 10.15789/2220-7619-AUR-15080

AN UMBRELLA REVIEW ON TREATMENTS AND THERAPEUTIC OPTIONS FOR COVID-19

SeyedAhmad SeyedAlinaghi[a],
Amir Masoud Afsahi[b],
Ayoob Molla[c],
Pegah Mirzapour[a],
Ramin Shahidi[c],
Haleh Siami[d],
Farid Farahani Rad[e],
Faeze Abbaspour[e],
Navid Mozafari[c],
Kamal Fakhredini[f],
Esmaeil Mehraeen[g,]
Omid Dadras[h]

[a] Iranian Research Center for HIV/AIDS (IRCHA), Tehran University of Medical Sciences (TUMS).
[b] University of California, San Diego (UCSD), California, USA.
[c] Bushehr University of Medical Sciences, Bushehr, Iran.
[d] Islamic Azad University, Tehran, Iran.
[e] Tehran University of Medical Sciences, Tehran, Iran.
[f] Behavioral Diseases Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran.
[g] Khalkhal University of Medical Sciences, Khalkhal, Iran.
[h] University of Bergen, Norway.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

ЗОНТИЧНЫЙ ОБЗОР ЛЕЧЕНИЯ И ТЕРАПЕВТИЧЕСКИХ ВАРИАНТОВ ПРИ COVID-19

СейедАхмад СейедАлинаги[1],

Амир Масуд Афсахи[2],

Аюб Молла[3],

Пега Мирзапур[1],

Рамин Шахиди[3],

Халех Сиами[4],

Фарид Фарахани Рад[5],

Фаэз Аббаспур[5],

Навид Мозафари[3],

Камаль Фахредини[6],

Исмаил Мехраин[7],

Омид Дадрас[8]

[1] Иранский исследовательский центр ВИЧ/СПИДа (IRCHA), Тегеранский университет медицинских наук (TUMS).

[2] Калифорнийский университет, Сан-Диего (UCSD), Калифорния, США.

[3] Университет медицинских наук Бушера, Бушер, Иран.

[4] Исламский университет Азад, Тегеран, Иран.

[5] Тегеранский университет медицинских наук, Тегеран, Иран.

[6] Центр исследования поведенческих заболеваний, Институт здравоохранения, Керманшахский университет медицинских наук, Керманшах, Иран.

[7] Халхалский университет медицинских наук, Халхал, Иран.

[8] Университет Бергена, Норвегия.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

Abstract

Introduction: As the COVID-19 pandemic continues to pose a significant challenge to global health, effective therapeutic options for preventing and treating the disease have become increasingly important. We aimed to provide an update on current treatments and therapeutic options for COVID-19 patients.

Methods: The purpose of this umbrella review is to explore the current treatments and therapeutic options for COVID-19 patients. Keywords and their combinations were searched across online databases in Embase, PubMed/MEDLINE, Web of Science, and Scopus spanning from July 1, 2020, through March 3, 2023. Publications were selected for data extraction in two steps based on the study inclusion/ exclusion criteria. The study adheres to the PRISMA checklist as well as NIH bias risk and quality assessment tool.

Results: In this review, 28 relevant articles were selected for the final qualitative synthesis. The majority of included studies had reported on the efficacy of Lopinavir/Ritonavir (n=4), Ivermectin (n=3), Baricitinib (n=2), Tocilizumab (n=2), Remdesivir (n=2), ACEI / ARB (n=2), Vitamin D (n=2), Molnupiravir (n=2), Traditional Chinese medicine (TCM) (n=2), Convalescent plasma transfusion (CPT) n=2) and hydroxychloroquine (n=2) in treating COVID-19. It appeared that Baricitinib, Remdesivir, ACEI/ARB, TCM, and CPT may have beneficial effects on reducing mortality, hospitalization duration, and disease severity in COVID-19 patients. Other interventions, such as Lopinavir/Ritonavir, Ivermectin, and Vitamin D, and Hydroxychloroquine did not show clear benefits or had inconclusive results.

Conclusion: This umbrella review provides a comprehensive overview of the current evidence on the effectiveness and safety of various pharmacological and non-pharmacological interventions for COVID-19. These results provide an updated overview of the current landscape for COVID-19 treatments, highlighting potential avenues for further research and clinical practice. It is crucial to continue monitoring emerging evidence and conducting rigorous studies to guide the development and optimization of therapeutic strategies against COVID-19.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

Keywords: COVID-19, SARS-CoV-2, Treatments, Therapeutic, Medicine, Umbrella review

Резюме

Введение: Поскольку пандемия COVID-19 продолжает представлять собой серьезную проблему для глобального здравоохранения, все более важными становятся эффективные терапевтические варианты профилактики и лечения этого заболевания. Мы стремились предоставить обновленную информацию о современных методах лечения для пациентов с COVID-19.

Методы: Целью данного обзора является изучение современных методов лечения и терапевтических возможностей для пациентов с COVID-19. Поиск ключевых слов и их комбинаций проводился в онлайн-базах данных Embase, PubMed/MEDLINE, Web of Science и Scopus с 1 июля 2020 г. по 3 марта 2023 г. Публикации отбирались для извлечения данных в два этапа на основе критериев включения / исключения. Исследование соответствует контрольному списку PRISMA, а также инструменту оценки риска и качества NIH.

Результаты: Для окончательного качественного синтеза в настоящем обзоре было отобрано 28 соответствующих статей. В большинстве включенных исследований сообщалось об эффективности лопинавира/ритонавира (n=4), ивермектина (n=3), барицитиниба (n=2), тоцилизумаба (n=2), ремдесивира (n=2), иАПФ/ БРА (n=2), витамин D (n=2), молнупиравир (n=2), традиционная китайская медицина (ТКМ) (n=2), переливание плазмы выздоравливающих (ППВ) n=2) и гидроксихлорохин (n=2)) при лечении COVID-19. Оказалось, что барицитиниб, ремдесивир, иАПФ/БРА, ТКМ и ППВ могут оказывать благотворное влияние на снижение смертности, продолжительности госпитализации и тяжести заболевания у пациентов с COVID-19. Другие вмешательства, такие как

 10.15789/2220-7619-AUR-15080

лопинавир/ритонавир, ивермектин, витамин D и гидроксихлорохин, не показали явных преимуществ или имели неубедительные результаты.

Заключение: Мы предоставили всесторонний обзор текущих данных об эффективности и безопасности различных фармакологических и нефармакологических вмешательств при COVID-19, акцентируясь потенциальных направлениях для дальнейших исследований и клинической практики. Крайне важно продолжать мониторинг новых данных и проводить тщательные исследования для разработки и оптимизации терапевтических стратегий против COVID-19.

Ключевые слова: COVID-19, SARS-CoV-2, лечение, терапия, медицина, зонтичный обзор.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

Introduction

The COVID-19 pandemic has posed a significant challenge to global health, with millions of cases and deaths reported worldwide, The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has become a global public health emergency (30,39). As the world continues to grapple with the pandemic, there has been a growing need for effective therapeutic options to prevent and treat COVID-19 (28, 35). Several potential therapeutic opportunities have emerged, including antiviral drugs, monoclonal antibody therapies, anti-inflammatory drugs, convalescent plasma therapy, and vaccines (7). In this context, ongoing research and development of treatments and prevention measures have become critical in managing the COVID-19 pandemic (12) and effective therapeutic options for preventing and treating the disease have become increasingly important (28, 24, 25).

The pandemic has highlighted the need to develop treatment guidelines based on current and reliable evidence, rather than relying solely on past experiences and theories. Although various potential therapeutic opportunities have emerged, including antiviral drugs, monoclonal antibody therapies, anti-inflammatory drugs, convalescent plasma therapy, and vaccines, it is essential to frequently review and revise these guidelines due to the rapid pace at which new evidence can emerge during a crisis (4). The rapidly changing nature of information during a crisis means that guidelines can quickly become outdated, and it is important to stay up-to-date on the latest developments in order to provide the best possible care. By continually revising guidelines, healthcare professionals can ensure that they are providing the most effective and evidence-based treatments to their patients (13, 17).

Against this background, It is crucial to emphasize the importance of ongoing research to fully understand the effectiveness and safety of COVID-19 treatment and prevention options. This review provides a brief overview of some of the potential options for COVID-19, highlighting benefits and the need for ongoing research to fully understand their effectiveness and the safety of current therapeutic options.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

1. Methods

This review investigated currently available treatments and therapeutic options for COVID-19 patients and elaborate on the implications and potential adverse effects. This study adheres to items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. **The risk of bias for included studies was assessed by the National Institute of Health (NIH) quality and bias risk assessment tool.**

2.1. Data sources

We performed a comprehensive search on the online database of Embase, PubMed/ MEDLINE, Web of Science, and Scopus. Combining the relevant keywords and search queries all the relevant articles published in the English language were browsed and retirieved from July 1st, 2020, to March 3rd, 2023. The comprehensive list of queries in different databases is provided in **Supplementary Material 1**. Here is an example of a search query in the PubMed/MEDLINE database,

(("COVID-19"[mesh] OR "SARS-CoV-2"[mesh] OR COVID-19[tiab] OR SARS-CoV-2[tiab] OR coronavirus disease 2019[tiab] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019 nCoV [tiab] OR SARS Coronavirus 2[tiab]) AND ("Therapeutics"[mesh] OR Therapeutic [tiab] OR Therapy [tiab] OR Therapies[tiab] OR Treatment[tiab] OR Medicine [tiab] OR Drug[tiab] OR Medication[tiab]) NOT (Vaccine[ti] OR Vaccination[ti]))

2.2. Study selection

To ensure the selection of the most appropriate studies, we employed two distinct selection steps. Initially, three research staff screened titles and abstracts of the retrieved articles. In the next step, three other researchers conducted a thorough full-text review of the initially selected articles. Pertinent publications that met the inclusion/ exclusion criteria were included for data extraction. The inclusion criteria were as follows: The study had to a systematic review, written in English, peer-reviewed prior to publication, and published in the allocated time period (July 1st

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

2020- March 3rd 2023). Studies were excluded if they were original articles, duplicated, non-human research models, ongoing experiments and/ or lacking published data, conference abstracts or abstracts without accessible full texts, preprint papers, editorial letters, case reports, or series.

2.3. Data extraction

Three researchers extracted the necessary data from the eligible articles. A preplanned spreadsheet was used to record the detailed information, which is presented in Table 2. Any potential duplicates were removed, and the accuracy of the extracted data was verified by other members of the research team.

2.4. Quality and bias risk evaluation

The quality and precision of the atudies and reported results were assured by adhering to the items outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Additionally, the National Institute of Health (NIH) quality and bias risk assessment tool was used to assess and minimize the potential risk of bias in the selected studies. Table 1 presents the results of the quality assessment. The questionnaire at the bottom of the table was used by two researchers to rate the included studies.

2. Results

In this review, we identified a total of 4,717 relevant sources. After an initial check, 805 duplicate articles were excluded, and the remaining 3,912 articles were screened based on the relevancy of titles and abstracts through which 3,561 resources were excluded. From the remaining 351 articles, 323 were excluded as they have not met the eligibility criteria. These excluded studies were non-English studies (n=32), enduring studies (n=53), systematic review protocols (n=24), non-human studies (n=85), studies unrelated to treatment and

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

medicine (n=113), and non-full-text studies (n=16). Ultimately, 28 articles most relevant to the study objective were selected for the final review.

Figure 1 -PRISMA 2020 flow diagram of study retrieval process

3.1 Available Treatment for COVID-19

A total of 28 potential treatment regimens were identified for COVID-19 as shown in **Table 2**. The majority of included studies reported on the efficacy of Lopinavir/Ritonavir (n=4), Ivermectin (n=3), Baricitinib (n=2), Tocilizumab (n=2), Remdesivir (n=2), ACEI / ARB (n=2), Vitamin D (n=2), Molnupiravir (n=2), Traditional Chinese medicine (TCM) (n=2), Convalescent plasma transfusion (CPT) n=2) and hydroxychloroquine (n=2) in treating COVID-19.

Despite many studies on *Lopinavir/Ritonavir*, which have shown no specific adverse effects, current research still lacks strong evidence regarding its antiviral effects against COVID-19. *Ivermectin* shows potential effectiveness in mild-moderate COVID-19 patients. However, further studies are needed. One study indicated that in the absence of antiviral treatments, cautious administration of Ivermectin can be considered. Studies showed that *Baricitinib* (which is a type of JAK inhibitor) along with Sarilumab, served as a good alternative for COVID-19 treatment and it can lead to a reduction in mortality rate among hospitalized patients with moderate-severe COVID-19. It appeared that *Molnupiravir*, which is a prodrug for Hydroxycitidine, could reduce the hospitalization and mortality rates in high-risk COVID-19 patients. Some studies have demonstrated the potential of *Chinese traditional and herbal medicine* as an alternative for the prevention, treatment, and rehabilitation of COVID-19 patients. Furthermore, recent studies have indicated that certain drugs can be beneficial in specific subgroups of COVID-19 patients. For instance, *ACE/ARB* has shown potential effectiveness in reducing ICU admission

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

and mortality rate among individuals with hypertension who were previously using ACE/ARB. Additionally, *Convalescent Plasma Therapy (CPT)* has demonstrated effectiveness in patients with hematological malignancies, while *Remdesivir* has shown positive outcomes in non-ventilated hospitalized patients. *Nirmatrelvir/Ritonavir*, sold under the name *Paxlovid*, a combination of the SARS-CoV-2 protease inhibitor nirmatrelvir, and ritonavir, a CYP3A4 inhibitor, is one of the best therapeutic choices for high-risk patients in reducing all-cause mortality and hospital admission. In people without prior or concomitant therapies low- to moderate-certainty evidence revealed that nirmatrelvir/ritonavir can be safe.

Table 1. Quality/Bias risk ratings of the included studies according to the NIH quality assessment tool

NIH = National Institutes of Health; CD = cannot determine; NR = not reported; NA = not applicable

*The NIH Quality Assessment Tool for Systematic reviews and Meta-Analysis (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) contains 8 questions: 1 = Is the review based on a focused question?, 2=Were eligibility criteria for included and excluded studies predefined and specified?, 3 = Did the literature search strategy use a comprehensive, systematic approach?, 4 = Were titles, abstracts and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?, 5 = Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?, 6 = Were the included studies listed along with important characteristics and results of each study?, 7 = Was publication bias assessed?, 8 = Was heterogeneity assessed

Table 2. Description of the findings reported in the eligible studies

Discussion

The main objective of this umbrella review was to evaluate and summarize the existing evidence on the potential treatments and therapeutic options for COVID-

 10.15789/2220-7619-AUR-15080

19 patients. The review provides a comprehensive overview of the current knowledge in this field. A total of 28 systematic reviews and meta-analyses were included in this review and encompassed a wide range of treatment modalities, including antiviral drugs, immunomodulators, JAK inhibitors, Convalescent plasma transfusion (CPT), Traditional Medicine and Supplementary medicine. The most frequently used therapies in selected studies were Lopinavir/Ritonavir (n=4), Ivermectin (n=3), Baricitinib (n=2), Tocilizumab (n=2), Remdesivir (n=2), ACEI / ARB (n=2), Vitamin D (n=2), Molnupiravir (n=2), Traditional Chinese medicine (TCM) (n=2), Convalescent plasma transfusion (CPT) (n=2) and hydroxychloroquine (n=2).

Lopinavir/Ritonavir is a combination of protease inhibitors that has been used to treat HIV infection and was also effective against SARS-CoV and MERS-CoV in vitro and in animal models (36). Some previous studies reported that there is no significant difference between Lopinavir/Ritonavir and standard care in terms of mortality, viral clearance, or adverse events (19). In our review, Lopinavir/Ritonavir did not show clear benefits in terms of hospitalization duration and time to negative PCR in mild diseases (27, 29, 32).

Ivermectin is an antiparasitic agent that inhibits the replication of viruses in vitro. The molecular hypothesis of Ivermectin's antiviral mode of action suggests an inhibitory effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in the early stages of infection (33). One of three studies that evaluated Ivermectin, indicated that it has potential effectiveness in treating mild to moderately ill patients. However, its role as an antiviral drug against COVID-19 in clinical setting is not clear yet as the other two studies were inconclusive (27, 33, 47).

Baricitinib is a Janus kinase (JAK1/JAK2) inhibitor developed to treat patients suffering from rheumatoid arthritis. JAK-STAT signaling is critical to multiple cellular processes, including survival, differentiation, and proliferation (45). The conclusion of two studies that examined Baricitinib was in line, as they concluded Baricitinib is an alternative to Tocilizumab -Which is a recombinant humanized anti-IL-6 receptor monoclonal antibody that has been approved for use

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

in patients with rheumatologic disorders and chimeric antigen receptor T cell-induced cytokine release syndrome (46) for reducing mortality in COVID-19 patients admitted to the hospital and undergoing corticosteroid treatment. Systemic JAK inhibitors reduce all-cause mortality in hospitalized individuals with moderate-severe COVID-19 (1, 15).

Remdesivir is a nucleotide analog that inhibits viral RNA polymerase and has broad-spectrum antiviral activity against several RNA viruses, including SARS-CoV-2 (3). Studies have shown that in non-ventilated hospitalized patients with COVID-19 who did not require ventilation, Remdesivir can decrease mortality. It is important to note that Remdesivir is associated with specific adverse effects, such as significant bradycardia, so rigorous attention is needed during the administration of this drug in COVID-19 patients (2, 27).

The *ACEI / ARB* drug class was analyzed in two studies included in this review. The findings of these studies were consistent. The first study examined the use of ACE/ARB among COVID-19 patients of East Asian descent and found no adverse outcomes. Additionally, ACEI/ARB use was associated with shorter hospitalization and reduced mortality rates. The beneficial effects of ACEI/ARB were more pronounced in individuals with hypertension, and the reduction in hospitalization was greater in females compared to males. In the second study, it was concluded that prior ACEI/ARB treatment was linked to lower hospital mortality, ICU admission, and the need for Intermittent Mandatory Ventilation (IMV) in COVID-19 patients (14, 20).

Two studies investigating the effects of *vitamin D* supplementation, with one study combining it with vitamin C, were included in this review. Vitamin D plays a role in modulating the innate immune response, while vitamin C possesses antioxidant, anti-inflammatory, antithrombotic, and immunomodulatory functions. Administration of vitamins C and D to COVID-19 patients did not demonstrate any influence on disease susceptibility, severity, or progression. Importantly, no adverse events were observed in the trials, indicating the safety of vitamin D supplements at the examined doses (26, 44).

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

Molnupiravir is an antiviral drug similar to Remdesivir, targeting the RNA-dependent RNA polymerase (RdRp) enzyme utilized by the coronavirus for transcription and replication of its viral RNA genome (43). Two reviews encompassing a total of 7 randomized controlled trials (RCTs) provide evidence that Molnupiravir shows promise as a valuable agent, significantly reducing the risk of hospitalization or death in high-risk/mild COVID-19 patients. Additionally, it may benefit non-pregnant, unvaccinated adults with COVID-19 who face an elevated risk of severity and hospitalization. Another advantageous feature of Molnupiravir is its cost-effectiveness. The drug has demonstrated good tolerance and safety with no significant adverse events reported in short-term use at doses ranging from 50-800 mg BID or a single dose up to 1600 mg (23, 42, 43).

Traditional Chinese Medicine (TCM) is a holistic approach that uses herbal formulas, acupuncture, moxibustion, and other modalities to treat various diseases based on the principles of yin-yang balance, qi circulation, and organ function. TCM has been widely used in China to prevent and treat COVID-19 patients with different disease stages and syndromes. Two comprehensive reviews, comprising a total of 76 randomized controlled trials (RCTs) and 101 reviews, have reached a consensus that TCM shows promise as an alternative approach for treatment, rehabilitation, and prevention. Furthermore, when used alone or in conjunction with conventional medicine, TCM has demonstrated benefits in alleviating symptoms among patients with acute respiratory infections. Notably, one intervention that emerged as commonly utilized was Xuebijing (XBJ) injection (18, 21).

Convalescent plasma therapy (CPT) involves the use of plasma collected from individuals who have recovered from COVID-19. This plasma contains neutralizing antibodies against the SARS-CoV-2 virus. CPT has been utilized as a passive immunotherapy for COVID-19 patients, aiming to transfer immunity from donors to recipients (10). One study has demonstrated that CPT can serve as an effective supportive therapy for COVID-19 patients with hematological malignancies. The findings indicate that CPT may lead to improved clinical outcomes, including higher survival rates, enhanced clearance of SARS-CoV-2, presence of anti-SARS-CoV-2

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

antibodies, shorter hospital discharge time, and better recovery after one month of CPT. Importantly, the treatment did not show any association with adverse events. (31, 41). Data on the effectiveness of *Hydroxychloroquine* as an antimalarial used for treating COVID-19 patients were inconclusive (27, 31). While there has been an umbrella study on the effects of Hydroxychloroquine and chloroquine therapy in COVID-19 (5), no umbrella review has compared different classes of therapeutic options.

In addition to the above-mentioned treatments, this umbrella review discussed other therapeutic options for COVID-19 patients. These include Thymosin alpha1 (Ta1), anticoagulants, other antivirals (such as Nirmatrelvir, Saquinavir, Favipiravir), Ultra-violet radiation therapy, Colchicine, Arbidol, N-acetyl cysteine (NAC), Ayurvedic medicines, JAK inhibitors (such as Tofacitinib, Ruxolitinib, Sarilumab), SSRI (Fluvoxamine), Clozapine, Quercetin and Anakinra (immunomodulator). Among these treatment options, Ayurvedic medicines, JAK inhibitors (such as Tofacitinib, Ruxolitinib, Sarilumab), SSRI (Fluvoxamine), colchicine, and Quercetin have shown to be beneficial in treating COVID-19 (6, 9, 15, 22, 38). On the other hand, NAC, anticoagulants, Clozapine, and Anakinra were non-beneficial (8, 11, 16, 34). In the case of Thymosin alpha1 (Ta1), the findings suggest that Ta1 therapy does not have a statistically significant impact on mortality. However, subgroup analyses indicated a beneficial effect on mortality in patients over 60 years of age, with a proportion of females less than 40%, and with severe COVID-19 (40).

The main limitations of this systematic review are the heterogeneity of the included studies in terms of design, population, intervention, comparator, outcome, and quality; the lack of meta-analysis due to the scarcity and diversity of data; and the possibility of publication bias due to the rapid emergence and dissemination of COVID-19 literature. Therefore, the results of this review should be interpreted with caution and updated regularly. Despite the extensive research conducted on treatments for COVID-19, there are still gaps and areas of uncertainty in the existing evidence. For example, there is limited evidence on the effectiveness of certain

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

antiviral drugs or immunomodulatory therapies. Additionally, the long-term effects of these treatments and their impact on specific patient populations, such as pregnant women or individuals with comorbidities, require further investigation. Therefore, more high-quality RCTs are needed to evaluate the efficacy and safety of these treatments and to identify the optimal dose, duration, timing, and combination of interventions for different subgroups of COVID-19 patients.

Conclusion

In conclusion, this umbrella review offers a comprehensive overview of the current evidence on the effectiveness and safety of various pharmacological and non-pharmacological interventions for COVID-19. Based on the included studies, we found that some interventions, such as Baricitinib, Remdesivir, ACEI/ARB, TCM, and CPT may have beneficial effects on reducing mortality, hospitalization duration, and disease severity in COVID-19 patients. However, the results should be interpreted with caution due to the heterogeneity and potential bias of the studies. Other interventions, such as Lopinavir/Ritonavir, Ivermectin, Vitamin D, and Hydroxychloroquine did not demonstrate clear benefits or provided inconclusive results. Therefore, additional high-quality randomized controlled trials are needed to confirm the efficacy and safety of these interventions, while also investigating optimal dosage, duration, and timing. Furthermore, future research should also consider the potential interactions, adverse events, and cost-effectiveness of the interventions, as well as the individual characteristics and preferences of the patients. The results of this study can be useful for clinicians and physicians who need evidence to choose the best treatment in a critical situation such as COVID-19.

Declarations

-*Ethics approval and consent to participate:* Not applicable

-*Consent to publication:* Not applicable

- *Availability of data and material:* The authors stated that all information provided in this article could be shared.

- *Competing interests:* The authors declare that there is no conflict of interest regarding the publication of this manuscript.

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

- *Funding:* This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

- *Authors' contributions:*

(1) The conception and design of the study: *Esmaeil Mehraeen, SeyedAhmad SeyedAlinaghi*

(2) Acquisition of data: *Ramin Shahidi, Ayoob Molla, Amir Masoud Afsahi*

(3) Analysis and interpretation of *data: Amir Masoud Afsahi*

(4) Drafting the article: *Esmaeil Mehraeen, Pegah Mirzapour, Haleh Siami, Farid Farahani Rad, Faeze Abbaspour Navid Mozafari, Kamal Fakhredini*

(5) Revising it critically for important intellectual content: *SeyedAhmad SeyedAlinaghi, Esmaeil Mehraeen*

(6) Final approval of the version to be submitted: *SeyedAhmad SeyedAlinaghi, Esmaeil Mehraeen*

- *Acknowledgments:* The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, and the University of Sydney.

 10.15789/2220-7619-AUR-15080

ТАБЛИЦЫ

Table 1. Quality/Bias risk ratings of the included studies according to the NIH quality assessment tool

Reference	Questions								Rating by reviewers	
	1	2	3	4	5	6	7	8	#1	#2
(1)	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Good	Good
(2)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Good
(6)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(8)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Good
(9)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(11)	Yes	Yes	Yes	NR	Yes	Yes	Yes	NA	Fair	Good
(14)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	Good
(15)	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Good	Fair
(16)	Yes	Yes	Yes	Yes	No	Yes	No	NA	Fair	Fair
(18)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(20)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(21)	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Fair	Good
(22)	Yes	Yes	Yes	No	No	Yes	No	NA	Fair	Fair
(23)	Yes	Yes	Yes	Yes	NR	Yes	No	NA	Good	Good
(26)	Yes	Yes	Yes	NR	Yes	Yes	No	NA	Fair	Fair
(27)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Good	Good
(29)	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Good	Good
(31)	Yes	Yes	Yes	Yes	No	Yes	No	NA	Fair	Good
(32)	Yes	Yes	Yes	Yes	No	Yes	NR	No	Fair	Fair
(34)	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	Fair	Fair
(33)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(37)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Fair
(38)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(40)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Fair
(41)	Yes	Yes	Yes	Yes	Yes	Yes	NR	No	Fair	Fair
(42)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Good
(44)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Fair
(47)	Yes	Yes	Yes	Yes	Yes	Yes	No	NA	Good	Fair

NIH = National Institutes of Health; CD = cannot determine; NR = not reported; NA = not applicable

*The NIH Quality Assessment Tool for Systematic reviews and Meta-Analysis (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) contains 8 questions: 1 = Is the review based on a focused question?, 2=Were eligibility criteria for included and excluded studies predefined and specified?, 3 = Did the literature search strategy use a comprehensive, systematic approach?, 4 = Were titles, abstracts and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?, 5 = Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?, 6 = Were the included studies listed along with important characteristics and results of each study?, 7 = Was publication bias assessed?, 8 = Was heterogeneity assessed?

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

Table 2. Description of the findings reported in the eligible studies

Reference	Country	Method (search date and searched databases)	Number of review studies	Current treatment/medicine	Therapeutic dose	Clinical considerations	Main findings
(1)	Brazil	Pubmed/ EMBASE/Cochrane library/MedRxiv October 7, 2020 – April 30, 2022	27 RCT	Baricitinib Sarilumab Tocilizumab	Not reported	Baricitinib has not been studied in severe renal failure and cannot be given in pregnancy	Baricitinib and Sarilumab are alternatives to Tocilizumab for reducing mortality in COVID-19 patients admitted to the hospital and undergoing corticosteroid treatment.
(2)	Switzerland	Pubmed/ EMBASE/Cochrane COVID-19 trial registry/ Clinical trial. gov/ International Clinical Trial Registry Platform/ preprint servers January 1, 2020 – April 11, 2022	9 RCT	Remdesivir	Not reported	Remdesivir has specific side effects (eg, severe bradycardia),	In non-ventilated hospitalized patients with COVID19 who did not require ventilation, Remdesivir demonstrated a decrease in mortality.
(6)	Pakistan	Pubmed/ The Cochrane Library / EMBASE Inception – October 5, 2022	6 RCT	Quercetin	Safe up to 500mg per day	Quercetin is a cheap and easily accessible therapeutic option for COVID-19 patient	The administration of Quercetin, especially in its phytosome formulation can provide benefits for COVID 19 patients by improving its bioavailability.
(8)	Germany	Medline/ EMBASE/Clinicaltrial.org/MedRxiv/WHO International Clinical Trial Registry Platform/CCSR Inception- December 13, 2021	5 RCT	Anakinra	Not reported	Anakinra might be beneficial in hospitalized patients with COVID-19 with low-flow/high-flow oxygen therapy and suPAR>6 ng/ml	When compared to placebo or standard care alone, Anakinra does not exhibit any impact on mortality, clinical improvement, worsening or safety outcomes in adult hospitalized patients with COVID 19
(9)	Canada	Medline/EMBASE/Pubmed/Web of science/CENTRAL/CINAHL/International pharmaceutial abstracts January 1, 2020- December 17, 2022	6 RCT 3Cohort study 1Case-Control 1Non-randomized clinical trial	SSRI(Fluvoxamine)	50-100mg Bid	100mg bid is more effective than 50mg bid	Fluvoxamine is a potential therapy in COVID19 out-patients with medium doses showing more favorable results in comparison with low doses.
(11)	Australia	Medline/EMBASE/Pubmed/PsycINFO November 2021- July7, 2022	8 Retrospective cohort 2 Prospective cohort 3 Cross-sectional study 1 Case-Control 1 Case-Series 3 Retrospective chart review	Clozapine	Not reported	There was a reduction in neutrophil level in Covid19 positive clozapine users	There is no evidence suggesting that the immune system of Clozapine users put them at risk of COVID 19. It is still crucial to closely monitor these patients.
(14)	China	Pubmed/Embase/Cochrane Library January 2000- May 2022	26 Retrospective cohort 2 Prospective cohort	ACEI / ARB	Not reported	The effect of ACEI/ARB is more obvious in HTN population. The reduction of hospitalization in female is more than male	Use of ACE/ARB among EAST-Asian COVID 19 patients did not show any adverse outcomes and was associated with shorter hospitalization and reduced mortality rates

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

(15)	Germany	Medline/ EMBASE/ClinicalTrials.gov/ WHO International Clinical Trials Registry Platform/medRxiv/ Cochrane Central Register of controlled trials/VA ESP/WHO Covid-19Global Literature Inception- February 2022	6 RCT	Janus Kinase Inhibitors: Baricitinib Tofacitinib Ruxolitinib	Not reported	There is no evidence on the efficacy and safety of systemic JAK inhibitors for non-hospitalized individuals	Systemic JAK inhibitors reduce all-cause mortality in hospitalized individuals with moderate-severe COVID 19.
(16)	Indonesia	Pubmed/Science direct Inception – October 4, 2021	6 RCT	Anticoagulants in prophylactic vs. intermediat/therapeutic doses	Not reported	The incidence of bleeding at the intermediate/therapeutic doses compared to the prophylactic dose	There was no significant differences in thromboembolic events or all-cause mortality
(18)	China	Campbell Library/ Cochrane Library/ EMBASE/ PubMed/ Web of Science/ CBM/ CNKI/ CQVIP/ WanFang Data Inception – March 23, 2022	76 RCT 50 Systematic Review	TCMs (Tradional chinese medicine)	Not reported	XBJ as a TCM was the most common intervention	In terms of treatment, rehabilitation and prevention TCM is a promising alternative.
(20)	China	PubMed/ the Cochrane Library/ Ovid/ Embase December 1, 2019-April 30, 2022	4 RCT 5 Retrospective cohort 1 Prospective cohort 1 Non-experimental comparative study	ACEI/ARB	Not reported	The effects of continuing ACE/ARB treatment may have been influenced by factors such as male sex and the presence of D.M	Previous ACEI/ARB treatment was associated with lower hospital mortality, ICU admission, and IMV in patients with COVID-19
(21)	China	CBM/ CNKI/ Wanfang/ PubMed/ Cochrane Library/ EMBASE /preprint platforms Date of database creation- March 31, 2021	51 Systematic Reviews	CHM (Chinese Herbal Medicine)	Not reported	clinical evidence of the benefits of CHM for acute respiratory infections such as COVID-19, SARS, and H1N1 seems more sufficient than other acute infections	Chinese herbal medicine, used alone or in combination with conventional medicine has benefits in relieving symptoms of patients with acute respiratory infections.
(22)	India	LitCOVID/ Google Scholar/ Science Direct/ EBSCO/ Scopus / Web of Science/ EMBASE Search date not reported	11 RCTs 4 Case reports 1 Case-series 4 Retrospective cohort 3 Non-randomized clinical trial 2 Pilot and prosspective comparative studies	Ayurvedic medicines and formulations: Ayush-64 Guduchi Ghana vati Chyawanprash	Not reported 500mg BD 500mg BD 12-24gr BD	Ayurvedic medicines have antiviral, antioxidant, anti-inflammatory, and immunomodulatory properties	Ayurvedic medicines can be combined with standard treatments to aid in early virus detection, accelerate recovery from COVID-19, expedite hospital discharge, and prevent further deterioration.
(23)	India	PubMed/ MedRxiv/ BioRxiv/ FDA/ ClinicalTrials. Gov/ ctri.nic.in / Google Scholar January 2021- March 2022	6 RCT : 4 Published 2 Unpublished	Molnupiravir	50-800 mg Bid Or Single dose Up to 1600mg	The drug is well tolerated and safe with no significant adverse events on short-term use	Clinical studies provide evidence that Molnupiravir significantly reduces the risk of hospitalization or death in high-risk mild COVID-19 patients

 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

 10.15789/2220-7619-AUR-15080

(26)	Germany	Pubmed/ Embase/ Scopus / Google Scholar No time constrain	9 RCTs 9 Retrospective cohorts 2 Prospective cohorts 2 Cross-sectional study 1 Case-control	Vitamin C and D Supplementation	Not reported	Vitamin D modulates the innate immune response Vitamin C has antioxidant, anti-inflammatory, antithrombotic, and immunomodulatory functions.	Administration of vitamins C and D in COVID-19 patients doesn't impact disease susceptibility, severity, and progression.
(27)	Iran	PubMed/ Scopus/ Web of Sciences Inception- January1, 2022	46 Reviews	Main intervention: Favipiravir Remdesivir Hydroxychloroq ine Ivermectin Lopinavir/Ritonavir Tocilizumab	Not reported	Not reported	The main limitations observed in the included studies were heterogeneity, sample size, follow-up, treatment variations, study design, definitions, synthesis, quality, and search methodology
(29)	Iran	PubMed/ Scopus/ Web of Sciences/Embase December 2019-March 2021	266 in Silico 34 in Vitro 15 in Vivo	Main intervention: Saquinavir Ritonavir Lopinavir Herbal medicine	Not reported	Discovering drugs that have multitarget antiviral and anti-inflammatory actions is crucial due to the nature of COVID19-Certain herbal medicine exhibit this potential.	For antiviral development, the main focus has been on targeting the protease and spike glycoprotein.
(31)	Greece	Pubmed/Medline and Embase September 2022	3 RCTs 4 Retrospective cohorts 1 Prospective cohort	N-acetyl cysteine (NAC)	The studies by Mousapour, Taher, and de Alencar used 1 g/12 h, 40 mg/kg/day, and 21 g (divided into two doses) respectively	Due to the limited certainty of evidence presented in the studies, it is not possible to provide recommendations for clinical practices.	In RCTs, the point estimates for hard clinical outcomes tend to be near the null effect line (lack of significant impact). Observational studies show heterogeneity, with certain studies suggesting positive outcomes.
(32)	India	Google Scholar January 2020 to May 2020	49 Studies	Hydroxychloroquine, Lopinavir and Ritonavir, Ultra-violet radiation therapy, Convalescent plasma transfusion (CPT) therapy.	Not reported	New drugs are in the premature stage of this pandemic. Further research is needed to fully understand the life cycle of n.COV and expedite the development of drugs and vaccines.	ICMR and NIH provide guidelines for Hydroxychloroquine and other antiviral drugs. Ongoing research includes natural products, herbs, combination therapy, UV radiation, MD simulations for vaccine development, and CPT.
(34)	USA	Google Scholar and PubMed and medRxiv Search date not reported	3 Cohort 1 Case-control 1RCT 2 Comparative studies	Arbidol, Lopinavir/Ritonavir	Not reported	Adverse reactions were rarely reported including ECG changes, GI symptoms, bacterial infections, and hepatic and renal dysfunction.	Antiviral regimens did not show clear benefits in terms of hospitalization duration and time to negative PCR in mild diseases.
(33)	Germany	Cochrane COVID-19 Study Register, Scopus, and WHO COVID-19 Global literature on coronavirus disease database Inception- July 2022	1 RCT 8 Ongoing studies	Nirmatrelvir combined with Ritonavir	Not reported	Ritonavir's role as a CYP3A4 inhibitor, makes Nirmatrelvir/Ritonavir prone to drug interactions, especially in patients with comorbidities.	Low certainty evidence suggests that Nirmatrelvir /Ritonavir reduces the risk of all-cause mortality, and hospital admission/death in high-risk, unvaccinated COVID-19 patients with symptom onset within 5 days. Low –moderate certainty

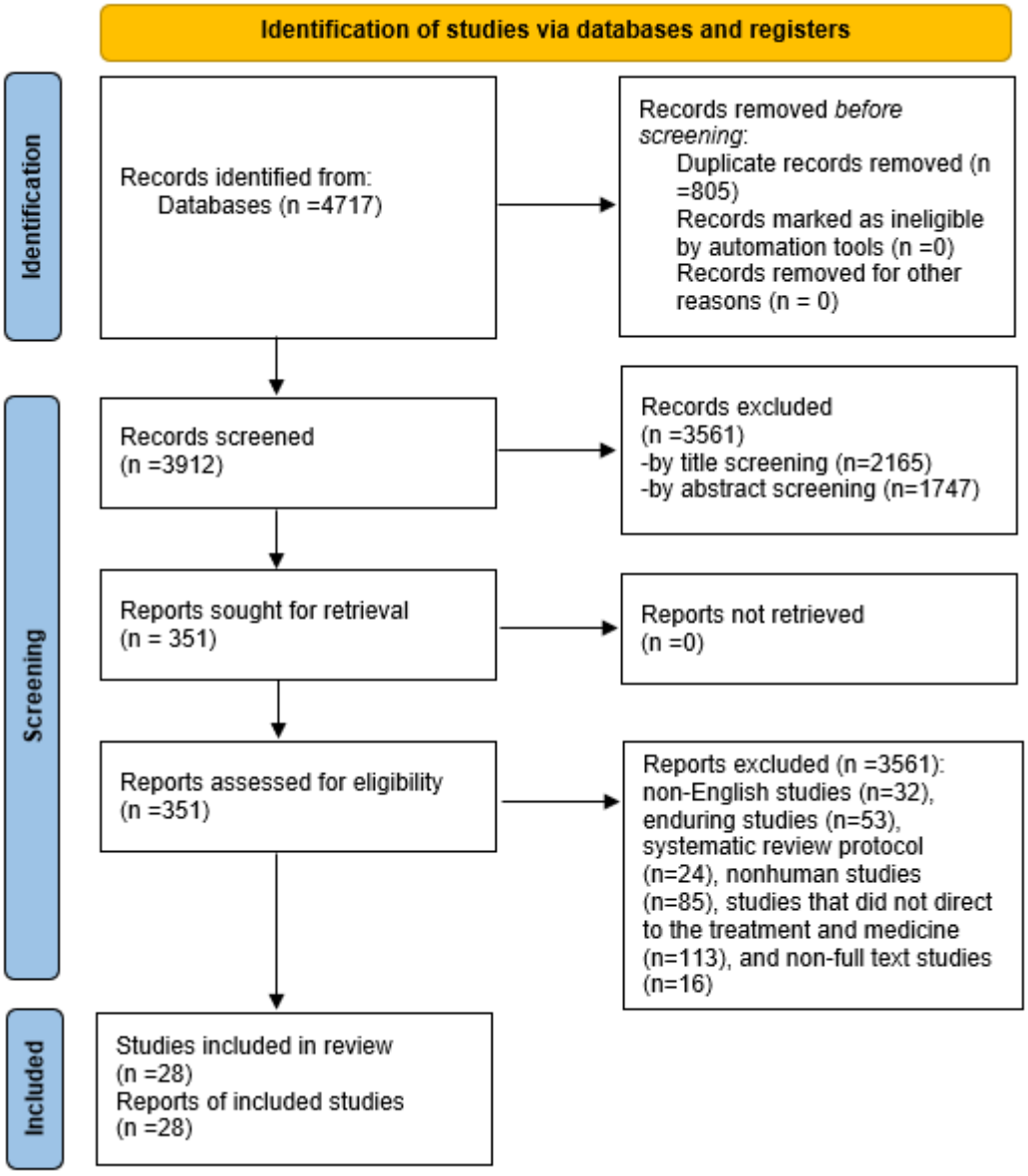
 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

							evidence suggests the safety of Nirmatrelvir /Ritonavir in patients without prior-concomitant therapies that rely on CYP3A4
(37)	USA	EMBASE, PubMed, medRxiv, Scopus, Prospero, and Google Scholar inception - February 2021	4 RCTs 2 Retrospective cohorts 2 Case-controls	Colchicine	Not reported	The use of Colchicine for treating COVID-19 is not recommended. Additional high-quality, multicenter RCTs are needed.	3 observational studies showed a decrease in all-cause mortality. 1 observational study showed a decrease in the risk of mechanical ventilation. 2 RCTs showed a reduction in hospitalization.
(38)	Germany	Cochrane COVID-19 Study Register, Web of Science (Emerging Citation Index and Science Citation Index), medRxiv, and Research Square Inception -May 2021	11 RCTs	Ivermectin	Not reported	The existing reliable evidence does not support the use of Ivermectin as an effective treatment or preventive measure for COVID-19.	Evidence for the effectiveness of Ivermectin in treating COVID-19 is currently uncertain for both in-patients and out-patients with limited/no beneficial effects in different aspects such as viral clearance-clinical improvement and adverse events.
(40)	China	PubMed, EMBASE, Cochrane Library, Web of Science databases Inception-October 25, 2022.	7 Retrospective cohorts 2 RCTs	Thymosin alpha1 (Ta1)	Not reported	This meta-analysis does not provide support for the utilization of Ta1 in hospitalized adult COVID-19 patients.	The meta-analysis results suggest that Ta1 therapy does not have a statistically significant impact on mortality. Subgroup analyses show a beneficial effect on mortality in patients >60 years with a proportion of females<40% and with severe COVID-19.
(41)	Australia	PubMed, Web of Science, ScienceDirect, and Scopus Inception- June 2022	5 Retrospective cohorts 12 Case reports 1 Case series	Convalescent plasma Therapy (CPT)	Not reported	CPT is an effective supportive therapy for COVID-19 patients with hematological malignancies	CPT may lead to improved clinical outcomes, including higher survival rates, enhanced clearance of SARS-COV-2, presence of anti-SARS-COV-2 antibodies, shorter hospital discharge time, and better recovery after one month of CPT. The treatment was not associated with adverse events.
(42)	India	PubMed, MedRxiv and Google Scholar October 2021- January 2022.	1 RCT 13 Preclinical studies	Molnupiravir	Not reported	Molnupiravir may benefit non-pregnant, unvaccinated adults with COVID-19 who face an elevated risk of severity and hospitalization.	Molnupiravir shows promise as a useful agent in reducing death and composite of hospitalization or death in high-risk adult patients with COVID-19. It offers the advantage of being cost-effective.
(44)	Spain	PubMed, Web of Science (WOS), the Cochrane COVID-19 Study Register, ClinicalTrials.gov-COVID-19 subset, and the WHO International Clinical Trials Registry Platform (ICTRP) Inception- May 2022	27 RCT	Vitamin D	Not reported	No adverse events were observed in the trials, indicating the safety of Vitamin D supplements within the examined doses.	No adverse events were observed in the trials. It can be concluded that Vitamin D supplementation using the doses and preparations examined, is safe.
(47)	China	Studies were not restricted by the year of publication, study site, drug dose, or control group	9 RCT	Ivermectin (IVM)	Not reported	In the absence of superior alternatives, clinicians should use IVM with caution in the clinical setting. Self-medication is not recommended for patients.	IVM shows potential effectiveness in treating mild to moderately ill patients. Its role as an antiviral drug in COVID-19 is still in the early stages of clinical application.

 10.15789/2220-7619-AUR-15080

РИСУНКИ

Figure 1 -PRISMA 2020 flow diagram of study retrieval process



 ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

Блок 1. Информация об авторе ответственном за переписку

Esmaeil Mehraeen, PhD, Health Information Management, Associate Professor, Department of Health Information Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran. Postal Code: 5681761351, Tel: +98-45-32426801, Fax: +98-45-32422305, E-mail: es.mehraeen@gmail.com

Исмаил Мехраин, доктор философии, управление медицинской информацией, доцент кафедры информационных технологий здравоохранения, Университет медицинских наук Халхал, Халхал, Иран. Почтовый индекс: 5681761351, тел.: +98-45-32426801, факс: +98-45-32422305, электронная почта: es.mehraeen@gmail.com

Блок 2. Информация об авторах

SeyedAhmad SeyedAlinaghi[a],
Amir Masoud Afsahi[b],
Ayoob Molla[c],
Pegah Mirzapour[a],
Ramin Shahidi[c],
Haleh Siami[d],
Farid Farahani Rad[e],
Faeze Abbaspour[e]
Navid Mozafari[c],
Kamal Fakhredini[f],
Esmaeil Mehraeen[g,]
Omid Dadras[h]

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

[a] MD, M.Phil, PhD, Clinical Epidemiologist, Associate Professor, Research Deputy of Iranian Research Center for HIV/AIDS (IRCHA), Iranian Institute for Reduction of High Risk Behaviors, Tehran University of Medical Sciences (TUMS), Tehran, Iran. E-mail: s_a_alinaghi@yahoo.com, pegah.mirzapour@yahoo.com, tamehrysaeed@gmail.com, elhamegzb75@gmail.com

[b] PhD, Department of Radiology, School of Medicine, University of California, San Diego (UCSD), California, USA. E-mail: amir.masoud.afsahi@gmail.com

[c] MD student, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran. E-mail: Ayoob.dpt87@gmail.com, dr.raminshahidi1@gmail.com, navidmozaffari97@gmail.com

[d] MD student, School of Medicine, Islamic Azad University, Tehran, Iran. E-mail: Haleh.siami@gmail.com,

[e] MD student, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. E-mail: farid.f.rad@gmail.com, absprfaeze@gmail.com,

[f] MD student, Behavioral Diseases Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran. E-mail: fakhredini1@gmail.com

[g] PhD, Health Information Management, Associate Professor, Department of Health Information Technology, Khalkhal University of Medical Sciences, Khalkhal, Iran. Postal Code: 5681761351, Tel: +98-45-32426801, Fax: +98-45-32422305, E-mail: es.mehraeen@gmail.com

[h] Dr, Department of Global Public Health and Primary Care, University of Bergen, Norway. E-mail: omiddadras@yahoo.com

СейедАхмад СейедАлинаги[1],

Амир Масуд Афсахи[2],

Аюб Молла[3],

Пега Мирзапур[1],

Рамин Шахиди[3],

Халех Сиами[4],

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

Фарид Фарахани Рад[5],

Фаэз Аббаспур[5],

Навид Мозафари[3],

Камаль Фахредини[6],

Исмаил Мехраин[7],

Омид Дадрас[8]

[1] доктор медицинских наук, магистр философии, доктор философии, клинический эпидемиолог, доцент, научный сотрудник Иранского исследовательского центра ВИЧ/СПИДа (IRCHA), Иранский институт снижения поведения высокого риска, Тегеранский университет медицинских наук (TUMS), Тегеран, Иран. Электронная почта: s_a_alinaghi@yahoo.com, pegah.mirzapour@yahoo.com, tamehrysaeed@gmail.com, elhamegzb75@gmail.com

[2] доктор философии, кафедра радиологии, медицинский факультет Калифорнийского университета, Сан-Диего (UCSD), Калифорния, США. Электронная почта: amir.masoud.afsahi@gmail.com

[3] студент медицинского факультета Бушерского университета медицинских наук, Бушер, Иран. Электронная почта: Ayoob.dpt87@gmail.com, dr.raminshahidi1@gmail.com, navidmozaffari97@gmail.com

[4] студент медицинского факультета Исламского университета Азад, Тегеран, Иран. Электронная почта: Haleh.siami@gmail.com,

[5] Студент медицинского факультета Тегеранского университета медицинских наук, Тегеран, Иран. Электронная почта: Farid.f.rad@gmail.com, absprfaeze@gmail.com,

[6] Студент, доктор медицинских наук, Центр исследования поведенческих заболеваний, Институт здравоохранения, Керманшахский университет медицинских наук, Керманшах, Иран. Электронная почта: fakhredini1@gmail.com

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

[7] Доктор философии, управление медицинской информацией, доцент кафедры информационных технологий здравоохранения, Халхалский университет медицинских наук, Халхал, Иран. Почтовый индекс: 5681761351, тел.: +98-45-32426801, факс: +98-45-32422305, электронная почта: es.mehraeen@gmail.com

[8] Доктор, департамент глобального общественного здравоохранения и первичной медико-санитарной помощи, Бергенский университет, Норвегия. Электронная почта: omiddadaras@yahoo.com

Блок 3. Метаданные статьи

AN UMBRELLA REVIEW ON TREATMENTS AND THERAPEUTIC OPTIONS FOR COVID-19

ЗОНТИЧНЫЙ ОБЗОР ЛЕЧЕНИЯ И ТЕРАПЕВТИЧЕСКИХ ВАРИАНТОВ ПРИ COVID-19

Сокращенное название статьи для верхнего колонтитула:

TREATMENTS AND THERAPEUTIC OPTIONS FOR COVID-19
ЛЕЧЕНИЕ И ТЕРАПЕВТИЧЕСКИЙ ВАРИАНТ ПРИ COVID-19

Keywords: COVID-19, SARS-CoV-2, Treatments, Therapeutic, Medicine, Umbrella review

Ключевые слова: COVID-19, SARS-CoV-2, лечение, терапия, медицина, зонтичный обзор.

Обзоры

Количество страниц текста – 10, количество таблиц – 2, количество рисунков – 1.

15.07.2023.

СПИСОК ЛИТЕРАТУРЫ

No.	Authors, Title	DOI/URL
1	Albuquerque AM, Eckert I, Tramujas L, Butler-Laporte G, McDonald EG, Brophy JM, Lee TC. Effect of tocilizumab, sarilumab, and baricitinib on mortality among patients hospitalized for COVID-19 treated with corticosteroids: a systematic review and meta-analysis. Clin Microbiol Infect. 2023 Jan;29(1):13-21. doi: 10.1016/j.cmi.2022.07.008. Epub 2022 Jul 19. PMID: 35863630; PMCID: PMC9293401.	https://pubmed.ncbi.nlm.nih.gov/35863630/
2	Amstutz A, Speich B, Mentré F, Rueegg CS, Belhadi D, Assoumou L, Burdet C, Murthy S, Dodd LE, Wang Y, Tikkinen KAO, Ader F, Hites M, Bouscambert M, Trabaud MA, Fralick M, Lee TC, Pinto R, Barratt-Due A, Lund-Johansen F, Müller F, Nevalainen OPO, Cao B, Bonnett T, Griessbach A, Taji Heravi A, Schönenberger C, Janiaud P, Werlen L, Aghlmandi S, Schandelmaier S, Yazdanpanah Y, Costagliola D, Olsen IC, Briel M. Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. Lancet Respir Med. 2023 May;11(5):453-464. doi: 10.1016/S2213-2600(22)00528-8. Epub 2023 Feb 21.	https://pubmed.ncbi.nlm.nih.gov/36828006/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	Erratum in: Lancet Respir Med. 2023 Aug;11(8):e77. PMID: 36828006; PMCID: PMC10156140.	
3	Ansems K, Grundeis F, Dahms K, Mikolajewska A, Thieme V, Piechotta V, Metzendorf MI, Stegemann M, Benstoem C, Fichtner F. Remdesivir for the treatment of COVID-19. Cochrane Database Syst Rev. 2021 Aug 5;8(8):CD014962. doi: 10.1002/14651858.CD014962. Update in: Cochrane Database Syst Rev. 2023 Jan 25;1:CD014962. PMID: 34350582; PMCID: PMC8406992.	https://pubmed.ncbi.nlm.nih.gov/34350582/
4	Areri H, Marshall A, Harvey G. Factors influencing self-management of adults living with HIV on antiretroviral therapy in Northwest Ethiopia: a cross-sectional study. BMC Infect Dis. 2020 Nov 23;20(1):879. doi: 10.1186/s12879-020-05618-y. PMID: 33228546; PMCID: PMC7686766.	https://pubmed.ncbi.nlm.nih.gov/33228546/
5	Celotto S, Veronese N, Barbagallo M, Ometto F, Smith L, Pardhan S, Barnett Y, Ilie PC, Soysal P, Lagolio E, Kurotschka PK, Tonelli R, Demurtas J. An umbrella review of systematic reviews with meta-analyses evaluating positive and negative outcomes of Hydroxychloroquine and chloroquine therapy. Int J Infect Dis. 2021 Feb;103:599-606. doi: 10.1016/j.ijid.2020.12.018. Epub 2020 Dec 11. PMID: 33316389; PMCID: PMC7833426.	https://pubmed.ncbi.nlm.nih.gov/33316389/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

6	Cheema HA, Sohail A, Fatima A, Shahid A, Shahzil M, Ur Rehman ME, Awan RU, Chinnam S, Nashwan AJ. Quercetin for the treatment of COVID-19 patients: A systematic review and meta-analysis. Rev Med Virol. 2023 Mar;33(2):e2427. doi: 10.1002/rmv.2427. Epub 2023 Feb 13. PMID: 36779438.	https://pubmed.ncbi.nlm.nih.gov/36779438/
7	Chinta S, Rodriguez-Guerra M, Shaban M, Pandey N, Jaquez-Duran M, Vittorio TJ. COVID-19 therapy and vaccination: a clinical narrative review. Drugs Context. 2023 Feb 7;12:2022-7-2. doi: 10.7573/dic.2022-7-2. PMID: 36793450; PMCID: PMC9914077.	https://pubmed.ncbi.nlm.nih.gov/36793450/
8	Dahms K, Mikolajewska A, Ansems K, Metzendorf MI, Benstoem C, Stegemann M. Anakinra for the treatment of COVID-19 patients: a systematic review and meta-analysis. Eur J Med Res. 2023 Feb 25;28(1):100. doi: 10.1186/s40001-023-01072-z. PMID: 36841793; PMCID: PMC9959952.	https://pubmed.ncbi.nlm.nih.gov/36841793/
9	Deng J, Rayner D, Ramaraju HB, Abbas U, Garcia C, Heybati K, Zhou F, Huang E, Park YJ, Moskalyk M. Efficacy and safety of selective serotonin reuptake inhibitors in COVID-19 management: a systematic review and meta-analysis. Clin Microbiol Infect. 2023 May;29(5):578-586. doi: 10.1016/j.cmi.2023.01.010.	https://pubmed.ncbi.nlm.nih.gov/36657488/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	Epub 2023 Jan 16. PMID: 36657488; PMCID: PMC9841740.	
10	Dhawan M, Priyanka, Parmar M, Angural S, Choudhary OP. Convalescent plasma therapy against the emerging SARS-CoV-2 variants: Delineation of the potentialities and risks. Int J Surg. 2022 Jan;97:106204. doi: 10.1016/j.ijsu.2021.106204. Epub 2021 Dec 30. PMID: 34974199; PMCID: PMC8717699.	https://pubmed.ncbi.nlm.nih.gov/34974199/
11	Giles G, Varghese S, Shymko G, Nguyen T, Waters F. Clozapine Therapy and COVID-19: A Systematic Review of the Prevalence Rates, Health Outcomes, Hematological Markers, and Patient Perspectives. Schizophr Bull. 2023 Jan 3;49(1):53-67. doi: 10.1093/schbul/sbac148. PMID: 36242537; PMCID: PMC9620749.	https://pubmed.ncbi.nlm.nih.gov/36242537/
12	Greene C, Wilson J, Griffin H, Tingle A, Cooper T, Semple MG, Enoch D, Lee A, Loveday H. The role of pandemic planning in the management of COVID-19 in England from an infection prevention and control perspective: results of a national survey. Public Health. 2023 Apr;217:89-94. doi: 10.1016/j.puhe.2023.01.028. Epub 2023 Feb 3. PMID: 36867987; PMCID: PMC9894767.	https://pubmed.ncbi.nlm.nih.gov/36867987/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

13	Hayden MK, Hanson KE, Englund JA, Lee F, Lee MJ, Loeb M, Morgan DJ, Patel R, El Alayli A, El Mikati IK, Sultan S, Falck-Ytter Y, Mansour R, Amarin JZ, Morgan RL, Murad MH, Patel P, Bhimraj A, Mustafa RA. The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Antigen Testing. Clin Infect Dis. 2023 Jan 26:ciad032. doi: 10.1093/cid/ciad032. Epub ahead of print. PMID: 36702617.	https://pubmed.ncbi.nlm.nih.gov/36702617/
14	Huang NX, Yuan Q, Fang F, Yan BP, Sanderson JE. Systematic review and meta-analysis of the clinical outcomes of ACEI/ARB in East-Asian patients with COVID-19. PLoS One. 2023 Jan 12;18(1):e0280280. doi: 10.1371/journal.pone.0280280. PMID: 36634085; PMCID: PMC9836310.	https://pubmed.ncbi.nlm.nih.gov/36634085/
15	Kramer A, Prinz C, Fichtner F, Fischer AL, Thieme V, Grundeis F, Spagl M, Seeber C, Piechotta V, Metzendorf MI, Golinski M, Moerer O, Stephani C, Mikolajewska A, Kluge S, Stegemann M, Laudi S, Skoetz N. Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev. 2022 Jun 13;6(6):CD015209. doi: 10.1002/14651858.CD015209. PMID: 35695334; PMCID: PMC9190191.	https://pubmed.ncbi.nlm.nih.gov/35695334/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

16	Kurniawati DR, Subagjo A, Djuari L. Efficacy and Safety of Prophylactic-Dose Anticoagulation Therapy with Intermediate-Therapeutic Doses in Covid-19 Patients. Indian Journal of Forensic Medicine & Toxicology. 2023;17(1):97-101.	https://medicopublication.com/index.php/ijfmt/article/view/18902
17	Liang W, Liang H, Ou L, Chen B, Chen A, Li C, Li Y, Guan W, Sang L, Lu J, Xu Y, Chen G, Guo H, Guo J, Chen Z, Zhao Y, Li S, Zhang N, Zhong N, He J; China Medical Treatment Expert Group for COVID-19. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. 2020 Aug 1;180(8):1081-1089. doi: 10.1001/jamainternmed.2020.2033. PMID: 32396163; PMCID: PMC7218676.	https://pubmed.ncbi.nlm.nih.gov/32396163/
18	Li Y, Qin Y, Chen N, Ge L, Wang Q, Aboudou T, Han J, Hou L, Cao L, Li R, Li M, Mi N, Xie P, Wu S, Hu L, Li X, Song Z, Ji J, Zhang Z, Yang K. Use of traditional Chinese medicine for the treatment and prevention of COVID-19 and rehabilitation of COVID-19 patients: An evidence mapping study. Front Pharmacol. 2023 Jan 19;14:1069879. doi: 10.3389/fphar.2023.1069879. PMID: 36744266; PMCID: PMC9892723.	https://pubmed.ncbi.nlm.nih.gov/36744266/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

19	RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020 Oct 24;396(10259):1345-1352. doi: 10.1016/S0140-6736(20)32013-4. Epub 2020 Oct 5. PMID: 33031764; PMCID: PMC7535623.	https://pubmed.ncbi.nlm.nih.gov/33031764/
20	Liu Q, Fu W, Zhu CJ, Ding ZH, Dong BB, Sun BQ, Chen RC. Effect of continuing the use of renin-angiotensin system inhibitors on mortality in patients hospitalized for coronavirus disease 2019: a systematic review, meta-analysis, and meta-regression analysis. BMC Infect Dis. 2023 Jan 24;23(1):53. doi: 10.1186/s12879-023-07994-7. PMID: 36694122; PMCID: PMC9872739.	https://pubmed.ncbi.nlm.nih.gov/36694122/
21	Luo X, Zhang Y, Li H, Ren M, Liu Y, Liu Y, Zhang Y, Kuang Z, Cai Y, Chen Y, Ni X. Clinical Evidence on the Use of Chinese Herbal Medicine for Acute Infectious Diseases: An Overview of Systematic Reviews. Front Pharmacol. 2022 Feb 25;13:752978. doi: 10.3389/fphar.2022.752978. PMID: 35281902; PMCID: PMC8914111.	https://pubmed.ncbi.nlm.nih.gov/35281902/
22	Maideen NMP, Balasubramanian R, Manavalan G, Balasubramanian K, Subramanian N, Murugesan T, Solaimalai VK. An Insight of Clinical Evidence of	https://pubmed.ncbi.nlm.nih.gov/35319399/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	Ayurveda Interventions in the Management of COVID-19 Patients. Infect Disord Drug Targets. 2022;22(6):e210322202491. doi: 10.2174/1871526522666220321152504. PMID: 35319399.	
23	Mali KR, Eerike M, Raj GM, Bisoi D, Priyadarshini R, Ravi G, Chaliserry LF, Janti SS. Efficacy and safety of Molnupiravir in COVID-19 patients: a systematic review. Ir J Med Sci. 2023 Aug;192(4):1665-1678. doi: 10.1007/s11845-022-03139-y. Epub 2022 Sep 10. PMID: 36087236; PMCID: PMC9463664.	https://pubmed.ncbi.nlm.nih.gov/36087236/
24	Mehraeen E, Oliaei S, SeyedAlinaghi S, Karimi A, Mirzapour P, Afsahi AM, Barzegary A, Vahedi F, Soleymanzadeh M, Behnezhad F, Javaherian M, Zargari G, Mirghaderi SP, Noori T, Sabatier JM. COVID-19 in Pediatrics: A Systematic Review of Current Knowledge and Practice. Infect Disord Drug Targets. 2022;22(5):e290921196908. doi: 10.2174/1871526521666210929121705. PMID: 34587889.	https://pubmed.ncbi.nlm.nih.gov/34587889/
25	Mehraeen E, Najafi Z, Hayati B, Javaherian M, Rahimi S, Dadras O, SeyedAlinaghi S, Ghadimi M, Sabatier JM. Current Treatments and Therapeutic Options for COVID-19 Patients: A Systematic	https://pubmed.ncbi.nlm.nih.gov/34313204/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	Review. Infect Disord Drug Targets. 2022;22(1):e260721194968. doi: 10.2174/1871526521666210726150435. PMID: 34313204.	
26	Migliorini F, Vaishya R, Eschweiler J, Oliva F, Hildebrand F, Maffulli N. Vitamins C and D and COVID-19 Susceptibility, Severity and Progression: An Evidence Based Systematic Review. Medicina (Kaunas). 2022 Jul 15;58(7):941. doi: 10.3390/medicina58070941. PMID: 35888660; PMCID: PMC9318801.	https://pubmed.ncbi.nlm.nih.gov/35888660/
27	Mohseni M, Ameri H, Arab-Zozani M. Potential limitations in systematic review studies assessing the effect of the main intervention for treatment/therapy of COVID-19 patients: An overview. Front Med (Lausanne). 2022 Sep 15;9:966632. doi: 10.3389/fmed.2022.966632. PMID: 36203750; PMCID: PMC9531544.	https://pubmed.ncbi.nlm.nih.gov/36203750/
28	Morishita M, Hojo M. Treatment options for patients with severe COVID-19. Glob Health Med. 2023 Apr 30;5(2):99-105. doi: 10.35772/ghm.2023.01024. PMID: 37128231; PMCID: PMC10130548.	https://pubmed.ncbi.nlm.nih.gov/37128231/
29	Mousavi S, Zare S, Mirzaei M, Feizi A. Novel Drug Design for Treatment of COVID-19: A Systematic Review of Preclinical Studies. Can J Infect Dis Med	https://pubmed.ncbi.nlm.nih.gov/36199815/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	Microbiol. 2022 Sep 25;2022:2044282. doi: 10.1155/2022/2044282. PMID: 36199815; PMCID: PMC9527439.	
30	Niranjan AK, Patel SK, Channabasappa NK, Rana J, Agrawal A, Kumar R, Pandey MK, Tiwari SP, Singh DR. Resurgence of cholera in the COVID-19 era: a global health concern. Ann Med Surg (Lond). 2023 Apr 4;85(4):1321-1322. doi: 10.1097/MS9.0000000000000415. PMID: 37113939; PMCID: PMC10129175.	https://pubmed.ncbi.nlm.nih.gov/37113939/
31	Pahari PK, Vyas S, Aman S, Singh U, Singh KP, Tiwari R, et al. Therapeutic Options for the Treatment of 2019-Novel Coronavirus in India: A Review. Coronaviruses. 2022;3(2):39-47.	https://www.eurekaselect.com/article/112059
32	Pantasri T, Ali MM, Ghouri MH, Alharbi AM, Alfahemi H. Role of Antiviral Drugs in Management of Mild and Moderate Coronavirus Disease-19: A Systematic Review. ADVANCEMENTS IN LIFE SCIENCES. 2022;9(3):270-6.	https://submission.als-journal.com/index.php/ALS/article/view/1268
33	Popp M, Reis S, Schießer S, Hausinger RI, Stegemann M, Metzendorf MI, Kranke P, Meybohm P, Skoetz N, Weibel S. Ivermectin for preventing and treating COVID-19. Cochrane Database Syst Rev. 2022 Jun 21;6(6):CD015017. doi:	https://pubmed.ncbi.nlm.nih.gov/35726131/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	10.1002/14651858.CD015017.pub3. PMID: 35726131; PMCID: PMC9215332.	
34	Paraskevas T, Kantanis A, Karalis I, Michailides C, Karamouzos V, Koniari I, Pierrakos C, Velissaris D. N-acetylcysteine efficacy in patients hospitalized with COVID-19 pneumonia: a systematic review and meta-analysis. Rom J Intern Med. 2023 Mar 16;61(1):41-52. doi: 10.2478/rjim-2023-0001. PMID: 36627753.	https://pubmed.ncbi.nlm.nih.gov/36627753/
35	Pashaei Z, SeyedAlinaghi S, Qaderi K, Barzegary A, Karimi A, Mirghaderi SP, Mirzapour P, Tantuoyir MM, Dadras O, Ali Z, Voltarelli F, Mehraeen E. Prenatal and neonatal complications of COVID-19: A systematic review. Health Sci Rep. 2022 Feb 15;5(2):e510. doi: 10.1002/hsr2.510. Retraction in: Health Sci Rep. 2023 Jul 26;6(7):e1451. PMID: 35224216; PMCID: PMC8844871.	https://pubmed.ncbi.nlm.nih.gov/35224216/
36	Patel TK, Patel PB, Barvaliya M, Saurabh MK, Bhalla HL, Khosla PP. Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. J Infect Public Health. 2021 Jun;14(6):740-748. doi: 10.1016/j.jiph.2021.03.015. Epub 2021 Apr 20. PMID: 34020215; PMCID: PMC8056786.	https://pubmed.ncbi.nlm.nih.gov/34020215/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

37	Reis S, Metzendorf MI, Kuehn R, Popp M, Gagyor I, Kranke P, Meybohm P, Skoetz N, Weibel S. Nirmatrelvir combined with ritonavir for preventing and treating COVID-19. Cochrane Database Syst Rev. 2022 Sep 20;9(9):CD015395. doi: 10.1002/14651858.CD015395.pub2. PMID: 36126225; PMCID: PMC9487421.	https://pubmed.ncbi.nlm.nih.gov/36126225/
38	Sanghavi D, Bansal P, Kaur IP, Mughal MS, Keshavamurthy C, Cusick A, Schram J, Yarrarapu SNS, Giri AR, Kaur N, Moreno Franco P, Abril A, Aslam F. Impact of colchicine on mortality and morbidity in COVID-19: a systematic review. Ann Med. 2022 Dec;54(1):775-789. doi: 10.1080/07853890.2021.1993327. PMID: 35258357; PMCID: PMC8920395.	https://pubmed.ncbi.nlm.nih.gov/35258357/
39	SeyedAlinaghi S, Karimi A, Barzegary A, Mojdeganlou H, Vahedi F, Mirghaderi SP, Shobeiri P, Ramezani M, Yousefi Konjdar P, Mirzapour P, Tantuoyir MM, Mehraeen E, Dadras O, Voltarelli F. COVID-19 mortality in patients with immunodeficiency and its predictors: a systematic review. Eur J Med Res. 2022 Oct 8;27(1):195. doi: 10.1186/s40001-022-00824-7. PMID: 36209202; PMCID: PMC9547631.	https://pubmed.ncbi.nlm.nih.gov/36209202/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

40	Shang W, Zhang B, Ren Y, Wang W, Zhou D, Li Y. Thymosin alpha1 use in adult COVID-19 patients: A systematic review and meta-analysis on clinical outcomes. Int Immunopharmacol. 2023 Jan;114:109584. doi: 10.1016/j.intimp.2022.109584. Epub 2022 Dec 13. PMID: 36527881; PMCID: PMC9754924.	https://pubmed.ncbi.nlm.nih.gov/36527881/
41	Shibeeb S, Ajaj I, Al-Jighefee H, Abdallah AM. Effectiveness of Convalescent Plasma Therapy in COVID-19 Patients with Hematological Malignancies: A Systematic Review. Hematol Rep. 2022 Dec 12;14(4):377-388. doi: 10.3390/hematolrep14040052. PMID: 36547236; PMCID: PMC9778836.	https://pubmed.ncbi.nlm.nih.gov/36547236/
42	Singh AK, Singh A, Singh R, Misra A. An updated practical guideline on use of molnupiravir and comparison with agents having emergency use authorization for treatment of COVID-19. Diabetes Metab Syndr. 2022 Feb;16(2):102396. doi: 10.1016/j.dsx.2022.102396. Epub 2022 Jan 13. PMID: 35051686; PMCID: PMC8755553.	https://pubmed.ncbi.nlm.nih.gov/35051686/
43	Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. Diabetes Metab Syndr. 2021 Nov-Dec;15(6):102329.	https://pubmed.ncbi.nlm.nih.gov/34742052/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	doi: 10.1016/j.dsx.2021.102329. Epub 2021 Oct 30. PMID: 34742052; PMCID: PMC8556684.	
44	Feiner Solís Á, Avedillo Salas A, Luesma Bartolomé MJ, Santander Ballestín S. The Effects of Vitamin D Supplementation in COVID-19 Patients: A Systematic Review. Int J Mol Sci. 2022 Oct 17;23(20):12424. doi: 10.3390/ijms232012424. PMID: 36293279; PMCID: PMC9604062.	https://pubmed.ncbi.nlm.nih.gov/36293279/
45	Van De Laar CJ, Oude Voshaar MAH, Fakhouri WKH, Zaremba-Pechmann L, De Leonardis F, De La Torre I, Van De Laar MAFJ. Cost-Effectiveness of a JAK1/JAK2 Inhibitor vs a Biologic Disease-Modifying Antirheumatic Drug (bDMARD) in a Treat-to-Target Strategy for Rheumatoid Arthritis. Clinicoecon Outcomes Res. 2020 Apr 15;12:213-222. doi: 10.2147/CEOR.S231558. PMID: 32346301; PMCID: PMC7167259.	https://pubmed.ncbi.nlm.nih.gov/32346301/
46	Wei Q, Lin H, Wei RG, Chen N, He F, Zou DH, Wei JR. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty. 2021 May 18;10(1):71. doi: 10.1186/s40249-021-00857-w. PMID: 34001244; PMCID: PMC8128625.	https://pubmed.ncbi.nlm.nih.gov/34001244/
47	Yang S, Shen S, Hou N. Is Ivermectin Effective in Treating COVID-19? Front Pharmacol. 2022 Jun	https://pubmed.ncbi.nlm.nih.gov/35800451/

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)

	21;13:858693. doi: 10.3389/fphar.2022.858693. PMID: 35800451; PMCID: PMC9253511.	

ISSN 2220-7619 (Print)
ISSN 2313-7398 (Online)