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Evaluating the Safety and Efficacy of Novel Antiviral Therapies for Emerging Infectious Diseases: A Systematic Review on COVID-19

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ABSTRACT

The SARS-CoV-2 infections had been treated with varied anti-viral therapies to improve patient clinical status and determine safety. There is lack of comprehensive consensus on determining the overall safety and clinical outcomes due to novel anti-viral therapies to synthesize evidence. The systematic review was conducted following PRISMA guidelines. The text words, keywords, and controlled-vocabulary words (MeSH terms were used to retrieve targeted keywords on PubMed, Embase, and Cochrane Library with the following limiters, e.g., studies in the English language, studies from 2020 to 2024, Open access studies, Peer-reviewed articles, and studies with full-text availability. This review included 30 randomized controlled trials of High quality to synthesize evidence with 10,941 patients with a mean age of 49 (ranging from 19 to 90) years, including 55% of males, to treat SARS-CoV-2 infectious patients with mild to severe severity. Remdesivir, Molnupiravir, tofacitinib, Baricitinib combine with Remdesivir, a combination of Favipiravir, Lopinavir, Ritonavir, Monoclonal antibodies (Lenzilumab, AZD 7442, Meplazumab, Bamlanivimab monotherapy and combination with etesevimab, REGEN-COV), Immunomodulators (Interferon-beta-1a, Peginterferon Lambda) is found to be effective and showed a statistically significant difference in improving clinical status by ensuring safety for patients with mild, moderate and severe SARS-CoV-2 infections($p<0.05$). Novel antiviral therapies Remdesivir, Molnupiravir, and specific monoclonal antibodies have been shown to have significant clinical efficacies in patients, which proves their importance in improving patient clinical status and safety outcomes. The conclusion indicated that these therapies are beneficial in enhancing the likelihood of clinical improvement with tolerable side effects.

Keywords: COVID-19; Efficacy; Novel Anti-Viral Therapies; Safety

Introduction

The outbreak of COVID-19 from the novel coronavirus, also known as SARS-CoV-2, increased global awareness of emerging infectious diseases. This pandemic has led to multi-omics analysis and database integration to analyze viruses and their evolution and develop early warning system strategies [1]. COVID-19 has also brought to the attention the necessity of enhancing the population's health literacy and competence in the proper communication channels to address the challenges presented by fake knowledge regarding the disease, which can impact public perception of the disease [2]. Moreover, the COVID-19 has highlighted the need to prioritize investment in public health, build resilient national capacities for early identification and response to threatening diseases, and use evidence for policy-making to improve preparedness in the face of the newly emerged threats as COVID-19 [3]. Thirdly, the continuous influence of new pathogenic diseases, such as coronaviruses that caused COVID-19, calls for international efforts to strengthen the measures of noticing and controlling biosecurity-related risks [4]. For the introduction of novel antiviral therapies for COVID-19, a global perspective should prioritize treatments. The treatment must focus on that hinder coronaviruses replication, target viral proteins or host-virus interface and can be in oral form for easy use especially in resource-poor settings [5]. Further research should focus on using existing drugs and creating new ones as combination therapies. It includes topical gels that prevent the virus from entering host cells, and newer classes of antiviral drugs to effectively target and treat viral diseases like COVID-19 including its variants [6].

Moreover, more focus should be directed towards preclinical drug development, investigating the use of nanotechnological approaches in drug delivery, using phytoconstituents, and polyherbal formulations for managing COVID-19 and subsequent emerging coronaviruses [7]. Novel antiviral therapies contain a range of drugs that intervene with viral life cycle stages and enhance immune regulation. Multiple novel approaches are being explored to inhibit the replication and spread of the virus (SARS-CoV-2), which is evident in the literature [8]. These approaches target the viral cell directly or modify the host cell processes to hinder virus replication [9]. The approaches are Nucleoside analogs (Target viral RNA polymerase) [10], Protease inhibitors [11], Monoclonal antibodies (Target Spike proteins) [12], and host cell targeting agents, e.g., Baricitinib [13]. The mechanism of action varies among all approaches according to their target action sites. The efficacy of Novel antiviral therapies varied among mild to severe COVID-19 patients. The nucleoside analogs Remdesivir, Molnupiravir, and Favipiravir have different mechanisms of action. Remdesivir and Favipiravir inhibit viral RNA-dependent RNA polymerase, and Molnupiravir induces errors in viral RNA replication. Nirmatrelvir and Ritonavir inhibited SARS-CoV-2's major protease (Mpro) and CYP3A to improve Nirmatrelvir pharmacokinetics [14]. Nirmatrelvir binds to SARS-CoV-2 to stop replication. Nirmatrelvir inhibits the viral protein-processing Mpro enzyme. This inhibits virus production and reduces COVID-19 severity [15].

Ritonavir, a CYP3A inhibitor, enhances SARS-CoV-2 pharmacokinetics. Hence, Paxlovid acts as inhibitors work together to reduce virus activity and augment COVID-19 treatment [14]. Sotrovimab, REGEN-COV (Casirivimab+Imedvimab), and Bamlanivimab are monoclonal antibodies that attach to the spike protein of SARS-CoV-2. They inhibit virus from entering cells and mediate the immune response [16,17]. When given early after a positive test, these antibodies reduce the risk of hospitalization or mortality among high-risk outpatients with mild to moderate COVID-19 [18]. Antibody fragments provide broader neutralization of SARS-CoV-2 variants and reduce the doses required to protect living organisms compared to mAbs [17]. However, host cell target agents (Baricitinib) a JAK inhibitor, have been used to treat COVID-19 to stop viral entry, reduce inflammation, and cytokines levels. Baricitinib inhibits virus-infected cells. It has been used to treat COVID-19 to control virus entrance, inflammation, and cytokine production [19]. Baricitinib targets cytokine in severe COVID-19 pneumonia, improving recovery rates in hospitalized patients [19]. Safety outcomes are also essential in determining these drugs' clinical and practical application among patients affected by the SARS-CoV-2 virus. New antiviral medicines have been thoroughly researched for COVID-19 therapy safety and efficacy. Remdesivir, Favipiravir, Lopinavir /Ritonavir, ribavirin, interferon, and Hydroxychloroquine have been tried clinically for different viral infections and have had mixed mortality and clinical outcomes.

The safety of these antiviral treatments requires determining adverse symptoms, including gastrointestinal issues, elevated blood uric acid levels, cough, respiration, and immunological reactions.

Rationale

Novel antivirals that target distinct viral replication stages can aid in the fight against COVID-19. Oral antivirals such as Evusheld, REGEN-COV, Bamlanivimab, etesevimab, Paxlovid, redeliver, Molnupiravir, favipiravir, dual oral protease inhibitor-ribavirin, and others target viral entry factors, viral replication, protein trafficking, post-translational modification, immunomodulation, and immune new etiotropic medications such as Molnupiravir, plitidepsin, and lopinavir/ritonavir remain in therapy regimens. Nonspecific immunoassays and broad-spectrum antivirals, such as RNases and RNAi, can also target viral genomes and proteins, paving the way for new antiviral therapies. Unusual COVID-19 treatments improve upon existing strategies and are acceptable.

The purpose of this review is to extract and synthesize evidence of novel antiviral therapies to determine the most effective treatment options for mild, moderate, and severe SARS-CoV-2 infection symptoms among hospitalized or outpatient departments. The focus was on clinical outcomes improvement, safety of each drug, viral clearance, mortality, incidence of disease, and return to home.

Objectives

The purpose of this review is to evaluate the efficacy, safety, and outcomes (viral load reduction, viral clearance) of novel antiviral therapies for the treatment of mild, moderate, and severe symptoms in SARS-CoV-2 patients.

Methodology

This is a systematic review that used PRISMA guidelines (Figure 1) [20] to assess the safety and efficacy of new antiviral therapies for infectious diseases like COVID-19.

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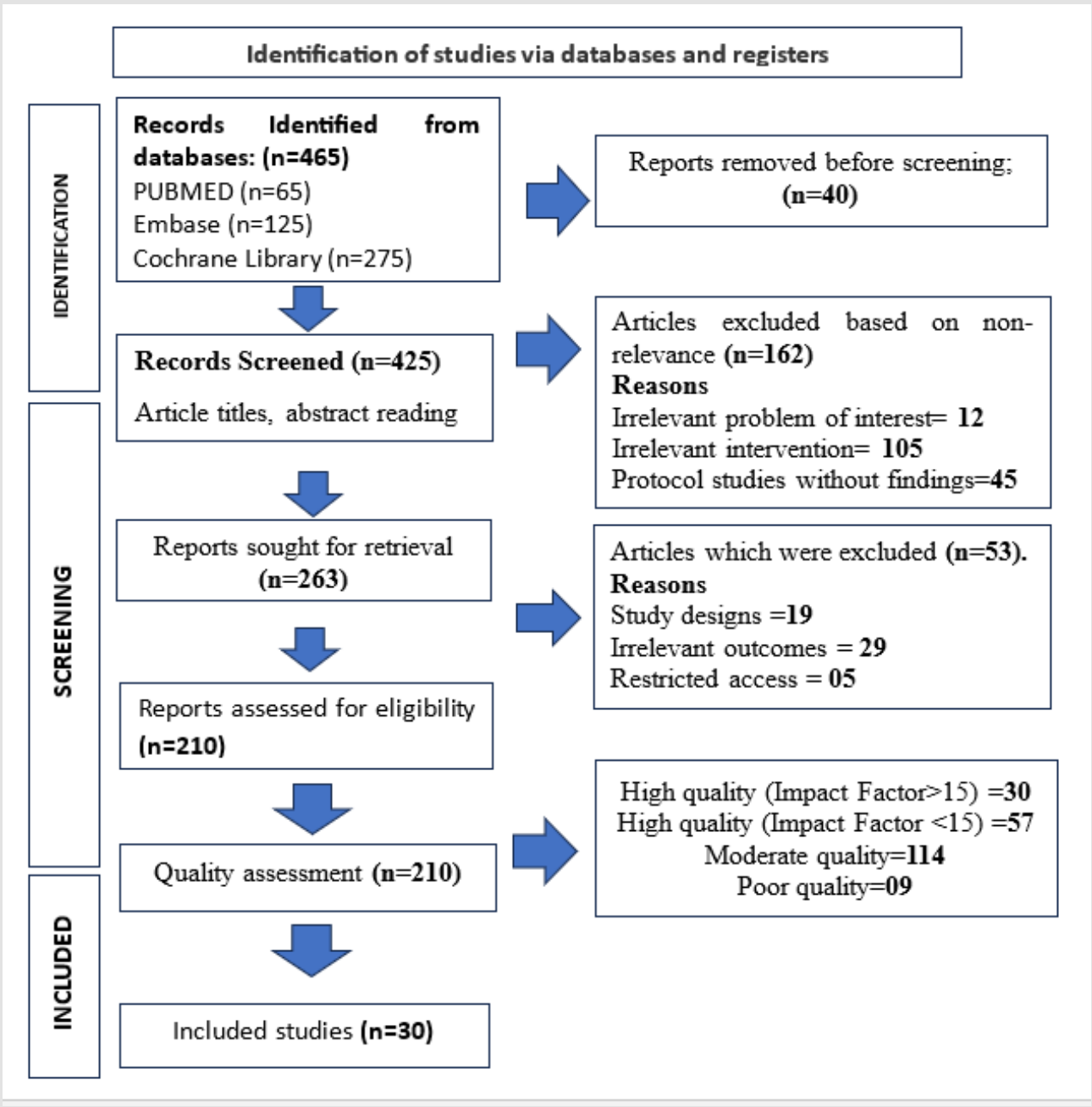

Figure 1: PRISMA flow chart.

Research Strategy

The text words, keywords, and controlled-vocabulary words (MeSH terms), e.g., "COVID-19 patients" OR "SARS-CoV-2 patients" AND "Novel anti-viral therapies" OR "anti-viral therapies" OR "Anti-viral agents" OR "Remdesivir" OR "Favipiravir" OR "Molnupiravir" OR Monoclonal antibodies" OR "Protease inhibitors" AND "standard of care" OR "placebo" AND "Safety" OR "Safety outcomes" OR "Effectiveness" OR "Clinical outcomes" OR "adverse events" OR "viral load" OR "Viral clearance" was used with appropriate use of Boolean operators "AND," "OR" to retrieve literature. The databases e.g. PubMed, Embase, and Cochrane Library were searched with the following limiters; studies in the English language, studies from 2014 to 2024, Open access studies, Peer-reviewed articles, and studies with full-text availability. The PICO framework was mentioned in (Table 1).

Table 1: Methodological quality and risk of bias assessment to determine strength of evidence.

Author	Year	Impact Factor JCR Clarivate (2024)	Risk of Bias	Evidence Strength (GRADE)	Evidence Commentary
(Peter Horby, et al [23])	2020	158.5	Low risk	High quality	Unblinded; randomized; uncontrolled; 1561 patients; is registered; provides data. This research has been cited 1009 times.
(Spinner, et al. [24])	2020	120.7	Low risk	High quality	Randomized; placebo-controlled; 596 patients; medium effect size; is registered; acknowledges limitations. This research has been cited 1061 times.
(Yeming Wang, et al. [25])	2020	98.4	Low risk	High quality	Multicentre; double-blind; randomized; placebo-controlled; 237 patients; medium effect size; is registered. This research has been cited 2963 times.
(Ivan Fan Ngai Hung ,et al. [36])	2020	98.4	Low risk	High quality	Phase 2; multicentre; randomized; control group; 127 patients; large effect size; is registered. This research has been cited 1266 times.
(Meagan P O'Brien et al. [37])	2021	158.5	Low risk	High quality	Double-blind; randomly assigned; placebo group; 2475 participants; medium effect size; is registered; provides data. This research has been cited 382 times.
(Jens Lundgren, et al. [39])	2021	158.5	Low risk	High quality	Double-blind; randomly assigned; placebo group; 300 patients; medium effect size; is registered; acknowledges limitations. This research has been cited 373 times.
(André C. Kalil, et al. [27])	2021	158.5	Low risk	High quality	Double-blind; randomized; placebo-controlled; 1033 patients; medium effect size; is registered. This research has been cited 1436 times.
(Patricia O Guimarães, et al. [47])	2021	158.5	Low risk	High quality	Unblinded; randomly assigned; placebo group; 289 patients; medium effect size; is registered. This research has been cited 365 times.
(Robert L Gottlieb al. [38])	2021	120.7	Low risk	High quality	Phase 2; double-blind; randomized; placebo group; 613 patients; acknowledges limitations. This research has been cited 836 times.
(Myron S. Cohen, et al. [39])	2021	120.7	Low risk	High quality	Phase 3; double-blind; randomized; placebo group; 1297 participants; medium effect size; is registered; acknowledges limitations. This research has been cited 170 times.
(Phillip Monk, et al. [48])	2021	76.2	Low risk	High quality	Phase 2; double-blind; randomized; placebo-controlled; 101 patients; medium effect size; is registered. This research has been cited 393 times.
(André C. Kalil, Aneesh K. Mehta et al. [28])	2021	76.2	Low risk	High quality	Phase 3; double-blind; randomized; placebo-controlled; 969 patients; low effect size; is registered. This research has been cited 124 times.
(Jordan J Feld, et al. [49])	2021	76.2	Low risk	High quality	Phase 2; double-blind; randomized; placebo-controlled; 30 patients; large effect size; is registered. This research has been cited 194 times.
(Huijie Bian et al. [40])	2021	39.3	Low risk	High quality	Phase 1; single-center; double-blinded; randomized; placebo-controlled; 59 subjects; is registered; acknowledges limitations; provides data. This research has been cited 44 times.
(Ivan O Rosas, et al. [29])	2021	27.1	Low risk	High quality	Phase 3; multicentre; double-blind; randomized; placebo-controlled; 649 enrolled patients; medium effect size; acknowledges limitations; provides data. This research has been cited 94 times.
(Andreas Barratt-Due, et al. [30])	2021	19.6	Low risk	High quality	Randomized; placebo group; 185 patients; is registered; acknowledges limitations; provides data. This research has been cited 88 times.
(Ruanne V Barnabas, et al. [51])	2021	19.6	Low risk	High quality	Multicentre; double-blind; randomized; control group; 407 participants; low effect size; is registered; acknowledges limitations; provides data. This research has been cited 79 times.
(Ilan S Schwartz, et al. [52])	2021	17.4	Low risk	High quality	Double-blind; randomized; placebo group; 89 participants; medium effect size; is registered; acknowledges limitations; provides data. This research has been cited 33 times.
(Myron J Levin, et al. [41])	2022	158.5	Low risk	High Quality	Phase 3; multicentre; double-blind; randomly assigned; placebo group; 3 trials, we enrolled adults; medium effect size; is registered; acknowledges limitations. This research has been cited 504 times.
(Angélica Jayk Bernal, et al. [46])	2022	158.5	Low risk	High Quality	Phase 3; double-blind; randomized; placebo-controlled; 1550 participants; medium effect size; is registered; acknowledges limitations. This research has been cited 1366 times.
(Jennifer Hammond, et al. [35])	2022	158.5	Low risk	High Quality	Phase 2; double-blind; randomized; placebo group; 2246 patients; is registered; acknowledges limitations. This research has been cited 1482 times.

(Robert L Gottlieb, et al. [31])	2022	158.5	Low risk	High Quality	Double-blind; randomized; placebo-controlled; 562 patients; medium effect size; is registered; acknowledges limitations. This research has been cited 829 times.
(Zelalem Temesgen, et al. [42])	2022	76.2	Low risk	High Quality	Phase 3; double-blind; randomized; placebo-controlled; 528 patients; medium effect size; is registered. This research has been cited 49 times.
(Florence Ader, et al. [32])	2022	56.3	Low risk	High quality	Phase 3; multicentre; randomized; control group; 857 participants; medium effect size; is registered. This research has been cited 252 times.
(Self, et al. [43])	2022	56.3	Low risk	High quality	Double-blind; randomized; placebo-controlled; 546 patients; low effect size; is registered. This research has been cited 153 times.
(Mila B Ortigoza, et al. [50])	2022	22.5	Low risk	High Quality	Multicentre; double-blind; randomized; placebo-controlled; 941 participants; is registered; acknowledges limitations. This research has been cited 68 times.
(Fischer, et al. [45])	2022	15.8	Low risk	High Quality	Phase 2a; multicentre; double-blind; randomized; placebo-controlled; 202 unvaccinated participants with confirmed SARS-CoV-2 infection and symptom duration; is registered. This research has been cited 264 times.
(Jens D Lundgren, et al. [44])	2022	19.6	Low risk	High Quality	Multicentre; unblinded; randomized; placebo-controlled; 314 participants; medium effect size; is registered; acknowledges limitations. This research has been cited 56 times.
(Karim Ali, et al. [33])	2022	17.4	Low risk	High quality	Multicentre; randomized; control group; 1282 patients; is registered; acknowledges limitations. This research has been cited 116 times.
(David M Lowe, et al. [34])	2022	15.8	Low risk	High Quality	Phase 2; double-blind; randomized; placebo-controlled; 240 participants; is registered; acknowledges limitations; provides data. This research has been cited 19 times.

Research Question Formulation

What is the efficacy, safety, outcomes (viral load reduction, viral clearance) of novel antiviral therapies for the treatment of mild, moderate, and severe symptoms in SARS-CoV-2 patients?

Inclusion Criteria

In this review, only RCTs in which adult patients of either gender diagnosed or suspected SARS-CoV-2 patients from 2020 to 2024 are included. All studies which are in English language, full text language, peer-reviewed, and open-access published in journals having more than 15 impact factors as per Clarivate journal citation report of web of science. The inclusion criteria of more than 15 impact factor are set to retrieve high impact factors randomized controlled trails studies to ensure robustness while synthesis evidence from high-impact factor journals. Only studies focused on novel antiviral therapies (including, but not limited to, Remdesivir, Molnupiravir, Favipiravir, and monoclonal antibodies) were selected.

Exclusion Criteria

Observational studies, case reports, case series, retrospective case series, retrospective chart reviews, Ambispective, systematic reviews, narrative reviews, meta-analyses, letters, editors, and communications were not included. Studies not in English language, paid, published in non-peer reviewed and having less than 15 impact factors were excluded. Studies which were focused on other than COVID-19 emerging infections were not considered.

Studies Selection Process

Two independent reviewers did the selection. In case of conflict, consensus was reached through discussion [21]. The initial recorded studies were screened through abstract and titles reading. The preset exclusion criteria excluded irrelevant studies. Third, eligibility criteria were determined by reading comprehensively in-depth articles as per pre-specified inclusion criteria. Methodological quality assessment was performed on included studies. To ensure reliability, high-quality studies published in journals with impact factors over 15 were selected.

Quality Assessment

Cochrane Risk of Bias 2.0 categorized studies as high, low, or some concern for bias [22]. GRADE assessed trial recommendation strength. Based on bias risk, GRADE assumptions were applied to determine evidence recommendation strength. High-quality studies had little risk of bias, while uncertain and high-risk studies were considered "moderate" and "low" quality evidence. This evidence-synthesizing systematic review included only high-quality studies [23].

Data Extraction and Synthesis

Data were extracted from included RCTs such as study designs, sample size characteristics (age, gender, disease duration, intervention, and controls), novel antiviral therapies, dosage, duration, comparator, outcomes measures, safety outcomes, clinical outcomes, objectives, contributions, and methodological quality assessment. The data was entered in an Excel spreadsheet. The datasheet also contained information about conflict of interest among authors, data availability, ethical concerns, and the number of times the articles were cited. The analysis of the studies was done using a systematic approach. A data was analyzed and synthesized based on thematic analysis approach withdrawing themes and sub-themes [22]. It involves the in-depth analysis of the convergence of these results and a

review through an iterative approach. The theme's critical appraisal aimed to analyze the evidence in order to ensure an informed, evidence-based understanding of novel clinical and safety outcomes for antiviral drugs.

Ethical Consideration

The review was conducted on humans using the Helinski declaration to ensure patient benefit. There was no conflict among the authors. The review was conducted in accordance with PRISMA guidelines to ensure the best evidence-based practice that other authors can replicate in the future (Figure 1). It will be published to disseminate the findings in the best interests of the public.

Results

This review synthesized evidence using PRISMA guidelines. PubMed, Embase, and Cochrane library databases yielded 465 articles using keywords, text words, and controlled vocabulary on the initial search. EndNote x9 identified and eliminated 40 duplicate articles. For screening, 425 articles were chosen. One hundred sixty-two irrelevant articles were deleted after title and abstract screening. Two hundred and ten RCTs met pre-specified inclusion criteria by reading in-depth research.

Risk of Bias Assessment

The methodological quality of 210 RCTs was examined using Cochrane risk of bias 2.0, which assessed five domains of each randomized controlled trial. ROB 2.0 tool classified RCTs into nine (09) high-risk and eighty-seven (87) low-risk, and 114 studies have uncertain risk of bias. Thirty (30) out of 87 low risks of bias RCTs were included in the review because these 30 RCTs retrieved from the journals that had impact factors of more than 15 according to Clarivate Journal citation analysis of Web of Science (Table 2).

Table 2: Characteristics of included studies.

Author	Year	Location	Sample Size	Age (mean ± SD)	Gender (% male)	Severity of Disease	Antiviral Therapy	Dosage	Duration (days)	Comparator	Primary Efficacy Outcome	Primary Safety Outcome	Effect Size (95% CI)	P-Value
(Peter Horby, et al. [23])	2020	UK	1561	65.4±15.3	62%	Mild to Severe	Hydroxy-chloroquine	200-800mg Tablet	3 to 10	usual-care	28 days mortality	Discharge from hospital within 28 days, Invasive mechanical ventilation	1.09 (0.97–1.23) rate ratio*	0.15
(Spinner, et al. [24])	2020	USA, Europe, Asia.	584	57 (interquartile range, 46-66)	61%	Moderate to severe	Remdesivir	200 mg (1st day), 100 mg/d IV	5 to 10	standard care	efficacy of on clinical status at 11th day	Discharge	1.65 (1.09-2.48)	0.02*
(Yeming Wang, et al. [25])	2020	China	237	65 years (IQR 56–71)	56%	Severe	Remdesivir	200 mg (1st day), 100 mg/d IV	10	placebo	clinical improvement within 28 days	Adverse events (102 (66%) Vs 50 (64%)	Hazard ratio 1.23(0.87-1.75)	0.24
(Ivan Fan Ngai Hung ,et al. [36]) al. (26)	2020	Hong Kong	127	52 years (IQR 32–62)	54%	mild to moderate	combination (lopinavir +ritonavir ribavirin)+ (interferon beta-1b) on alternate days	(400 mg+100 mg+400 mg every 12 h)+ 3 doses 8 million IU IF-beta-1b	14-days	oral lopinavir–ritonavir	negative RT-PCR result for SARS-CoV-2	self-limited nausea and diarrhoea with no difference between groups for adverse effects	Hazard Ratio 4·37(1·86–10·24)	0·0010*
(Meagan P O'Brien et al. [37])	2021	USA	1505	42.9	45.90%	severe	REGEN-COV (casirivimab imdevimab)	1200 mg SC	2-4 weeks	placebo	development of symptomatic SARS-CoV-2 infection through day 28	reduction in symptomatic disease & high viral load	RR 81.4%	0.001*
(Jens Lundgren, et al. [39])	2021	USA	314	Median 61 (49–71)	56%	Moderate to severe	LY-CoV555+ Remdesivir	7000 mg	5 to 9 days	placebo	sustained recovery during a 90-day period, favourable pulmonary outcomes (similar)	Similar Safety outcome odds ratio 1.56;(0.78 to 3.10) P = 0.20	Odds ratio 0.85(0.56-1.29)	0.45

(André C. Kalil, et al. [27])	2021	USA (55 sites), Singapore (4), South Korea (2), Mexico (2), Japan, Spain, UK Denmark	1033	55.4	63.10%	severe	Combination (baricitinib+Remdesivirr)	Remdesivir 200 mg IV at day one, maintenance dose of 100mg/d up to 10 days, Baricitinib 4mg/d until 14 days	10 to 14	placebo	time to recovery, clinical status at day 15	few side effects in combination -5 points (-9.8 to -0.3; p=0.03)	rate ratio rcovery1.16 (1.01 to 1.32)	0.03*
(Patricia O Guimarães, et al. [47])	2021	Brazil 15 sites	289	56±14	65.10%	Moderate to severe	tofacitinib (effective lower risk of death and resp failure)	10 mg	14 days	placebo	occurrence of death or respiratory failure through 28 days	Adverse effects (14.1% vs 12%)	risk ratio, 0.63(0.41-0.97)	0.04*
(Robert L Gottlieb al. [38])	2021	USA	577	44.7+15.7	45.40%	mild to moderate	Bamlanivimab alone **VS** Combination (Bamlanivimab etesevimab)	700 mg, 2800 mg, 7000 mg, (2800+2800 each in combination)	11 (±4 days)	placebo	Change in SARS-CoV-2 log viral load at day 11 (±4 days).	Hypersensitivity reactions in 9 patients of bamlanivimab, 2 combination treatment, and 1 placebo), no death reported.	-0.57 (95% CI, -1.00 to -0.14;	0.01* significant only for combination group
(Myron S. Cohen, et al. [39])	2021	USA	966	53.0 (range, 18-104)	25.30%	Moderate to severe	Bamlanivimab monotherapy	single infusion 4200 mg	8 weeks	placebo	incidence of COVID-19 with moderate or worse	Rate of adverse effect (20.1% vs 18.9%); UTI (2% vs 2.4%); hypertension (1.2% vs 1.7%); All 5 deaths occur in placebo group	odds ratio 0.43 (0.28-0.68)	<0.001*
(Phillip Monk, et al. [48])	2021	nine UK sites	101	57·1+13·26	59%	Severe	interferon beta-1a (SNG001) (6 MIU)	I-neb nebulizer/d	14 to 28 days	placebo	change in clinical condition on the WHO Ordinal Scale for Clinical Improvement	Headache (15% vs 10%), three deaths in placebo group, none in SNG001 as it reported as well tolerated.	odds ratio 2·32(1·07-5·04)	**0·033***
(André C. Kalil, Aneesh K. Mehta et al. [28])	2021	Japan, Mexico, Singapore, South Korea, USA	969	58·7+15·9	58%	Moderate to severe	interferon beta-1a plus Remdesivir	200 mg at day 1 (100 mg up to 10 days) Remdesivir, four doses of 44 microgram Interferon beta 1a	10 to 28 days	placebo plus Remdesivir	time to recovery, change in clinical condition on the WHO Ordinal Scale for Clinical Improvement	Compared to placebo Remdesivir, patients who needed high-flow oxygen at baseline experienced 69% vs 39% adverse effects and 60% vs 24% significant adverse effects.	Time to recovery 5 days in both groups (rate ratio of interferon beta-1a plus Remdesivir group vs placebo plus Remdesivir 0·99 (0·87-1·13)	0·88
(Jordan J Feld, et al. [49])	2021	Canada	60	Mean 46 (IQR 32–54)	42%	mild-to-moderate	peg interferon lambda	subcutaneous injection 180 µg	7 days	Placebo	negative (SARS-CoV-2) RNA on day 7, adjusted viral load	well tolerated, and adverse events; Two individuals met the threshold of grade 3 increase, one in each group	Lambda group more likely to had undetectable viral load at day 7, odds ratio 4·12 (1·15-16·73)	0·029*

(Huijie Bian et al. [40])	2021	China, USA, Pakistan, Brazil, Mexico	167	Median 47 (18–80)	70.10%	severe	Meplazumab	0.12 mg/kg	14 to 29 days	Placebo	Mortality, viral load, cytokines levels, clinical improvement	89.5% shortness of breath,78.4% cough, 69.8% fatigue or unwell, 97.5% no ICU or HDU stay, no patient undergo invasive mechanical ventilation	Compared to placebo, the 0.12 mg/kg group had a significant increase in response rate (16.0% and 8.0%, respectively), clinical improvement (30.9%), and negative rates (viral load) on day 29 (53.9%, 81.0%, 91.7%, and 65.2%, respectively).	<0.05*
(Ivan O Rosas, et al. [29])	2021	USA, UK, Spain, Brazil, Russia	649	60.1±13.3 58.2±13.3	63.28%	severe	Tocilizumab+ Remdesivir	8 mg/kg	28 to 60 days	placebo+ Remdesivir	time for ready for discharge or when they achieved category 1 on 7 point OSCI scale	By day 28, 128 (29.8%) tocilizumab plus remdesivir and 72 (33.8%) placebo plus remdesivir patients had serious adverse events, and 78 (18.2%) and 42 (19.7%) died.	Median time "ready for discharge" was 14 (95% CI 12-15) days with tocilizumab plus remdesivir and 14 (95% CI 11-16) days with placebo plus remdesivir; ; Cox proportional hazards ratio 0.97 (95% CI 0.78-1.19)	0.74
(Andreas Barratt-Due, et al. [30])	2021	Norway	185	59.8+15.3	65.70%	Moderate to severe	Remdesivir+SOC	200 mg loading dose, 100 mg maintainence	9 to 10 days	Hydroxychloroquine (800mg to 400mg)+ SOC	In-hospital mortality; the degree of respiratory failure and inflammation; and viral clearance in the oropharynx.	There were no significant changes in hospitalization mortality. SARS-CoV-2 load in the oropharynx decreased significantly in the first week, with equivalent 10-day virus levels in the remdesivir, HCQ, and SoC groups. Both drugs didn't influence plasma or serum inflammatory variables or respiratory failure.	mean viral load 2(1.6%), in-hospital mortality was 6.6%	>0.05
(Ruanne V Barnabas, et al. [51])	2021	USA	671	39 ((IQR), 27 to 51)	40%	Severe	Hydroxychloroquine	(400 mg/d for 3 days followed by 200 mg/d	11 days	Ascorbic acid (500 mg/d followed by 250 mg/d) as a placebo-equivalent control.	PCR-confirmed incident SARS-CoV-2 infection	adverse events were higher in the hydroxychloroquine group than the control group (66 (16.2%) versus 46 (10.9%), respectively; P = 0.026)	Hazard ratio 1.10(0.73 to 1.66)	>0.20
(Ilan S Schwartz, et al. [52])	2021	Canada	148	46.7 ± 11.5 46.9 ± 11.0	55.40%	severe	Hydroxychloroquine			Placebo	The composite of hospitalization, invasive mechanical ventilation or death within 30 days. serious adverse events and mortality	4(3.6%) patients met primary outcomes in HCQ treated for Hospitalization and discharge	Serious adverse events 3(3.3%), Emesis 5(5.5%) Hospitilaization 3(3.3%) in HCQ treated, none in placebo	0.6

(Myron J Levin, et al. [41])	2022	USA, UK, Belgium, France, Sweden	5197	53.5±15.0	53.90%	severe	combination AZD7442 (tixagevimab and cilgavimab)	300 mg	83 days	Placebo	incidence of adverse events, symptomatic Covid-19 confirmed by TR-PCR	Symptomatic Covid-19 occurred in 8(0.2%) AZD7442 group and 17(1.0%) in placebo., Five severe or serious Covid-19 cases and two deaths occurred in the placebo group.	relative risk reduction, 76.7% (46.0 to 90.0)	<0.001*
(Angélica Jayk Bernal, et al. [46])	2022		1433	43.0 (18–90)	48.70%	mild-to-moderate	Molnupiravir	800 mg	5 days	Placebo	incidence hospitalization or death at day 29, incidence of adverse effects	death; 1 in Molnupiravir, 9 in placebo, adverse events; 30.4% vs 33%(placebo)	the risk of hospitalization for any cause or death through day 29 was lower with Molnupiravir 7.3% VS 14.1%, difference, -6.8 percentage points; (-11.3 to -2.4)	0.001*
(Jennifer Hammond, et al. [35])	2022	USA, UK, Mexico	2246	46.00 (18.00–88.00)	51.10%	severe	Nirmatrelvir ritonavir	Nirmatrelvir (300 mg), ritonavir (100 mg)	6 days	placebo	hospitalization or death from any cause through day 28, viral load, and safety	(Study group; placebo); Total Death;(0 vs 13(placebo), viral load (-0.868 log10 copies per milliliter) lower in intervention group, Adverse events (22.6% vs 23.9%), serious adverse event (1.6% vs 6.6%), adverse events lead to discontinuation (2.1% vs 4.2%), Dysgeusia (5.6% vs 0.3%), diarrhea (3.1% vs 1.6%)	Hospitalization or death by day 28 was 6.32% points lower in the Nirmatrelvir group than in the placebo group (-9.04 to -3.59)	<0.001*
(Robert L Gottlieb, et al. [31])	2022	USA, Germany, Spain, UK	562	50 years,	52.10%	moderate-to-severe	Remdesivir	(200 mg on day 1 and 100 mg on days 2 and 3)	3 to 28 days	placebo	hospitalization or death from any cause by day 28, safety end point was any adverse event	No patient died in Remdesivir group, Adverse events (42.3% vs 46.3%)	Hospitalization or death (Remdesivir; Placebo), (0.7% vs 5.3%) (Hazard ratio, 0.13; 0.03 to 0.59;)	0.008*
(Zelalem Temesgen, et al. [42])	2022	USA, Brazil	479	61+14	65%	moderate-to-severe	Lenzilumab	600 mg per dose	28 days	Placebo	survival without invasive mechanical ventilation, Adverse events for safety evaluation	At least one adverse event (27% vs 33%) grade 3 in severity based on CTCAE criteria. No death was reported.	Survival without mechanical ventilation (Lenzilumab Vs Placebo; 84% vs 78%); hazard ratio 1·54(1·02-2·32)	0.04*
(Florence Ader, et al. [32])	2022	France, Belgium, UK, Austria, Portugal, Luxembourg	857	64 (54–73)	70%	moderate-to-severe	Remdesivir+standard of care	200 mg loading dose, 100 mg maintainence	10 to 15 days	standard of care	Clinical status at day 15 measured by the WHO seven-point ordinal scale and safety.	No difference in adverse events (0.48),Three (03) deaths due to emdesivi.	(odds ratio 0·98(0·77-1·25)	0.85

(Self, et al. [43])	2022	USA, Denmark, Switzerland, Poland	536	61 (50–74), 60 (49–70), 61 (50–71)	57.50%	moderate-to-severe	Sotrovimab	500 mg dose of Sotrovimab	7, 14, 28 days	(Placebo group) and (BRII-196 plus BRII-198), 1000mg of each	time to sustained clinical recovery, Safety was based on composite of death, serious adverse events, incident organ failure, and serious coinfection up to day 90 after randomisation	Clinical recovery; (placebo;85%; sotrovimab;88%;BRII-196 plus BRII-198;88%), Safety outcomes (placebo;27%); sotrovimab;23%;BRII-196 plus BRII-198;26%) Death (7%;8%;9%) respectively at 90 day met.	Sotrovimab;1·12 (I 0·91–1·37) , BRII-196 plus BRII-198;1·08 (0·88–1·32).	>0.05
(Mila B Ortigoza, et al. [50])	2022	USA	941	63 years (IQR, 52-73)	59.10%	moderate-to-severe	COVID-19 convalescent plasma (CCP)	250 mL of CCP or equivalent volume of placebo (normal saline)	14 to 28 days	Placebo	The 11-point World Health Organization (WHO) Ordinal Scale for Clinical Improvement on day 14, Efficacy of CCP was defined as a cumulative adjusted odds ratio (cOR) less than 1 and a clinically meaningful effect as cOR less than 0.8.	Adverse events (placebo;8.2%, CCP;9.4%) p=0.57, Transfusion reactions (Placebo; 0.4%, CCP;1.7%) p=0.06	Heterogeneity of treatment effect: at day 28, cORs were 0.72 (95% CrI, 0.46-1.13; P(cOR<1) = 93%); 0.65 (95% CrI, 0.41 to 1.02; P(cOR<1) = 97%) for those not receiving remdesivir and not receiving corticosteroids at randomization.	1.0
(Fischer, et al. [45])	2022	USA	202	19 to 82 years	48.50%	Severe	Molnupiravir	200 mg; 400mg; 800mg	4 weeks	placebo	Time to viral RNA clearance, viral load clearance, Infectious virus detection	well tolerated among all dose 200 to 800 mg, Adverse event (Molnupiravir 200mg; 47.8%; 400mg; 32.3%; 800mg; 20%; placebo;29%),1(1.6%) patient lead to hypoxia which died eventually	Median Time to viral RNA clearance (Molnupiravir-800mg;14 days, Placebo; 15 days). Viral clearance (Molnupiravir-800mg;92.5%, Placebo; 80.3%), Infectious virus (1.9% vs 16.7%)	<0.016*

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(Jens D Lundgren, et al. [44])	2022	USA	314	61 (49, 71)	56%	Moderate to severe	Bamlanivimab	7000 mg	4 weeks to 90 days	placebo	"pulmonary" and "pulmonary-plus" assessed at day 5, serological and virological assay, time to sustained recovery, mortality, serious adverse events, end organ disease, and serious infections	Composite outcome safety (Bamlanivimab; 28%; placebo; 19%)	Sustained recovery (Bamlanivimab; 88%; placebo;90%), sHR=0.99 (95% CI:0.79–1.22; p=0.89) Sustained recovery in (Bamlanivimab nAb negative; 91%;85%, Bamlanivimab nAb positive 87%: placbo 96%)	0.89
(Karim Ali, et al. [33])	2022	Canada	1282	65(53-77)	59.80%	Moderate to severe	Remdesivir+SOC	200 mg loading dose, 100 mg maintainence	14 to 28 days	Standard care	in hospital mortality, clinical severity, oxygen- and ventilator-free days (at 28 d), incidence of new oxygen or mechanical ventilation use, duration of hospital stay, and adverse event rate	No difference in safety events, mechanical ventilation (Remdesivir;8%: SOC;15%)	in hospital mortality (Remdesivir+SOC; 18.7%; SOC alone: 22.6%), −3.9 (−8.3 to 1.03), secondary outcomes improved, not difference found regard to mortality	0.09
(David M Lowe, et al. [34])	2022	UK	240	40.0+12.2	51.20%	mild to moderate	favipiravir+plcebo, lopinavir-ritonavir	Favipiravir 200-mg, lopinavir--ritonavir (200-mg/ 50-mg)	5 days	Favipiravir, placebo	viral load at Day 5	Treatment related adverse event (57%), While comparing lopinavir-ritonavir monotherapy (93%); favipiravir+ lopinavir-ritonavir (88%) reported majority of adverse events	the mean viral load in the favipiravir+plcebo arm had changed by −0.57 log10 (95% CI −1.21 to 0.07, p = 0.08) and in the lopinavir-ritonavir+-placebo arm by −0.18 log10 (95% CI −0.82 to 0.46, p = 0.58) compared to the placebo arm at Day 5, More participants had undetectable virus at Day 5 in the favipiravir+placebo arm compared to placebo only (46.3% versus 26.9%, odds ratio (OR): 2.47, 95% CI 1.08 to 5.65; p = 0.03)	0.03*

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

The 30 included RCTs were of low risk of bias RCTs. Therefore, it was upgraded to High quality according to the GRADE tool assumptions. Moreover, 114 RCTs that had unclear risk of bias have downgraded the quality of evidence to "moderate quality." However, the remaining 09 RCTs were of high risk of bias and rated as "low quality" (Table 2).

Characteristics of Included Studies

The characteristics of included 30 RCTs, categorized as "high quality," had 10,941 patients with a mean age of 49 years ranging between 19 and 90 years. The majority of patients were in middle or late adulthood. The gender distribution is almost equally among groups, with 55% of whom were males. Each RCT compared novel antiviral therapies with standard of care, usual care, and placebo. The effect of each novel therapy had an equal comparator to determine the significance of novel antiviral therapies that are mentioned in Table 3. The key highlights and findings are also presented in Table 3.

Table 3: Key findings and highlights of included studies.

Author	Year	Findings
(Peter Horby, et al. [23])	2020	The results suggest that patients in the Hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98)
(Spinner, et al. [24])	2020	On day 11, patients in the 5-day Remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; P = .02) Nausea (10% vs 3%), hypokalemia (6%)
(Yeming Wang, et al. [25])	2020	Eligible patients were adults (aged ?18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment of 12 days or less, oxygen saturation of 94% or less on room air or a ratio of arterial ox
(Ivan Fan Ngai Hung ,et al. [36])	2020	The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days (IQR 5-11)) than the control group (12 days; hazard ratio 4·37 (95% CI 1·86-10·24), p=0·0010)
(Meagan P O'Brien et al. [37])	2021	The primary efficacy end point was the development of symptomatic SARS-CoV-2 infection through day 28 in participants who did not have SARS-CoV-2 infection (as measured by rtRNA-PCR assay)
(Jens Lundgren, et al. [39])	2021	The percentage of patients with the primary safety outcome (a composite of death, serious adverse events, or clinical grade 3 or 4 adverse events through day 5) was similar in the LY-CoV555 group and the placebo group (19% and 14%, respectively; odds ratio
(André C. Kalil, et al. [27])	2021	Patients receiving Baricitinib had a median time to recovery of 7 days (95% confidence interval (CI), 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P = 0.03), and 30% higher odds of
(Patricia O Guimarães, et al. [47])	2021	The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval (CI), 0.41 to 0.97; P = 0.04)
(Robert L Gottlieb al. [38])	2021	Findings In the phase 2 portion of a randomized phase 2/3 clinical trial with 577 patients, there was no significant difference in change in viral load with 3 different doses of Bamlanivimab monotherapy compared with placebo; treatment with a combination.
(Myron S. Cohen, et al. [39])	2021	Bamlanivimab significantly reduced the incidence of COVID-19 in the prevention population compared with placebo (8.5% vs 15.2%; odds ratio, 0.43 (95% CI, 0.28-0.68); P < .001; absolute risk difference, -6.6 (95% CI, -10.7 to -2.6) percentage points)
(Phillip Monk, et al. [48])	2021	Patients receiving SNG001 had greater odds of improvement on the OSCI scale (odds ratio 2·32 (95% CI 1·07–5·04); p=0·033) on day 15 or 16 and were more likely than those receiving placebo to recover to an OSCI score of 1 (no limitation of activities)
(André C. Kalil, Aneesh K. Mehta et al. [28])	2021	Combination treatment with Baricitinib and Remdesivir was safe and superior to Remdesivir alone for hospitalized Covid-19 patients, showing faster recovery and improved clinical status. Baricitinib plus Remdesivir was superior to Remdesivir alone.
(Jordan J Feld, et al. [49])	2021	The decline in SARS-CoV-2 RNA was greater in those treated with peg interferon lambda than placebo from day 3 onwards, with a difference of 2·42 log copies per mL at day 7 (p=0·0041)
(Huijie Bian et al. [40])	2021	The meplazumab treatment significantly improved the discharged (P = 0.005) and case severity (P = 0.021), and reduced the time to virus negative (P = 0.045) in comparison to the control group

(Ivan O Rosas, et al. [29])	2021	Median time from randomization to hospital discharge or "ready for discharge" was 14 (95% CI 12–15) days with Tocilizumab plus Remdesivir and 14 (95% CI 11–16) days with placebo plus Remdesivir (log-rank P = 0.74; Cox proportional hazards ratio 0.97 (95
(Andreas Barratt-Due, et al. [30])	2021	Difference in daily viral decrease rate, 0.113 (95% CI, –0.001 to 0.227) Difference in daily viral decrease rate, 0.028 (95% CI, –0.084 to 0.139) In addition to a large difference in sample size and only Remdesivir and HCQ used as active treatment
(Ruanne V Barnabas, et al. [51])	2021	The frequency of participants experiencing adverse events was higher in the Hydroxychloroquine group than the control group (66 (16.2%) versus 46 (10.9%), respectively; P = 0.026). The delay between exposure, and then baseline testing and the first dose of
(Ilan S Schwartz, et al. [52])	2021	Statistical analysis the absolute effect size was estimated based on the Italian experience, assuming that up to 20% of the Alberta population (4.4 million) could acquire SARS-CoV-2 infection (n = 840 000), that 16% of those infected (n = 134 400) could r
(Myron J Levin, et al. [41])	2022	Symptomatic Covid-19 occurred in 8 of 3441 participants (0.2%) in the AZD7442 group and in 17 of 1731 participants (1.0%) in the placebo group (relative risk reduction, 76.7%; 95% confidence interval (CI), 46.0 to 90.0; P<0.001); extended follow-up at a m
(Angélica Jayk Bernal, et al. [46])	2022	The superiority of Molnupiravir was demonstrated at the interim analysis; the risk of hospitalization for any cause or death through day 29 was lower with Molnupiravir (28 of 385 participants (7.3%)) than with placebo (53 of 377 (14.1%)) (difference, ?6.8
(Jennifer Hammond, et al. [35])	2022	In the planned interim analysis of patients treated within 3 days after symptom onset (modified intention-to treat population, comprising 774 of the 1361 patients in the full analysis population), the incidence of Covid-19–related hospitalization or death
(Robert L Gottlieb, et al. [31])	2022	Covid-19-related hospitalization or death from any cause occurred in 2 patients (0.7%) in the Remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval (CI), 0.03 to 0.59; P = 0.008)
(Zelalem Temesgen, et al. [42])	2022	Survival without invasive mechanical ventilation to day 28 was achieved in 198 (84%; 95% CI 79-89) participants in the Lenzilumab group and in 190 (78%; 72-83) patients in the placebo group, and the likelihood of survival was greater with Lenzilumab than
(Florence Ader, et al. [32])	2022	The difference between treatment groups was not significant (odds ratio 0·98 (95% CI 0·77-1·25); p=0·85) There was no significant difference in the occurrence of serious adverse events between treatment groups (Remdesivir, 135 (33%) of 406 vs control,
(Self, et al. [43])	2022	At day 5, neither the Sotrovimab group nor the BRII-196 plus BRII-198 group had significantly higher odds of more favorable outcomes than the placebo group on either the pulmonary scale (adjusted odds ratio Sotrovimab 1·07 (95% CI 0·74-1·56); BRII-196.
(Mila B Ortigoza, et al. [50])	2022	The statistical analysis plan specified that the DSMB consider stopping the trial for success with P (cumulative adjusted odds ratio (cOR)<1) greater than or equal to 95% and P(cOR<0.8) greater than or equal to 50% (statistical analysis plan in Supplement
(Fischer, et al. [45])	2022	Infectious virus (secondary endpoint) was detected in swabs from 1.9% of the 800-mg Molnupiravir group compared with 16.7% of the placebo group at day 3 of treatment (P =0.016) At day 5 of treatment, infectious virus was not isolated
(Jens D Lundgren, et al. [44])	2022	Patients were followed for 90 days for sustained recovery (defined as discharge to home and remaining home for 14 consecutive days) and a composite safety outcome (death, serious adverse events, organ failure, or serious infections). Among 314 participants
(Karim Ali, et al. [33])	2022	Among patients assigned to receive Remdesivir, in-hospital mortality was 18.7%, compared with 22.6% in the standard-of-care arm (relative risk (RR) 0.83 (95% confidence interval (CI) 0.67 to 1.03), and 60-day mortality was 24.8% and 28.2%, respectively (9
(David M Lowe, et al. [34])	2022	In the primary analysis, the mean viral load in the Favipiravir placebo arm had changed by -0.57 log10 (95% CI -1.21 to 0.07, p = 0.08) and in the lopinavir-ritonavir+placebo arm by -0.18 log10 (95% CI -0.82 to 0.46, p = 0.58) compared to the placebo arm

Types of Anti-Viral Therapies Evaluated

In this review, combination of Protease inhibitors (Nirmatrelvir and Ritonavir), (Lopinavir Ritonavir), Polymerase inhibitors (Remdesivir), Nucleoside analogue (Molnupiravir), Monoclonal antibodies (Bamlanivimab monotherapy and combination with etesevimab, Sotrovimab, Lenzilumab), Immunomodulators (Interferon, Tofacitinib, Hydroxychloroquine) novel antiviral therapies were used. Each study compared novel anti-viral therapy as an intervention with the standard of care, placebo, or control group with an equal ratio of 1:1. These novel antiviral therapies had effectively treated patients of mild, moderate, and severe SARS-CoV-2 affected patients. It also reported improvements in clinical outcomes and related side effects or adverse events due to each novel antiviral therapy.

Efficacy and Safety Outcomes of Novel Anti-Viral Therapies

Remdesivir

Remdesivir has been used in trials [24-33] to determine its efficacy. In all these trials, dosages of 200 mg for day one and a maintenance dose of 100mg were given among patients for a duration of 10 to 14 days to assess improvement in clinical outcomes such as hospital mortality, respiratory symptoms reduction, and clinical improvement score. Only two trials, (Gottlieb, et al. [31]); (Spinner, et al. [24]) found statistically significant differences while comparing it with the standard of care, usual care, or placebo ($p<0.05$) [24, 31]. However, the remaining studies showed no statistical difference ($p>0.05$). During assessment of the safety of Remdesivir, only (Ader, et al. [32]) reported three deaths due to remdesivir comparing its effect with the standard of care [32]. There is no significant difference in adverse events reported due to Remdesivir when given among patients with the standard of care and placebo in any of the above-mentioned trials. However, (Kalil, et al. [27,28]), [27, 28] both applied combination therapy of interferon beta-1a and baricitinib with remdesivir. (Kalil, et al [28]) found that Remdesivir showed better efficacy in combination with Baricitinib than prescribed alone. Therefore, a faster recovery has been evident when this combination is prescribed among SARS-CoV-2 patients. On the other hand, (Kalil, et al [27]) demonstrate that the combination of interferon beta-1a and remdesivir did not demonstrate superiority over remdesivir alone in hospitalized COVID-19 pneumonia (p=0.88) [28].

Protease Inhibitors

The effect size and safety outcomes for protease inhibitors were compared in the three included studies, taking into account differences in dosage, duration, and severity of the disease. (Lowe, et al. [34]) studied the efficacy of Favipiravir alongside lopinavir-ritonavir, involving 240 participants with mild to moderate COVID-19 from the UK [34]. The study revealed a notable viral load reduction (OR: 2. 47, p = 0. 03), although they are characterized by high adverse events, especially those on lopinavir-ritonavir monotherapy (93%). In a randomized trial by (Hammond, et al. [35]), 2246 hospitalized severe COVID-19 patients from the USA, UK, and Mexico received ivermectin. The intervention group had a lower incidence of hospitalization or death by day 28 ($p<0.001$), lower viral load, and fewer severe adverse events [35]. However, (Hung, et al. [36]) from Hong Kong involving 127 patients with mild to moderate COVID-19 prescribed lopinavir-ritonavir, ribavirin, and IFN beta-1b. They reported a significantly lower hazard ratio of reporting RT-PCR negative compared to the control group (p = 0. 0010) with minimal side effects [36]. The findings suggest that protease inhibitors can be effectively used with other therapies, and their efficacy and safety may significantly differ. Among them, Nirmatrelvir and ritonavir were deemed to have a strong indication for use in severe cases, with reported reductions in severe outcomes and a favorable safety profile [34-36].

Monoclonal Antibodies

The drugs belonging to monoclonal antibodies had been used in nine included RCTs with varying efficacy and safety outcomes. (O'Brien, et al. [37]) recently studied the impact of REGEN-COV (Casirivimab and Imdevimab) in severe COVID-19: a 1200 mg vitamin D subcutaneous dose proved effective in decreasing the emergence of symptomatic SARS-CoV-2 infection by day 28 with an RR of 81 [37]. On the other hand, (Gottlieb, et al. [38]) evaluated Bamlanivimab alone and its combination with Etesevimab in moderate to mild cases [38]. The study showed that the combination treatment decreased the viral load of SARS-CoV-2 at day 11 (p=0. 01), while Bamlanivimab alone did not make a statistically significant difference. (Cohen, et al. [39]) state that in moderate to severe conditions, Bamlanivimab monotherapy reduced moderate or worse COVID-19 by having an odd ratio of 0. 43($p<0. 001$), and it pointed out that all five of the deaths were in the placebo group [39]. Furthermore, it is agreed that all five of the deaths were in the placebo group (p=0.00). Another study of Bian et al. [40] on Meplazumab in severe settings also highlighted better clinical efficacy and significantly greater response rate compared with the placebo ($p<0. 05$) [40]. (Rosas, et al. [29]) conducted research on Tocilizumab plus Remdesivir with severe COVID-19 patients and concluded that median time to discharge was similar to placebo plus Remdesivir (p=0.74) [29]. (Levin, et al. [41]) also revealed that AZD7442 (tixagevimab and cilgavimab) in severe cases reduced the risk of having symptomatic COVID-19 infections by 76.7%, $p < 0. 001$ [41].

(Temesgen, et al. [42]) studied the efficacy of Lenzilumab in moderate to severe cases that led to an improvement of the primary efficacy endpoint of time to ventilator support or death (HR 1. 54; p 0. 04) [42]. In the study by (Self, et al. [43]), they evaluated the efficacy of Sotrovimab and realized that there were no variations in the clinical recovery or safety profile of the participants who received Sotrovimab as compared to the placebo group ($p>0.05$) [43]. Last, but not least, (Lundgren, et al. [44)], examining high-dose Bamlanivimab in moderate and severe SARS-CoV-2, observed that the likelihood of sustained recovery or any rate of perceived safety was no different from placebo (p=0. 89) [44]. The results suggested that monoclonal antibodies, including REGEN-COV and AZD7442, reduce SARS-CoV-2 symptoms and enhance clinical outcomes such as mortality, impairment, and discharge. The overall response varied among RCTs as most findings were not statistically significant and showed lower efficacy. Still, these studies did not analyze confounding variables that may impact treatment efficacy. Monoclonal antibody safety is substantial as most of the deaths occurred in placebo groups, or (Rosas, et al. [29]) reported 18.8% deaths in Tocilizumab plus Remdesivir group, which needed to be studied or distinguished [29]. There were no serious adverse effects, ensuring its safety. Researchers may utilize these to vaccinate the populace to reduce SARS-CoV-2 severity.

Nucleoside Analogue

The efficacy and safety of Nucleoside analogues, e.g., Molnupiravir, were investigated in two trials. (Fischer, et al. [45]) conducted trial on severe COVID-19. In this trail three doses of Molnupiravir were used: 200mg, 400mg, and 800mg, for four weeks. The study found that Molnupiravir was well-tolerated across all doses, with adverse events reported as follows: 47.4% for 200 mg, 32% for 400 mg, 3% for 800 mg, and 20% for the placebo: 29%. Another study pointed out one death in the Molnupiravir group; the patient experienced hypoxia. The time duration of treatment was 14 days in the 800 mg Molnupiravir group versus 15 days in the placebo arm. A viral clearance was much superior in the 800 mg group at 92.5% than the placebo group (80.3%). The number of participants positive for infectious virus count was remarkably lower in the 800 mg group (p < 0. 016). However, (Jayk Bernal, et al. [46]) focused on minimizing symptoms of COVID-19 and prescribed Molnupiravir at a dosage of 800 mg for only five days. This placed the proportion of patients who experienced a hospitalization or death by day 29 at a lower 7.3% in the Molnupiravir group as opposed to the placebo group 14.8%, (HR; -11. 3 to -2. 4), p=0.001. In the analysis, patients in the intervention group had a better improvement score than the control group. Mortality was reported as 1 with Molnupiravir and 9 with placebo group. The incidence of adverse events was somewhat lower in the Molnupiravir arm (30.4%) than in the placebo arm (33%). To conclude, Molnupiravir effectively treats mild, moderate, and severe SARS-CoV-2 infection with fewer side effects with only one case of mortality.

Immunomodulators

Five trials evaluated the efficacy of Immunomodulators in treating SARS-CoV-2 infections [47-50]. (Guimarães, et al. [47]) found Tofacitinib (10mg) for fourteen days as effective in lowering risk of death and respiratory failure while treating moderate to severe SARS-CoV-2 patients via reduction in inflammation and immune-mediated response in tissues (Janus-Kinase mechanism) as compared to placebo. The difference is statistically significant as p=0.04; however, 14.1% side effects were reported as compared to 12% side effects in placebo group [47]. Interferon beta-1a (SNG001) for nebulized therapy in severe COVID-19 was studied by (Monk, et al. [48]). They observed betterment in clinical status and no mortality associated with the treatment [48]. However, (Kalil, et al. [28]) gave interferon beta-1a together with remdesivir to moderate-severe patients. There was no difference in recovery duration but increased side effects in patients requiring high-flow oxygen [28]. A recent study by (Feld, et al. [49]) studied the efficacy of subcutaneous peg interferon lambda in mild to moderate cases. Which showed a significant reduction in viral load by day 7 [49]. (Mila B Ortigoza, et al. [50]) studies the effect of COVID-19 convalescent plasma. The use of COVID-19 convalescent plasma did not demonstrate a significant overall effectiveness in improving the clinical condition of hospitalized COVID-19 patients who needed non-invasive supplementary oxygen. However, it is possible that convalescent plasma with high levels of antibodies may have had some benefits during the early stages of the pandemic [50].

Overall, all the studies noted interferon and tofacitinib treatment to be significant effective in terms of improvement in clinical outcomes based on disease severity, time, and dose of interferon administered (p<0.05) except when Interferon beta-1a prescribed with remdesivir (p=0.88). Although, COVID-19 convalescent plasma showed no significant difference but higher levels antibodies may be beneficial which direct future researchers to do further studies which may validate the finding.

Hydroxychloroquine (HCQ)

HCQ dose, intensity, treatment time, and safety issues vary widely between existing published researches. In an open, non-comparative, 3–10-day UK trial; (Horby, et al. [23]) prescribed orally HCQ at 200-800 mg/day to COVID-19 patients. No substantial changes in adverse events and 28-day mortality rate were seen between HCQ and standard care (rate ratio: 1.09; 95% CI 0. 97–1. 23). In 671 severe COVID-19 patients (Barnabas, et al. [51]) [51] in the US randomly given HCQ (400 mg first and then 200 mg daily for 11 days) to a placebo-equivalent ascorbic acid control. The study found 16.2% adverse events in the HCQ group compared to 10.9% in control patients (P = 0.26). However, the hazard ratio of <0.20 did not affect clinical end goals. (Schwartz, et al. [52]) employed HCQ to assess hospitalization, invasive mechanical ventilation, and 30-day death in 148 Canadian severe COVID-19 patients. Despite increased rates of significant side events such as emesis and hospitalization, there was no statistical difference in primary outcomes between HCQ and placebo groups, with a hazard ratio of 0.6 at 95% CI. Overall, no statistically significant difference was found for HCQ. Patient clinical outcomes suggest that HCQ therapy depend on the patient's condition and disease severity, requiring rigorous research to characterize the effectiveness of SARS-CoV-2 treatment.

Discussion

This review included 30 randomized controlled trials of High quality to synthesize evidence. The 10,941 patients with a mean age of 49 (ranging from 19 to 90) years, including 55% of males were included in this review to treat with mild to severe SARS-CoV-2 patients. Multiple novel antiviral therapies were used in the included trials. Remdesivir, Molnupiravir, tofacitinib, Baricitinib combine with Remdesivir, a combination of Favipiravir, Lopinavir, Ritonavir, Monoclonal antibodies (Lenzilumab, AZD 7442, Meplazumab, Bamlanivimab monotherapy and combination with etesevimab, REGEN-COV), Immunomodulators (Interferon-beta-1a, Peg interferon Lambda, Tofacitinib) is found to be effective and showed a statistically significant difference in improving clinical status by ensuring safety for patients with mild, moderate and severe SARS-CoV-2 patients. However, Hydroxychloroquine, Sotrovimab, Tocilizumab, and Interferon beta-1a in combination with remdesivir showed statistically insignificant differences. These find-

ings underscore the diverse, varied effectiveness and safety of these novel anti-viral therapies highlighting the necessity for tailored therapeutic intervention based on patients-specific factors, disease severity, age, and rigorous clinical assessment of patients. While comparing the findings of the review with existing literature, Remdesivir showed significant improvement in clinical outcomes and ensured safety. It showed less in-hospital mortality and emphasized its influential role.

Which is aligned with (Wang, et al. [53]) who also found that Remdesivir is effective in vitro coronavirus treatment by inhibiting viral replication and supporting that claim. Another study (Gordon, et al. [54]) also emphasized the effectiveness of improving clinical status. (Feng, et al. [55]) showed that Remdesivir is effective due to its higher viral genetic diversity inhibition among immunocompromised patients, aligning with the review emphasis on patients-specific factors because (Karim Ali, et al. [33]) found significant statistics for Remdesivir in comparison to the standard care of patients [33]. However, the variance in effectiveness may all depend upon patient profile and severity and confounding variables. This is the limitation of this review because it only reported that variance. Furthermore, novel antiviral therapies for monoclonal antibodies showed statistically significant effects in SARS-CoV-2 treatment, except for Sotrovimab and Tocilizumab. Similarly, Immunomodulators also showed statistically significant differences alone, but when Remdesivir is prescribed, its efficacy decreases. The effectiveness variance may be dependent upon immune response, disease severity, age, and confounding variables. Overall, the Immunomodulators and monoclonal antibodies are the safest among all novel antiviral therapies, as no death or mortality is reported in any single trial. Fewer side effects are reported, with no serious adverse event reported in any trial. It is also considered as the best option to treat SARS-CoV-2 patients with severe and critical severity of symptoms. The findings align with the meta-analysis systematic review of (Wungu, et al. [56]), emphasizing that monoclonal antibodies are viable options for severe or critical SARS-CoV-2 infections. A research team suggests that monoclonal antibodies are less aggressive in terms of mortality and are also beneficial in mild to moderate SARS-CoV-2. Although some monoclonal antibodies showed less response, it may be due to the uncertain immune response of patients.

Therefore, future research must address this question and explore treatment options. However, the effectiveness of novel antiviral therapies' varied responses may be due to the provirus effects of some specific factors, such as aryl hydrocarbon receptors, that provide insights into how they impact the efficacy of antiviral therapies [57]. Moreover, (Giovannoni, et al. [58]) also claimed similar factors which may impede antiviral efficacy. Therefore, the literature debates that these sorts of factors must be answered in future research to determine efficacy by regressively analyzing factors that may influence efficacy. Moreover, (Weston, et al. [59] also emphasized that broad antiviral SARS-CoV2) activity approved by the FDA highlights the importance of repurposed novel anti-viral therapies and also offers diverse perspectives on therapeutic options. To conclude, the findings ensure the overall efficacy and safety of SARS-CoV-2 patients through novel antiviral therapies. It specifically emphasizing the direct focus of health professionals, physicians, and policymakers on establishing guidelines with a special focus on tailored intervention based on patient-specific factors, disease severity, and other confounding variables.

Limitations

Several limitations inherent to this review must be considered when considering the evidence synthesis. First, the original protocols could have been constrained among RCTs, and the adaptations due to the dynamic COVID-19 crisis might have introduced heterogeneity in the study settings and objectives. Thus, problems such as few RCTs with small sample sizes or a majority of RCT's short follow-up duration in many individual trials precluded drawing definitive conclusions concerning safety and efficacy. Additionally, the studies were performed earlier when no vaccines had been developed, leaving out vaccinated persons and making the results less generalizable to the contemporary vaccinated population. Despite using pre-specified inclusion criteria and critically appraising the quality of the included studies, the application of the random-effects model for meta-analysis was still hampered by the heterogeneity of treatment efficacy. Further, the patient data across different studies and the variability of the types of populations, stages of disease, and therapeutic approaches utilized also limit the homogeneity among results. More importantly, the review needs to discuss factors affecting effectiveness.

Implications and Future Recommendation

Nevertheless, some limitations are in place. The management of SARS-CoV-2 relies on the conclusions drawn from this review. Available evidence indicates that Remdesivir, Molnupiravir, and other monoclonal antibodies enhance the clinical outcomes and safety of COVID-19 treatment across various disease severities. These drugs have shown significant efficacy in treating COVID-19, particularly in severe cases necessitating intensive treatment. The dangers and benefits mentioned here maintain the importance of tailoring a medical treatment plan according to age, other medical conditions, and the severity of the sickness. When evaluating the impact of these antiviral medications, healthcare practitioners, policymakers, and clinical guidelines should consider the variables. The evaluation also advocates for further investigation into the effectiveness of these medications in individuals who have been vaccinated, as well as any other circumstances that may complicate the analysis. Further research on these factors will be necessary to enhance the management of COVID-19 and improve patient outcomes in contemporary practice.

Conclusion

In conclusion, this systematic review comprehensively discusses the effectiveness and side effects of multiple novel antiviral medications for viral SARS-CoV-2 infections at various disease stages. Drugs such as Remdesivir, Molnupiravir, Tofacitinib and specific monoclo-

nal antibodies have been shown to have substantial clinical efficacies depending upon the disease severity of patients. It proves their importance in improving patient health care, clinical outcomes and reducing side effects. Although a few therapies like Hydroxychloroquine and some monoclonal antibodies (Sotrovimab, Tocilizumab) are found to have no clinically significant benefit, the overall synthesis indicated that these therapies are beneficial in enhancing the likelihood of clinical improvement with tolerable side effects. This has provided direction toward the need for individualized intervention strategies for patients with different characteristics such as the severity of SARS-CoV-2, and confounding factors, as indicated by the review. However, the following issues result from confounding variables attributable to the heterogeneous outcomes and interventions with varied effect sizes. The mentioned antiviral therapies should be incorporated into clinical practice guidelines. Further studies should consider focusing on factors together with various aspects highlighted in discussion with therapeutic outcomes to maximize the care of SARS-CoV-2 infected patients.

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