Title: A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus–A Possible Reference for Coronavirus Disease-19 Treatment Option.


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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jmv.25729.

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Author contributions: TT Yao and JD Qian wrote the article, include the concept of this article, definition of intellectual content and data acquisition; WY Zhu contributed for data acquisition; Y Wang and GQ Wang designed and reviewed the manuscript for its intellectual content.

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Funding: This work was supported by awards from the Scientific Research Seed Fund of Peking University First Hospital (#2018SF049 to JD Qian) and the National Natural Science Foundation of China (#81870417 to YW).

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Conflict of interest: The authors declare no conflict of interest.

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A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus–A Possible Reference for Coronavirus Disease-19 Treatment Option

Abstract

In the past few decades, coronaviruses have risen as a global threat to public health. Currently, the outbreak of coronavirus disease-19 (COVID-19) from Wuhan caused a worldwide panic. There are no specific antiviral therapies for COVID-19. However, there are agents that were used during the SARS and MERS epidemics. We could learn from SARS and MERS. Lopinavir (LPV) is an effective agent that inhibits the protease activity of coronavirus. In this review, we discuss the literature on the efficacy of LPV in vitro and in vivo, especially in
patients with SARS and MERS, so that we might clarify the potential for the use of LPV in patients with COVID-19.

**Keywords:** Lopinavir; Coronavirus; COVID-19; SARS; MERS.

**Introduction**

In recent years, novel coronavirus infections have emerged periodically in various countries around the world. Severe acute respiratory syndrome coronavirus (SARS-CoV) occurred in 2002, infecting 8,422 people and causing 916 deaths during the epidemic.[1] Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in 2012.[2] At the end of December 2019, a total of 2499 laboratory-confirmed cases of Middle East respiratory syndrome (MERS), including 861 associated deaths were reported globally.[3] At the end of 2019, novel coronavirus pneumonia (NCP) emerged in Wuhan and spread rapidly. The pathogen was confirmed new coronavirus, which was officially named COVID-19 by the world health organization (WHO). As of February 21, 2020, a total of 76,395 confirmed cases have been reported, and 2,348 patients are reported to have died. Currently, there is no specific antiviral treatment for COVID-19. Therefore, identifying drug treatment options as soon as possible is critical for the response to the COVID-19 outbreak.

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SARS-CoV, MERS-CoV and COVID-19 belong to the same genera of CoV and all are beta-CoV. COVID-19 shares 79.5% sequence identity with SARS-CoV.\(^4\) Therefore, the existing treatment LPV for SARS and MERS may be helpful for developing COVID-19 therapeutics.

Proteinase is a key enzyme in CoV polyprotein processing. In recent years, research on SARS-CoV and MERS-CoV protease inhibitors has been carried out in vitro and in vivo. Lopinavir (LPV) is a proteinase inhibitor. Both peak (9.6 \(\mu\)g/ml) and trough (5.5 \(\mu\)g/ml) serum concentrations of LPV inhibit SARS-CoV.\(^5\) LPV also blocks a post entry step in the MERS-CoV replication cycle.\(^6\) Ritonavir (RTV) inhibits the CYP3A-mediated metabolism of LPV, thereby increasing the serum concentration of LPV. Lopinavir /Ritonavir (LPV/r) is a combination of lopinavir and ribavirin. The antiviral activity of LPV/r is similar to that of LPV alone, suggesting that the effect is largely driven by LPV.\(^7,8\) In this review, we analyze the efficacy of LPV or LPV/r in patients with SARS-CoV and MERS-CoV, which may be useful as a reference for COVID-19 treatment option.

1. In vitro and animal studies

1.1 In vitro studies of SARS

An analysis of molecular dynamics simulations showed that the SARS-CoV 3CLpro enzyme could be inhibited by the combination lopinavir and ritonavir.\(^9\) A
binding analysis of the main SARS coronavirus proteinase with LPV showed that half of lopinavir is left outside the catalytic site, and the efficacy of lopinavir may be poor.[10] Another study showed that neither lopinavir nor ritonavir has an effect on the replication of SARS-CoV.[11]

However, studies have revealed that lopinavir has antiviral activity. The EC50 of LPV for the plaque reduction assay is 6 µg/ml in the Vero cell line. The selectivity index (SI) of LPV is 8 to 32.[12] In vitro activity against SARS–CoV has been demonstrated for lopinavir at 4 µg/ml after 48 h of incubation. Cytopathic inhibition has been achieved down to a concentration of lopinavir 1 µg/ml combined with ribavirin at 6.25 µg/ml and data suggested that this combination may be synergistic against SARS–CoV in vivo.[13]

1.2 Animal studies of SARS

There have been some animal studies of SARS,[14] however, no study of lopinavir or ritonavir has been performed.

1.3 In vitro studies of MERS

In an in vitro study, LPV inhibited MERS-CoV-induced cytopathic effect (CPE) with an EC50 of 8.0 µM (SI= 3.1), and a maximal protective effect (89% inhibition) was observed at a dose of 12 µM.[6] However, an in vitro study showed that LPV was not effective. LPV showed a suboptimal EC50 in the initial
cytopathic effect inhibition assay and was therefore not evaluated further.\cite{15}

Another in vivo study of MERS showed that EC50 values generated for lopinavir and ritonavir were 11.6 and 24.9 μM with CC50 values >50 μM, the SI for LPV and RTV was > 4.3 and > 2, respectively.\cite{7} Compared with RDV and IFNβ, LPV has inferior in vitro antiviral activity. RTV does not significantly enhance the antiviral activity of LPV in vitro.\cite{7}

1.4 Animal studies of MERS

For the MERS-CoV mouse model, prophylactic LPV/r combined with IFNβ slightly reduced the viral loads.\cite{7} However, therapeutic LPV/r and IFNβ improved pulmonary function, but failed to reduce viral replication and lung hemorrhaging. This in vivo evidence is suggestive of the potential for LPV/r to treat MERS-CoV infections. When LPV/r was combined with IFNβ, the antiviral activity (EC50 = 160 IU/ml) was indistinguishable from that of IFNβ alone (EC50 = 175 IU/ml, P = 0.62). This suggests that the observed in vitro antiviral activity of the LPV/r- IFNβ combination against MERS-CoV is dominated by IFNβ when LPV/r is used at clinically relevant concentrations.

Chan et al. explored the therapeutic potential of LPV/r and/or IFNβ in common marmosets.\cite{16} Animals treated with LPV/r alone or in combination with interferonβ1b had better clinical scores, less weight reduction and less pulmonary
infiltrate than untreated animals. Furthermore, necropsied lung and extrapulmonary tissues from the treated group had lower mean viral loads than those from the control group.

The in vitro studies and animal studies of SARS and MERS were summarized in Table 1.

2. Clinical studies

2.1 SARS

In a preliminary report, there were no deaths at 30 days after the onset of symptoms among 34 patients treated with LPV/r (400 mg ritonavir and 100 mg lopinavir) in combination with ribavirin initially, compared to 10% mortality in 690 patients taking only ribavirin. Twenty-one percent of 33 patients who received LPV/r as a rescue therapy died, whereas 42% of 77 patients who received ribavirin alone died. However, these results were given only as a presentation, and no formal paper was published. Thus, the evidence is not credible.

A retrospective matched cohort study including 1052 SARS patients (75 treated patients and 977 control patients) showed that the addition of LPV/r as an initial treatment was associated with a reduced death rate (2.3%) and intubation rate (0%) compared with that in a matched cohort who received standard treatment (11.0% and 15.6%, respectively, $P<0.05$). In addition, the rate and dose of
pulsed methylprednisolone were decreased. These SARS patients were retrospectively matched with control subject. Matching was performed with respect to age, sex, the presence of comorbidities, lactate dehydrogenase level, and the use of pulsed steroid therapy. However, the mortality, oxygen desaturation and intubation rates of the subgroup of patients who received lopinavir-ritonavir as rescue therapy were not different from those in the matched cohort and patients who received an increased dose of pulsed methylprednisolone. This result suggests that the combination of lopinavir and ribavirin has a synergistic effect for the treatment of SARS; it may play an essential role in the early phase of the infection. The viral replication phase peaks around day 10.\textsuperscript{19} LPV/r use within this replication window decreases the peak viral load and the subsequent immune response.

Another retrospective matched cohort study of SARS patient also revealed that the rate of acute respiratory distress syndrome (ARDS) or death was significantly lower in the LPV/r combination treatment group (1/41, 2.4%) than the historical controls (32/111, 28.8%) on day 21.\textsuperscript{13} In addition, the LPV/r group had a progressive decrease in the viral load, an early rise in the lymphocyte count, a reduction in the cumulative dose of pulsed methylprednisolone, and fewer episodes of nosocomial infections. These findings show that LPV/r, when...
combined with ribavirin, may be an effective agent against SARS. The summary of the effects of LPV in SARS patients is shown in Table 2.

2.2 MERS

A MERS patient who received LPV/r, ribavirin and interferon had a resolution of viremia after 2 days of treatment.\textsuperscript{[20]} However, the patient eventually died from septic shock 2 months and 19 days after the initial diagnosis. Another 64-year-old MERS patient from Korea was also treated with LPV/r, ribavirin and interferon. After 6 days of antiviral therapy, negative PCR result in the serum sample, sputum samples and swab samples were achieved.\textsuperscript{[21]} The patient was discharged on day 13 of admission after achieving complete recovery. These two simple cases may show that LPV is effective against MERS. However, they do not exclude the possibility of other combination therapies being effective or spontaneous improvement occurring. The treatment effect of LPV/r against MERS is still controversial.

A retrospective study enrolled healthcare workers (HCWs) with high-risk exposure to MERS-CoV pre-isolation pneumonia and revealed that an effective postexposure prophylaxis (PEP) strategy including LPV/r may limit the spread of infection.\textsuperscript{[22]} PEP therapy was associated with a 40% decrease in the risk of infection with no severe adverse events during treatment. PEP therapy was a
significant factor that reduced the risk of MERS-CoV infection in HCWs. This finding may indirectly reflect the antiviral effect of LPV/r. Moreover, a combination regimen of interferon + ribavirin + LPV/r was recommended officially for MERS therapy in Korea, where MERS began to spread in 2015.[23]

Without randomized controlled trials, determining treatment is difficult due to patient and treatment variability as well as a lack of appropriately matched controls. The combination of LPV/r and interferon was considered in a randomized control trial in Saudi Arabia.[24] Enrollment began in November 2016 and the results are not yet available. The summary of LPV research in MERS patients is shown in Table 3.

2.3 COVID-19

There are no reported in vitro studies of COVID-19. Four patients with COVID-19 were given antiviral treatment including LPV/r. After treatment, three patients showed significant improvement in pneumonia associated symptoms, two of whom were confirmed to be COVID-19 negative and discharged, and one of whom was negative for the virus at the first test.[25] This study shows the positive effects of LPV/r therapy. Two reviews, including a Chinese review and communication showed that LPV may be drug treatment option for COVID-19.[26,27] However, a retrospectively study enrolled 134 NCP (Novel coronavirus pneumonia) patients revealed that there is no significant difference...
between LPV/r treated group (n=52), Abidol treated group (n=34) and control
group (n=48) in improving symptom or in reducing viral loads. The negative
rate of COVID-19 nucleic acid on the 7 day was 71.8%, 82.6% and 77.1%,
respectively ($P=0.79$). The efficacy of LPV/r antiviral treatment warrants further
verification in future studies. Nine randomized controlled trials of LPV/r in
patients with COVID-19 have been registered in China up to February 22 (Table
4). Currently, the combination of LPV/r is a recommended antiviral regimen in the
latest version of the Diagnosis and Treatment of Pneumonia Caused by
COVID-19 issued by the National Health Commission of the People's Republic of
China.

**Discussion**

Currently, there are no FDA-approved treatments for any human CoV infection.
Upon the emergence of SARS-CoV and MERS-CoV, patients were administered
off-label antivirals. Most in vitro studies have shown that SARS-CoV could be
inhibited by LPV and that the EC50 of LPV is acceptable. Furthermore, two
retrospective matched cohort studies of SARS patients revealed that LPV/r plays
an essential role in the clinical outcome, especially in the early stage.
LPV/r-treatment alone or in combination with interferon had improved clinical
outcomes in experiments involving common marmosets and in some MERS

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patient. However, we need to wait for more clinically valid evidence to confirmed the positive value of LPV for COVID-19 treatment.

Although most of the data indicate the efficacy of LPV, adverse reactions should be kept in mind. Diarrhea, nausea and asthenia are the most frequently reported reactions in patients receiving LPV therapy. Elevated total bilirubin, triglyceride and hepatic enzyme levels have also been reported. A retrospective study of MERS showed that the most common symptoms and laboratory tests of LPV/r PEP were diarrhea (40.9%), nausea (40.9%), stomatitis (18.2%), fever (13.6%), anemia (45.0%), leukopenia (40.0%) and hyperbilirubinemia (100%). However, the symptoms and laboratory tests returned to normal after LPV therapy ceased.

The protease inhibitor LPV could be an effective treatment based on experience accumulated from the SARS and MERS outbreaks. The treatment of CoV patients with LPV/r improved their outcomes. LPV/r may be a potential treatment option for COVID-19. Additional studies are needed to gain further insights into the origin, tropism, and pathogenesis of COVID-19.

Conflict of interest: The authors declare no conflict of interest.

Author contribution: TT Yao and JD Qian wrote the article, include the concept of this article, definition of intellectual content and data acquisition; WY Zhu

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contributed for data acquisition; Y Wang and GQ Wang designed and reviewed the manuscript for its intellectual content.

Acknowledgments: This study was supported by the Scientific Research Seed Fund of Peking University First Hospital (#2018SF049 to JD Qian) and the National Natural Science Foundation of China (#81870417 to YW).

ORCID: Gui-Qiang Wang http://orcid.org/0000-0003-0515-7974

Reference


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15. Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, Li PT, Dai J, Mok FK, Chen H, Hayden FG, Yuen KY. Broad-spectrum antivirals for the


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Table 1. A summary of in vitro and animal studies of SARD and MERS.

<table>
<thead>
<tr>
<th></th>
<th>In vitro</th>
<th>Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SARS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r could inhibit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS-CoV 3CLpro enzyme</td>
<td>No study of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td></td>
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<tr>
<td><strong>MERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV inhibit MERS-CoV-induced CPE with an EC50 of 8.0 μM (SI= 3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic LPV/r combines with IFNβ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7)</td>
<td></td>
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</tr>
</tbody>
</table>

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| (10) | The efficacy of LPV to SARS coronavir us could be poor | (15) | LPV were not effective in the initial cytopathic effect inhibition assay | Therapeutic LPV/r and IFNβ Improves pulmonary function |
| (11) | Neither LPV nor RTV had an effect on the replication of SARS-CoV | (7) | The EC50 values generated for LPV were 11.6 μM (SI > 4.3). RTV does not significantly enhance the antiviral activity of LPV in vitro | (16) | LPV/r-treated alone or combination with interferonβ 1b Better clinical scores |
| (12) | The EC50 of LPV was 6 μg/ml (SI was 8 to 32) | | | Less weight reduction |
| (13) | There is activity against SARS-CoV with combination of | | | Less pulmonary infiltrate |
| | | | | Lower viral loads in lung |

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LPV 1
µg/ml and
RBV 6.25
µg/ml

Abbreviation: SARS-CoV, Severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; LPV, lopinavir; RTV, ritonavir; LPV/r, lopinavir/ ritonavir; RBV, ribavirin; INF, interferon; EC50, 50% effective inhibitory concentration; SI, selectivity index; CPE, cytopathic effect.

Table 2. A summary of the studies on the use of lopinavir therapy in SARS patients.

<table>
<thead>
<tr>
<th>Reference Type</th>
<th>Patients</th>
<th>Ribavirin</th>
<th>Corticosteroids</th>
<th>Lopinavir</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference Type</td>
<td>Patients</td>
<td>Ribavirin</td>
<td>Corticosteroids</td>
<td>Lopinavir</td>
<td>Outcome</td>
</tr>
<tr>
<td>Cohan et al., 2003</td>
<td>10 to 14 days (2.4 g oral loading dose, followed by 1.2 g orally every 8 hours, or 8 mg/kg intravenously every 8 hours)</td>
<td>21 days (starting dosage: hydrocortisone 100-200 mg every 6-8 hours, or methylprednisolone 3 mg/kg/day, depending on the severity).</td>
<td>10 to 14 days of lopinavir 400 mg/ritonavir 100 mg orally every 12 hours</td>
<td>Desaturation rate (SaO2 95%) [%]</td>
<td>Intubation rate (%)</td>
</tr>
<tr>
<td>Initial therapy (44)</td>
<td>68.2</td>
<td>0*</td>
<td>2.3</td>
<td>1.6*</td>
<td></td>
</tr>
<tr>
<td>Control (634)</td>
<td>84.5</td>
<td>11.0*</td>
<td>15.6*</td>
<td>3.0*</td>
<td></td>
</tr>
<tr>
<td>Rescue therapy</td>
<td>93.5</td>
<td>9.7</td>
<td>12.3</td>
<td>3.8*</td>
<td></td>
</tr>
<tr>
<td>Control (343)</td>
<td>92.1</td>
<td>18.1</td>
<td>14.0</td>
<td>3.0*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C hu et Re tro 5</th>
<th>14 days (4 g oral loading dose followed by 1.2 g orally every 8 hours, or 8 mg/kg intravenously every 8 hours)</th>
<th>21 days (starting dosage: hydrocortisone 100-200 mg every 6-8 hours, or methylprednisolone 3 mg/kg/day, depending on severity)</th>
<th>14 days of lopinavir 400 mg/ritonavir 100 mg orally every 12 hours</th>
<th>ARD S/death rate (%)</th>
<th>Viral load and lymphocyte count</th>
<th>No soci om al inf ec ti ons (%)</th>
<th>Mean pulsed methyl prednisolone dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical control group</td>
<td>28.8</td>
<td>/</td>
<td>25.2</td>
<td>2.0 g</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Indicates a significant difference, \( P<0.05 \).
Table 3. A summary of the studies on the use of lopinavir therapy in MERS patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Type</th>
<th>Patient Age</th>
<th>Ribavirin</th>
<th>Pegylated Interferon</th>
<th>Intubation</th>
<th>Lopinavir</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al., 2016</td>
<td>1 patient, 64M</td>
<td>7 days, 2 g loading dose followed by 1.2 g every 8 hours per day orally</td>
<td>Pegylated interferon 180 µg/0.5 ml, subcutaneously on day 4 of admission</td>
<td>7 days, LPV/r (400/100 mg twice daily), per oral</td>
<td>Fever was absent. PCR results of serum samples, sputum samples and swab samples were all negative 6 days after antiviral therapy. The patient was discharged on day 13 of admission after achieving complete recovery.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sempere et al., 2014</td>
<td>1 patient, 69M</td>
<td>Ribavirin (2000 mg p.o. loading dose, followed by 1200 mg p.o. every 8 hour for 8 days)</td>
<td>Pegylated interferon 180 g subcutaneously once per week for 12 days</td>
<td>10 days, LPV/r (400/100 mg twice daily), per oral</td>
<td>Viremia resolved after 2 days of treatment but ultimately died from septic shock.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Therapy was initiated between days 1 and 3 after the last unprotected exposure to a MERS patient. PEP therapy was associated with a 40% decrease in the risk of infection. There were no severe adverse events during PEP therapy.

Table 4. Clinical trials of LPV in patients with 2019-nCoV registered in China (up to February 22).

<table>
<thead>
<tr>
<th>Registration number</th>
<th>Registration date</th>
<th>Institution</th>
<th>Title</th>
<th>Enrolment date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi CT R20</td>
<td>1/23</td>
<td>Wuhan Infectious Diseases</td>
<td>A randomized, open-label, blank-controlled trial for the efficacy and safety of lopinavir-ritonavir and</td>
<td>2020/1/10</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Page</th>
<th>Hospital/Medical</th>
<th>Treatment/Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
<td>Hospital</td>
<td>interferon-alpha 2b in hospitalization patients with novel coronavirus pneumonia (COVID-19)</td>
</tr>
<tr>
<td>293</td>
<td>Sichuan People's Hospital, Sichuan Academy of Medical Sciences</td>
<td>A real-world study for lopinavir/ritonavir (LPV/r) and emtritabine (FTC) / Tenofovir alafenamide Fumarate tablets (TAF) regimen in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
</tr>
<tr>
<td>08</td>
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<tr>
<td>Chi 2020</td>
<td>Tongji Hospital, Huazhong University of Science and Technology</td>
<td>A randomized, open-label study to evaluate the efficacy and safety of Lopinavir-Ritonavir in patients with mild 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
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<td>CT /2/3</td>
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<td>000</td>
<td>University of Technology</td>
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<tr>
<td>295</td>
<td>Zhejiang University School of Medicine</td>
<td>A randomized, open-label, controlled trial for evaluating of the efficacy and safety of Darunavir/Cobicistat or Lopinavir/Ritonavir combined with thymosin al1 in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)</td>
</tr>
<tr>
<td>41</td>
<td></td>
<td></td>
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<tr>
<td>Chi 2020</td>
<td>The First Affiliated Hospital of Zhejiang Medical College</td>
<td>Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP) patients</td>
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<tr>
<td>CT /2/4</td>
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<tr>
<td>R20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>000</td>
<td>University of Zhejiang Medical College</td>
<td>A multicenter, randomized, open-label, positive-controlled trial for the efficacy and safety of recombinant cytokine gene-derived protein injection combined with abidole, lopinavir/litonavir in the</td>
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<tr>
<td>CI</td>
<td>Year</td>
<td>Affiliation</td>
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</tr>
<tr>
<td>73</td>
<td>2020</td>
<td>University</td>
</tr>
<tr>
<td>296</td>
<td>2020</td>
<td>Hospital</td>
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<tr>
<td>297</td>
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<td>Hospital</td>
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