingwen therapy presents potential clinical benefits and contributes significantly to epidemic control and patient well-being.

The ongoing spread of the COVID-19 pandemic compels the research community to continue exploring therapeutic approaches. This article emphasizes the use of Molnupiravir and Lianhua Qingwen in treating COVID-19, showcasing their potential to inhibit viral replication, alleviate symptoms, and reduce hospitalization rates. Our review of the literature and statistical analysis supports several conclusions. Molnupiravir, as a ribonucleoside analog, has the potential to inhibit COVID-19 replication. In combination with Lianhua Qingwen, we observed a decrease in viral load and a declining trend in laboratory nucleic acid test results. However, while we found positive results, further research is needed to fully understand the efficacy and safety of Molnupiravir, especially in combination therapy. Moreover, Lianhua Qingwen's potential in early treatment, with its ability to alleviate symptoms and regulate the body's response, is promising. Combining Chinese and Western medicine for improved therapeutic effects and reduced adverse reactions is gaining traction among scholars.

\textbf{Limitation of the Study}

Currently, research primarily focuses on the combination of Lianhua Qingwen and conventional Western medicine in the treatment of COVID-19, as well as the standalone use of Lianhua Qingwen for COVID-19 treatment. Up to now, we have not identified additional literature on the combined use of Molnupiravir and Lianhua Qingwen in the integrated Chinese and Western medicine treatment of COVID-19. It is undeniable that our study has a relatively small number of cases, but it is unique and innovative. We employed rigorous methodological approaches in both study design and implementation, including detailed data collection and analysis processes, as well as statistical methods, to ensure the reliability of our study results. Our research fills a knowledge gap in existing literature and provides novel insights and approaches to the combined use of Molnupiravir and Lianhua Qingwen in the integrated Chinese and
Western medicine treatment of COVID-19. It is important to emphasize that our study is preliminary and exploratory, limited to the mentioned treatment protocols. Its intent is to offer initial evidence and provide a foundation and direction for future larger-scale studies. We hope that this research will pave the way for new approaches to the treatment of COVID-19, offering valuable insights for clinical practice.

In conclusion, our study offers new insights into COVID-19 treatment, particularly in early infection stages. The combination of Molnupiravir and Lianhua Qingwen therapy presents potential clinical benefits and contributes significantly to epidemic control and patient well-being. However, it is important to emphasize that the efficacy and safety of these drugs should be supported and validated through further scientific studies to ensure their reliability in clinical practice. Multicenter clinical trials should be reinforced to explore the full potential of these drugs in the ever-evolving landscape of COVID-19 and to safeguard global public health.

Conclusion

In this study, we have substantiated the efficacy of Molnupiravir and Lianhua Qingwen in effectively curtailing the replication of SARS-CoV-2, thereby furnishing substantial and compelling evidence of their effectiveness.

Declarations

Ethics Approval and Consent to Participate

This study was conducted with the approval of The First People's Hospital of Yunnan Province, Affiliated Hospital of Kunming University of Science and Technology. All participants gave written informed consent. All research studies on humans (individuals, samples, data) have been performed in accordance with the principles stated in the Declaration of Helsinki.

Consent For Publication

Not applicable

Availability Of Data and Materials

The datasets generated during this study are available for release upon a substantiated request, and it is ensured that all patient-specific data has undergone de-identification to preserve confidentiality.

Competing Interests

The authors declare that they have no competing interests in this work.

Author Contributions
Min Tang is the co-first authors of this manuscript, and Tao Rui and Ning Xu are the corresponding author. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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**References**


