CoLab Network

Remdesivir for the Treatment of COVID-19 in the Outpatient Setting

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Key Messages

Remdesivir is fully or conditionally accepted to treat COVID-19 in many places around the world, including Canada.

We reviewed the current evidence on the potential benefits and harms of using remdesivir to treat COVID-19 in nonhospitalized patients in settings similar to Canada. We included 1 randomized controlled trial and 9 observational studies comparing remdesivir to other antivirals (molnupiravir or nirmatrelvir-ritonavir), placebo, or no treatment.

Findings suggest remdesivir lowers the risk of COVID-19–related hospitalization compared with placebo in patients with mild to moderate SARS-CoV-2 infection who are not vaccinated, particularly males and patients aged 60 or older. One randomized controlled trial at low risk of bias saw this risk reduction. However, results should be interpreted with caution because of the small sample size and limited generalizability to the current Canadian setting.

The observational studies did not adjust for underlying factors. The likelihood of treatment outcomes across different treatment groups is affected by various patient characteristics, including the severity of COVID-19 disease, vaccination status, time from symptoms or diagnosis to treatment, and comorbidities. Therefore, results may be confounded and should be interpreted with caution.

Findings suggest remdesivir has variable efficacy in reducing hospitalization. Two observational studies saw a protective effect, while 1 study saw no significant reduction. All are at a serious risk of bias.

Findings suggest remdesivir does not lower the risk of all-cause deaths or COVID-19–related deaths compared to no treatment. Three observational studies at critical risk of bias reported these findings.

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Stakeholders:
One clinician with content expertise provided comments on this report.

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Abbreviations

AE	adverse event
CI	confidence interval
ED	emergency department
FLU-PRO	inFLUenza Patient-Reported Outcome
HR	hazard ratio
ICU	intensive care unit
IQR	interquartile range
mAb	monoclonal antibody
MD	mean difference
NA	not applicable
OR	odds ratio
PICOS	population, intervention, comparator, study design
PRESS	Peer Review of Electronic Search Strategies
RCT	randomized controlled trial
ROB	risk of bias
ROBINS-I	Risk of Bias in Non-randomised Studies of Interventions
RR	relative risk
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SE	standard error

Introduction and Rationale

Background and Rationale

Several drug treatments for COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are approved for use in Canada. Currently, the federal government, through the Public Health Agency of Canada, is responsible for the procurement and allocation of the following drugs for COVID-19 that are in demand by federal, provincial, and territorial health care systems: nirmatrelvir-ritonavir (Paxlovid), remdesivir (Veklury), and tocilizumab (Actemra).

There is a need to gather post-market drug information and evidence to explore options for procurement, allocation, and equitable distribution of COVID-19 drugs to facilitate future discussions regarding access to these drugs within Canadian health care systems. This report focuses on the current state of evidence for remdesivir in the outpatient setting.

Table 1 outlines the approved indications for remdesivir in Canada.

Rationale
PHAC currently sources and distributes COVID-19 drugs for Canada's health care systems. Gathering post-market evidence on their safety and efficacy is important to help determine fair access in the future.

Table 1

Approved Indication for Remdesivir (Veklury)

Approved use	Presentation and manufacturer	Administration
Remdesivir (Veklury)		
Hospitalized adults and pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen. Nonhospitalized adults and pediatric patients (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.	Powder for solution for infusion, 100 mg/vial (5 mg/mL when reconstituted) Gilead Sciences Canada, Inc.	Day 1: single loading dose of 200 mg intravenously Day 2 onward: 100 mg given once daily intravenously • For hospitalized adults and adolescents with pneumonia requiring supplemental oxygen: The total duration of treatment should be at least 5 days and not more than 10 days. • For nonhospitalized adults who are at increased risk of progressing to severe COVID-19: Treatment should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset. The total duration of treatment should be 3 days.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Source: Product monograph for Veklury (June 13, 2023).

Objectives

The objective is to evaluate the efficacy, effectiveness, and safety of remdesivir for the treatment of COVID-19 in nonhospitalized adults (outpatients).

Policy Questions

1. What is the efficacy, effectiveness, and safety of remdesivir in nonhospitalized patients with COVID-19?
2. Which nonhospitalized patients are most likely to benefit from treatment with remdesivir?

Research Questions

This clinical review addressed the above-cited policy questions by exploring the following research questions:

1. What is the efficacy of remdesivir in nonhospitalized patients with COVID-19?
2. What is the real-world effectiveness of remdesivir in populations where clinical data (i.e., RCTs) are lacking?
3. What is the real-world safety of remdesivir in nonhospitalized patients with COVID-19?
4. What are the characteristics of patients (e.g., comorbidities) associated with improved outcomes in the treatment of COVID-19 with remdesivir?
5. What are the characteristics of patients (e.g., comorbidities) that are associated with risk of adverse outcomes when treated with remdesivir?

Methods

Methods
We used a rapid systematic review approach looking at randomized clinical trials and comparative observational studies. We selected studies for inclusion using criteria from the PICOS framework.

The research questions were addressed using a rapid systematic review approach. The review broadly followed the methods of the Cochrane Handbook for Systematic Reviews for Interventions[1] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.[2]

Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's Peer Review of Electronic Search Strategies (PRESS) checklist. The complete search strategy is presented in Appendix 1.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. The Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the population, intervention, comparator, and study design (PICOS) framework and research questions. The main search concept was remdesivir. The US National Institutes of Health's clinicaltrials.gov trials registry was also searched.

CADTH-developed search filters were applied to limit retrieval to all clinical trials and observational studies. The observational filter was modified to remove terms for cross-sectional studies, prevalence studies, case studies, and case reports. The search was limited to English- or French-language documents. Conference abstracts were excluded from the search results.

The initial search was completed on May 1, 2023. Regular alerts updated the database literature searches until June 19, 2023.

Eligibility Criteria

Studies that met the PICOS criteria were selected for inclusion (Table 2).

Table 2

Selection Criteria

Criteria	Description
Population	Nonhospitalized adults with COVID-19
Interventions	Remdesivir with usual care (e.g., steroids, antibiotics, diuretics, oseltamivir)
Comparators	• Nirmatrelvir-ritonavir • Molnupiravir • Inhaled glucocorticoids or budesonide • Usual care (e.g., steroids, antibiotics, diuretics, oseltamivir) • No therapy • Placebo
Outcomes	Efficacy and effectiveness • emergency department visit without hospitalization • hospitalization and length of stay • intensive care unit admission • ICU length of stay • time from symptom onset to emergency department visit • time from symptom onset to hospitalization • need for ventilation • post–COVID-19 condition (long COVID) • rebound COVID-19 (at 7 days and at 30 days) • adherence to treatment • time to symptom resolution Safety • death (including survival, all-cause mortality) • serious adverse events (total, thrombocytopenia, acute liver injury, acute kidney injury) • withdrawal due to adverse events
Study designs	Completed phase II/III RCTs or higher Nonrandomized controlled clinical trials and cohort studies
Setting[a]	Canada or studies with a similar health care system as Canada: Australia, Greece, Italy, Nordic countries (Denmark, Norway, Finland, Iceland, Sweden), Japan, Netherlands, New Zealand, Portugal, Spain, the UK, the US

ICU = intensive care unit; RCT = randomized controlled trial.

[a] PHAC indicated preference for results from countries with similar health care systems and context for comparability, in particular, countries with a decommodified health care system. Other countries included were high-income countries in the Organization for Economic Cooperation and Development (i.e., the US, the UK, Australia).

Studies not reporting any outcomes of interest or with a setting not considered to be similar to the Canadian health care system were excluded, along with noncomparative cohort studies, protocols for studies in progress or without results, terminated studies, registered studies in progress, editorials, letters, commentaries, conference abstracts, presentations, theses, preprints, duplicate studies, and studies not reported in English or French. Studies from settings outside of the list in Table 1 were excluded.

Eligibility Criteria
Population: nonhospitalized adults with COVID-19. Intervention: remdesivir with usual care. Comparator: no therapy, placebo, usual care, nirmatrelvir–ritonavir, molnupiravir, or inhaled glucocorticoids or budesonide.

Population and Subgroups

The population of interest was nonhospitalized adults (outpatients) with COVID-19.

Studies that enrolled mixed populations with both eligible and ineligible patients (e.g., mixed inpatients and outpatients) were included if separate data were reported for the population of interest (i.e., outpatients) or the population of interest accounted for at least 80% of all study patients.

The population subgroups of interest were

- age (> 65 years)
- sex or gender
- vaccination status
- patients who are immunocompromised
- number of comorbidities
- Indigenous Peoples
- groups considered to be underserved or equity-deserving (those who are unhoused; people with lower socioeconomic status; people living in rural, remote, or geographic-disparate settings; racialized groups; refugee or newcomer status).

Intervention and Comparators

The intervention of interest was remdesivir (with usual care, which could include steroids, antibiotics, diuretics, and/or oseltamivir).

The eligible comparators were:

- nirmatrelvir-ritonavir
- molnupiravir
- inhaled glucocorticoids or budesonide
- usual care (e.g., steroids, antibiotics, diuretics, oseltamivir)
- no therapy
- placebo

Studies in which remdesivir was used as a background treatment or was part of a multicomponent intervention and/or those studies in which the effect of remdesivir could not be isolated were excluded.

Outcomes Definition

The primary efficacy and effectiveness outcomes of interest were:

- incidence of emergency department (ED) visits without hospitalization
- incidence of hospitalizations
- hospital length of stay
- incidence of intensive care unit (ICU) admissions
- ICU length of stay
- time from symptom onset to ED visit
- time from symptom onset to hospitalization
- need for ventilation
- post–COVID-19 condition (long COVID)
- rebound COVID-19 (at 7 days and at 30 days)
- adherence to treatment
- time to symptom resolution.

The safety outcomes of interest were

- Death (including survival, all-cause mortality)
- Serious adverse events (SAEs) (total)
- Thrombocytopenia SAE: A normal blood platelet count or level in adults ranges from 150,000/µL to 450,000/µL. The severity of the thrombocytopenia levels is separated into mild, moderate, or severe:
  - mild: blood platelet count between 101,000/µL and 140,000/µL
  - moderate: blood platelet count between 51,000/µL and 100,000/µL
  - severe: blood platelet count between 51,000/µL and 21,000/µL.[3]
- Acute liver injury SAE: Acute injury could be a named event or SAE or some study-reported parameter involving alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), international normalized ratio, total protein, or albumin.
- Acute kidney injury SAE: For acute kidney or renal injury, we extracted what was reported as acute kidney injury as well as creatinine clearance or definitions of injury. Normal clearance rates 97 mL/minute to 137 mL/minute (1.65 mL/second to 2.33 mL/second) for males and 88 mL/minute to 128 mL/minute (1.496 mL/second to 2.18 mL/second) for females.
- Withdrawal due to AEs

Outcomes were extracted at the end of study unless otherwise noted.

Study Designs

The following study designs were eligible for inclusion:

- randomized controlled trials (RCTs) (phase II/III or higher)
- nonrandomized controlled clinical trials
- controlled cohort studies.

Study Selection Process

Two independent reviewers applied the eligibility criteria to each title and abstract identified in the literature search. All records deemed potentially relevant by at least 1 reviewer were obtained in full-text format. The eligibility criteria were applied to the full-text records by both reviewers independently, and a final decision about eligibility was made. Conflicts were resolved by discussion. The reviewers were not blinded to study authors or centre of publication before study selection. Study screening and assessment of eligibility were facilitated and standardized using DistillerSR (Evidence Partners).

Quality Assessment

Risk of bias assessments were completed by 1 reviewer and verified by a second reviewer. Any disagreements were resolved by consensus. The original, primary publication for each unique included study was used for the assessments, with supplementary data obtained from the study protocol, companion reports, and ClinicalTrials.gov records if necessary.

Randomized Controlled Trials

We applied the Cochrane Collaboration's Risk of Bias tool (ROB v.1.0) to the included RCTs that reported at least 1 outcome of interest.[4] The ROB tool addresses 6 specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues.

Each domain included 1 or more specific entries in an ROB table, and a standardized form was created and applied in line with the Cochrane Collaboration's ROB template. Assessments were based on prespecified questions addressing the adequacy of the study for each domain, which resulted in judgments of low, high, or unclear risk of bias.

For each unique RCT, we assessed the quality of the original primary publication with additional details sought from supporting literature (e.g., published protocol, ClinicalTrials.gov records) if necessary.

Assessments were performed by 1 reviewer and verified by a second reviewer. Disagreements were resolved by consensus.

Observational Studies

We applied the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I)[5] tool developed by the Cochrane Collaboration to assess the potential bias inherent in each included study with a cohort design, in which individuals who received different interventions were followed over time. This tool consists of 7 domains that evaluate the presence of bias: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. Detailed guidance on using the ROBINS-I tool was followed (ROBINS-I: detailed guidance).[6] Each domain was assessed individually, resulting in judgments of low, moderate, serious, or critical risk of bias or of no information. An overall judgment of risk of bias was determined by evaluating the 7 domains using a predefined algorithm (refer to Table 2 for detailed guidance).

Unlike randomized controlled studies, which are better suited for inferring causality between interventions and outcomes, cohort studies provide valuable insights on outcomes that are challenging to measure in clinical settings, occur in patient populations excluded from RCTs, or comprise safety signals requiring large or specific patient populations for detection. These studies often explore different effects of an intervention using various analytical approaches for the same outcome. However, using the ROBINS-I tool for multiple outcomes of interest can introduce complexity and consume considerable time. To streamline our efforts, we operationalized the outcomes of interest into those that are objectively and subjectively measured and further categorized the effects (estimates) of interest as either unadjusted or adjusted. When a study reported both subjectively and objectively measured outcomes, or reported adjusted or unadjusted effects, we would conduct various assessments to address the different levels of bias risk.

In addition, we collected key information on significant confounders and cointerventions from each study, which served as supplementary support for our evaluation of potential bias.

Publication Bias

Publication bias was not assessed.

Applicability

Applicability of the study findings to the Canadian setting was evaluated based on a review of key demographic and clinical variables of the included studies, including age, sex or gender, race, ethnicity, comorbidities, vaccination status, and COVID-19 variant. To evaluate the applicability of the study results to the Canadian health care system today, we followed and applied the 4-step process suggested by Atkins et al.[7] to assess the applicability of studies. In particular, in a PICO statement, we identified the key study characteristics to consider that could be collected and interpreted.

Data Extraction

Data were extracted by 1 reviewer by use of piloted and standardized data abstraction forms, and the extracted data were verified for accuracy by a second reviewer. Any disagreements were resolved by consensus.

The original primary publication for each included study was used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records if necessary to address the research questions. In situations in which multiple publications for a unique study were available (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study), the most recently adjudicated data for each outcome were extracted, with preference given to published records.

The following data were extracted:

- Study characteristics, including publication year, study design, registration number, countries, study delivery and follow-up time, funding sources, and COVID-19 variant at the time of study
- Participant information, including eligibility criteria, sample size, sex or gender, age, race or ethnicity, immunocompromised or health status, vaccination status, underserved or equity-deserving status, reported comorbidities
- Intervention characteristics, including name, duration, dose, detailed description of cointervention, and definitions of usual care
- Results and related definitions for the outcomes of interest as previously listed.

When outcome data were reported with multiple follow-up time points, we extracted data from all time points.

Data Analyses and Synthesis

A descriptive summary of study selection, quality assessment, and study and patient characteristics is presented for each included RCT that reported at least 1 outcome of interest.

We used a random-effects model to synthesize the data for outcomes measured in 2 or more studies using similar definitions, even when high heterogeneity was indicated by large I^2 values. This was because we expected that clinical heterogeneity across studies may exist, such as different study designs, severity of disease, comorbidities, settings, and cointerventions. For observational studies, we also used the random-effects model to synthesize the raw data, calculating effect measures including pooled relative risks (RRs) and Peto odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The random-effects model was used to synthesize pooled effect measures and CIs adjusted for confounding factors using the generic inverse variance method, based on the adjusted effect measures and their standard errors (SEs). For these primary analyses, data for RCTs and observational studies were described separately, and data for different study designs were compared but not combined.

Identifying the reasons for heterogeneity of results across the studies, using subgroup and meta-regression techniques, was not possible because of the limited information available. Clinical heterogeneity was assessed across studies by documenting and reviewing the variation of the characteristics of the study patients by severity of condition, demographics, and setting; the interventions in the implementation (e.g., dose or intensity), experience of practitioners, and nature of control (placebo, none, standard of care); and in the outcomes by measurement methods, event definition, cut-points, and follow-up duration.

Sensitivity Analysis

No sensitivity analyses were performed.

Results of Clinical Evaluation

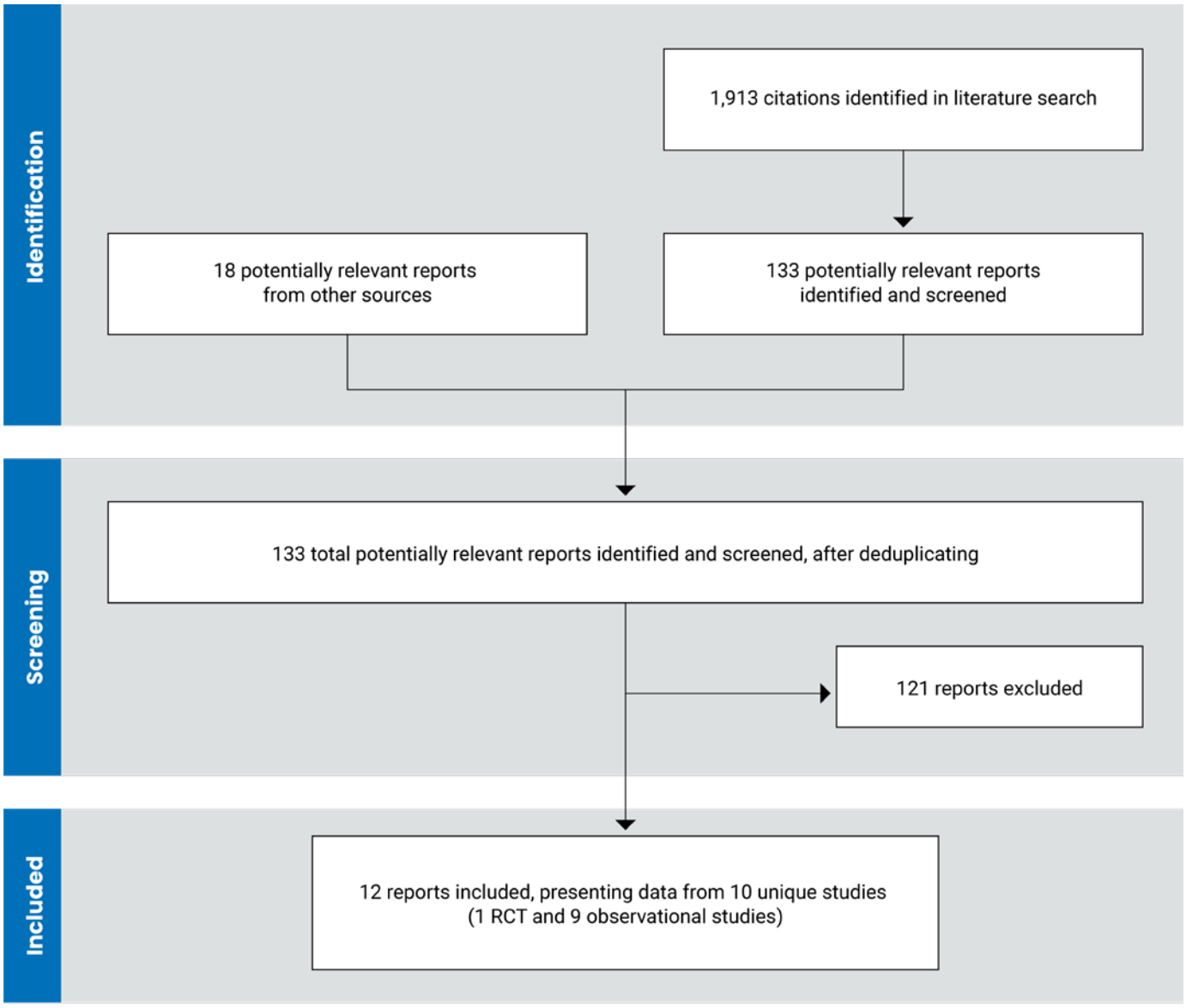
Selection of Primary Studies

A total of 1,913 citations were identified in the literature search. Following screening of titles and abstracts, 1,780 citations were excluded, and 133 potentially relevant records were retrieved for full-text review. Of these, 121 were excluded for various reasons, and 12 records reporting 10 unique primary studies met the inclusion criteria (1 RCT and 9 observational studies) (Figure 1). There were 3 reports for the 1 RCT; the main report[8] was used because the 2 companion reports (referenced in Appendix 2) did not provide additional data for this review. The list of included studies is provided in Appendix 2 and the list of excluded studies in Appendix 3.

Included Studies
Ten unique studies across 12 publications are included in the final analysis: 1 RCT and 9 comparative observational studies.

Figure 1

PRISMA Flow Chart of Selected Reports



Study Characteristics

The characteristics of the studies of interest for this report are summarized in Table 3, Table 4, Table 5, and Table 6. A summary and additional characteristics of these studies are described subsequently.

Summary

Study Design

There are 10 studies included for this review: 1 RCT[8] and nine observational studies. The latter consists of 3 prospective[9-11] and 6 retrospective cohort studies.[12-17] Eight of 9 cohort studies enrolled eligible patients in similar periods, with the earliest study start date in December 2021 and the latest study end date in October 2022 (i.e., during theOmicron variant spread). The remaining cohort study included both a pre-Omicron and Omicron study period from March 2021 to July 2022; however, the Omicron period was still predominant.[15] The RCT (PINETREE) was conducted between September 2020 and April 2021 before the emergence of the Delta variant as the dominant circulating strain.[8]

Key Point
Data were collected during the Omicron wave for 8 of the included observational studies. The remaining observational study had both a pre-Omicron and Omicron study period. The RCT was done before the Delta variant.

Country of Origin

The PINETREE trial was a multicentre RCT conducted in the US, Spain, Denmark, and the UK.[8] Six of 9 cohort studies were conducted in Italy,[9,10,12,15-17] and the remaining 3 were conducted in Canada,[11] the US,[13] and Spain.[14] Infectious disease clinics and infusion facilities were the outpatient settings reported in 6 studies,[8,9,12,13,16,17] while university hospitals or COVID-19 day hospital were reported in 3 studies.[10,14,15] One Canadian cohort study was conducted in an organ transplant[11] recipient population.

Patient Population

Patients with confirmed SARS-CoV-2 infection were included in all 10 studies and tested by antigen or real-time reverse-transcription polymerase chain reaction in 4 studies.[8,10,13,16] Nonhospitalized patients with mild to moderate COVID-19 disease (i.e., not requiring

oxygen therapy) for less than 7 days and with 1 or more risk factors for progression to severe illness were eligible for early antiviral treatment in those studies. Two cohort studies focused on patients with underlying hematologic malignancies,[15,16] while 1 focused on organ transplant recipients.[11] Patients who were asymptomatic, hospitalized, or previously received treatment for COVID-19 or supplemental oxygen were excluded. Two studies were designed to include patients between ages 12 and 18 years;[8,13] however, only 8 adolescents (1.4%) were reported with limited data in the RCT,[8] and no separate information was reported for adolescents in the cohort study.[13] The sizes of the study populations of interest varied from 73 to 1,118 patients from eligible arms by excluding the patients who received sotrovimab,[13,14,16,17] monoclonal antibodies (mAbs),[15] or combined treatments[14] across the 10 studies.

Interventions

Five 2-arm studies[8,11-14] compared remdesivir with placebo, nirmatrelvir-ritonavir, control groups without remdesivir, control groups without antiviral, or no treatment; four 3-arm studies[9,10,15,17] compared remdesivir with molnupiravir and nirmatrelvir-ritonavir; and one 4-arm study[16] had the same 3 arms plus an untreated control group. Remdesivir was administered in a 3-day regimen intravenously with the recommended dose of 200 mg on the first day, followed by 100 mg on days 2 and 3. There was no further information on the administration of the other antiviral treatments and control groups without remdesivir treatment, except for oral molnupiravir 800 mg and oral nirmatrelvir-ritonavir 300 mg/100 mg twice daily for 5 consecutive days reported in 1 cohort study[10] and 3 days for placebo in the RCT.[8] Immunosuppressant therapies were reported as cointerventions in 3 studies,[11,14,16] primarily for patients with underlying cancers or organ transplants.

Dosing
Remdesivir was given intravenously for 3 days, with the recommended dose of 200 mg on the first day followed by 100 mg on days 2 and 3 for all studies.

Outcomes

Eight studies reported hospitalizations due to COVID-19 progression, 6 reported any events leading to drug discontinuation or withdrawal,

5 reported all-cause mortality, and 4 reported death due to COVID-19 progression. The other outcomes were reported in 3 studies or fewer, including length of hospitalization (3 studies), ICU admission (3 studies), progression to oxygen requirement (3 studies), any SAEs (3 studies), rebound of symptoms after antiviral discontinuation (2 studies), ED visits (1 study), mechanical ventilation (1 study), COVID-19–related sequelae (1 study), persistence of symptoms, and acute liver injury (1 study). These outcomes were followed until 28 to 30 days after the first positive test in 8 studies,[8-11,13,14,16,17] whereas a longer follow-up of 90[12] and 180 days[15] was considered in 2 cohort studies.

Randomized Controlled Trial

Gottlieb et al. (2022) (PINETREE)

Summary
The RCT compared remdesivir with a placebo. Patients with at least 1 risk factor for progression to severe disease (age 60 or older, obesity, or coexisting medical conditions) were included.

Gottlieb et al. (2022)[8] reported the findings of PINETREE, a randomized, double-blind, placebo-controlled trial of remdesivir in nonhospitalized patients with COVID-19 who had symptom onset within the previous 7 days and who had at least 1 risk factor for disease progression (age ≥ 60 years, obesity, or coexisting medical conditions). The study was conducted in 64 sites in the US, Spain, Denmark, and the UK. The PINETREE trial was funded by Gilead Sciences. Details about this RCT are provided in Table 3.

Patients eligible for enrolment in the PINETREE trial were 12 years or older, had at least 1 preexisting risk factor for progression to severe COVID-19 or were 60 years or older with or without other risk factors. All patients had at least 1 ongoing symptom consistent with COVID-19 (with onset of the first symptom within 7 days before randomization) and had a SARS-CoV-2 infection confirmed by a molecular diagnostic assay within 4 days before screening. Risk factors considered were hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, or sickle cell disease. The details of the inclusion and exclusion criteria are provided in Table 3. Recruitment took place between October 2020 and April 2021.

The trial protocol was to enrol a total of 1,264 patients, allowing for sample size re-estimation at the interim analysis after approximately 50% of participants had completed the day 28 visit because of uncertainties about the event rates for hospitalization and death rates in the placebo arm. However, the trial was terminated early due to feasibility of study enrolment and the noted "changing needs of non-hospitalized participants." This decision was not based on efficacy or safety concerns. Consequently, the trial data were analyzed when 584 patients had been randomized into the study, of which 22 did not receive infusion. Patients were randomly assigned in a 1:1 ratio to remdesivir 200 mg administered by IV infusion on the first day of treatment followed by 100 mg remdesivir administered by IV infusion on days 2 and 3, or to matching placebo administered by daily intravenous (IV) infusions for 3 days. Remdesivir (and placebo) infusions were administered to patients at the site under close supervision or in the participant's home by a home health service provider.

Randomization was stratified according to residence in a skilled nursing facility (yes or no), age (< 60 years or ≥ 60 years), and country (US or outside the US). The use of other treatments was documented, although concomitant use of other investigational or approved drugs for SARS-CoV-2, such as lopinavir-ritonavir and interferon, were not permitted. However, use of these medications for an approved indication other than SARS-CoV-2 infection was permitted. The use of hydroxychloroquine or chloroquine for any indication was also not permitted.

The primary efficacy end point was initially a composite of hospitalization for any cause or death from any cause by day 14 and was modified during the study to be a composite of hospitalization related to COVID-19 or death from any cause by day 28 in response to comments from the Food and Drug Administration. The primary safety end point was any AE.

Table 3

Characteristics of the Randomized Controlled Trial

Characteristic	Gottlieb et al. (2022) (PINETREE)[8]
Trial registration number	NCT04501952
Status	Complete, published
Study period	September 18, 2020, to April 8, 2021
Study design	Randomized, double-blind, placebo-controlled trial
Locations	64 sites in the US, Spain, Denmark, and the UK Sites included outpatient infusion facilities, skilled nursing facilities, and some home infusions
Randomized, N	584
Inclusion criteria	Eligible patients were 12 years or older with at least 1 pre-existing risk factor for progression to severe COVID-19 or were 60 years or older with or without other risk factors.
Exclusion criteria	Patients were ineligible for any of the following reasons • they were receiving or were expected to receive supplemental oxygen or hospital care at the time of screening • they had a previous hospitalization for COVID-19 • they had previously received treatment for COVID-19 (including investigational drugs) • they had received a SARS-CoV-2 vaccine.
Intervention	IV remdesivir (200 mg on day 1 and 100 mg on days 2 and 3)
Comparator	• Placebo (daily IV infusions for 3 days) • No additional details reported
Treatment duration	3 days
Follow-up	14 days and 28 days
Primary end point	The primary efficacy end point was a composite of hospitalization related to COVID-19 (as determined by site investigators, who were unaware of trial group assignments, and defined as ≥ 24 hours of acute care) or death from any cause by day 28. The primary efficacy end point was initially a composite of hospitalization for any cause or death from any cause by day 14 and was modified on January 14, 2021, in response to comments from the Food and Drug Administration. Trial blinding was maintained. The primary safety end point was any adverse event.

Characteristic	Gottlieb et al. (2022) (PINETREE)[8]
Secondary end points	Secondary end points included: • composite of COVID-19–related medically attended visits or death from any cause by days 14 and 28 • COVID-19–related hospitalizations by days 14 and 28 • time-weighted average change in nasopharyngeal SARS-CoV-2 viral load from baseline to day 7 • time to alleviation of baseline COVID-19 symptoms (with alleviation defined as mild or absent symptoms) compared with those reported on the baseline FLU-PRO Plus questionnaire completed before the first infusion. Post hoc analyses were also conducted for: • hospitalization for any cause by day 28 • time to alleviation of baseline COVID-19 symptoms as reported on FLU-PRO Plus questionnaire completed on the day of the first infusion, either before or after the infusion.
Relevant VOC reported	Variants before the B.1.617.2 (Delta) variant of SARS-CoV-2 emerged as the dominant circulating strain.

FLU-PRO = inFLUenza Patient-Reported Outcome; RCT = randomized controlled trial; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VOC = variant of concern.

Cohort Studies

Pinargote-Celorio et al. (2022)

Pinargote-Celorio et al. (2022)[14] reported findings from a single-centre, retrospective, observational cohort study involving the implementation of an outpatient clinical pathway for patients with SARS-CoV-2 infection receiving early treatment within the Spanish health system. The clinical pathway involved patients who attended a COVID-19 day hospital and met the indication for the use of authorized drugs at the time of the study (January 1, 2022, to June 30, 2022), including sotrovimab, remdesivir, or nirmatrelvir-ritonavir. Treatments were administered in the day hospital or at home, for those individuals unable to travel, and the effectiveness of the drugs used for treatment was assessed.

A total of 262 individuals were referred from different levels of care and were included in the cohort following detection through an

Summary
The 9 observational studies included 3 prospective and 6 retrospective cohorts. Each compared remdesivir with usual care to 1, 2, or 3 different comparators. Hospitalization due to COVID-19 was the most reported outcome.

automated system based on a patient database, daily results from a SARS-CoV-2 microbiology test results registry, and daily cross-referencing of both to identify candidates for treatment. Other medical specialties, accident and ED, and primary care databases were also used to identify possible candidates. Actual referrals were done through telephone or hospital consultation system. The investigators noted the study likely underestimated the percentage of patients treated versus referred because there were initial difficulties with patient registration and the referral pathways were not fully structured and were being managed mainly through telephone contact. Although treatments were compared, this descriptive study lacked a formal control group, which does not allow for a full evaluation of treatment effectiveness.

The primary end point was hospitalization and/or death by 30 days (excluding those that occurred in the first 24 hours of treatment). Other end points evaluated were grade 2 or 3 toxicity and treatment discontinuation. Participants were followed up by telephone by a team of nurses until symptoms resolved or 30 days was reached.

An established protocol was noted, but no citation or source was provided, and it could not be obtained. The investigators did not receive any funding for the study.

Del Borgo et al. (2023)

Del Borgo et al. (2023)[9] reported on a single-centre prospective, observational cohort study of nonhospitalized individuals with mild to moderate COVID-19, confirmed through a positive nasopharyngeal swab for SARS-CoV-2, and who had 1 or more risk factors for progression to severe illness, as defined by European Medicines Agency (EMA) and Agenzia italiana del farmaco guidelines. These risk factors included body mass index greater than 30 kg/m^2, diabetes mellitus, chronic kidney failure, immunodeficiency, neurological disease, cardiovascular disease, lung disease, older than 65 years, hospitalization for another disease, chronic hepatopathy, active oncological disease, and hemoglobinopathy. The study centre

was located in Central Italy at a hospital-based early COVID-19 clinic. The study recruited patients who received IV remdesivir, oral molnupiravir, or nirmatrelvir-ritonavir between January 2022 and October 2022 when all 3 treatments were available and when variants of concern — Omicron BA.1, BA.2, BA.4, and BA.5 — were prevalent in Italy.

Recruitment for the study was done through general practitioners, hospital specialists, or self-referral through a regional phone system. Patients were screened for risk factors, demographics, and medications or conditions that could interact with or preclude use of the study medications. Oral therapy with molnupiravir or nirmatrelvir-ritonavir was not considered if patients were dysphagic or preferred IV therapy with remdesivir. Remdesivir was administered over 2 hours and monitored in the clinic or, if an oral antiviral was the intervention of choice, it was dispensed to a patient's relative.

A total of 1,118 participants were treated with the study medications and followed prospectively (remdesivir: n = 230; molnupiravir: n = 499; nirmatrelvir-ritonavir: n = 398). Clinical end point data were collected after 30 days of therapy via telephone. A diary was also provided to all patients in which they could record symptoms, AEs, and vital signs. Individuals who received remdesivir were interviewed and monitored for AEs during their infusion. If telephone follow-up failed, clinical data were collected through a regional COVID-19 platform and/or medical records.

The primary end point was clinical progression, defined as progression to pneumonia, acute respiratory distress syndrome, COVID-19–related death, or non-COVID-19–related death. This composite outcome was collected in all patients treated and in a subgroup of patients who were immunocompromised (n = 320). Secondary end points were the persistence of symptoms at 30 days and time to negativization (i.e., seronegative status). It is unclear if the subgroup of patients who were immunocompromised was planned a priori because no protocol was available.

Mikulska et al. (2023)

Mikulska et al. (2023)[15] conducted a retrospective study of consecutive individuals who had hematological malignancies (including recipients of a hematopoietic stem cell transplant and chimeric antigen receptor T-cell therapy) treated for mild to moderate COVID-19 between March 2021 and July 2022. Two centres in Italy provided early treatment to symptomatic individuals with nationally authorized mAbs or antivirals administered as soon as possible after COVID-19 diagnosis and before developing respiratory failure that required oxygen treatment due to SARS-CoV-2 infection. In addition, all patients, regardless of COVID-19 status, received counselling regarding the appropriate preventive measures, early symptom recognition, the importance of early testing, and the need to report any positive results promptly to the care hematologist so appropriate treatment could be prescribed by an infectious disease consultant.

At the time of the study, the nationally authorized time limits defining early treatment varied: 10 days from symptom onset for bamlanivimab combined with etesevimab and for casirivimab combined with imdevimab or sotrovimab, 7 days for remdesivir, and 5 days for nirmatrelvir-ritonavir and molnupiravir. Remdesivir was authorized for early treatment in Italy in December 2021, and the investigators reported there were no study drug shortages. Choice of treatment was up to the treating physician taking into account a patients' individual characteristics; however, oral nirmatrelvir-ritonavir was noted as the first choice and remdesivir was noted as a second choice by the investigators. Investigators noted that circulating variants of concern at the time of referral were also considered. Individuals were treated at the referral centre or at home, and remdesivir IV infusions were administered in an outpatient setting with 1 dose per day for 3 days.

The primary end point was a composite of treatment failure defined as progression to severe COVID-19 requiring oxygen supplementation, corresponding to grade 4 or higher on the

WHO COVID Outcomes Scale, or COVID-19–related death. Secondary end points were the duration of SARS-CoV-2 positivity, COVID-19–associated mortality, and 90-day mortality. Investigators identified outcomes during the pre-Omicron and Omicron periods and tracked number of vaccine doses for participants. The total cohort size was 328 individuals; of these, 208 received antiviral treatments (remdesivir: n = 59; nirmatrelvir-ritonavir: n = 116; molnupiravir: n = 33).

No funding was provided for the study and no protocol was located.

Solera et al. (2023)

Solera et al. (2023)[11] reported findings from a single-centre, prospective cohort study conducted during an Omicron BA.2 wave (April and May 2022) at the University Health Network Organ Transplant Program in Toronto, Ontario. Investigators followed consecutive adult patients with a single-organ transplant who had a confirmed COVID-19 diagnosis and received remdesivir within 7 days of symptom onset (early treatment) for a minimum of 30 days or until the end of the disease course. The diagnosis of COVID-19 was made using rapid antigen tests; this was confirmed with a polymerase chain reaction test for only those patients who were eventually hospitalized.

All patients who had a transplant were considered high risk for severe disease progression. They were treated according to Ontario provincial guidelines at the time. All decisions regarding treatment were made by the care team in the hospital's COVID-19 care virtual clinic by a nurse or physician specializing in transplant care together with a transplant infectious disease physician who took into consideration the individual patients' wellness and other risk factors. Individuals who received remdesivir were given a 200 mg IV infusion on day 1 followed by 100 mg on days 2 and 3. Those patients who did not receive remdesivir were offered supportive care only, nirmatrelvir-ritonavir, or mABs for early treatment or they were offered supportive care only if time since symptom onset was greater than 7 days.

The primary end point was COVID-19–related hospitalizations longer than 24 hours within 30 days of symptom onset. Additional end points included need for supplemental oxygen (new need or increase in requirement), ICU admission, mechanical ventilation, and all-cause mortality. Primary analyses estimated the risk of each end point based on having received remdesivir treatment as an outpatient using adjusted hazard ratios (HRs) and the number needed to treat to prevent 1 hospital admission. Investigators used the Cox proportional hazard regression model to estimate the lung transplant–adjusted HR for hospitalization associated with outpatient remdesivir treatment.

No funding was received for this study. Some study authors reported receiving research or clinical trial grants and advisory fees from pharmaceutical manufacturers, but none of the declared grants or fees were from Gilead.

Colaneri et al. (2022)

Colaneri et al. (2022)[16] reported findings from a single-centre, retrospective, observational cohort study conducted in Northern Italy. The study assessed early treatment for high-risk individuals with hematological malignancies (myeloma, Hodgkin or non-Hodgkin lymphoma, chronic and acute leukemia, paroxysmal nocturnal hemoglobinuria, amyloidosis, and myelodysplastic syndrome or myeloproliferative neoplasms) and mild to moderate COVID-19 for preventing hospitalizations and reducing SARS-CoV-2 shedding. Comparisons were made across treatments administered, including nirmatrelvir-ritonavir, remdesivir, sotrovimab, and molnupiravir (only provided to individuals not eligible for any other drug) and to patients who did not receive any treatment. Hospitalized patients, those requiring oxygen therapy for COVID-19, and asymptomatic individuals were excluded.

Data for individuals evaluated were collected between December 23, 2021, and April 30, 2022. Investigators noted that the vast majority of cases were due to the Omicron variant. The primary end point was

hospitalization by day 28. Other end points were reported as length of SARS-CoV-2 viral shedding in patients receiving versus not receiving early therapies, and the effect of early treatment in patients with hematologic malignancies with negative SARS-CoV-2 antibodies.

The appropriate therapy for individuals was chosen by the treating infectious disease specialist according to eligibility criteria and the availability of each drug's pilot sheet. Data for 88 patients were extracted (treated: n = 55; nontreated: n = 33). Of those patients who were treated, 15 received remdesivir (27%), 10 received nirmatrelvir-ritonavir (18%), and 15 received molnupiravir (27%). Data for number of vaccination doses received and days from last vaccination were collected.

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Manciulli et al. (2023)

Manciulli et al. (2023)[17] reported findings from a retrospective cohort study including outpatients receiving early treatment for COVID-19 in 11 infectious diseases units in the Tuscany region of Italy between January 1, 2022, and March 31, 2022, when the Omicron sublineages BA.1 and BA.2 were circulating. Those outpatients who were eligible had received sotrovimab, remdesivir, nirmatrelvir-ritonavir, or molnupiravir, had at least 1 risk factor according to AIFA criteria, and had mild to moderate COVID-19 according to the WHO criteria. This study included children from a pediatric infectious disease centre.

Referrals came from hospital specialists, general practitioners, COVID-19 home treatment centres, or ED physicians. End points in the trial were treatment completion, AEs, and hospitalization or death due to COVID-19 progression at day 28. A total of 781 individuals

received treatment and were included in the study; assignment to the treatment groups was described as nonrandomized (remdesivir: n = 142; sotrovimab: n = 314; molnupiravir: n = 205; nirmatrelvir-ritonavir: n = 120).

A survival analysis between different treatment groups was carried out using Kaplan-Meier curves and the log-rank test. Multivariable Cox proportional hazards regression was performed to identify independent predictors of the composite outcome (28-day hospitalization and/or death related to COVID-19). A propensity score analysis using inverse probability of treatment weighting was done to assess the average treatment effect of sotrovimab, nirmatrelvir-ritonavir, and molnupiravir compared with remdesivir. Covariates to generate the propensity score included sex or gender; age; chronic comorbidities, such as obesity, chronic kidney disease, chronic heart disease, chronic obstructive pulmonary disease, cancer, cognitive impairment, diabetes, and immunosuppression; smoking habit; vaccination status, categorized as "not vaccinated" (none or incomplete primary schedule) or "vaccinated" (complete primary schedule with or without a booster dose); and latency between symptoms onset to antiviral administration, categorized as either 3 days or less or more than 3 days. Investigators arbitrarily decided to consider remdesivir as a reference variable because patients in this treatment group had the most events (hospitalization and/or death). Standardized differences were used to compare balance in baseline covariates between the 4 treatment groups before and after weighing by the inverse probability of treatment.

No external research funding was received. One author reported research funding and personal honorariums outside the current study from Merck, Sharp & Dohme, ViiV Healthcare, GlaxoSmithKline, and Gilead.

Tiseo et al. (2023)

Tiseo et al. (2023)[10] conducted a single-centre, prospective, observational cohort study between January 1, 2022, and July 1, 2022 in Pisa, Italy. The study included 562 outpatients with COVID-19 and at least 1 risk factor for disease progression. The study was conducted in an outpatient clinic during the spread of the Omicron variant in Italy.

Individuals received nirmatrelvir-ritonavir, remdesivir, or molnupiravir according to Agenzia italiana del farmaco indications at the time, varied by timing, route of administration, and contraindications. Patients were eligible if they did not require supplemental oxygen therapy, were not hospitalized due to COVID-19, and had mild to moderate COVID-19. Asymptomatic patients were not included. All included individuals were followed for 30 days from their first positive nasopharyngeal swab and were contacted by telephone on day 7 and day 30 from the start of treatment. The primary end point was a composite of death or hospitalization for COVID-19. Secondary end points were occurrence of AEs and a negative nasopharyngeal swab within 10 days of the first positive test. Discontinuation due to AEs was also collected.

A one-way analysis of variance and multivariable Cox proportional hazards regression analysis was performed for the primary outcome to explore differences among the 3 treatment groups. Variables statistically significant in the univariable analysis ($P < 0.05$) and those deemed of clinical relevance were entered in the multivariable model, including age 80 years or older, comorbidities, time from start of symptoms to antiviral treatment, immunosuppression, and adequate COVID-19 vaccination. For the secondary outcomes, the proportion of events were described in the 3 groups.

No funding was received, and some study authors declared honorariums, advisory fees, and or grants from various manufacturers, but noted that declarations were outside the submitted work and did not affect the scientific objectivity of the work.

Piccicacco et al. (2022)

Piccicacco et al. (2022)[13] reported findings of a single-centre, retrospective cohort study conducted between December 27, 2021 to February 4, 2022, during the Omicron (B.1.1.529) surge, in an ambulatory infusion clinic at Tampa General Hospital (Tampa, Florida). A total of 260 patients with confirmed COVID-19 infection were included.

Patients were eligible if they were classified as having mild to moderate symptoms for 7 days or less at the time of inclusion and they were at high-risk for progression to severe COVID-19 and had not previously received a COVID-19–directed oral antiviral or community-administered mAbs. Individuals received remdesivir or sotrovimab for 3 days or received no treatment and were followed for 29 days. The control cohort consisted of randomly selected high-risk outpatients who did not receive remdesivir or sotrovimab because they declined treatment, were unable to be contacted for scheduling, had transportation issues, or had a major drug interaction with remdesivir. Although eligible patients could be 12 years or older, there was no further information on the adolescents in this study. The primary outcome was a composite of COVID-19–related hospitalizations and ED visits within 29 days from symptom onset; secondary outcomes included the incidence of each component of the primary end point, 29-day all-cause mortality, and AEs in the treatment cohorts.

One-way analysis of variance and 3 × 2 chi-square test was used to assess differences between patients who received treatment versus those who did not receive treatment. The percentage of patients who were hospitalized or visited the ED by day 29 was determined with Kaplan-Meier analysis.

The authors stated this study was carried out as part of their routine work. The authors also mentioned that patient compliance with 3 consecutive days of remdesivir at their infusion clinic was better than anticipated, with 95% of patients completing all 3 infusions.

Mazzitelli et al. (2023)

Mazzitelli et al. (2023)[12] reported on a retrospective cohort study conducted between February 9 to May 31, 2022, during the Omicron variant infection period in the Infectious and Tropical Diseases Unit of Padua University Hospital (Padua, Italy). The study included 681 patients consecutively referred to the centre with COVID-19 infection who were at high risk of progression.

Eligible patients did not require oxygen therapy for COVID-19 within 7 days from symptom onset and had at least 1 risk factor for developing severe COVID-19: oncological or hematological disease in the active phase, chronic renal failure, severe pulmonary disease, primary or acquired immunodeficiency, obesity, severe cardiovascular disease, uncontrolled diabetes mellitus, or age older than 65 years. Patients who received a concomitant treatment with nirmatrelvir-ritonavir, molnupiravir, or mABs were excluded. Individuals received remdesivir for 3 days or no antiviral treatment (control group) and were followed for 3 months. For the control group, the reasons for not receiving early remdesivir were patient's choice, logistic issues (i.e., inability to reach the centre for 3 consecutive days), or they were unable to be scheduled for the treatment course. The primary outcomes were progression of COVID-19 to oxygen requirement, hospitalizations, and deaths; secondary outcomes were time to clinical recovery, time to microbiological cure, AEs, prevalence of "postacute COVID-19 syndrome," and onset of new SARS-CoV-2 infection.

Multivariable analyses included statistically significant variables from univariable analyses ($P < 0.05$) plus a priori determined biologically relevant variables (e.g., age, sex or gender, and time from COVID-19 signs and symptoms onset to health care access, diagnosis, and treatment).

Funding was not reported; however, authors declared no conflict of interest.

Table 4

Characteristics of Cohort Studies 1

Characteristic	Pinargote-Celorio et al. (2022)[14]	Del Borgo et al. (2023)[9]	Mikulska et al. (2023)[a15]
Name	NA	NA	NA
Publication year	2022	2023	2023
Design	Retrospective cohort study	Prospective cohort study	Retrospective cohort study
Country	Spain	Italy	Italy
Setting (no centres)	COVID-19 day hospital	Clinic for early COVID-19 at an Italian hospital	Two university hospitals
Study period	January 1, 2022, to June 30, 2022	January 5, 2022, to October 3, 2022	March 2021 to July 2022
Relevant VOCs reported	Omicron variant	Omicron BA.1, BA.2, BA.4 and BA.5 prevalent	Including pre-Omicron and Omicron period; Omicron predominance
Participants, n[b]	218 (of 262 total reported)	1,118	208 eligible (of 328 total reported)
Population	Patients in the outpatient department who had SARS-CoV-2 infection and high risk of progression	Nonhospitalized patients with mild to moderate COVID-19 disease and ≥ 1 risk factors for progression to severe illness	Patients with hematologic malignancies who received early therapy for mild to moderate COVID-19 (i.e., not requiring oxygen therapy); the first treated COVID-19 episode
Exclusions	Patients on combination therapy	Patients treated with early remdesivir (3-day scheme) who were hospitalized for other diseases than COVID-19 illness or were in the emergency department	Patients who received early treatment with both antivirals and anti-spike mABs
Intervention (participants who received intervention, n)	Remdesivir (124)	Remdesivir (230)	Remdesivir (59)
Duration of treatment	3 days	3 days	NR
Comparator(s) (participants who received comparator, n)	Nirmatrelvir-ritonavir (94)	Molnupiravir (499) Nirmatrelvir-ritonavir (389)	Molnupiravir (33) Nirmatrelvir-ritonavir (116)
Duration of treatment	NR	NR	NR

Characteristic	Pinargote-Celorio et al. (2022)[14]	Del Borgo et al. (2023)[9]	Mikulska et al. (2023)[a15]
Cointerventions	43.8% of patients received the treatment of biologic immunomodulators: anti-CD20, anti-TNF, other biologics, JAK inhibitors, and protein kinase inhibitors	NR	NR
Follow-up time	30 days	30 days	30, 90, and 180 days after SARS-CoV-2 infection
Outcomes reported	• Hospitalization within 30 days after treatment • Hospitalization due to COVID progression • All-cause or related 30-day mortality • Patients requiring noninvasive ventilation • Patients requiring admission to the critical care unit	• All-cause mortality (related and not related to COVID-19) • COVID-19–related mortality • All-cause mortality for subgroup who were immunocompromised • Any serious adverse event • Any events leading to drug discontinuation or withdrawal • Post–COVID-19 condition: persistence of symptoms at 30 days (adjusted)	• Treatment failure (composite outcome, defined as progression to severe COVID-19 requiring oxygen supplementation, corresponding to grade 4 or higher on the WHO COVID Outcomes Scale or COVID-19–related death)
Description of usual care	NR	NR	NR

CD20 = cluster of differentiate 20; JAK = Janus kinase; mAB = monoclonal antibody; NR= not reported; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TNF = tumour necrosis factor; VOC = variant of concern.

[a] Mikulska et al.[15] included a mixed population of patients who could be treated in or out of hospital; no separate data were provided, and no proportion of outpatients was reported.

[b] Eligible patient arms only.

Table 5

Characteristics of Cohort Studies 2

Characteristic	Solera et al. (2023)[11]	Colaneri et al. (2022)[16]	Manciulli et al. (2023)[17]
Name	NA	NA	FEDERATE Cohort
Publication year	2023	2022	2023
Design	Single-centre prospective cohort study	Single-centre retrospective cohort study	Retrospective cohort study
Country	Canada	Italy	Italy
Setting (no centres)	University Health Network Organ Transplant Program in Toronto	One of the infectious disease outpatient clinics of a hospital	11 infectious disease units
Study period	April 1, 2022, to May 5, 2022	December 23, 2021, to April 30, 2022	January 1, 2022, to March 31, 2022
Relevant VOCs reported	Omicron BA.2	Vast majority of COVID-19 cases due to the Omicron variant	Omicron sublineages BA.1 and BA.2
Participants, n[a]	192	73 eligible (of 88 total reported)	67 eligible (of 781 total reported)
Population	All adult organ transplant recipients with a confirmed diagnosis of symptomatic COVID-19	Adult patients with hematologic malignancies who tested positive for SARS-CoV-2 with mild to moderate COVID-19 diseases, including outpatients and patients admitted for reasons other than COVID-19	Patients with mild or moderate COVID-19 infection who had at least 1 risk factor and received sotrovimab, remdesivir, nirmatrelvir-ritonavir, or molnupiravir in an outpatient setting
Exclusions	Patients diagnosed with COVID at the time of admission or during hospitalization	Patients hospitalized for COVID-19 and/or requiring oxygen therapy for COVID-19 at the first clinical evaluation; asymptomatic patients	Patients hospitalized for reasons other than COVID-19 at the time of treatment, without a risk factor for severe COVID-19, who were asymptomatic or had severe or critical disease
Intervention (participants who received intervention, n)	Remdesivir (86)	Remdesivir (15)	Remdesivir (142)
Duration of treatment	3 days	3 days	NR
Comparator(s) (participants who received comparator, n)	Control group without remdesivir (106)	Molnupiravir (15) Nirmatrelvir-ritonavir (10) Nontreated (33)	Molnupiravir (205) Nirmatrelvir-ritonavir (120)

Characteristic	Solera et al. (2023)[11]	Colaneri et al. (2022)[16]	Manciulli et al. (2023)[17]
Duration of treatment	NR	NR	NR
Cointerventions	Immunosuppressants: • prednisone • tacrolimus • cyclosporine • mycophenolate • azathioprine • sirolimus	Immunosuppressive therapies: • rituximab • obinutuzumab • methotrexate • CHOP • CHOEP • ABVD • Poli-chemotherapy (VCR, Ara-C, Ida, EDX, cisplatin, endamustine) • VD (bortezomib dexamethasone) • eculizumab • tyrosine kinase inhibitors • others (daratumumab, isatuximab, IMIDs, brentuximab, Ab anti-PD1-PDL1)	NR
Follow-up time	A minimum period of 30 days or until the end of the disease course (complete clinical recovery or death)	28 days	28 days
Outcomes reported	• Hospitalization due to COVID-19 progression (adjusted	• 28-day hospital admission due to COVID-19 (adjusted)	• Death due to COVID-19 progression • Hospitalization due to COVID-19 progression • Discontinuation lead by drug intolerance
Description of usual care	Supportive care only (no active antiviral or anti-inflammatory)	NR	NR

ABVD = chemotherapy with doxorubicin, bleomycin, vinblastine, dacarbazine; Ara-C = cytarabine; CHOP = chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone; CHOEP = chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; EDX = cyclophosphamide; IMID = immunomodulatory drugs; NR = not reported; PD1 = programmed cell death protein 1; PDL1 = programmed cell death receptor ligand 1; VCR = vincristine; VD = bortezomib plus dexamethasone; VOC = variant of concern.

[a] Eligible participant arms only.

Table 6

Characteristics of Cohort Studies 3

Characteristic	Tiseo et al. (2023)[10]	Piccicacco et al. (2022)[13]	Mazzitelli et al. (2023)[12]
Name	PISA cohort	NA	NA
Publication year	2023	2022	2023
Design	Prospective cohort study	Single-centre retrospective cohort study	Retrospective cohort study
Country	Italy	US	Italy
Setting (no centres)	University Hospital of Pisa	Ambulatory infusion clinic, Tampa General Hospital	Infectious and Tropical Diseases Unit of Padua University Hospital
Study period	January 1, 2022, to July 1, 2022	December 27, 2021, to February 4, 2022	February 9, 2022, to May 31, 2022
Relevant VOCs reported	During Omicron variant spread	Omicron (B.1.1.529 surge)	> 85% Omicron variant
Participants, n[a]	562	172 eligible (of 260 total reported)	681
Population	Consecutive outpatients with documented COVID-19 who received 1 authorized antiviral treatment if they did not require supplemental oxygen therapy, were not hospitalized due to COVID-19, had mild to moderate COVID-19, and had at least 1 of the risk factors associated with progression to severe disease.	All patients had confirmed COVID-19 infection (either by antigen or PCR testing), were aged ≥ 12 years, and weighed ≥ 40 kg. All patients were classified as having mild to moderate symptoms for ≤ 7 days at the time of inclusion and were at high-risk for progression to severe COVID-19 in the outpatient setting.	Adult patients with COVID-19 at high risk of COVID-19 progression, consecutively referred to the centre, not hospitalized for COVID-19, and not requiring oxygen therapy for COVID-19 within 7 days from symptom onset, with at least 1 of the conditions representing risk factors for developing severe COVID-19.
Exclusions	Asymptomatic patients	Patient had received a COVID-19–directed oral antiviral (e.g., nirmatrelvir-ritonavir or molnupiravir), community-administered mAbs or if there were limited records for follow-up	Patient had received a concomitant treatment with oral antiviral agents nirmatrelvir-ritonavir or molnupiravir or received mAbs
Intervention (participants who received intervention, n)	Remdesivir (196)	Remdesivir (82)	Remdesivir (316)

Characteristic	Tiseo et al. (2023)[10]	Piccicacco et al. (2022)[13]	Mazzitelli et al. (2023)[12]
Duration of treatment	3 days	3 days	3 days
Comparator(s) (participants who received comparator, n)	• Molnupiravir (114) • Nirmatrelvir-ritonavir (252)	Control group without treatment (90)	Control group without antiviral treatment (365)
Duration of treatment	5 days	NR	NR
Cointerventions	NR	NR	NR
Follow-up time	30 days from the first positive nasopharyngeal swab	29 days	3 months
Outcomes reported	• 30-day mortality due to COVID-19 • Hospitalization due to COVID-19 progression • Rebound of symptoms after antiviral discontinuation • Any adverse events leading to drug discontinuation or withdrawal • AST or ALT increase	• Hospitalization at 29 days • Emergency department visit without hospitalization at 29 days • Hospitalization at 14 days • Emergency department visit without hospitalization at 14-days • All-cause mortality at 29 days • Any serious adverse event • Any events leading to drug discontinuation or withdrawal	• COVID-19–related death • ICU admission • Length of hospitalization • Post–COVID-19 condition: sequelae per patient (1 month after) • Post–COVID-19 condition: sequelae per patient (3 months after) • Rebound COVID-19 or SARS-CoV-2 reinfection • Any events leading to drug discontinuation or withdrawal Adjusted • progression to hospitalization • progression to oxygen requirement • post–COVID-19 condition: COVID-19–related sequelae (1 month after) • post–COVID-19 condition: COVID-19–related sequelae (3 months after)
Description of usual care	NR	NR	NR

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ICU = intensive care unit; mAB = monoclonal antibody; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; VOC = variant of concern.

[a] Eligible participant arms only.

Patient Characteristics

The basic characteristics of patients are summarized in Table 7, Table 8, Table 9, and Table 10. The median or mean age ranged from 50 years to 69 years, and 38.5% to 53.4% of the patients were females. COVID-19 vaccination status was reported in all 9 observational studies, although varied percentages were presented in the different treatment groups, whereas the RCT study excluded patients who were vaccinated.[8] The number of patients who were immunocompromised and patients with comorbidities were reported in all studies and were of varied proportions. Limited information on race or ethnicity was reported in 3 studies.[8,13,14] The median time from symptom onset to treatment was from 2 days to 5 days for remdesivir in 5 studies,[8,10,12,13,17] 3 days for molnupiravir and nirmatrelvir-ritonavir in 2 studies,[10,17] and 5 days in the placebo group in the RCT.[8]

Vaccination Status
The 9 observational studies reported varied percentages of COVID-19 vaccination. The RCT excluded vaccinated patients, making the study less generalizable to the current Canadian setting.

Randomized Controlled Trial

Table 7

Characteristics of Patients in the Randomized Controlled Trial

Characteristic	Gottlieb et al. (2022) (PINETREE)[8]
Trial registration number	NCT04501952
Status	Complete, published
Study period	September 18, 2020, to April 8, 2021
Study design	Randomized, double-blind, placebo-controlled trial
Locations	64 sites in the US, Spain, Denmark, and the UK. Sites included outpatient infusion facilities, skilled nursing facilities, and some home infusions.
Randomized, N	584
Inclusion criteria	Eligible patients were 12 years or older with at least 1 pre-existing risk factor for progression to severe COVID-19 or were 60 years or older with or without other risk factors.

Characteristic	Gottleib et al. (2022) (PINETREE)[8]	
Exclusion criteria	Patients were ineligible for any of the following reasons • they were receiving or were expected to receive supplemental oxygen or hospital care at the time of screening • they were previously hospitalized for COVID-19 • they previously received treatment for COVID-19 (including investigational agents) • they received a SARS-CoV-2 vaccine	
Intervention	Remdesivir	Placebo
Number of patients	292	292
Age (years), mean (SD)	50 (15)	51 (15)
Female, n (%)	131 (47.0)	138 (48.8)
Race or ethnicity, n (%)		
White	228 (81.7)	224 (79.2)
Hispanic or Latino	123 (44.1)	112 (39.6)
Black	20 (7.2)	22 (7.8)
American Indian or Alaska Native[a]	15 (5.4)	21 (7.4)
Asian, Native Hawaiian, or Pacific Islander[a]	7 (2.5)	7 (2.5)
Other	3 (1.1)	2 (0.7)
Patients who were immunocompromised, n (%)	14 (5.0)	9 (3.2)
Vaccination status	This trial excluded patients who had received SARS-CoV-2 vaccines	
Underserved or equity-deserving groups, n (%)	NR	NR
Patients with comorbidities, n (%)	NR	NR
Categories of comorbidities, n (%)		
Diabetes mellitus	173 (62.0)	173 (61.1)
Obesity	154 (55.2)	156 (55.1)
Hypertension	138 (49.5)	130 (45.9)

Characteristic	Gottlieb et al. (2022) (PINETREE)[8]	
Chronic lung disease	67 (24.0)	68 (24.0)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)
Immune compromised	14 (5.0)	9 (3.2)
Current cancer:	12 (4.3)	18 (6.4)
Chronic kidney disease (mild or moderate)	7 (2.5)	11 (3.9)
Chronic liver disease	1 (0.4)	1 (0.4)
Time from symptom onset to remdesivir or health care visit (days), median (IQR)	5 (3 to 6)	5 (4 to 6)

IQR = interquartile range; NR = not reported; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation.

[a] This grouping of race or ethnicity was taken directly from the Gottlieb et al. (PINETREE)[8] article.

Cohort Studies

Table 8

Characteristics of Patients (Cohort Studies 1)

Characteristic	Pinargote-Celorio et al. (2022)[a,14]		Del Borgo et al. (2023)[9]			Mikulska et al. (2023)[15]		
	Remdesivir	Nirmatrelvir-ritonavir	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir
Age (years), median	60 (IQR, 46 to 71.3)	62 (IQR, 44.8 to 74.5)	66 (range, 18 to 98)	78 (range, 21 to 103)	64 (range, 17 to 104)	66 (range, 16 to 89)		
Female, n (%)	56 (45.2)	59 (62.8)	116 (50.4)	247 (49.5)	167 (42.9)	133 (40.5)		
Race or ethnicity, n (%)	Spanish 244 (93.1)		NR			NR		
Patients who were immunocompromised, n (%)	83 (66.9)	56 (59.6)	94 (40.9)	97 (19.4)	129 (33.2)	NR		
Vaccination status	Vaccination with booster dose: n = 104 (83.9%)	Vaccination with booster dose: n = 80 (85.1%)	Incomplete vaccinal status: n = 32 (13.9%)	Incomplete vaccinal status: n = 26 (5.2%)	Incomplete vaccinal status: n = 24 (6.2%)	Anti-SARS-CoV-2 vaccination: n = 330 (91.7%) Doses: median = 3 (range, 0 to 4)		
Underserved or equity-deserving groups, n (%)	NR		NR			NR		
Patients with a comorbidity	Only reported n (%) for each category		Only reported n (%) for each category			Number of comorbidities (unclear measurement): median = 1 (range, 0 to 5)		

Characteristic	Pinargote-Celorio et al. (2022)[a,14]		Del Borgo et al. (2023)[9]			Mikulska et al. (2023)[15]		
	Remdesivir	Nirmatrelvir-ritonavir	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir
Categories of comorbidities	• Arterial hypertension • Diabetes mellitus • Body mass index > 30 • Smoking • Cardiovascular • Chronic kidney disease • Dialysis • Cardiovascular disease • Chronic lung disease • Asthma		• Cardiovascular disease • Neurological disease • Chronic kidney disease			• Acute myeloid leukemia • Acute lymphoid leukemia • Non-Hodgkin lymphoma • Hodgkin disease • Chronic lymphocytic leukemia • Multiple myeloma • Myelodysplastic syndrome • Myelofibrosis • Other (aplastic anemia = 4; CML = 3; other = 3)		
Time from symptom onset to remdesivir or health care visit	NR		NR			Days from symptoms onset to treatment: median = 2 (range, 0 to 13)		

CML = chronic myelogenous leukemia; IQR = interquartile range; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Study was a 3-arm study that included sotrovimab, which is not eligible in this report. These data are not reported; however, information on nationality and comorbidities were reported in the study only for the total number of participants (i.e., all 3 arms).

Table 9

Characteristics of Patients (Cohort Studies 2)

Characteristic	Solera et al. (2023)[11]		Colaneri et al. (2022)[a,16]				Manciulli et al. (2023)[b,17]		
	Remdesivir	Not treated	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir	Not treated	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir
Age (years)	Mean = 52.3 (SD = 13)	Mean = 54.7 (SD = 14)	Median = 63 (IQR, 49.0 to 71.2)				Median = 67.4 (IQR, 52 to 78.9)	Median = 68.9 (IQR, 57.3 to 79.9)	Median = 66.9 (IQR, 50.3 to 75.6)
Female, n (%)	38 (44.2)	36 (34)	47 (53)				83 (58.5)	87 (42.4)	69 (57.5)
Race or ethnicity, n (%)	NR		NR				NR		
Patients who were immunocompromised, n (%)	Reported immunosuppressive therapies Majority were on triple immunosuppression with prednisone, mycophenolate, and a calcineurin inhibitor		Reported immunosuppressive therapies, including rituximab, obinutuzumab, methotrexate, CHOP, CHOEP, ABVD, Poli-chemotherapy (VCR, Ara-C, Ida, EDX, cisplatin, bendamustine), VD (bortezomib-dexamethasone), eculizumab, tyrosine kinase inhibitors, others (daratumumab, isatuximab, IMIDs, brentuximab, Ab anti-PD1-PDL1)				n = 51 (35.9%)	n = 26 (12.7%)	n = 46 (38.3%)
Vaccination status (number of doses)	< 3: n = 8 (9.3%) ≥ 3: n = 78 (90.7%)	< 3: n = 11 (10.4%) ≥ 3: n = 95 (89.6%)	For all treated patients: mean = 2.6 (SD = 0.8)[a]			Mean = 2.7 (SD = 0.5)	0: n = 17 (12%) 1: n = 2 (1.4%) Full: n = 24 (16.9%) Booster: n = 98 (69.1%)	0: n = 24 (11.7%) 1: n = 3 (1.5%) Full: n = 46 (22.4%) Booster: n = 132 (64.4%)	0: n = 3 (2.5%) 1: n =1 (0.8%) Full: n = 7 (5.8%) Booster: n = 109 (90.8%)
Underserved or equity-deserving groups, n (%)	NR		NR				NR		
Patients with comorbidities, mean SD	1.9 (1.2)	2.2 (1.4)	1.5 (1.2)				NR (Only n and % reported for each category)		

Characteristic	Solera et al. (2023)[11]		Colaneri et al. (2022)[a,16]				Manciulli et al. (2023)[b,17]		
	Remdesivir	Not treated	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir	Not treated	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir
Categories of comorbidities	• Hypertension • Diabetes mellitus • Body mass index > 30 • Coronary artery disease Chronic cardiac failure • Chronic lung disease • Chronic kidney disease • Active systemic malignancy • Other immunodeficiency		• Neoplasia • Chronic kidney disease • Cardiovascular disease • Hypertension • Diabetes mellitus • Lung disease • Hepatitis C antibodies • Obesity • Smoking				• Obese • Pregnant • Chronic kidney disease • Coronary heart disease • Cancer • Chronic obstructive pulmonary disease • Cognitive impairment • Stroke • Diabetes		
Time from symptom onset to remdesivir or health care visit	NR		NR				Time to treatment: median = 4 (IQR, 2 to 5)	Time to treatment: median = 3 (IQR, 2 to 4)	Time to treatment: median = 3 (IQR, 2 to 3)

IQR = interquartile range; NR = not reported; SD = standard deviation.

[a] Study had 4 treatments under "treated" patients, including the 3 that are listed and sotrovimab, which was not eligible in this report, so we did not report these data. However, some baseline information was reported for the combined treated groups (i.e., all 4 treatments).

[b] This is a 4-arm study, including sotrovimab, which was not eligible in this report, so we did not report these data. Children from a pediatric infectious disease centre were also included in the study and no separate data reported but there seem to be very few children included based on the IQR for age.

Table 10

Characteristics of Patients (Cohort Studies 3)

Characteristic	Tiseo et al. (2023)[10]			Piccicacco et al. (2022)[13]		Mazzitelli et al. (2023)[12]	
	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir	Remdesivir	Molnupiravir	Remdesivir	Molnupiravir
Age (years)	Median = 69.5 (IQR, 57.75 to 80)	Median = 69.5 (IQR, 57.75 to 80)	Median = 65 (IQR, 51.25 to 75.75)	Mean = 58 (SD = 14.2)	Mean = 55.2 (SD = 16.8)	Median = 69 (IQR, 57 to 78)	Median = 63 (IQR, 52 to 74)
Female, n (%)	83 (42.3)	52 (45.6)	125 (49.6)	45 (54.9)	44 (49)	174 (55.1)	191 (52.3)
Race or ethnicity, n (%)	NR			• Caucasian: 51 (62.2) • African American: 15 (18.3) • Hispanic: 6 (7.3) • Other: 10 (12.2)	• Caucasian: 55 (61) • African American: 20 (22.3) • Hispanic: 14 (15.6) • Other: 1 (1.1)	NR	
Patients who were immunocompromised or immunodeficient, n (%)	55 (28.1)	20 (17.5)	54 (21.4)	53 (64.6)	66 (73.3)	92 (29.1)	60 (16.4)
Vaccination status	Adequate COVID-19 vaccination: n = 151 (77%) Time from the last COVID-19 vaccine dose (days): median 122 (IQR, 85 to 178)	Adequate COVID-19 vaccination: n = 85 (74.6%) Time from the last COVID-19 vaccine dose (days): 136 (IQR, 82 to 189)	Adequate COVID-19 vaccination: n = 219 (86.9%) Time from the last COVID-19 vaccine dose (days): median = 137 (IQR, 93 to 172)	Initial: n = 68 (83%) Booster: n = 36 (43.9%) Unvaccinated: n = 14 (17%)	Initial: n = 59 (65.6%) Booster: n = 32 (35.6%) Unvaccinated: n = 31 (34.4%)	Vaccination against SARS-CoV-2: n = 250 (79.1%)	Vaccination against SARS-CoV-2: n = 193 (52.9%)
Underserved or equity-deserving groups, n (%)	NR			NR		NR	

Characteristic	Tiseo et al. (2023)[10]			Piccicacco et al. (2022)[13]		Mazzitelli et al. (2023)[12]	
	Remdesivir	Molnupiravir	Nirmatrelvir-ritonavir	Remdesivir	Molnupiravir	Remdesivir	Molnupiravir
Patients with comorbidities	Number of comorbidities, n (%) • ≤ 1: 25 (12.8) • ≥ 2: 170 (86.7) • ≥ 3: 118 (60.2)	Number of comorbidities, n (%) • ≤ 1: 26 (22.8) • ≥ 2: 88 (77.2) • ≥ 3: 61 (53.5)	Number of comorbidities, n (%) • ≤ 1: 78 (31) • ≥ 2: 174 (69) • ≥ 3: 93 (36.9)	Only reported specific category with n (%)		Comorbidities per patient (n): median = 2 (IQR, 1 to 3)	Comorbidities per patient (n): median = 1 (IQR, 1 to 2)
Categories of comorbidities	• Obesity • Chronic lung disease • Immunosuppression (primary or acquired) • Diabetes mellitus • Arterial hypertension • Cardiovascular disease • Cerebrovascular disease • Solid cancer • Hematological disease • Chronic liver disease • Autoimmune disease • Solid organ transplant • Neurological disease			• Chronic kidney disease • Hypertension • Cardiovascular disease • Chronic lung disease		NR	
Time from symptom onset to remdesivir or health care visit	Time from symptom onset to antiviral treatment (days): median = 4 (IQR, 3 to 5)	Time from symptom onset to antiviral treatment (days): median = 3 (IQR, 2 to 4)	Time from symptom onset to antiviral treatment (days): median = 3 (IQR, 2 to 4)	Time from symptom onset to first dose (days): mean = 4 (SD = 1.4)	No remdesivir given	Time from symptom onset to early remdesivir (days): median = 2 (IQR, 2 to 3)	No remdesivir given

IQR = interquartile range; NR = not reported; SD = standard deviation.

Data Analysis and Synthesis

Randomized Controlled Trial

The results reported on the outcomes of interest in the randomized controlled trial, as well as additional results calculated based on the reported study results, are provided in Table 11. In Appendix 4, the results are provided with the study authors' conclusions.

Findings Suggest
Remdesivir lowers the risk of COVID-19–related hospitalization in nonvaccinated patients compared to a placebo. Males and patients aged 60 or older are likely to benefit most from this risk reduction.

Gottlieb et al. (2022)[8] found all COVID-19–related hospitalizations occurred by day 14 (2 patients hospitalized with remdesivir vs. 15 with placebo) and the risk of COVID-19–related hospitalization was statistically significantly lower in the group who received remdesivir than in the group who received placebo (HR = 0.13; 95% CI, 0.03 to 0.59) and (RR = 0.14; 95% CI, 0.031 to 0.59). In an adjusted analysis, there was a statistically significant reduction in COVID-19–related hospitalizations for remdesivir compared with placebo for the subgroup of patients aged 60 years or older (HR = 0.11; 95% CI, 0.01 to 0.86) and for males (HR = 0.11; 95% CI, 0.01 to 0.84), but not for the subgroup of patients who were Hispanic or Latino (HR = 0.26; 95% CI, 0.06 to 1.22).

We calculated the median and IQR time to hospitalization from supplemental data (remdesivir: median = 4 days [IQR, 2.5 to 7.5] placebo: median = 6.5 days; [IQR, 3 to 9]) and estimated the mean and SD of this measure based on the median, IQR, and study sample size with the formula proposed by Wan et al.[18] and found no statistically significant difference between remdesivir and placebo (mean difference [MD] = −1.50 days; 95% CI, −6.51 to 3.51) (Table 11).

Gottlieb et al. (2022) found no deaths from any cause by day 28 for both remdesivir and placebo.

Table 11

Results for Outcomes of Interest in the Randomized Controlled Trial

Reported results on outcomes of interest in Gottlieb et al. (2022)[8]	Additional results calculated based on reported study results[a]
COVID-19–related hospitalization by day 28,[b] n (%) • Remdesivir (n = 279): 2 (0.7) • Placebo (n = 283):15 (5.3) • HR = 0.13 (95% CI, 0.03 to 0.59)[c] All COVID-19–related hospitalizations occurred by day 14.	COVID-19–related hospitalization by day 14 • Remdesivir vs. placebo • Unadjusted RR = 0.14 (95% CI, 0.031 to 0.59)
ICU admission among hospitalized patients, n (%) • Remdesivir (n = 279): 3 (1) • Placebo (n = 283): 3 (1)	ICU admission • Remdesivir vs. placebo • Unadjusted RR = 1.01 (95% CI, 0.21 to 4.98)
Time to hospitalization (reported as individualized day of hospitalization from time of randomization), median (IQR) • Remdesivir (n = 5): 4 (2.5 to 7.5)[d] • Placebo (n = 18): 6.5 (3 to 9)	Length of hospitalization (days) • Remdesivir vs. placebo • Unadjusted MD = −1.50 (95% CI, −6.51 to 3.51)
Death from any cause by day 28,[e] n (%) • Remdesivir (n = 279): 0 (0) • Placebo (n = 283): 0 (0) • HR (95% CI): not calculated	Death by day 28 • Remdesivir vs. placebo • Unadjusted RR (95% CI): Not estimable
Any SAE,[f] n (%) • Remdesivir (n = 279): 5 (1.8) • Placebo (n = 283): 19 (6.7)	Serious adverse event • Remdesivir vs. placebo • Unadjusted RR = 0.27 (95% CI, 0.10 to 0.71)
Adverse event leading to discontinuation of trial regimen, n (%) • Remdesivir (n = 279): 2 (0.7) • Placebo (n = 283): 5 (1.8)	Drug discontinuation due to adverse event • Remdesivir vs. placebo • Unadjusted RR = 0.41 (95% CI, 0.079 to 2.07)

CI = confidence interval; HR = hazard ratio; MD = mean difference; RR = risk ratio; SAE = serious adverse event.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] No patients in either group died by day 28; therefore, the results for the composite outcome could be used for our single outcome of interest (COVID-19–related hospitalization).

[c] Cox proportional hazards model with the baseline stratification factors as covariates (i.e., residence in a skilled nursing facility [yes or no], age [< 60 years or ≥ 60 years], and country [inside or outside US]) was used to estimate HR and 95% CI.

[d] Only 2 patients in the remdesivir arm were considered to have been hospitalized because of COVID-19 (2 and 3 days, respectively). Non-COVID-19–related causes were atrial fibrillation, cardiac failure congestive, and angina pectoris.

[e] Authors provided the outcome (transfer, discharged, or death) for all hospitalized patients; only 1 patient in the placebo group died as of day 59.

[f] Severity grades were defined according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

Cohort Studies

These results are for the outcomes of interest reported in the cohort studies; additional results were calculated based on these reported study results and are provided in Table 12. Many of the reported results on effect estimates and all of the additional results have not been adjusted for possible differences between the cohorts that could distort the relationship between the cohorts and the outcome under consideration (i.e., confounding). This should be considered when interpreting the results. In Appendix 4 the reported results are provided with the study authors conclusions.

ED visits without hospitalization: ED visits without hospitalization was reported in 1 study (Piccicacco et al. [2022][13]), and no adjustment for possible confounding factors was made when the remdesivir and control (no treatment) cohorts were compared. The study reported that patients treated with remdesivir were statistically significantly less likely to visit the ED within 29 days of treatment compared with patients in the control group (OR = 0.2; 95% CI, 0.04 to 0.94).

Findings Suggest
Remdesivir lowers the number of emergency department visits but, interpretation is limited as it was only reported in 1 study and there were no adjustments done for underlying factors.

Hospitalization: Hospitalization was reported in 7 studies (Piccicacco et al. [2022],[13] Manciulli et al. [2023],[17] Tiseo et al. [2023],[10] Pinargote-Celorio et al. [2022],[14] Mazzitelli et al. [2023],[12] Colaneri et al. [2022],[16] and Solera et al. [2023][11]). Only 3 studies included results from an adjusted analysis for the specific outcome of hospitalization (Mazzitelli et al. [2023],[12] Colaneri et al. [2022],[16] and Solera et al. [2023][11]). Mazzitelli et al. (2023)[12] and Solera et al. (2023)[11] found that remdesivir statistically significantly reduced hospitalization compared with control. Mazzitelli et al. (2023)[12] found that remdesivir statistically significantly reduced progression to hospitalization compared with no antiviral treatment (adjusted OR = 0.049; 95% CI, 0.015 to 0.163), and Solera et al. (2023)[11] found that remdesivir statistically significantly reduced COVID-19–related hospitalization by 30 days compared with no remdesivir (adjusted HR = 0.12; 95% CI, 0.03 to 0.57). Colaneri et al. (2022)[16] found that none of the early treatments including remdesivir statistically significantly reduced 28-day hospital admissions compared with no treatment (adjusted HR = 1.16, P = 0.83).

Findings Suggest
Remdesivir has variable efficacy in reducing hospitalizations. We see a protective effect in 2 studies, but 1 study found no significant reduction compared with the control. All 3 studies adjusted for underlying factors.

The study by Piccicacco et al. (2022)[13] included hospitalizations but the authors made no adjustment for possible confounding factors when comparing the remdesivir and control (no treatment) cohorts. This authors found there was no statistically significant difference for hospitalizations within 29 days of symptom onset for patients who received remdesivir compared with the control group who received no treatment (RR = 0.72; 95% CI, 0.28 to 1.78).

Two studies, Manciulli et al. (2023)[17] and Tiseo et al. (2023)[10] compared COVID-19–related hospitalizations by 28 and 30 days, respectively, for remdesivir versus molnupiravir, but the authors made no adjustment for possible confounding for this specific outcome. Both Manciulli et al. (2023)[17] and Tiseo et al. (2023)[10] found the difference between treatment groups was not statistically significant (remdesivir: RR = 2.53 [95% CI, 0.75 to 8.47]; molnupiravir: RR = 5.82 [95% CI, 0.75 to 44.85]). The combined RR indicated a statistically significant lower rate of COVID-19–related hospitalizations for molnupiravir than remdesivir (RR = 3.14; 95% CI, 1.11 to 8.88) (Figure 2). Although Manciulli et al. (2023)[17] and Tiseo et al. (2023)[10] did not conduct multivariate-adjusted analyses for the hospitalization outcome, they did conduct this analysis on the composite outcome of hospitalization or death.

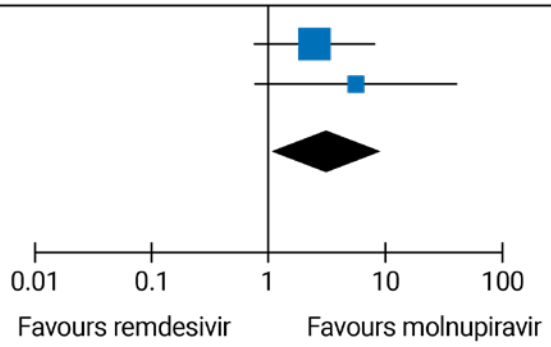
Findings Suggest
Molnupiravir and nirmatrelvir-ritonavir are more effective at lowering the rate of hospitalization compared with remdesivir. We saw this effect after combining the risks, but without adjusting for underlying factors.

Figure 2

Meta-Analysis of COVID-19–Related Hospitalization for Remdesivir Versus Molnupiravir — Unadjusted Risk Ratio[a]

Study or Subgroup	Remdesivir Events	Remdesivir Total	Molnupiravir Events	Molnupiravir Total	Weight	Risk Ratio M-H, Random, 95% CI
Manciulli, 2023	7	142	4	205	74.0%	2.53 [0.75 , 8.47]
Tiseo, 2023	10	196	1	114	26.0%	5.82 [0.75 , 44.85]
Total (95% CI)		**338**		**319**	**100.0%**	**3.14 [1.11 , 8.88]**
Total events	17		5			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.50$, df = 1 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

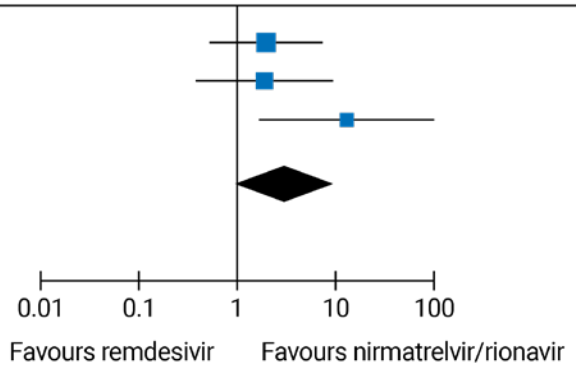
In 3 studies (Manciulli et al. [2023],[17] Tiseo et al. [2023],[10] and Pinargote-Celorio et al. [2022][14]), the authors compared remdesivir versus nirmatrelvir-ritonavir in an unadjusted analysis for the outcome of COVID-19–related hospitalizations by 28, 30, and 30 days respectively. Both Manciulli et al. (2023)[17] and Pinargote-Celorio et al. (2022)[14] found that the difference between treatment groups was not statistically significant (RR = 1.97 [95% CI, 0.52 to 7.46] and RR = 1.90 [95% CI, 0.38 to 9.56], respectively), whereas Tiseo et al. (2023)[10] found a statistically significant difference favouring nirmatrelvir-ritonavir. The combined unadjusted RR indicated a statistically significant lower rate of COVID-19–related hospitalizations for nirmatrelvir-ritonavir compared with remdesivir (RR = 3.01; 95% CI, 1.00 to 9.11) (Figure 3).

Figure 3

Meta-Analysis of COVID-19–Related Hospitalization for Remdesivir Versus Nirmatrelvir-Ritonavir — Unadjusted Risk Ratio[a]

Study or Subgroup	Remdesivir Events	Total	Nirmatrelvir/ritonavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Manciulli, 2023	7	142	3	120	43.3%	1.97 [0.52 , 7.46]
Pinargote-Celorio, 2022	5	124	2	94	33.3%	1.90 [0.38 , 9.56]
Tiseo, 2023	10	196	1	252	23.3%	12.86 [1.66 , 99.59]
Total (95% CI)		**1170**		**1157**	**100.0%**	**3.01 [1.00 , 9.11]**
Total events	22		6			

Heterogeneity: Tau² = 0.27; Chi² = 2.78, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel;.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

Length of hospitalization: Length of hospitalization was reported in 2 studies, and the authors of both studies did not adjust for possible confounding factors when the remdesivir and no remdesivir cohorts were compared. Both Mazzitelli et al. (2023)[12] and Solera et al. (2023)[11] did not find a statistically significant difference between remdesivir and no remdesivir on duration of hospitalization. We estimated the mean and SD based on the median, IQR, and study sample size with the formula proposed by Wan et al.[18] and combined the data, which showed a similar result of no statistically significant difference between the cohorts (MD = −1.72; 95% CI, −9.16 to 5.71) (Figure 4).

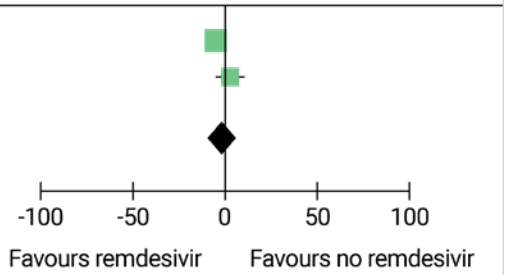
Findings Suggest
Remdesivir does not lower the length of hospitalization or number of ICU admissions compared with no treatment. The studies did not account for underlying factors.

Figure 4

Meta-Analysis of Length of Hospitalization in Days[a] — Unadjusted Mean Difference

Study or Subgroup	Remdesivir Mean	SD	Total	No remdesivir Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Mazzitelli, 2023	7.667	2.963	3	12.667	14.074	56	74.0%	-5.00 [-9.98 , -0.02]
Solera, 2023	11	4.444	2	8.333	8.148	13	26.0%	2.67 [-4.92 , 10.25]
Total (95% CI)			**5**			**69**	**100.0%**	**-1.72 [-9.16 , 5.71]**

Heterogeneity: Tau^2 = 18.67; Chi^2 = 2.74, df = 1 (P = 0.10); I^2 = 64%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



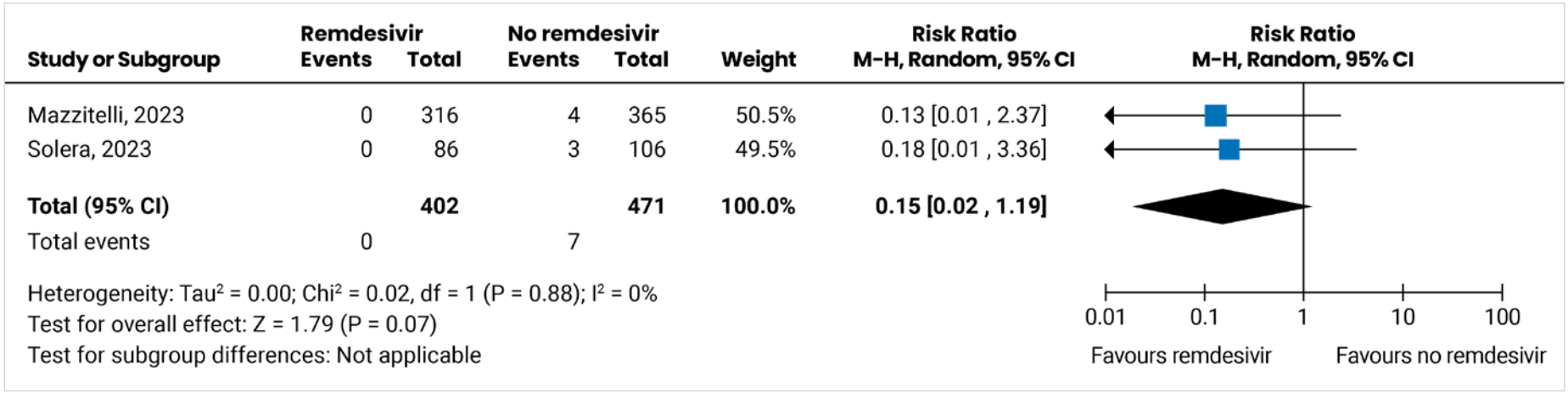
CI = confidence interval; IV = inverse variance.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

ICU admission: ICU admissions was reported in 3 studies (Mazzitelli et al. [2023],[12] Pinargote-Celorio et al. [2022],[14] and Solera et al. [2023][11]) and the authors made no adjustment for possible confounding of the groups being compared. Mazzitelli et al. (2023)[12] stated that the rare occurrence of ICU admission did not allow for enough power to test the difference in ICU admissions between the group who received remdesivir and the control group who received no antiviral treatment (RR = 0.13; 95% CI, 0.007 to 2.37). Solera et al. (2023)[11] reported no ICU admissions in the group who received remdesivir and 3 (2.8%) in the no remdesivir group (RR = 0.18; 95% CI, 0.009 to 3.36). We combined the raw frequency data from these 2 studies, and the combined analysis did not find a statistically significant decrease in ICU admissions for remdesivir compared with no remdesivir (RR = 0.15; 95% CI, 0.02 to 1.19) (Figure 5). Pinargote-Celorio et al. (2022)[14] compared remdesivir with nirmatrelvir-ritonavir; there were no ICU admissions in both groups.

Figure 5

Meta-Analysis of ICU Admission for Remdesivir Versus No Remdesivir — Unadjusted Risk Ratio[a]



CI = confidence interval; M-H = Mantel-Haenszel.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

Need for supplemental oxygen: Three studies (Mazzitelli et al. [2023],[12] Pinargote-Celorio et al. [2022],[14] and Solera et al. [2023][11]) included the need for supplemental oxygen. Only Mazzitelli et al. (2023)[12] reported the result adjusted for sex, immunodeficiency, number of comorbidities per patient, and time from COVID-19 onset to diagnosis. The adjusted result showed that early remdesivir treatment compared with no antiviral treatment in the control group was independently associated with a lower risk of progression to oxygen (adjusted OR = 0.034; 95% CI, 0.008 to 0.144). Solera et al. (2023)[11] found no statistically significant difference in the need for supplemental oxygen when comparing remdesivir and no remdesivir (HR = 0.21; 95% CI, 0.02 to 2.03), but it is unclear if this was based on an adjusted or unadjusted analysis. Pinargote-Celorio et al. (2022)[14] compared remdesivir with nirmatrelvir-ritonavir and found no patients in either group required noninvasive ventilation.

Findings Suggest
Early treatment with remdesivir may lower the need for supplemental oxygen compared with no treatment. This effect is seen in 1 study that adjusted for underlying factors, but not in another study with no adjustment.

Post–COVID-19 condition: Two studies on post–COVID-19 condition compared treatment cohorts after adjusting for possible confounding factors. Mazzitelli et al. (2023)[12] reported that patients in the group treated with early remdesivir group compared with the group who received no antiviral treatment had statistically significantly fewer COVID-19–related sequelae at both the 1-month (adjusted OR = 0.147; 95% CI, 0.089 to 0.242) and 3-month (adjusted OR = 0.181; 95% CI, 0.105 to 0.312) follow-ups. Del Borgo et al. (2023)[9] found patients treated with remdesivir had statistically significantly higher persistence of symptoms at 30 days compared with those treated with molnupiravir (OR = 0.46; 95% CI, 0.30 to 0.71) or nirmatrelvir-ritonavir (OR = 0.56; 95% CI, 0.37 to 0.85).

Findings Suggest
Remdesivir may reduce COVID-19 aftereffects compared with no treatment, whereas molnupiravir is better at reducing persistent symptoms. Remdesivir is comparable to other antivirals for symptom rebound.

Rebound COVID-19: In an unadjusted analysis, Tiseo et al. (2023)[10] and Mazzitelli et al. (2023)[12] reported on rebound COVID-19; they found no statistically significant difference between remdesivir and molnupiravir (RR = 0.11; 95% CI, 0.005 to 2.31) and nirmatrelvir-ritonavir (RR = 0.11; 95% CI, 0.006 to 1.97). In particular, Tiseo et al. (2023)[10] reported on rebound of symptoms after antiviral discontinuation at 30 days and found no rebound in group treated

with remdesivir approximately 2% of patients treated with molnupiravir and nirmatrelvir-ritonavir experienced a rebound of symptoms.

Death: Death was reported in 7 studies (Manciulli et al. [2023],[17] Tiseo et al. [2023],[10] Piccicacco et al. [2022],[13] Mazzitelli et al. [2023],[12] Pinargote-Celorio et al. [2022],[14] Del Borgo et al. [2023],[9] and Solera et al. [2023][11]). For the comparison of the treatment cohorts for each of these studies, the authors did not adjust for potential confounding factors. Piccicacco et al. (2022),[11,13] included comparisons between remdesivir and no remdesivir or no antiviral treatment on all-cause deaths; No statistically significant difference was found when considered individually (RR = 0.37 [95% CI, 0.015 to 8.85] and RR = 0.25 [95% CI, 0.012 to 5.06], respectively) or when combined (RR = 0.30; 95% CI, 0.03 to 2.66) for this unadjusted analysis (Figure 6). Similarly, the combined result for the Peto OR indicated a nonstatistically significant reduction in all-cause mortality for remdesivir compared with no remdesivir/no antiviral treatment (OR = 0.16; 95% CI, 0.02 to 1.53). Mazzitelli et al. (2023)[12] made a similar comparison but for COVID-19–related deaths and found no statistically significant difference (RR = 0.28; 95% CI, 0.06 to 1.35).

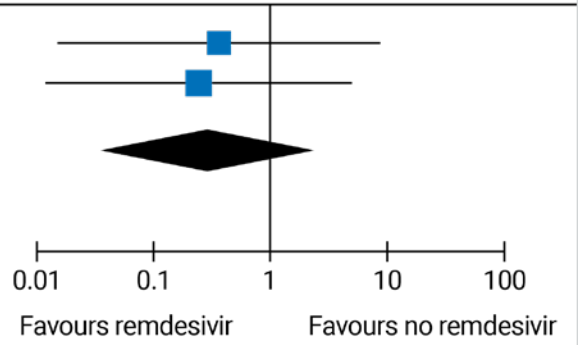
Findings Suggest
Remdesivir does not lower the risk of all-cause or COVID-19–related deaths compared with no treatment. The studies did not account for underlying factors.

Figure 6

Meta-Analysis of All-Cause Death for Remdesivir Versus No Remdesivir — Unadjusted Risk Ratio[a]

Study or Subgroup	Remdesivir Events	Remdesivir Total	No remdesivir Events	No remdesivir Total	Weight	Risk Ratio M-H, Random, 95% CI
Piccicacco, 2022	0	82	1	90	47.4%	0.37 [0.02 , 8.85]
Solera, 2023	0	86	2	106	52.6%	0.25 [0.01 , 5.06]
Total (95% CI)		**168**		**196**	**100.0%**	**0.30 [0.03 , 2.66]**
Total events	0		3			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

Three studies[9,10,17] compared remdesivir and molnupiravir on COVID-19–related deaths at 28 or 30 days from start treatment, and when considered individually or when combined in an unadjusted analysis, no statistically significant difference was found (RR = 0.99; 95% CI, 0.15 to 6.50) (Figure 7). The combined result for the Peto OR was similar (OR = 1.20; 95% CI, 0.25 to 5.72).

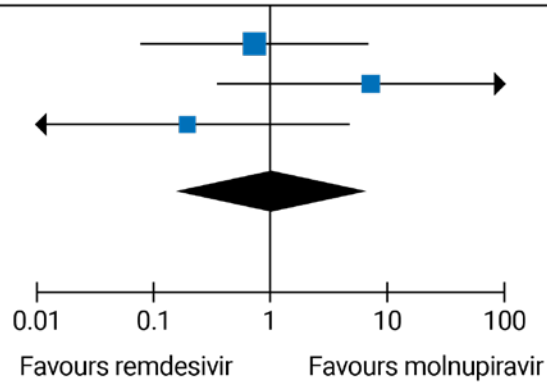
Findings Suggest
Remdesivir is comparable to other antivirals in reducing COVID-19–related deaths. The studies did not account for underlying factors.

Figure 7

Meta-Analysis of COVID-19–Related Deaths for Remdesivir Versus Molnupiravir — Unadjusted Risk Ratio[a]

Study or Subgroup	Remdesivir Events	Remdesivir Total	Molnupiravir Events	Molnupiravir Total	Weight	Risk Ratio M-H, Random, 95% CI
Borgo, 2023	1	230	3	499	43.9%	0.72 [0.08 , 6.91]
Manciulli, 2023	2	142	0	205	29.2%	7.20 [0.35 , 148.91]
Tiseo, 2023	0	196	1	114	26.9%	0.19 [0.01 , 4.74]
Total (95% CI)		**568**		**818**	**100.0%**	**0.99 [0.15 , 6.50]**
Total events	3		4			

Heterogeneity: $Tau^2 = 0.77$; $Chi^2 = 2.75$, df = 2 (P = 0.25); $I^2 = 0\%$
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



M-H = Mantel-Haenszel; CI = confidence interval.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

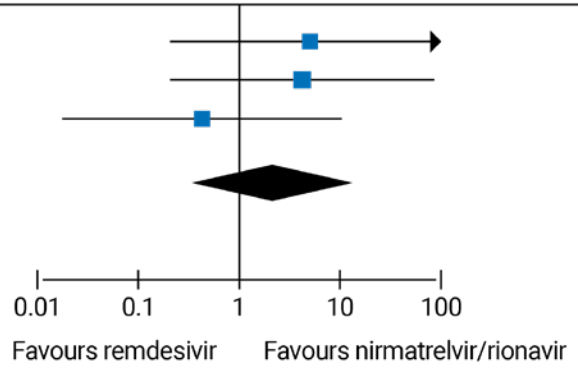
Three studies[9,10,17] compared remdesivir and nirmatrelvir-ritonavir on COVID-19–related deaths at 28 or 30 days and, when considered individually or when combined, no statistically significant difference was found (RR = 2.15; 95% CI, 0.35 to 13.13) in this unadjusted analysis (Figure 8). The combined result for the Peto OR was similar (OR = 3.12; 95% CI, 0.43 to 22.69). Pinargote-Celorio et al. (2022)[14] reported on the comparison of remdesivir and nirmatrelvir-ritonavir and found no events for the outcome of all-cause 30-day mortality in either groups.

Figure 8

Meta-Analysis of COVID-19–Related Deaths for Remdesivir Versus Nirmatrelvir-Ritonavir — Unadjusted Risk Ratio[a]

Study or Subgroup	Remdesivir Events	Remdesivir Total	Nirmatrelvir/ritonavir Events	Nirmatrelvir/ritonavir Total	Weight	Risk Ratio M-H, Random, 95% CI
Borgo, 2023	1	230	0	389	32.1%	5.06 [0.21 , 123.82]
Manciulli, 2023	2	142	0	120	35.8%	4.23 [0.21 , 87.28]
Tiseo, 2023	0	196	1	252	32.1%	0.43 [0.02 , 10.45]
Total (95% CI)		**568**		**761**	**100.0%**	**2.15 [0.35 , 13.13]**
Total events	3		1			

Heterogeneity: Tau² = 0.00; Chi² = 1.45, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel.

[a] Results have not been adjusted for variables that may distort the relationship between the treatments and the outcome and caution in interpreting must be exercised.

Any serious adverse event: Any SAE was reported in 2 studies (Piccicacco et al. [2022][13] and Del Borgo et al. [2023][9]). The authors of both studies reported rare cases (zero or 1) of SAE without further analysis.

Drug discontinuation: Drug discontinuation was reported in 4 studies (Manciulli et al. [2023],[17] Tiseo et al. [2023],[10] Mazzitelli et al. [2023],[12] and Del Borgo et al. [2023][9]). Discontinuation was uncommon in all studies.

Acute liver injury: Acute liver injury–related outcomes were reported in 1 study. Tiseo et al. (2023)[10] found that AST and ALT increased in 1 patient in the molnupiravir group and none in the remdesivir and nirmatrelvir-ritonavir group.

Key Finding
Serious adverse events and drug discontinuation were uncommon in the studies that reported these safety outcomes. Acute liver injury outcomes were only reported in 1 study, with no injuries for remdesivir.

Table 12

Results for Outcomes of Interest in Cohort Studies

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Emergency department visit without hospitalization	
Piccicacco et al. (2022)[13]	
COVID-19–related 29 day ED visit, within 29 days from symptom onset (initial COVID-19 diagnosis made in the ED did not count as an ED visit), n (%) • 14 days ◦ Remdesivir (n = 82): 1 (1.2) ◦ No treatment control (n = 90): 6 (6.7) ◦ P = 0.05[c] • 29 days ◦ Remdesivir (n = 82): 2 (2.4) ◦ No treatment control (n = 90): 10 (11.1) ◦ P = 0.04 ◦ Unadjusted OR = 0.2 (95% CI, 0.04 to 0.94) ◦ Absolute risk reduction: 8.7% ◦ Number needed to treat: n = 12 (95% CI, 6.3 to 72.9)	COVID-19–related ED visit by day 29 • Remdesivir vs. control • Unadjusted RR = 0.22 (95% CI, 0.050 to 0.97)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Hospitalization	
Piccicacco et al. (2022)[13]	
Hospitalization, n (%) • 14 days ◦ Remdesivir (n = 82): 4 (5) ◦ No treatment) control (n = 90): 8 (8.9) ◦ P = 0.27[c] • 29 days ◦ Remdesivir (n = 82): 7 (8.5) ◦ No treatment control (n = 90): 11 (12.2) ◦ P = 0.58[c]	Hospitalization by day 29 • Remdesivir vs. control • Unadjusted RR = (95% CI): • RR = 0.70; 95% CI, 0.28 to 1.72
Manciulli et al. (2023)[17]	
Hospitalization due to COVID-19 progression by day 28, n (%) • Remdesivir (n = 142): 7 (4.9) • Molnupiravir (n = 205): 4 (1.9) • Nirmatrelvir-ritonavir (n = 120): 3 (2.5)	Hospitalization due to COVID-19 by day 28 • Remdesivir vs. molnupiravir • Unadjusted RR = 2.53 (95% CI, 0.75 to 8.47) Hospitalization due to COVID-19 by day 28 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 1.97 (95% CI, 0.52 to 7.46)
Tiseo et al. (2023)[10]	
Hospitalization due to COVID-19 by day 30, n (%) • Remdesivir (n = 196): 10 (5.1) • Molnupiravir (n = 114): 1 (0.9) • Nirmatrelvir-ritonavir (n = 252): 1 (0.4) • P = 0.002 (test for multiple comparisons)	Hospitalization due to COVID-19 by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 5.82 (95% CI, 0.75 to 44.85) Hospitalization due to COVID-19 by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 12.86 (95% CI, 1.66 to 99.59)
Pinargote-Celorio et al. (2022)[14]	
All-cause hospitalization by day 30 post treatment, n (%) • Remdesivir (n = 124): 8 (6.5) • Nirmatrelvir-ritonavir (n = 94): 3 (3.2) **Hospitalization due to COVID-19 progression by day 30 post treatment**, n (%) • Remdesivir (n = 124): 5 (4) • Nirmatrelvir-ritonavir (n = 94): 2 (2.1)	Hospitalization by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 2.02 (95% CI, 0.55 to 7.41) Hospitalization due to COVID-19 by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 1.90 (95% CI, 0.38 to 9.56)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Mazzitelli et al. (2023)[12]	
Progression to hospitalization, unclear follow-up,[d] n (%) • Remdesivir (n = 316): 3 (0.9) • No antiviral treatment control treatment (n = 365): 56 (15.3) **Adjusted result**[e] • Early remdesivir vs. control (reference): • Adjusted OR = 0.049 (95% CI, 0.015 to 0.163, P < 0.001)	NC
Colaneri et al. (2022)[16]	
28-day hospital admission • **Adjusted result**[f] ◦ Number of patients: remdesivir (n = 15); not treated (n = 33) ◦ Remdesivir vs. nontreated (reference): HR = 1.16 (SE = 0.71; P = 0.83)	NC
Solera et al. (2023)[11]	
COVID-19–related hospitalization by day 30, n (%) • Remdesivir (n = 86): 2 (2.3%) • No remdesivir (n = 106): 13 (12.3%) • P = 0.013 **Adjusted result**[g] • Remdesivir vs. without remdesivir (reference) • HR = 0.12 (95% CI, 0.03 to 0.57; P = 0.007) • NNT to prevent admission = 15.2 (95% CI, 13.6 to 31.4)	Hospitalization due to COVID-19 by day 30 • Remdesivir vs. no remdesivir • Unadjusted RR = 0.19 (95% CI, 0.044 to 0.82)
Length of hospitalization (days)	
Mazzitelli et al. (2023)[12]	
Length of hospitalization (days), median (IQR)[h] • Remdesivir (n = 3): 3 (8 to 12) • No remdesivir (n = 56): 14 (10 to 29) • P = 0.299	Length of hospitalization (days) • Remdesivir vs. no remdesivir • Unadjusted MD = −5.00 (95% CI, −9.98 to −0.02)
Solera et al. (2023)[11]	
Duration of hospitalization (days), median (IQR) • Remdesivir (n = 2): 11 (8 to 14) • No remdesivir (n = 13): 6 (4 to 15)	Length of hospitalization (days) • Remdesivir vs. no remdesivir • Unadjusted MD = 2.67 (95% CI, −4.92 to 10.25)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
ICU admission	
Mazzitelli et al. (2023)[12]	
ICU admission, unclear follow-up, n (%) • Remdesivir (n = 316): 0 (0) • No antiviral treatment control (n = 365): 4 (1.1)[i]	ICU admission (day unclear) • Remdesivir vs. control • Unadjusted RR = 0.13 (95% CI, 0.007 to 2.37)
Pinargote-Celorio et al. (2022)[14]	
Patients required admission to the critical care unit by day 30, n (%) • Remdesivir (n = 124): 0 (0) • Nirmatrelvir-ritonavir (n = 94): 0 (0)	ICU admission by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = not estimable
Solera et al. (2023)[11]	
ICU admission at day 30, n (%) • Remdesivir (n = 86): 0 (0) • No remdesivir (n = 106): 3 (2.8)	ICU admission by day 30 • Remdesivir vs. no remdesivir • Unadjusted RR = 0.18 (95% CI, 0.009 to 3.36)
Need for supplemental oxygen	
Mazzitelli et al. (2023)[12]	
Progression to oxygen requirement, unclear follow-up, n (%) • Remdesivir (n = 316): 2 (0.6) • No antiviral treatment control (n = 365): 56 (15.3) • Remdesivir vs. control (reference) • OR = 0.035 (95% CI, 0.009 to 0.145 (unadjusted), P < 0.001) **Adjusted result**[e] • Early remdesivir vs. control (reference) • Adjusted OR = 0.034 (95% CI, 0.008 to 0.144; P < 0.001)	NC
Pinargote-Celorio et al. (2022)[14]	
Patients required noninvasive ventilation, n (%) • Remdesivir (n = 124): 0 (0) • Nirmatrelvir-ritonavir (n = 94): 0 (0)	Require noninvasive ventilation • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR Not estimable

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Solera et al. (2023)[11]	
Need for supplemental oxygen (including both patients who needed to start oxygen therapy and those with oxygen at baseline whose requirement increased), n (%) • Remdesivir (n = 86): 1 (1.2) • No remdesivir (n = 106): 4 (1.8) • HR = 0.21 (95% CI, 0.02 to 2.03; P = 0.38) • (unclear if unadjusted or adjusted) **Mechanical ventilation**, n (%) • Remdesivir (n = 86): 0 (0) • No remdesivir (n = 106): 2 (1.9)	Need for supplemental oxygen • Remdesivir vs. no remdesivir • Unadjusted RR = 0.31 (95% CI, 0.035 to 2.71) Mechanical ventilation • Remdesivir vs. no remdesivir • Unadjusted RR = 0.25 (95% CI, 0.012 to 5.06)
Post–COVID-19 condition	
Mazzitelli et al. (2023)[12]	
COVID-19—related sequelae, 1 month after, n (%) • Remdesivir (n = 314): 27 (8.6) • No antiviral treatment control (n = 365): 155 (43.4) • P = 0.001 **Adjusted result**[j] • Among 671 survivors, early remdesivir vs. control (reference) • Adjusted OR = 0.147 (95% CI, 0.089 to 0.242) • P = 0.001 **Number of sequelae per patient**, 1 month after, median (IQR)[k] • Remdesivir (n = 27):1 (1 to 2) • No antiviral treatment control (n = 155): 1 (1 to 2) • P = 0.525 **COVID-19—related sequelae**, 3 months after, n (%) • Remdesivir (n = 314): 21 (6.7) • No antiviral treatment control (n = 365): 108 (30.3) • P < 0.001 **Adjusted result**[l] • Among 671 survivors, early remdesivir vs. control (reference): • Adjusted OR = 0.181 (95% CI, 0.105 to 0.312) • P < 0.001 **Number of sequelae per patient**, 3 months after, median (IQR)[k] • Remdesivir (n = 21): 1 (1 to 2) • No antiviral treatment control (n = 108): 1 (1 to 2) • P = 0.754	NC

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Del Borgo et al. (2023)[9]	
Persistence of symptoms at 30 days (e.g., dyspnea, arthromyalgia, fever, cough, rhinitis, gastrointestinal problems, asthenia) • Number of patients: remdesivir (n = 230), molnupiravir (n = 499), nirmatrelvir-ritonavir (n = 389) **Adjusted result** • Molnupiravir vs. remdesivir (reference): OR = 0.46 (95% CI, 0.30 to 0.71, P = 0.001) • Nirmatrelvir-ritonavir vs. remdesivir (reference): OR (95% CI): OR = 0.56 (95% CI, 0.37 to 0.85, P = 0.006)	NC
Rebound COVID-19 (at 7 days and at 30 days)	
Tiseo et al. (2023)[10]	
Rebound of symptoms after antiviral discontinuation, 30 days, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 109): 2 (1.8) • Nirmatrelvir-ritonavir (n = 236): 5 (2.1) • P = 0.130 (test for multiple comparison)	Rebound of COVID-19 symptoms by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 0.11 (95% CI, 0.005 to 2.31) Rebound of COVID-19 symptoms by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.11 (95% CI, 0.006 to 1.97)
Mazzitelli et al. (2023)[12]	
SARS-CoV-2 reinfection within 3 months, n (%) • Remdesivir (n = 316): 5 (1.6) • No antiviral treatment control (n = 365): 22 (6.2) • P = 0.003	SARS-CoV-2 reinfection at 3 months • Remdesivir vs. control • Unadjusted RR = 0.26 (95% CI, 0.10 to 0.69)
Death	
Manciulli et al. (2023)[17]	
Death due to COVID-19 progression, by day 28, n (%) • Remdesivir (n = 142): 2 (1.4) • Molnupiravir (n = 205): 0 (0) • Nirmatrelvir-ritonavir (n = 120): 0 (0)	Death due to COVID-19 by day 28 • Remdesivir vs. molnupiravir • Unadjusted RR = 7.20 (95% CI, 0.35 to 148.91) Death due to COVID-19 by day 28 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 4.23 (95% CI, 0.21 to 87.28)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Tiseo et al. (2023)[10]	
30-day mortality due to COVID-19, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 114): 1 (0.9) • Nirmatrelvir-ritonavir (n = 252): 1 (0.4) • P = 0.453 (test for multiple comparison)	Death due to COVID-19 by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 0.19; 95% CI, 0.008 to 4.74 Death due to COVID-19 by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.43; 95% CI, 0.018 to 10.45
Del Borgo et al. (2023)[9]	
All-cause mortality (COVID-19 and no COVID-19) by day 30, n (%) • Remdesivir (n = 230): 2 (0.9%) • Molnupiravir (n = 499): 7 (1.4%) • Nirmatrelvir-ritonavir (n = 389): 4 (1%) • P = 0.785	Death by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 0.62 (95% CI, 0.13 to 2.96) Death by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.85 (95% CI, 0.16 to 4.58)
COVID-19 mortality by day 30, n (%) • Remdesivir (n = 230): 1 (0.4%) • Molnupiravir (n = 499): 3 (0.6%) • Nirmatrelvir-ritonavir (n = 389): 0 (0%) • P = 0.261	Death due to COVID-19 by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 0.72 (95% CI, 0.076 to 6.91) Death due to COVID-19 by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 5.06 (95% CI, 0.21 to 123.82)
Pinargote-Celorio et al. (2022)[14]	
All-cause 30-day mortality, n (%) • Remdesivir (n = 124): 0 (0) • Nirmatrelvir-ritonavir (n = 94): 0 (0)	Death by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = not estimable
Mazzitelli et al. (2023)[12]	
COVID-19–related death, unclear follow-up, n (%) • Remdesivir (n = 316): 2 (0.6) • No antiviral treatment control (n = 365): 8 (2.2) • P = 0.092	Death due to COVID-19 (day unclear) • Remdesivir vs. control • Unadjusted RR = 0.29 (95% CI, 0.062 to 1.35)
Piccicacco et al. (2022)[13]	
29-day all-cause mortality, n (%) • Remdesivir (n = 82): 0 (0) • No treatment control (n = 90): 1 (1.1) • P = 0.39[c]	Death by day 29 • Remdesivir vs. control • Unadjusted RR = 0.37 (95% CI, 0.015 to 8.85)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Solera et al. (2023)[11]	
All-cause mortality by day 30, n (%) • Remdesivir (n = 86): 0 (0) • No remdesivir (n = 106): 2 (1.9)	Death by day 30 • Remdesivir vs. no remdesivir • Unadjusted RR = 0.25 (95% CI, 0.012 to 5.06)
Any serious adverse event	
Piccicacco et al. (2022)[13]	
Serious adverse event requiring intervention, n (%) • Remdesivir (n = 82): 1 (1.2) • No treatment control (n = 90): NR	NC
Del Borgo et al. (2023)[9]	
Severe adverse effects according to European Medicines Agency definition, n (%) • Remdesivir (n = 230): 0 (0) • Molnupiravir (n = 499): 0 (0) • Nirmatrelvir-ritonavir (n = 389): 0 (0)	Severe adverse effects • Remdesivir vs. molnupiravir • Unadjusted RR = not estimable Severe adverse effects • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = not estimable
Drug discontinuation	
Manciulli et al. (2023)[17]	
Discontinuation by drug intolerance, n (%) • Remdesivir (n = 142): 3 (2.1) • Molnupiravir (n = 205): 5 (2.5) • Nirmatrelvir-ritonavir (n = 120): 0 (0)	Discontinuation by drug intolerance • Remdesivir vs. molnupiravir • Unadjusted RR = 0.87 (95% CI, 0.21 to 3.57) Discontinuation by drug intolerance • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 5.92 (95% CI, 0.31 to 113.54)
Tiseo et al. (2023)[10]	
Discontinuation, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 109): 4 (3.7) • Nirmatrelvir-ritonavir (n = 236): 5 (2.1) • P = 0.043	Drug discontinuation • Remdesivir vs. molnupiravir • Unadjusted RR = 0.062 (95% CI, 0.003 to 1.14) Drug discontinuation • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.11 (95% CI, 0.006 to 1.97)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a,b]
Del Borgo et al. (2023)[9]	
Voluntarily interrupted early treatment with antiviral drugs, n (%) • Remdesivir (n = 230): 0 (0) • Molnupiravir (n = 499): 5 (1) • Nirmatrelvir-ritonavir (n = 389): 6 (2)	Voluntarily drug interruption • Remdesivir vs. molnupiravir • Unadjusted RR = 0.20 (95% CI, 0.011 to 3.54) Voluntarily drug interruption • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.13 (95% CI, 0.007 to 2.29)
Mazzitelli et al. (2023)[12]	
AE-related discontinuation, unclear follow-up, n (%) • Remdesivir (n = 316): 5 (1.6%) • No antiviral treatment control (n = 365): NR	NC
Acute liver injury	
Tiseo et al. (2023)[10]	
AST and ALT increase (2 × ULN) by day 30, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 109): 1 (0.9) • Nirmatrelvir-ritonavir (n = 236): 0 (0) • P = 0.137	AST and ALT increase (2 × ULN) by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 0.19 (95% CI, 0.008 to 4.53) AST and ALT increase (2 × ULN) by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = not estimable
Treatment failure	
Mikulska et al. (2023)[15]	
Treatment failure defined as progression to severe COVID-19 requiring oxygen supplementation, corresponding to grade 4 or higher on the WHO COVID Outcomes Scale, or COVID-19–related death. Categories of the WHO 7-point ordinal scale are: (1) not hospitalized, no limitations on activities; (2) not hospitalized, limitation on activities; (3) hospitalized, not requiring supplemental oxygen; (4) hospitalized, requiring supplemental oxygen; (5) hospitalized, on noninvasive ventilation or high flow oxygen devices; (6) hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygen (ECMO); (7) death. Secondary outcomes were the length of SARS-CoV-2 positivity, COVID-19–associated mortality, and overall 90-day mortality, n (%) • Remdesivir (n = 59): 2 (3.4) • Molnupiravir (n = 33): 4 (12.1) • Nirmatrelvir-ritonavir (n = 116): 6 (5.2) This outcome is not listed in the PICOS statement, but this is the only outcome reported in this study that was related to the outcomes of interest.	Treatment failure • Remdesivir vs. molnupiravir • Unadjusted RR = 0.28 (95% CI, 0.054 to 1.45) Treatment failure • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.66 (95% CI, 0.14 to 3.15)

AE = adverse event; ALT = alanine transaminase; ARR = absolute risk reduction; AST = aspartate aminotransferase: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; mAB = monoclonal antibody; MD = mean difference; M-H = Mantel Haenszel; NC = no calculation; NNT = number needed to treat; NR = not reported; OR = odds ratio; RR = relative risk; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SE = standard error; ULN = upper limit of normal.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Since these additional calculations are based on unadjusted data, the resulting effect estimates will be unadjusted, and interpretation must be made with caution.

[c] Not adjusted; this P value corresponds to a comparison of the 3 treatment groups remdesivir, sotrovimab and control; sotrovimab is not eligible.

[d] Although the follow-up was not clearly reported, author stated that all hospitalizations occurred within the first 10 days from COVID-19 symptom onset. As this study had 1 month and 3 month follow-up, 1 month was used for comparisons with other studies.

[e] Multivariable analyses were used to compute univariate significant variables (P < 0.05) plus biological relevant variables by linear and binary regressions (entry method). Factors adjusted: sex, immunodeficiency, number of comorbidities per patient, time from COVID-19 onset to diagnosis.

[f] Multivariable Cox proportional hazards regression model for 28-day hospital admission considering the impact of each treatment and adjusting for sex, age, number of underlying comorbidities, and number of anti-SARS-CoV-2 vaccinations performed.

[g] Cox proportional hazards regression model. Due to the low rate of events for hospitalization, proportional hazards models were adjusted solely for lung transplant status.

[h] These data are only for hospitalized patients (early remdesivir [n = 3] versus no early remdesivir [n = 56]). For the 3 hospital admissions in the remdesivir group, 2 ended with death and 1 was hospitalized for 4 days.

[i] Reported percentage of ICU admission was only from hospitalized patients; P = 0.858 reported for the comparison among hospitalized patients.

[j] Multivariable analyses were used to compute univariate significant variables (P < 0.05) plus biological relevant variables by linear and binary regressions. Factors adjusted: age, any previous SARS-CoV-2 immunity, chronic renal disease, immunodeficiency, time from COVID-19 onset to diagnosis, and number of comorbidities per patient.

[k] In patients with sequelae only (month 1: early remdesivir [n = 27] vs. no early remdesivir [n = 155]; month 3: early remdesivir [n = 21] vs. no early remdesivir [n = 108]).

[l] Multivariable analyses with factors adjusted: age, any previous SARS-CoV-2 immunity, cardiovascular disease, chronic renal disease, immunodeficiency, time from COVID-19 onset to diagnosis, and number of comorbidities per patient.

Subgroup Analysis

Subgroups
Analysis for subgroups of interest was not feasible because of insufficient data. Only 1 study presented results for specific subgroups.

Data reported were insufficient for the analyses of the subgroups of interest. If available, we summarized the subgroup analysis result from individual studies (Table 13). Some of the reported results on effect estimates and all of the additional results have not been adjusted for possible differences between the cohorts that could distort the relationship between the treatments and the outcome under consideration (i.e., confounding); this should be considered when interpreting the results. In Appendix 4 the results are provided with the study authors' conclusions.

Gottlieb et al. (2022)[8] presented results for subgroups including age 60 years and older, male, and ethnic group (not Hispanic or Latino and Hispanic or Latino). This study found the composite event of hospitalization and death (i.e., hospitalization as no deaths occurred) was lower in the group treated with remdesivir than in the group treated with placebo for those aged 60 years and older or males. Del Borgo et al. (2023)[9] presented results for group of patients who were immunocompromised and found no statistically significant difference for the 3 groups of treatment (remdesivir, molnupiravir, nirmatrelvir-ritonavir) in terms of all-cause mortality.

Table 13

Subgroup Analysis Reported on Outcomes of Interest

Reported results on subgroups and outcomes of interest	Additional results calculated based on reported study results[a,b]
COVID-19–related hospitalization	
Gottlieb et al. (2022)[8]	
COVID-19–related hospitalization by subgroups, n (%) **Subgroups: Age, sex, and ethnicity** **Both raw data and adjusted HR** • Age ≥ 60 years: ◦ Remdesivir (n = 83): 1 (1.2) ◦ Placebo (n = 87): 9 (10.3) ◦ HR = 0.11 (95% CI, 0.01 to 0.86) • Male sex ◦ Remdesivir (n = 148): 1 (0.7) ◦ Placebo (n = 145): 9 (6.2) ◦ HR = 0.11 (95% CI, 0.01 to 0.84) • Ethnic group: Not Hispanic or Latino ◦ Remdesivir (n = 146): 2 (1.4) ◦ Placebo (n = 158): 8 (5.1) ◦ HR = 0.26 (95% CI, 0.06 to 1.22) • Ethnic group: Hispanic or Latino ◦ Remdesivir (n = 123): 0 (0) ◦ Placebo (n = 112): 6 (5.4) ◦ HR = NR The authors reported the subgroups only for the primary efficacy outcome (a composite outcome of COVID-19–related hospitalization and death) by day 28. Because there was no death in either group, the numbers of patients for the composite outcome could be used for our single outcome of interest: COVID-19–related hospitalization. Cox proportional hazards model with the baseline stratification factors as covariates (i.e., residence in a skilled nursing facility [yes or no], age [< 60 years or ≥ 60 years], and country [in- and outside US]) was used to estimate HRs and 95% CIs. For subgroups with no events in the remdesivir group, estimates could not be accurately calculated and omitted.	NC

Reported results on subgroups and outcomes of interest	Additional results calculated based on reported study results[a,b]
Death	
Del Borgo et al. (2023)[9]	
All-cause mortality (COVID-19 and no COVID-19) by day 30, n (%) **Subgroup: Patients who were immunocompromised** • Remdesivir (n = 94): 1 (1.1) • Molnupiravir (n = 97): 2 (2.1) • Nirmatrelvir-ritonavir (n = 129): 4 (3.1) • P = 0.587	Subgroup: immunocompromised Death by day 30 • Remdesivir vs. molnupiravir • Unadjusted RR = 0.52 (95% CI, 0.048 to 5.59) Subgroup: immunocompromised Death by day 30 • Remdesivir vs. nirmatrelvir-ritonavir • Unadjusted RR = 0.34 (95% CI, 0.039 to 3.02)

CI = confidence interval; HR = hazard ratio; NC = no calculation; RR = relative risk.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Since some of these additional calculations are based on unadjusted data, the resulting effect estimates will be unadjusted; interpretation must be made with caution.

Summary of Critical Appraisal

Randomized Controlled Trial

We reported the risk of bias assessment for the RCT in Table 14. The adequate sequence generation and allocation concealment were judged as unclear because of lack of information on randomization methods and allocation process. All other areas were judged as low risk.

Risk of Bias Assessment
Overall, the RCT is at low risk of bias, with unclear bias in sequence generation and allocation.

Table 14

Risk of Bias Assessment for the Included Randomized Controlled Trial

ID	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Gottlieb et al. (2022)	Unclear	Unclear	**Low**	**Low**	**Low**	**Low**	**Low**

ROB = risk of bias.

Note: Low = low ROB; high = high ROB; unclear = unclear ROB.

Cohort Studies

We assessed 9 cohort studies, comprising 3 prospective and 6 retrospective studies, using the ROBINS-I tool. The evaluated outcomes in all studies were considered objective, and the majority of their results were unadjusted. Among these studies, 8 were evaluated for a set of unadjusted outcomes, resulting in an overall critical risk of bias primarily attributed to confounding. Despite the identification of several important confounders in these studies, they were not adequately controlled for in relation to the outcomes evaluated in this evidence synthesis (Table 15). The interpretation of the domain level ROB judgments are as follows: low = the study is comparable to a well-performed randomized trial; moderate = the study is sound for a nonrandomized study but cannot be considered comparable to a well-performed randomized trial; serious = the study has some important problems; and critical = the study is too problematic to provide any useful evidence on the effects of the intervention.[5]

Risk of Bias Assessment
The risk of bias across the observational studies ranged from serious to critical. The studies failed to account for underlying factors, which may distort the results.

Four studies included adjusted estimates that accounted for identified confounders, resulting in improved judgments, ranging from moderate to serious risk of bias due to confounding.[9,11,12,16] These studies were deemed to have a serious risk of bias, primarily stemming from a serious risk of bias in the classification of interventions, which is likely differential misclassification of the intervention status related to the outcome or the risk of the outcome. This bias was present in all 4 studies because the assignment of treatment was susceptible to influence from prescribers' prior knowledge of the outcome. Specifically, prescribers tended to avoid assigning treatments that were highly related to a particular outcome, thus deviating from a random assignment process.

Table 15

Risk of Bias Assessment for Included Cohort Studies

Author (year)	List of outcomes assessed	ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions)							
		1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended interventions	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall bias
Pinargote-Celorio et al. (2022)	• Hospitalization: day 30 post-treatment • Hospitalization: due to COVID-19 progression • All-cause or related 30-day mortality • Patients required noninvasive ventilation • Patients required admission to the critical care unit	Critical RoB	Low RoB	Serious RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Critical RoB
Borgo et al. (2023)	• All-cause mortality (COVID-19 and no COVID-19) • COVID-19 mortality • All-cause mortality for immunocompromised subgroup • Any serious adverse event • Any events leading to drug discontinuation or withdrawal	Critical RoB	Low RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Low RoB	Critical RoB
Borgo et al. (2023) (adjusted[a])	• Post—COVID-19 condition: persistence of symptoms at 30 days	Moderate RoB	Low RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Low RoB	Serious RoB

Author (year)	List of outcomes assessed	ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions)							
		1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended interventions	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall bias
Mikulska et al. (2023)	• Treatment failure (a composite outcome, defined as progression to severe COVID-19 requiring oxygen supplementation, corresponding to grade 4 or higher on the WHO COVID Outcomes Scale, or COVID-19—related death.)	Critical RoB	Low RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Low RoB	Critical RoB
Solera et al. (2023)	• All-cause mortality • ICU admission • Need for supplemental oxygen • mechanical ventilation	Critical RoB	Low RoB	Serious RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Critical RoB
Solera et al. (2023) (adjusted)	• Hospitalization due to COVID-19 progression	Serious RoB	Low RoB	Serious RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Serious RoB
Colaneri et al. (2022) (adjusted)	• 28-day hospital admission due to COVID-19	Serious RoB	Low RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Serious RoB	Serious RoB
Manciulli et al. (2023)	• Death due to COVID-19 progression • Hospitalization due to COVID-19 progression • Discontinuation lead by drug intolerance	Critical RoB	Serious RoB	Serious RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Critical RoB

Author (year)	List of outcomes assessed	ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions)							
		1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended interventions	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall bias
Tiseo et al. (2023)	• 30-day mortality due to COVID-19 • Hospitalization due to COVID-19 progression • Rebound of symptoms after antiviral discontinuation • Any adverse events leading to drug discontinuation or withdrawal • AST/ALT increase	Critical RoB	Low RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Low RoB	Critical RoB
Piccicacco et al. (2022)	• Hospitalization: 29 day • Emergency department visit without hospitalization: 29 day • Hospitalization: 14 day • Emergency department visit without hospitalization: 14 day • All-cause mortality: 29 day • Any serious adverse event • Any events leading to drug discontinuation or withdrawal	Critical RoB	Serious RoB	Serious RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Critical RoB

Author (year)	List of outcomes assessed	ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions)							
		1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended interventions	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result	Overall bias
Mazzitelli et al. (2023)	• COVID-19—related death • ICU admission • Length of hospitalization • Post—COVID-19 condition: number of sequelae per patient (1 month after) • Post—COVID-19 condition: number of sequelae per patient (3 months after) • Rebound COVID-19: SARS-CoV-2 reinfection within 3 months • Any events leading to drug discontinuation or withdrawal	Critical RoB	Low RoB	Serious RoB	Serious RoB	Low RoB	Moderate RoB	Low RoB	Critical RoB
Mazzitelli et al. (2023) (adjusted)	• Progression to hospitalization (adjusted) • Progression to oxygen requirement • Post—COVID-19 condition: COVID-19—related sequelae (1 month after) • Post—COVID-19 condition: COVID-19—related sequelae (3 months after)	Serious RoB	Low RoB	Serious RoB	Serious RoB	Low RoB	Low RoB	Low RoB	Serious RoB

[a] The studies which provided adjusted results for the outcomes evaluated were noted (adjusted) under their study names; the remaining studies without this note were provided unadjusted results.

Discussion

Summary of Evidence

Key Point
We did not identify any studies in the literature that compared remdesivir with inhaled glucocorticoids or budesonide.

The aim of this rapid systematic review was twofold: to determine the efficacy and effectiveness for remdesivir in nonhospitalized patients with COVID-19 and to establish whether the use of remdesivir is safe in the outpatient setting. The project scope was informed by engaging with clinical experts and decision- and policy-makers to better understand the considerations for treatment with remdesivir in the outpatient setting and the potential health system impacts. A total of 10 publications met the final inclusion criteria, which reported findings from 1 RCT[8] on the use of remdesivir or placebo and 9 cohort studies[9-17] comparing remdesivir to other antiviral treatments (molnupiravir or nirmatrelvir-ritonavir) or to no antiviral treatment. No studies were identified in the literature search with comparisons to inhaled glucocorticoids or budesonide (outside of any reported use as standard of care).

Patients were eligible to receive remdesivir treatment in the included studies due to mild to moderate COVID-19 disease and that they were at risk for progression to severe illness based on their health status or age. Two cohort studies included patients at high risk for progression to severe COVID-19 disease due to hematological malignancies and 1 due to organ transplant. Other studies may have included these populations within a broader context of at-risk populations. Patients in the RCT may be less generalizable to the current Canadian setting because the patients were unvaccinated and the trial was completed before the Omicron variants became prominent. Few patients in the RCT (1.4%) were adolescents. The number of Indigenous Peoples who participated in the study is only documented for centres in the US, and with a noninformative and unusual grouping "American Indian or Alaska Native." The study populations are broadly generalizable to patients with mild to moderate COVID-19, although local differences in standard of care

and access to health care where the studies were conducted may vary and/or differ from the Canadian guidelines.

Most planned analyses were not feasible owing to the paucity of data for the outcomes of interest and/or the limitations in the cohort study data. Analyses of data including or consisting entirely of data which did not consider variables that may distort the relationship between remdesivir and the health effects of interest are presented for exploratory purposes only if no data were available, and readers should use extreme caution when reviewing and interpreting these results.

Key Point
Most of the analyses we planned were not feasible because of the lack of data for the outcomes of interest and/or because of the limitations in the observational data. Results should be interpreted with caution.

The risk of bias in the included RCT was low yet unclear for sequence generation and allocation.[8] The risk of bias across the range of included cohort studies ranged from serious to critical risk of bias.[9-17] The overall limitation of the included cohort studies was failing to account for variables that could distort the association between the studied treatments and the health outcomes of interest.

Variants

The Omicron variant of SARS-CoV-2 was first identified in November 2021 and it quickly surpassed the Delta variant to become the predominant cause of COVID-19 globally.[13] Antivirals played a key role in COVID-19 treatment during the Omicron surge.[9,11,13,15] The included studies vary in their overlap with the surge of the Omicron variant worldwide, and therefore, vary in how generalizable the results are based on more recent variants of concern. The single RCT included[8] was conducted between September 2020 and April 2021 before the Omicron and Delta variants or subvariants emerged as dominant circulating strains of COVID-19. Among the 9 cohort studies included, only 1 retrospective cohort study had coverage in both the pre-Omicron and Omicron time periods (March 2021 to July 2022). However, results showed that none of the included patients treated with antiviral drugs received them in the pre-Omicron period. The remaining 8 cohort studies were conducted in similar time periods between December 2021 and October 2022, and indicated

Variants
All the observational studies provided real-world evidence of early remdesivir treatment in the Omicron era. The RCT was conducted before the emergence of the Omicron and Delta variants and subvariants.

that all (or the majority of) patients were infected by Omicron variants, although testing for variants and subvariants was uncommon. Mazzitelli et al.[12] assumed all patients were Omicron-infected based on period random sampling and sequencing showing prevalence of Omicron variants in more than 85% cases (i.e., variant testing was not performed for all patients). Two additional cohort studies[10,15] reported no systematic identification of the SARS-CoV-2 variants or not excluding patients possibly infected with another variant. Regardless, all the cohort studies included in this review provided real-world evidence of early remdesivir treatment in the Omicron era.

Vaccination Status

Vaccination is fundamental to prevent progression to severe COVID-19 disease and it remains the most powerful option against developing severe COVID-19 illness.[9,12] Reporting of details to assess the completeness or currency of patients' vaccination status varied in the included studies. The language used and the definitions implemented were difficult to match against definitions used in official capacities internationally. In the only included RCT, patients who were vaccinated were excluded.[8] Vaccination status in study participants was reported in many different ways in the included cohort studies. Of the 9 cohort studies included, 7 report that 81% to 94% of study patients had adequate, complete, or full vaccinations (one study reported a median of 3 doses and a second study a mean of 2.6 doses).[15,16] Median days from the last vaccine dose ranged from 122 to 137 days across the 3 treatment arms in another cohort study.[10] The same study defined patients with "nonadequate vaccination" as those who were unvaccinated or who had only received a single vaccination.[10] Two of the included cohort studies reported 83% and 79.1% of patients received initial vaccination in the remdesivir groups, while 65.5% and 52.9% received initial vaccination in the untreated control groups.[12,13]

Vaccination Status
Of the 9 observational studies, 7 reported between 81% and 94% of the patients in the study had adequate, complete, or full vaccinations. Vaccinated patients were excluded from the RCT.

There are some imbalances in vaccine status highlighted in the

included cohort studies. Mazzitelli et al.[12] found that vaccination was significantly higher in the patients who were treated than in the patients who were not treated. Piccicacco et al.[13] similarly documented that a higher proportion of patients were unvaccinated in the untreated control group; 58% (18 of 31) of the patients who were unvaccinated in the control group refused treatment and 35.5% (11 out of 31) were unavailable for scheduling for treatment. Thus, patients with vaccine hesitancy were less likely to seek drug treatment. One study mentioned that the data on the full immunization schedules of all participants was not retrieved and patients might have received different combinations of vaccines, which could influence any measured COVID-19 outcomes.[17] Data from the included cohort studies were likely to be broadly reflective of the vaccination status in the general population; however, these were insufficiently reported to conduct any subgroup analyses based on vaccine status.

Remdesivir, Comparators, and Cointerventions

The PINETREE trial[8] was a placebo-controlled RCT of remdesivir treatment in outpatients. The 9 included cohort studies had a number of comparators: 4 studies compared remdesivir to a single treatment of nirmatrelvir-ritonavir,[14] a control group without remdesivir,[11] a control group without antiviral treatments,[12] or no treatment;[13] 4 studies[9,10,15,17] compared remdesivir to molnupiravir and nirmatrelvir-ritonavir; and 1 study[16] compared remdesivir to molnupiravir and nirmatrelvir-ritonavir, and a nontreated control group. Three of the 9 cohort studies were prospective cohort studies, and 6 were retrospective cohort study designs. Although all 9 cohort studies were comparative cohorts, their comparisons were not well-controlled. The risk of bias was assessed as critical for all outcomes presented with unadjusted results and serious for outcomes presented with adjusted results.

Standard of care was not adequately described in any of the 10 included studies. Cointerventions were noted in some studies

Standard of Care
The 10 studies compared remdesivir with usual care to other antiviral treatments, no antiviral treatment, or a placebo (the RCT). The standard of care was not adequately described in any of the 10 studies.

but were not consistently or comprehensively reported. Immunosuppressant therapies were reported as cointerventions in 3 cohort studies[11,14,16] conducted in patients with underlying hematological cancers or history of organ transplant. Solera et al.,[11] a Canadian cohort study in organ transplant recipients, reported that the majority of the patients were on triple immunosuppressants with prednisone, mycophenolate, and a calcineurin inhibitor, and that maintenance prednisone treatment was a variable associated with a higher frequency of hospitalization.

The authors of the included studies reported that the decision to administer any antiviral therapy was dependent on several factors, including patients' health status and characteristics, potential drug-drug interactions, and overall immunosuppression, considering both personal preference and the judgment of physicians.[9-11,17] In the study by Del Borgo et al., the authors noted that molnupiravir was the preferred choice for older patients instead of nirmatrelvir-ritonavir or remdesivir, and attributed this to noticeable drug interactions with other treatments that are a barrier to prescription of this drug for people aged 75 or older.[9] One cohort study observed that patients with hematologic disease, who had received an organ transplant, or who were affected by immunodeficiency were treated with remdesivir or nirmatrelvir-ritonavir, whereas molnupiravir was used for patients with neurological and cardiovascular diseases and chronic kidney failure.[9]

Remdesivir is administered intravenously by a qualified health professional over 3 days: 200 mg on the first day and 100 mg on days 2 and 3. The infusion is administered over 30 minutes, and the patient is monitored for an additional 15 to 30 minutes after the infusion.[19] The included studies described the administration of remdesivir in the outpatient setting in varying levels of detail. Participants in the RCT were able to access the 3-day infusion through skilled nursing facilities, outpatient infusion centres, and some home visits. Pinargote-Celorio et al. described the implementation of a novel outpatient clinical pathway for patients

with SARS-CoV-2 infection through a day hospital in Spain. Antiviral treatments were provided in the day hospital or at home for individuals unable to travel.[14] Other studies described administration through hospital-based COVID-19 clinics for outpatients,[9] a referral centre,[15] or home.[15]

Several studies noted that parenteral administration of remdesivir is less practical than oral compounds and requires health services equipped with nursing staff and/or the ability to care for patients who cannot travel to specialty outpatient centres.[10,16,17] Solera et al. noted that the lack of an infusion centre in their area and not being able to access an infusion centre were barriers to patients receiving remdesivir within 7 days of symptoms onset.[11] Two cohort studies also reported difficulties contacting patients for scheduling within 7 days of symptoms onset and that patients had transportation issues while trying to access outpatient infusion centres or refusal of treatment.[11,13]

Severity of COVID-19 Infection and Risk Factors for Progression to Severe COVID-19 Disease

Various guidelines are available to guide the treatment of patients with COVID-19.[20-24] All 10 studies followed these guidelines and focused treatment on nonhospitalized patients with mild to moderate COVID-19 disease who were approximately 7 days from symptoms onset and who had 1 or more risk factors for progression to severe illness.

Severity of Infection
All 10 studies included nonhospitalized patients with mild to moderate COVID-19 infection, who were approximately 7 days after their first symptoms and had 1 or more risk factors for severe disease.

All 10 included studies focused on eligible outpatients, although some inpatients were included in some of the cohort studies. Colaneri et al.[16] included outpatients and 8 patients admitted to hospital for reasons other than COVID-19 in their study; in their study, Mikulska et al.[15] included both outpatients and inpatients (12%) who were already admitted to hospital for "chemotherapy or haematopoietic stem cell transplant in whom they could not exclude that already present a specific symptoms were caused or aggravated by SARS-CoV-2 infection."

Definitions for "mild to moderate" COVID-19 disease were based on patients not requiring oxygen therapy,[8,10,12,15,16] WHO criteria,[17] or was not stated.[9,11,13,14] All patients in the included studies had at least 1 risk factor for developing severe COVID-19. Two studies[15,16] focused on the patients with hematologic malignancies, and 1 study[11] focused on organ transplant recipients. At baseline, various risk factors noted in the published guidelines were collected by investigators in the 10 included studies, including age older than 65, BMI greater than 30, diabetes mellitus, chronic kidney disease, immunodeficiency, neurological diseases, cardiovascular diseases, lung diseases, hospitalization for other diseases, chronic hepatopathy, active oncological diseases, and hemoglobinopathies. A post hoc subgroup analysis for the PINETREE RCT focused on the heterogeneity of the treatment effect of remdesivir by number of baseline risk factors and was evaluated by pooling data from all treatment groups.[25] In the subanalysis results, remdesivir demonstrated efficacy for preventing COVID-19 hospitalization in patients regardless of baseline risk factor burden.[25]

Adults aged 60 years or older are at higher risk for severe COVID-19 illness, and all included studies considered age as a key risk factor (median or mean age ranged from 50 years to 69 years). The RCT and 1 cohort study were designed to include patients aged between 12 years and 18 years;[8,13] there were 8 adolescents (1.4%) included in the RCT with limited data and no subgroup analyses reported.[8] No separate information or results were reported for adolescents in the cohort study.[13] In the 10 included studies, 38.5% to 53.4% of the patients were females. Very little information was presented for any underserved or equity-deserving groups beyond baseline characteristics or health status. The PINETREE trial provided baseline patient characteristics on race and ethnicity, including 36.7% who were "American Indian or Alaskan Native."[8]

Study Design and Risk of Bias

Key Information
The RCT was funded by Gilead Sciences, the manufacturer of remdesivir.

PINETREE is a randomized, double-blind, placebo-controlled trial. The PINETREE trial enrolled patients from 64 sites in the US, Spain, Denmark, and the UK; 94.5% of patients lived in the US. It was funded by Gilead Sciences, the manufacturer of remdesivir. Study procedures were described in the published record and supplemented by content in the accompanying protocol. The quality of the RCT was unclear for sequence generation and allocation concealment because no details were provided beyond a basic randomization ratio (1:1) and planned stratification variables. The study was assessed to have a low risk of bias across all other bias domains. The planned primary outcome in the original study protocol was all-cause hospitalization; this was changed when the protocol was updated to a primary composite of death or COVID-19–related hospitalization. The determination of the reason for hospitalization was not well-described and may be prone to subjective decision making and bias; however, all-cause hospitalization is still reported in the trial. The PINETREE trial was stopped for administrative reasons at 44.5% of the planned enrolment, and it is uncertain how this impacted the results.[8]

Study Population
In the RCT, 94.5% of the enrolled patients lived in the US. Six of the observational studies collected data in Italy, and the remaining 3 collected data in Canada, the US, and Spain.

Six of 9 cohort studies were conducted in Italy;[8,9,11,14-16] the remaining 3 were conducted in Canada,[11] the US,[12] and Spain.[13] Three prospective and 6 retrospective cohort study designs were used in the included studies. In all 9 included cohort studies, the risk of bias was assessed as critical for all outcomes presented with unadjusted results and as serious for outcomes presented with adjusted results. Residual confounding among the treatment groups is a large concern, and confounding by indication cannot be ruled out. Six of the 9 cohort studies were retrospective, and most of the outcomes reported in the included studies were not adjusted. In addition, the selection of antiviral treatment was affected by knowledge of the outcome from guidance, physicians, and patients in each included cohort study, which led to a rating of serious risk of bias in the classification of interventions domain. Small sample sizes made it difficult to determine whether specific comorbidities were independently associated with the primary outcome.[13,16] It also

could be perceived as unethical to withhold treatment to conduct a placebo-controlled study in a real-world setting.[13]

Results from the included PINETREE trial[8] were used to inform recommendations for a 3-day course of IV remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) as a treatment option for nonhospitalized individuals at high risk for progression to severe disease in many international COVID-19 guidelines, including the NIH and WHO guidelines. Currently, 3 antiviral drugs (remdesivir, molnupiravir, and nirmatrelvir-ritonavir) are available for patients with SARS-CoV-2 infection with this indication.[9,11,16,17]

In summary, 9 cohort studies displayed the available real-world evidence of early remdesivir treatment for predominantly vaccinated high-risk outpatients infected with the Omicron variant of SARS-CoV-2, whereas the PINETREE data could not be generalized to the vaccinated population with Omicron infection.

Interpretation of Clinical Results

Efficacy: RCT

No deaths from any cause by day 28 occurred in the group treated with remdesivir or with placebo. All COVID-19–related hospitalizations occurred by day 14, with more occurring in the placebo group than group treated with remdesivir. Based on the composite of these 2 outcomes, the risk of COVID-19–related hospitalization or death from any cause by day 28 was statistically significantly lower in the group treated with remdesivir than in the placebo group. In addition, for patients older than 60 years or male sex, the incidence of the composite outcome of COVID-19–related hospitalization and death was statistically significantly lower in those treated with remdesivir than with placebo.[8]

Efficacy
Results from the RCT suggest remdesivir reduces the risk of COVID-19–related hospitalization compared with a placebo. This risk reduction is notable in males and those aged 60 or older. Interpret with caution due to the small sample size.

Effectiveness: Cohort Studies

Hospitalization: The adjusted results from the studies by Mazzitelli et al. (2023)[12] and Solera et al. (2023)[11] showed that treatment with remdesivir reduced hospitalizations compared with no remdesivir treatment. Colaneri et al. (2022)[16] found none of the early treatments, including remdesivir, significantly reduced the risk of hospitalization.

Length of hospitalization: No effect was found in reducing the length of hospitalization for the cohort who received remdesivir versus the cohort who did not receive remdesivir. The sample size was small in both the Mazzitelli et al. (2023)[12] and Solera et al. (2023)[11] study, and the confidence interval was wide because these data were only based on patients that progressed to hospitalization.

ED visits: Piccicacco et al. (2022)[13] found patients treated with remdesivir were less likely to visit the ED within 29 days from symptom onset than patients who were not treated with remdesivir or sotrovimab.

ICU admission: In the study by Mazzitelli et al. (2023),[12] there was insufficient power to test the difference between groups. In the study by Solera et al. (2023),[11] there were no ICU admissions in the remdesivir group compared to the untreated group. The combined

Effectiveness
Observational study findings suggest that remdesivir may reduce hospitalization, the likelihood of ED visits, the need for supplemental oxygen, and COVID-19 aftereffects compared with no treatment. Interpret with caution.

RR of these 2 studies showed no statistically significant difference between treatment with remdesivir and no treatment with remdesivir. In addition, Pinargote-Celorio et al. (2022)[14] reported no ICU admissions in both the group treated with remdesivir and the group treated with nirmatrelvir-ritonavir.

Oxygen requirement: The adjusted result from the study by Mazzitelli et al. (2023)[12] showed that early remdesivir treatment was independently associated with a lower risk of progression to supplemental oxygen.

Post–COVID-19 condition: Mazzitelli et al. (2023)[12] found that patients in the early remdesivir group reported reduced prevalence of COVID-19–related sequelae at both 1- and 3-month follow-ups. Del Borgo et al. (2023)[9] found that patients treated with molnupiravir and nirmatrelvir-ritonavir had fewer persistence of symptoms at 30 days compared with patients treated with remdesivir.

Rebound COVID-19: Tiseo et al. (2023) found 2% of patients treated with nirmatrelvir-ritonavir or molnupiravir experienced a rebound of symptoms by 30 days after antiviral discontinuation. No patients treated with remdesivir experienced a rebound. None of these data analyses were adjusted.

Death: No adjusted results were provided for death, although 7 studies reported this outcome. The unadjusted combined data of 2 studies[11,13] that compared remdesivir and no remdesivir or no antiviral treatment did not find a statistically significant difference for COVID-19–related deaths. Mazzitelli et al. (2023)[12] made a similar comparison for COVID-19–related deaths and found no statistically significant difference.

Safety

In the studies by Piccicacco et al. (2022)[13] and Del Borgo et al. (2023),[9] there were rare cases of SAE (zero or 1) with no further analysis conducted. Discontinuation was uncommon according to data from the studies by Manciulli et al. (2023), Tiseo et al. (2023), Mazzitelli et al. (2023), and Del Borgo et al. (2023).[9,10,12,17] There were

Safety
Serious adverse events and drug discontinuation were uncommon in the studies that reported these safety outcomes. Acute liver injury outcomes were only reported in 1 study, with no injuries for remdesivir.

no cases of acute liver injury (reported as AST and ALT increase) for remdesivir or for nirmatrelvir-ritonavir, whereas there was 1 patient with acute liver injury in the group treated with molnupiravir.[10] None of these data were analysed with adjusted methods or allow for further analysis in this report.

Strengths and Limitations of the Systematic Review

Strengths

We designed, implemented, and conducted a rapid systematic review and meta-analysis following the best practices as outlined in the *Cochrane Handbook of Systematic Reviews of Interventions*.[1] The literature search was continuously updated to include the most recent studies published up to June 19, 2023. The systematic review was specific to the Canadian context and included real-world evidence.

Strengths
This review was specific to the Canadian context and included real-world evidence.

Limitations

Two main limitations of this report were the lack of identified clinical evidence for some key subgroups of interest and the varying clinical end point definitions which limited the analyses that could be conducted. Another limitation is the potential for confounding due to the inability to adjust for variables distorting associations between treatments and the outcomes of interest. Unadjusted results are reported in many of the cohort studies for important outcomes; however, some reports included adjusted analyses on outcomes not included in this report.[10,17] Due to the paucity of data from RCTs, this report relied heavily on observational studies. Many of the effect estimates combined in meta-analyses were not from confounder-adjusted analyses. Although these data are presented in the interest of transparency to provide a complete synthesis of the evidence available, we strongly recommend interpreting these results with caution. We only included published data, which may exclude information available in preprints or grey literature. Although we conducted comprehensive searches for evidence, there were few primary studies eligible for inclusion. The decision to restrict inclusion to settings similar to the Canadian health system optimized applicability to Canada but did result in studies being excluded that may have contributed additional data to this review.

Limitations
There are 2 main limitations to this review: the lack of clinical evidence for some of the key populations of interest, subgroups, and clinical end points, and the inability or failure to adjust for underlying factors.

Conclusions and Implications for Decision- or Policy-Making

What Is the Efficacy, Effectiveness, and Safety of Remdesivir in Nonhospitalized Patients With COVID-19?

To determine the efficacy, effectiveness, and safety of remdesivir in nonhospitalized patients with COVID-19, a systematic review of controlled clinical trials and real-world studies was undertaken. One RCT and 9 cohort studies were included in this review. Due to the rapid review format of the review, no formal evidence grading was used to assess the trustworthiness of the reported effects.

The 1 RCT investigated the use of remdesivir or placebo in a group of patients with COVID-19 who were unvaccinated and had 1 or more risk factors for progression to severe disease. Although the allocation procedures are unclear, there are no other concerns over risk of bias in this study. Based on this single study, remdesivir administered to any nonhospitalized patients may reduce the risk of hospitalization at 14 days. This reduction is most noteworthy in populations older than 60 years and in males, but firm conclusions cannot be made because only 2 participants were considered to be hospitalized for COVID-19. Due to the small number of participants, we are unable to form any conclusions regarding length of hospitalization and ICU admission among hospitalized patients. We are unable to make any conclusions regarding the reported safety of remdesivir in outpatient settings because the data reported in the only RCT is difficult to interpret. The number of severe AEs and withdrawals due to AEs was higher in the placebo group, but few details on these AEs were provided in the trial report. We may infer that SAEs were not likely increased due to the administration of remdesivir because all trial participants received the same standard of care. Due to the quantity and quality of the reported data, conclusions could not be drawn on death.

A total of 9 cohort studies reported real-world experience with early remdesivir treatment for outpatients with COVID-19 at high risk for

Implications
Study findings are limited because of small sample sizes, uncontrolled underlying factors, and conflicting results. Further evidence is needed to make any firm conclusions.

severe outcomes due to age older than 60 years or comorbidity. In these studies, various comparisons were made with placebo, molnupiravir, and nirmatrelvir-ritonavir. All the included cohort studies were assessed to be at serious or critical risk for bias due to inadequate consideration for potential variables that may distort the relationship between remdesivir or the comparators and any effectiveness or safety outcomes reported. This limits our confidence in the reported findings relevant to this review. Therefore, no conclusions can be drawn regarding ED visits without hospitalization, length of hospitalization, ICU admission, rebound COVID-19, and SAEs (total or specific). Drug discontinuation was very uncommon.

In the studies that reported findings using appropriate analyses (i.e., considered variables that may distort the effect of remdesivir on the clinical end points), there are conflicting results about the effect of remdesivir on hospitalization and post–COVID-19 condition. The results in the 1 appropriately analyzed study suggest that hospitalizations may be reduced in patients treated compared with patients who take no antiviral medication within 10 days from COVID-19 symptom, but there is very limited information regarding follow-up duration. No firm conclusions can be made about the effect of remdesivir on progression to oxygen use or noninvasive ventilation as there are inadequate details reported and conflicting results presented in the included cohort studies.

Which Nonhospitalized Patients Are Most Likely to Benefit From Treatment With Remdesivir?

Patient health status plays a pivotal role in COVID-19 treatment because it may influence both antiviral selection and any health outcome effects. Results from the current review do consider individuals at higher risk for severe outcomes due to COVID-19 because the studies included participants who were immunocompromised, had a health status that places them at higher risk, or are in an adult age group considered to be at

higher risk. Although we considered age, sex and gender, and whether the study included Indigenous Peoples or underserved or equity-deserving groups of nonhospitalized individuals with COVID-19, the study data reported were insufficient for any pooled analyses for any of the subgroups of interest. The only exception was in the included clinical trial; there were fewer hospitalizations in populations older than age 60 and in males when treated with remdesivir versus placebo. No differences were found when Hispanic or Latino participants were compared with non-Hispanic or Latino participants. Firm conclusions regarding the efficacy of remdesivir for preventing hospitalizations in populations older than 60 years or males could not be drawn because only 2 study participants were considered by investigators to have been hospitalized for COVID-19. One cohort study presented a subgroup analysis based on participants who were immunocompromised who took remdesivir, molnupiravir, or nirmatrelvir-ritonavir; however, no conclusions can be drawn from the presented data because the analyses failed to consider variables that could distort the effect of remdesivir on the clinical end points.

What Other Considerations Are There for Decision- or Policy-Making Related to Outpatient Treatment With Remdesivir?

The included real-world studies collected data from participants during periods when the Omicron variant was reported as a dominant strain in the studies; however, not all study participants in these studies were tested or confirmed to have the SARS-CoV-2 Omicron variant. Participants were predominantly vaccinated, and many of the cohort participants were described as having a complete vaccination profile, being "boosted," or having more than 2 vaccinations on average. The proportions of individuals without vaccination or with incomplete vaccination status varied across the studies and the groups compared. The only RCT included was initiated before the emergence of the Omicron variant, and all study participants were unvaccinated. As such, these limitations affect generalization to vaccinated populations with Omicron infections and should be taken into consideration in making any conclusions.

References

1. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews for interventions, version 5.1. 0. London (GB): The Cochrane Collaboration; 2011: https://handbook-5-1.cochrane.org/. Accessed 2023 Jul 2.
2. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178-189.
3. Cleveland Clinic. Thrombocytopenia. 2022; https://my.clevelandclinic.org/health/diseases/14430-thrombocytopenia#:~:text=Thrombocytopenia%20levels%20are%3A,and%2021%2C000%20microliters%20of%20blood. Accessed 2023 Jul 2.
4. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
5. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
6. Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I). London (GB): The Cochrane Collaboration; 2023: https://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions. Accessed 2023 Jul 2.
7. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1198-1207.
8. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. 2022;386(4):305-315.
9. Del Borgo C, Garattini S, Bortignon C, et al. Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use. *Viruses*. 2023;15(4):21.
10. Tiseo G, Barbieri C, Galfo V, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. *Infect Dis Ther*. 2023;12(1):257-271.
11. Solera JT, Arbol BG, Bahinskaya I, Marks N, Humar A, Kumar D. Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the omicron BA.2 wave. *Am J Transplant*. 2023;23(1):78-83.
12. Mazzitelli M, Trunfio M, Sasset L, et al. Risk of hospitalization and sequelae in patients with COVID-19 treated with 3-day early remdesivir vs. controls in the vaccine and Omicron era: A real-life cohort study. *J Med Virol*. 2023;95(3):e28660.
13. Piccicacco N, Zeitler K, Ing A, et al. Real-world effectiveness of early remdesivir and sotrovimab in the highest-risk COVID-19 outpatients during the Omicron surge. *J Antimicrob Chemother*. 2022;77(10):2693-2700.
14. Pinargote-Celorio H, Otero-Rodriguez S, Gonzalez-de-la-Aleja P, et al. Mild SARS-CoV-2 infection in vulnerable patients: implementation of a clinical pathway for early treatment. *Enferm Infecc Microbiol Clin*. 2023;30:30.
15. Mikulska M, Testi D, Russo C, et al. Outcome of early treatment of SARS-CoV-2 infection in patients with haematological disorders. *Br J Haemato*l. 2023;20:20.

16. Colaneri M, Pieri TC, Roda S, et al. Assessing the Efficacy of Early Therapies against SARS-CoV-2 in Hematological Patients: A Real-Life Study from a COVID-19 Referral Centre in Northern Italy. *J Clin Med*. 2022;11(24):15.

17. Manciulli T, Spinicci M, Rossetti B, et al. Safety and Efficacy of Outpatient Treatments for COVID-19: Real-Life Data from a Regionwide Cohort of High-Risk Patients in Tuscany, Italy (the FEDERATE Cohort). *Viruses*. 2023;15(2):05.

18. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.

19. Administration of Remdesivir for COVID-19. Geneva (CH): World Health Organization; 2022: https://apps.who.int/iris/bitstream/handle/10665/359761/WHO-2019-nCoV-Therapeutics-Remdesivir-Poster-B-2022.1-eng.pdf. Accessed 2023 Jul 18.

20. Uso degli antivirali per COVID-19. Rome (IT): Agenzia Italiana del Farmaco; 2023: https://www.aifa.gov.it/web/guest/uso-degli-antivirali-orali-per-covid-19. Accessed 2023 Jul 18.

21. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. (updated April 20, 2023). Bethesda (MD): National Institutes of Health; 2023: https://www.covid19treatmentguidelines.nih.gov/. Accessed 2023 Jul 18.

22. Clinical practice guideline summary: recommended drugs and biologics in adult patients with COVID-19. Toronto (ON): Ontario COVID-19 Science Advisory Table; 2022: https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-11-0/. Accessed 2023 Jul 2.

23. IDSA guidelines on the treatment and management of patients with COVID-19. Arlington (VA): Infectious Diseases Society of America; 2021: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 2023 Jul 2.

24. Lamontagne F, Stegemann M, Agarwal A, et al. A living WHO guideline on drugs to prevent covid-19. *BMJ*. 2021;372.

25. Brown SM, Katz MJ, Ginde AA, et al. Consistent Effects of Early Remdesivir on Symptoms and Disease Progression Across At-Risk Outpatient Subgroups: Treatment Effect Heterogeneity in PINETREE Study. *Infect Dis Ther*. 2023;12(4):1189-1203.

Authors

Clinical Review

George A. Wells acted as the principal investigator by developing and leading the approach and contributed to validation of the results, interpretation of the results, drafting, and finalizing the report.

Xiaoqin Wang contributed by screening studies; extracting data; analyzing and interpreting results, figures, and tables; and drafting and revising the report.

Joan Peterson contributed by screening studies, verifying data, drafting tables, and drafting and revising the report.

Zemin Bai contributed by screening studies, verifying data, assessing risk of bias, drafting tables, and drafting and revising the report.

Shannon Kelly contributed to the conceptualization and design of the approach, provided research oversight, and contributed to the interpretation of results and drafting and finalizing the report.

Melissa Brouwers contributed to the choice of topic, question refinement, protocol, interpretation of the data, and review and refinement of the report.

Research Information Science

Hannah Loshak designed and executed the literature search strategy, monitored search alerts, prepared the search methods section and appendix, managed referencing of the report, and provided final approval to the version of the report submitted for publication.

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Reviewers

Shu-Ching Hsieh contributed by assessing risk of bias and reviewing the draft report.

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Conflicts of Interest

George A. Wells disclosed the following:

Payment as Advisor or Consultant

Thermedical: Ablation system and catheter needle 2021

VBI Vaccines Inc.: Coronavirus Vaccine 2020. Design and analysis advice for preparation of FDA submission.

Other

VBI Vaccines Inc.: Coronaviurs Vaccine 2020. Data Safety Monitoring Board – Member.

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Other

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For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.

Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946 to present)
- Embase (1974 to present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: May 1, 2023

Alerts: Monthly search update provided prior to project completion

Search filters applied: randomized controlled trials; controlled clinical trials, observational studies

Limits

- Language limit: English- and French-language
- Conference abstracts: excluded

Table 16

Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1 (remdesivir* or Veklury* or Redyx* or gs-5734 or gs5734 or gs-465124 or gs465124 or gs-829143 or gs829143 or 3QKI37EEHE).ti,ab,kf,ot,hw,nm,rn.

2 exp Covid-19/ or SARS-CoV-2/

3 (coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)

4 (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARS-COV2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.

5 ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,ot.

6 ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot.

7 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot.

8 or/2-7

9 1 and 8

10 9 use medall

11 *remdesivir/ or (remdesivir* or Veklury* or Redyx* or gs-5734 or gs5734 or gs-465124 or gs465124 or gs-829143 or gs829143).ti,ab,kf,dq.

12 exp Coronavirus disease 2019/

13 sars-related coronavirus/ or SARS coronavirus/

14 (coronavirinae/ or betacoronavirus/ or coronavirus infection/) and (epidemic/ or pandemic/)

15 (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,hw,ot.

16 ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,hw,ot.

17 ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot.

18 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot.

19 or/12-18

20 11 and 19

21 20 use oemezd

22 (conference abstract or conference review).pt.

23 21 not 22
24 10 or 23
25 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
26 Randomized Controlled Trial/
27 exp Randomized Controlled Trials as Topic/
28 "Randomized Controlled Trial (topic)"/
29 Controlled Clinical Trial/
30 exp Controlled Clinical Trials as Topic/
31 "Controlled Clinical Trial (topic)"/
32 Randomization/
33 Random Allocation/
34 Double-Blind Method/
35 Double Blind Procedure/
36 Double-Blind Studies/
37 Single-Blind Method/
38 Single Blind Procedure/
39 Single-Blind Studies/
40 Placebos/
41 Placebo/
42 Control Groups/
43 Control Group/
44 (random* or sham or placebo*).ti,ab,hw,kf.
45 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
46 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
47 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
48 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
49 allocated.ti,ab,hw.
50 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
51 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
52 (pragmatic study or pragmatic studies).ti,ab,hw,kf.
53 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.

54 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
55 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
56 or/25-55
57 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
58 (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
59 Multicenter Study.pt.
60 Clinical Studies as Topic/
61 exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
62 Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
63 Randomization/
64 Random Allocation/
65 Double-Blind Method/
66 Double Blind Procedure/
67 Double-Blind Studies/
68 Single-Blind Method/
69 Single Blind Procedure/
70 Single-Blind Studies/
71 Placebos/
72 Placebo/
73 Control Groups/
74 Control Group/
75 Cross-Over Studies/ or Crossover Procedure/
76 (random* or sham or placebo*).ti,ab,hw,kf.
77 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
78 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
79 (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
80 (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
81 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
82 (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.
83 ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.

84 ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
85 allocated.ti,ab,hw.
86 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
87 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
88 (pragmatic study or pragmatic studies).ti,ab,hw,kf.
89 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
90 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
91 trial.ti,kf.
92 or/57-91
93 exp animals/
94 exp animal experimentation/
95 exp models animal/
96 exp animal experiment/
97 nonhuman/
98 exp vertebrate/
99 [animal.po.]
100 or/93-99
101 exp humans/
102 exp human experiment/
103 [human.po.]
104 or/101-103
105 100 not 104
106 92 not 105
107 epidemiologic methods.sh.
108 epidemiologic studies.sh.
109 observational study/
110 observational studies as topic/
111 clinical studies as topic/
112 controlled before-after studies/
113 historically controlled study/
114 interrupted time series analysis/
115 national longitudinal study of adolescent health/

116 cohort studies/
117 cohort analysis/
118 longitudinal studies/
119 longitudinal study/
120 prospective studies/
121 prospective study/
122 follow-up studies/
123 follow up/
124 followup studies/
125 retrospective studies/
126 retrospective study/
127 case-control studies/
128 exp case control study/
129 observational study/
130 quasi experimental methods/
131 quasi experimental study/
132 (observational study or validation studies or clinical study).pt.
133 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
134 cohort*.ti,ab,kf.
135 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
136 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.
137 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.
138 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.
139 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.
140 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
141 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf.
142 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
143 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
144 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.
145 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf.

146 (quasi adj (experiment or experiments or experimental)).ti,ab,kf.
147 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.
148 or/107-147
149 56 or 106 or 148
150 24 and 149
151 remove duplicates from 150
152 limit 151 to (english or french)

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

Search results: 17 Studies found for: remdesivir | "COVID-19" | Completed Studies

Appendix 2: List of Included Studies

Note that this appendix has not been copy-edited.

Table 17

Included Studies

Study	Citation
Randomized controlled trial	
PINETREE	Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *New Engl J Med*. 2022;386(4):305-315. **[Main report]**
	Brown SM, Katz MJ, Ginde AA, et al. Consistent Effects of Early Remdesivir on Symptoms and Disease Progression Across At-Risk Outpatient Subgroups: Treatment Effect Heterogeneity in PINETREE Study. I*nfect Dis Ther*. 2023;12(4):1189-1203.
	Pan DZ, Odorizzi PM, Schoenichen A, et al. Remdesivir improves biomarkers associated with disease severity in COVID-19 patients treated in an outpatient setting. *Commun Med (Lond)*. 2023;3(1):2.
Cohort studies	
NA	Mazzitelli M, Trunfio M, Sasset L, et al. Risk of hospitalization and sequelae in patients with COVID-19 treated with 3-day early remdesivir vs. controls in the vaccine and Omicron era: A real-life cohort study. *J Med Viro*l. 2023;95(3):e28660.
	Piccicacco N, Zeitler K, Ing A, et al. Real-world effectiveness of early remdesivir and sotrovimab in the highest-risk COVID-19 outpatients during the Omicron surge. *J Antimicrob Chemother*. 2022;77(10):2693-2700.
	Del Borgo C, Garattini S, Bortignon C, et al. Covid-Group Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use. *Viruses*. 2023;15(4):1025.
	Pinargote-Celorio H, Otero-Rodriguez S, Gonzalez-de-la-Aleja P, et al. Mild SARS-CoV-2 infection in vulnerable patients: implementation of a clinical pathway for early treatment. *Enferm Infecc Microbiol Clin*. 2023;30: S2529-993X(23)00090-4.
	Mikulska M, Testi D, Russo C, et al. Outcome of early treatment of SARS-CoV-2 infection in patients with haematological disorders. *Br J Haematol*. 2023;201(4):628-639.
	Tiseo G, Barbieri C, Galfo V, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. *Infect Dis Ther*. 2023;12(1):257-271.
	Colaneri M, Pieri TC, Roda S, et al. Assessing the Efficacy of Early Therapies against SARS-CoV-2 in Hematological Patients: A Real-Life Study from a COVID-19 Referral Centre in Northern Italy. *J Clin Med*. 2022;11(24):7452.
	Solera JT, Arbol BG, Bahinskaya I, Marks N, Humar A, Kumar D. Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the omicron BA.2 wave. *Am J Transplant*. 2023;23(1):78-83.
	Manciulli T, Spinicci M, Rossetti B, et al. Safety and Efficacy of Outpatient Treatments for COVID-19: Real-Life Data from a Regionwide Cohort of High-Risk Patients in Tuscany, Italy (the FEDERATE Cohort). *Viruses*. 2023;15(2):438.

Appendix 3: List of Excluded Studies

Note that this appendix has not been copy-edited.

Table 18

Excluded Studies

Reason for exclusion	Citation
Population not of interest	Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826.
	Jen HH, Chang WJ, Lin TY, et al. Evaluating Clinical Efficacy of Antiviral Therapy for COVID-19: A Surrogate Endpoint Approach. *Infect Dis Ther*. 2021;10(2):815-825.
	Colombo CJ, Colombo, RE, Maves RC, et al. Performance Analysis of the National Early Warning Score and Modified Early Warning Score in the Adaptive COVID-19 Treatment Trial Cohort. *Crit Care Explor*. 2021;3(7):e0474.
	Thiede JM, Gress AR, Libby SD, et al. Immune Profiling to Determine Early Disease Trajectories Associated With Coronavirus Disease 2019 Mortality Rate: A Substudy from the ACTT-1 Trial. *J Infect Dis*. 2021;223(8):1339-1344.
	Fintzi, J., Bonnett, T., Sweeney, D. A., Huprikar, N. A., Ganesan, A., Frank, M. G., McLellan, S. L. F., Dodd, L. E., Tebas, P., Mehta, A. K. Deconstructing the Treatment Effect of Remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: Implications for Critical Care Resource Utilization. *Clin Infect Dis*. 2022;74(12):2209-2217.
	Paules CI, Gallagher SK, Rapaka RR, et al. Remdesivir for the Prevention of Invasive Mechanical Ventilation or Death in Coronavirus Disease 2019 (COVID-19): A Post Hoc Analysis of the Adaptive COVID-19 Treatment Trial-1 Cohort Data. *Clin Infect Dis*. 2022;74(7):1260-1264.
	Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11):1048-1057.
	WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*. 2022;399(10399):1941-1953.
	Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511.
	Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ*. 2022;194(7):E242-E251.
	Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: A randomized controlled trial. [rench]. *CMAJ*. 2022;194(7):E713-E723.
	Lau VI, Fowler R, Pinto R, et al. Cost-effectiveness of remdesivir plus usual care versus usual care alone for hospitalized patients with COVID-19: an economic evaluation as part of the Canadian Treatments for COVID-19 (CATCO) randomized clinical trial. *CMAJ Open*. 2022;10(3):E807-E817.

Reason for exclusion	Citation
Population not of interest (continued)	Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis*. 2022;22(2):209-221. Lingas G, Neant N, Gaymard, A, et al. Effect of remdesivir on viral dynamics in COVID-19 hospitalized patients: a modelling analysis of the randomized, controlled, open-label DisCoVeRy trial. *J Antimicrob Chemother*. 2022;77(5):1404-1412. Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Mentre F, Burdet C. Final results of the DisCoVeRy trial of remdesivir for patients admitted to hospital with COVID-19. *Lancet Infect Dis*. 2022;22(6):764-765. Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, et al. Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 : A Randomized Trial. *Ann Intern Med*. 2021;174(9):1261-1269. Lerum TV, Maltzahn NN, Aukrust P, et al. Persistent pulmonary pathology after COVID-19 is associated with high viral load, weak antibody response, and high levels of matrix metalloproteinase-9. *Sci Rep*. 2021;11(1):23205. Nevalainen OPO, Horstia S, Laakkonen S, et al. Effect of remdesivir post hospitalization for COVID-19 infection from the randomized SOLIDARITY Finland trial. *Nat Commun*. 2022;13(1):6152.
Intervention not of interest	Brown SM, Peltan I, Kumar N, et al. Hydroxychloroquine versus azithromycin for hospitalized patients with COVID-19: Results of a randomized, active comparator trial. *Ann Am Thorac Soc*. 2021;18(4):590-597. Temesgen Z, Kelley CF, Cerasoli F, et al. C reactive protein utilisation, a biomarker for early COVID-19 treatment, improves lenzilumab efficacy: results from the randomised phase 3 'LIVE-AIR' trial. *Thorax*. 2022;06:06. I-SPY COVID Consortium. Report of the first seven agents in the I-SPY COVID trial: a phase 2, open label, adaptive platform randomised controlled trial. *EClinicalMedicine*. 2023;58:101889. Shah T, McCarthy M, Nasir I, et al. Colchicine and high-intensity rosuvastatin in the treatment of non-critically ill patients hospitalised with COVID-19: a randomised clinical trial. *BMJ Open*. 2023;13(2):e067910. Jain MK, De Lemos JA, McGuire DK, et al. Atovaquone for treatment of COVID-19: A prospective randomized, double-blind, placebo-controlled clinical trial. *Front Pharmaco*l. 2022;13:1020123. DiNubile MJ, Parra S, Salomo AC, Levinson SL. Adjunctive Recombinant Human Plasma Gelsolin for Severe Coronavirus Disease 2019 Pneumonia. *Open Forum Infect Dis*. 2022;9(8):ofac357. Fintzi J, Bonnett T, Tebas P, et al. Unraveling the Treatment Effect of Baricitinib on Clinical Progression and Resource Utilization in Hospitalized COVID-19 Patients: Secondary Analysis of the Adaptive COVID-19 Treatment Randomized Trial-2. *Open Forum Infect Dis*. 2022;9(7):ofac219. Coutre SE, Barnett C, Osiyemi O, et al. Ibrutinib for Hospitalized Adults With Severe Coronavirus Disease 2019 Infection: Results of the Randomized, Double-Blind, Placebo-Controlled iNSPIRE Study. *Open Forum Infect Dis*. 2022;9(5):ofac104. Roshon M, Lemos-Filho L, Cherevka H, Goldberg L, Salottolo K, Bar-Or D. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of a Novel Inhaled Biologic Therapeutic in Adults with Respiratory Distress Secondary to COVID-19 Infection. *Infect Dis Ther*. 2022;11(1):595-605. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab Efficacy and Safety in Newly Hospitalized Covid-19 Subjects: Results from the Live-Air Phase 3 Randomized Double-Blind Placebo-Controlled Trial. *medRxiv*. 2021; 2021.05.01.21256470. [non-peer reviewed preprint]

Reason for exclusion	Citation
Intervention not of interest (continued)	Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*. 2022;10(9): 888-899.
	Barkauskas C, Mylonakis E, Poulakou G, et al. Efficacy and Safety of Ensovibep for Adults Hospitalized With COVID-19 : A Randomized Controlled Trial. *Ann Intern Med*. 2022;175(9):1266-1274.
	ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. *Lancet Respir Med*. 2022;10:972-984.
	Nickols NG, Mi Z, DeMatt E, et al. Effect of Androgen Suppression on Clinical Outcomes in Hospitalized Men With COVID-19: The HITCH Randomized Clinical Trial. *JAMA Netw Open*. 2022;5(4):e227852.
	ITAC (INSIGHT 013) Study Group. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. *Lancet*. 2022;399(10324):530-540.
	Ortigoza MB, Yoon H, Goldfeld KS, et al. Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(2):115-126.
	Lundgren JD, Grund B, Barkauskas CE, et al. Responses to a Neutralizing Monoclonal Antibody for Hospitalized Patients With COVID-19 According to Baseline Antibody and Antigen Levels : A Randomized Controlled Trial. *Ann Intern Med*. 2022;175(2):234-243.
	Temesgen Z, Burger CD, Baker J, et al. Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebo-controlled trial. *Lancet Respir Med*. 2022;10(3):237-246.
	Branch-Elliman W, Ferguson R, Doros G, et al. Subcutaneous sarilumab for the treatment of hospitalized patients with moderate to severe COVID19 disease: A pragmatic, embedded randomized clinical trial. *PLoS One*. 2022;17(2):e0263591.
	Perlin DS, Neil GA, Anderson C, et al. Randomized, double-blind, controlled trial of human anti-LIGHT monoclonal antibody in COVID-19 acute respiratory distress syndrome. *J Clin Invest*. 2022;132(3):e153173.
	Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(12):1365-1376.
	Menichetti F, Popoli P, Puopolo M, et al. Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Netw Open*. 2021;4(11):e2136246.
	Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270.
	Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418.
	Ade, F, Peiffer-Smadja N, Poissy J, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-beta-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clin Microbiol Infect*. 2021;27(12):1826-1837.
	Lundgren JD, Grund B, Barkauskas CE, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(10):905-914.
	Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*. 2021;384(9):795-807.

Reason for exclusion	Citation
Intervention not of interest (continued)	Mazzotta V, Cozzi Lepri A, Colavita F, et al. Viral load decrease in SARS-CoV-2 BA.1 and BA.2 Omicron sublineages infection after treatment with monoclonal antibodies and direct antiviral agents. *J Med Virol*. 2023;95(1):e28186.
	Cacho J, Nicolas D, Bodro M, et al. Use of remdesivir in kidney transplant recipients with SARS-CoV-2 Omicron infection. *Kidney Int*. 2022;102(4):917-921.
	Kilcoyne A, Jordan E, Zhou A, et al. Clinical and economic benefits of lenzilumab plus standard of care compared with standard of care alone for the treatment of hospitalized patients with COVID-19 in the United States from the hospital perspective. *J Med Econ*. 2022;25(1):160-171.
	Bertuccio P, Degli Antoni M, Minisci D, et al. The impact of early therapies for COVID-19 on death, hospitalization and persisting symptoms: a retrospective study. *Infection*. 2023;6:1-12.
	Green ACA, Curtis HJ, Higgins R, et al. Trends, variation, and clinical characteristics of recipients of antiviral drugs and neutralising monoclonal antibodies for covid-19 in community settings: retrospective, descriptive cohort study of 23.4 million people in OpenSAFELY. *BMJ Med*. 2023;2(1):e000276.
	Scotto R, Buonomo AR, Iuliano A, et al. Remdesivir Alone or in Combination with Monoclonal Antibodies as an Early Treatment to Prevent Severe COVID-19 in Patients with Mild/Moderate Disease at High Risk of Progression: A Single Centre, Real-Life Study. *Vaccines (Basel)*. 2023;11(2):200.
	Lasagna A, Albi G, Figini S, et al. Long-COVID in Patients with Cancer Previously Treated with Early Anti-SARS-CoV-2 Therapies in an Out-of-Hospital Setting: A Single-Center Experience. *Cancers (Basel)*. 2023;15(4):1269.
	Raad II, Hachem R, Masayuki N, et al. International multicenter study comparing COVID-19 in patients with cancer to patients without cancer: Impact of risk factors and treatment modalities on survivorship. *eLife*. 2023;12:e81127.
	Biscarini S, Villa S, Genovese C, et al. Safety Profile and Outcomes of Early COVID-19 Treatments in Immunocompromised Patients: A Single-Centre Cohort Study. *Biomedicines*. 2022;10(8):2002.
	Jia X, Cao S, Lee AS, et al. Anti-nucleocapsid antibody levels and pulmonary comorbid conditions are linked to post-COVID-19 syndrome. *JCI Insight*. 2022;7(13):e156713.
	Hall VG, Al-Alahmadi G, Solera, JT, et al. Outcomes of SARS-CoV-2 Infection in Unvaccinated Compared With Vaccinated Solid Organ Transplant Recipients: A Propensity Matched Cohort Study. *Transplantation*. 2022;106(8):1622-1628.
Setting not of interest	Hadadi A, Ajam A, Montazeri M, et al. Effects of Remdesivir on in-Hospital and Late Outcomes of Patients With Confirmed or Clinically Suspected COVID-19: A Propensity Score-Matched Study. *Acta Medica Iranica*. 2022;60(7):407-412.
	Popescu C, Andrei AI, Ciresa A, Sturza F, Duna F, Popescu GA. Early Use of Remdesivir in Obese Male Patients with Covid-19 Can Improve the Prognosis. *Farmacia*. 2022;70(1):76-80.
	Taghavi MR, Tavanaei Tamanaei T, Oghazian MB, et al. Effectiveness of Fortified Garlic Extract Oral Capsules as Adjuvant Therapy in Hospitalized Patients with Coronavirus Disease 2019: A Triple-Blind Randomized Controlled Clinical Trial. *Curr Ther Res Clin Exp*. 2023;98:100699.
	Bansode S, Singh PK, Tellis M, et al. A Comprehensive Molecular and Clinical Investigation of Approved Anti-HCV Drugs Repurposing against SARS-CoV-2 Infection: A Glaring Gap between Benchside and Bedside Medicine. *Vaccines (Basel)*. 2023;11(3):515.
	Galal MW, Ahmed M, Shao Y, et al. The Use of Mebendazole in COVID-19 Patients: An Observational Retrospective Single Center Study. *Adv Virol*. 2022:3014686.

Reason for exclusion	Citation
Setting not of interest (continued)	Amoushahi A, Moazam E, Tabatabaei AR, et al. Efficacy and Safety of Inhalation of Nebulized Ethanol in COVID-19 Treatment: A Randomized Clinical Trial. *Cureus*. 2022;14(12):e32218.
	Mortaz E, Jamaati H, Dezfuli NK, et al. Changes in PD-1- and CTLA-4-bearing blood lymphocytes in ICU COVID-19 patients treated with Favipiravir/Kaletra or Dexamethasone/Remdesivir: a pilot study. *Iranian J Allergy Asthma Immunol*. 2023;22(1):99-109.
	Kasiri H, Ghazaiean M, Rouhani N, Naderi-Behdani F, Ghazaeian M, Ghodssi-Ghassemabadi R. The effects of colchicine on hospitalized COVID-19 patients: A randomized, double-blind, placebo-controlled clinical trial. *J Investif Med*. 2023;71(2):124-131.
	Tam AR, Zhang RR, Lung KC, et al. Early Treatment of High-Risk Hospitalized Coronavirus Disease 2019 (COVID-19) Patients With a Combination of Interferon Beta-1b and Remdesivir: A Phase 2 Open-label Randomized Controlled Trial. *Clin Infect Dis*. 2023;76:e216-e226.
	Mousapour P, Hamidi Farahani R, Mosaed R, Asgari A, Hazrati E. Efficacy and safety of acetylcysteine for the prevention of liver injury in COVID-19 intensive care unit patients under treatment with remdesivir. *Gastroenterol Hepatol Bed Benc*h. 2022;15(3):241-248.
	Mohiuddin Chowdhury ATM, Kamal A, Abbas KU, et al. Efficacy and Outcome of Remdesivir and Tocilizumab Combination Against Dexamethasone for the Treatment of Severe COVID-19: A Randomized Controlled Trial. *Front Pharmacol*. 2022;13:690726.
	Panda PK, Singh BO, Moirangthem B, et al. Antiviral Combination Clinically Better Than Standard Therapy in Severe but Not in Non-Severe COVID-19. *Clin Pharmacol*. 2021;13:185-195.
	Gupta S, Dixit PK, Ghana P, et al. Open-label randomized control trial of hydroxychloroquine in patients with moderate to severe coronavirus disease 2019 infection. *Med J Armed Forces India*. 2021;77(Suppl 2):S305-S311.
	Mahajan L, Singh AP, Gifty. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. *Indian J Anaesth*. 2021;65(Suppl 1):S41-S46.
	Aryan H, Farahani RH, Chamanara M, et al. Evaluation of the efficacy of oral nano-silymarin formulation in hospitalized patients with COVID-19: A double-blind placebo-controlled clinical trial. *Phytother Res*. 2022;36(10):3924-3931.
	Essai CATCO (Canadian Treatments for COVID-19); pour le Réseau de recherche clinique de l'Association pour la microbiologie médicale et l'infectiologie Canada (AMMI Canada) le Groupe canadien de recherche en soins intensifs (CCCTG). Remdésivir chez les patients hospitalisés pour la COVID-19 au Canada: essai clinique randomisé et contrôlé. *CMAJ*. 2022;194(2):E713-E723.
	Guzman-Esquivel J, Galvan-Salazar HR, Guzman-Solorzano HP, et al. Efficacy of the use of mefenamic acid combined with standard medical care vs. standard medical care alone for the treatment of COVID-19: A randomized double-blind placebo-controlled trial. *Int J Mol Med*. 2022;49(3):29.
	Shohan M, Nashibi R, Mahmoudian-Sani MR, et al. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: A randomized controlled trial. *Eur J Pharmacol*. 2022;914:174615.
	Fakharian A, Barati S, Mirenayat M, et al. Evaluation of adalimumab effects in managing severe cases of COVID-19: A randomized controlled trial. *Int Immunopharmacol*. 2021;99:107961.
	Martin-Onraet A, Barrientos-Flores C, Vilar-Compte D, Perez-Jimenez C, Alatorre-Fernandez P. Use of remdesivir for COVID-19 in patients with hematologic cancer. *Clin Exp Med*. 2022;12:1-8.
	Hajimoradi M, Sharif Kashani B, Dastan F, et al. Remdesivir associated sinus bradycardia in patients with COVID-19: A prospective longitudinal study. *Front Pharmacol*. 2022;13:1107198.

Reason for exclusion	Citation
Setting not of interest (continued)	Rajme-Lopez S, Martinez-Guerra BA, Zalapa-Soto J, et al. Early Outpatient Treatment With Remdesivir in Patients at High Risk for Severe COVID-19: A Prospective Cohort Study. *Open Forum Infect Dis*. 2022;9(10):ofac502. Aksak-Was BJ, Chober D, Serwin K, et al. Remdesivir Reduces Mortality in Hemato-Oncology Patients with COVID-19. *J Inflamm Res*. 2022;15:4907-4920. Kim T, Joo DH, Lee SW, Lee J, Lee SJ, Kang J. Real-World Efficacy of Regdanvimab on Clinical Outcomes in Patients with Mild to Moderate COVID-19. *J Clin Med*. 2022;11(5):1412. Gupta V, Ingawale S, Bhondve A, et al. Clinical Study of Use of Remdesivir and Tocilizumab in Severely Ill COVID-19 Patients. *J Assoc Physicians India*. 2021;69(7):14-19. Elec AD, Oltean M, Goldis P, et al. COVID-19 after kidney transplantation: Early outcomes and renal function following antiviral treatment. *Int J Infect Dis*. 2021104:426-432.
Study design not of interest	Fintzi J, Bonnett T, Sweeney DA, et al. Deconstructing the Treatment Effect of Remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: Implications for Critical Care Resource Utilization. *Clin Infect Dis*. 2022;74(12):2209-2217. Department of Error: Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*. 2022;400(10362). Ohsfeldt R, Kelton K, Klein T, et al. Cost-Effectiveness of Baricitinib Compared With Standard of Care: A Modeling Study in Hospitalized Patients With COVID-19 in the United States. *Clin Ther*. 2021;43(11):1877-1893.e4. Bauer RN, Teterina A, Shivram H, et al. Prognostic value of severe acute respiratory syndrome coronavirus-2 viral load and antibodies in patients hospitalized with COVID-19. *Clin Transl Sci*. 2023;16(6):1049-1062. Pilgram L, Appel KS, Ruethrich MM, et al. Use and effectiveness of remdesivir for the treatment of patients with covid-19 using data from the Lean European Open Survey on SARS-CoV-2 infected patients (LEOSS): a multicentre cohort study. Infection. 2023;51(4):1033-1049. Potter GE, Bonnett T, Rubenstein K, et al. Temporal Improvements in COVID-19 Outcomes for Hospitalized Adults: A Post Hoc Observational Study of Remdesivir Group Participants in the Adaptive COVID-19 Treatment Trial. *Ann Intern Med*. 2022;175(12):1716-1727. Olender SA, Walunas TL, Martinez E, et al. Remdesivir Versus Standard-of-Care for Severe Coronavirus Disease 2019 Infection: An Analysis of 28-Day Mortality. *Open Forum Infect Dis*. 2021;8(7):ofab278. Bajema KL, Wang XQ, Hynes DM, et al. Early Adoption of Anti-SARS-CoV-2 Pharmacotherapies Among US Veterans With Mild to Moderate COVID-19, January and February 2022. *JAMA Netw Ope*n. 2022;5(11):e2241434. Tran A, Rochwerg B. In adults hospitalized with COVID-19, adding baricitinib vs. dexamethasone to remdesivir did not differ for MV-free survival. *Ann Intern Med*. 2022;175(10):JC115. Marrone A, Nevola R, Sellitto A, et al. Remdesivir Plus Dexamethasone Versus Dexamethasone Alone for the Treatment of Coronavirus Disease 2019 (COVID-19) Patients Requiring Supplemental O2 Therapy: A Prospective Controlled Nonrandomized Study. *Clin Infect Dis*. 2022;75(1):e403-e409. Rosenberg K. Remdesivir in The Treatment of COVID-19. *Am J Nurs*. 2021;121(1):55. Olender SA, Perez KK, Go AS, et al. Remdesivir for Severe Coronavirus Disease 2019 (COVID-19) Versus a Cohort Receiving Standard of Care. *Clin Infect Dis*. 2021;73(11):e4166-e4174.

Reason for exclusion	Citation
Study design not of interest (continued)	Mikulska M, Sepulcri C, Dentone C, et al. Triple combination therapy with two antivirals and monoclonal antibodies for persistent or relapsed SARS-CoV-2 infection in immunocompromised patients. *Clin Infect Dis*. 2023;77(2):280-286.
	Li X, Zhou L, Gaggl M, et al. Remdesivir for COVID-19 and acute kidney injury: disproportionality analysis of data from the U.S. Food and Drug Administration Adverse Event Reporting System. *Int J Clin Pharm*. 2023;45(2):509-514.
	Shimizu H, Kawase J, Hayashi M, Imaizumi K, Ito Y, Okazawa M. COVID-19 symptom-onset to diagnosis and diagnosis to treatment intervals are significant predictors of disease progression and hospitalization in high-risk patients: A real world analysis. *Respir Investig*. 2023;61(2):220-229.
	Wu B, Luo M, Wu F, He Z, Li Y, Xu T. Acute Kidney Injury Associated With Remdesivir: A Comprehensive Pharmacovigilance Analysis of COVID-19 Reports in FAERS. *Front Pharmacol*. 2022;13:692828.
	Zhou Y, Li J, Wang L, Zhu X, Zhang M, Zheng J. Acute Kidney Injury and Drugs Prescribed for COVID-19 in Diabetes Patients: A Real-World Disproportionality Analysis. *Front Pharmacol*. 2022;13:833679.
	Rafaniello C, Ferrajolo C, Sullo MG, et al. Cardiac events potentially associated to remdesivir: An analysis from the european spontaneous adverse event reporting system. *Pharmaceuticals (Basel)*. 2021;14(7):611.
	Liao SH, Hung CC, Chen CN, et al. Assessing efficacy of antiviral therapy for COVID-19 patients: A case study on remdesivir with bayesian synthesis design and multistate analysis. *J Formos Med Assoc*. 2021;120(Supplement 1):S77-S85.
	Tang H, Zhou L, Li X, et al. Drug-induced liver injury associated with lopinavir-ritonavir in patients with COVID-19: a disproportionality analysis of U.S. food and drug administration adverse event reporting system (FAERS) data. *Int J Clin Pharm*. 2021;43(4):1116-1122.
	Touafchia A, Bagheri H, Carrie D, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. *Clin Microbiol Infect*. 2021;27(5):791.e5-791.e8.
	Watanabe JH, Kwon J, Nan B, Abeles SR, Mehta SR. Examination of Medication Use Patterns by Age Group, Comorbidity, and Month in COVID-19 Positive Patients in a Large Statewide Health System During the Pandemic in 2020. *J Pharm Technol*. 2022;38(2):75-87.
	Mastruzzo C, Commodari E, Grasso U, et al. Early Stage Combination Treatment with Methylprednisolone Pulse and Remdesivir for Severe COVID-19 Pneumonia. *Int J Environ Res Public Health*. 2023;20(2):1081.
	Gliga S, Lubke N, Killer A, et al. Rapid Selection of Sotrovimab Escape Variants in Severe Acute Respiratory Syndrome Coronavirus 2 Omicron-Infected Immunocompromised Patients. *Clin Infect Dis*. 2023;76(3):408-415.
	De Vito A, Colpani A, Saderi L, et al. Impact of Early SARS-CoV-2 Antiviral Therapy on Disease Progression. *Viruses*. 2022;15(1):71.
	Kilcoyne A, Jordan E, Thomas K, et al. Clinical and Economic Benefits of Lenzilumab Plus Standard of Care Compared with Standard of Care Alone for the Treatment of Hospitalized Patients with Coronavirus Disease 19 (COVID-19) from the Perspective of National Health Service England. *Clinicoecon Outcomes Res*. 2022;14:231-247.
	Zhao Y, Zhang J, Zheng K, et al. Serious Cardiovascular Adverse Events Associated with Hydroxychloroquine/Chloroquine Alone or with Azithromycin in Patients with COVID-19: A Pharmacovigilance Analysis of the FDA Adverse Event Reporting System (FAERS). *Drugs Real World Outcomes*. 2022;9(2):231-241.
	Fusaroli M, Raschi E, Gatti M, De Ponti F, Poluzzi E. Development of a Network-Based Signal Detection Tool: The COVID-19 Adversome in the FDA Adverse Event Reporting System. *Front Pharmacol*. 2021;12:740707.

Reason for exclusion	Citation
Study design not of interest (continued)	Kikuchi K, Nangaku M, Ryuzaki M, et al. Survival and predictive factors in dialysis patients with COVID-19 in Japan: a nationwide cohort study. *Ren Replace Ther*. 2021;7(1):59.
	Elshaboury RH, Monk MM, Bebell LM, et al. Remdesivir use and outcomes during the FDA COVID-19 emergency use authorization period. *Ther Adv Infect Dis*. 2021;8:20499361211046669.
	Shields AM, Anantharachagan A, Arumugakani G, et al. Outcomes following SARS-CoV-2 infection in patients with primary and secondary immunodeficiency in the UK. *Clin Exp Immunol*. 2022;209(3):247-258.
	Villamarin M, Marquez-Algaba E, Esperalba J, et al. Preliminary Clinical Experience of Molnupiravir to Prevent Progression of COVID-19 in Kidney Transplant Recipients. *Transplantation*. 2022;106(11):2200-2204.
	Panagopoulos P, Petrakis V, Trypsianis G, Papazoglou D. Early 3-day course of remdesivir in vaccinated outpatients with SARS-CoV-2 infection. A success story. *J Chemother*. 2022;34(8):550-553.
	Gutierrez R, Mendez-Figueroa H, Biebighauser JG, Bhalwal A, Pineles BL, Chauhan SP. Remdesivir use in pregnancy during the SARS-CoV-2 pandemic. *J Matern Fetal Neonatal Med*. 2022;35(25):9445-9451.
	Wiley Z, Ross-Driscoll K, Wang Z, Smothers L, Mehta AK, Patzer RE. Racial and Ethnic Differences and Clinical Outcomes of Patients With Coronavirus Disease 2019 (COVID-19) Presenting to the Emergency Department. *Clin Infect Dis*. 2022;74(3):387-394.
	Huynh DN, Millan A, Quijada E, John D, Khan S, Funahashi T. Description and Early Results of the Kaiser Permanente Southern California COVID-19 Home Monitoring Program. *Perm J*. 2021;25:20.281.
	Garcia-Vidal C, Alonso R, Camon AM, et al. Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19. *J Antimicrob Chemother*. 2021;76(12):3296-3302.
	Singh A, Kamath A. Assessment of adverse events associated with remdesivir use for coronavirus disease 2019 using real-world data. *Expert Opin Drug Saf*. 2021;20(12):1559-1564.
	Rivera DR, Peters S, Panagiotou OA, et al. Utilization of COVID-19 Treatments and Clinical Outcomes among Patients with Cancer: A COVID-19 and Cancer Consortium (CCC19) Cohort Study. *Cancer Discov*. 2020;10(10):1514-1527.

Appendix 4: Reported Results on Outcomes of Interest With Conclusions From Authors of Included Studies

Note that this appendix has not been copy-edited.

In Table 19, the reported results on the outcomes of interest from the RCT are presented as in Table 11. In addition, concluding comments by the study investigators are provided as reported in the RCT. This provides a summary of the perspective of the investigators on the results of their study. However, even though the RCT report has been peer-reviewed, caution in reading these comments must be exercised since investigators may have overinterpreted the associations and causality of their results.

Table 19

Reported Results on Outcomes of Interest for the Randomized Controlled Trials With Study Authors' Conclusion

Reported results on outcomes of interest in Gottlieb et al. (2022)[8]	Study authors' conclusion
COVID-19–related hospitalization by day 28[b] n (%) • Remdesivir (n = 279): 2 (0.7) • Placebo (n = 283):15 (5.3) • HR = 0.13 (95% CI, 0.03 to 0.59)c All Covid-19–related hospitalizations occurred by day 14.	"All Covid-19–related hospitalizations occurred by day 14." (page 308)

Reported results on outcomes of interest in Gottlieb et al. (2022)[8]	Study authors' conclusion
COVID-19–related hospitalization by subgroups, n (%) **Subgroups: Age, sex, and ethnicity** **Both raw data and adjusted HR** • Age ≥ 60 years: ◦ Remdesivir (n = 83): 1 (1.2) ◦ Placebo (n = 87): 9 (10.3) ◦ HR = 0.11 (95% CI, 0.01 to 0.86) • Male sex ◦ Remdesivir (n = 148): 1 (0.7) ◦ Placebo (n = 145): 9 (6.2) ◦ HR = 0.11 (95% CI, 0.01 to 0.84) • Ethnic group: Not Hispanic or Latino ◦ Remdesivir (n = 146): 2 (1.4) ◦ Placebo (n = 158): 8 (5.1) ◦ HR = 0.26 (95% CI, 0.06 to 1.22) • Ethnic group: Hispanic or Latino ◦ Remdesivir (n = 123): 0 (0) ◦ Placebo (n = 112): 6 (5.4) ◦ HR = NR The authors reported the subgroups only for the primary efficacy outcome (a composite outcome of COVID-19–related hospitalization and death) by day 28. Because there was no death in either group, the numbers of patients for the composite outcome could be used for our single outcome of interest: COVID-19–related hospitalization. Cox proportional hazards model with the baseline stratification factors as covariates (i.e., residence in a skilled nursing facility [yes or no], age [< 60 years or ≥ 60 years], and country [in- and outside US]) was used to estimate HRs and 95% CIs. For subgroups with no events in the remdesivir group, estimates could not be accurately calculated and omitted.	"In prespecified subgroup analyses, the incidence of a primary efficacy endpoint event was lower in the remdesivir group than in the placebo group." (page 308) According to the authors, age and sex were prespecified subgroups.
ICU admission among hospitalized patients, n (%) • Remdesivir (n = 279): 3 (1) • Placebo (n = 283): 3 (1)	No specific interpretation for this outcome.
Time to hospitalization (reported as individualized day of hospitalization from time of randomization), median (IQR) • Remdesivir (n = 5): 4 (2.5 to 7.5)[d] • Placebo (n = 18): 6.5 (3 to 9)	No specific interpretation for this outcome.

Reported results on outcomes of interest in Gottlieb et al. (2022)[8]	Study authors' conclusion
Death from any cause by day 28[e], n (%) • Remdesivir (n = 279): 0 (0) • Placebo (n = 283): 0 (0) • HR (95% CI): not calculated	"No patients in either group died by day 28" (page 308) Regarding the composite outcome, the authors concluded the following "… we found that patients who received a 3-day course of remdesivir had an 87% lower risk of Covid-19–related hospitalization or death from any cause by day 28 and an 81% lower risk of Covid-19–related medically attended visits or death from any cause by day 28 than patients who received placebo." (page 310)
Any SAE[f], n (%) • Remdesivir (n = 279): 5 (1.8) • Placebo (n = 283): 19 (6.7)	"Among nonhospitalized patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo."(page 305)
Adverse event leading to discontinuation of trial regimen, n (%) • Remdesivir (n = 279): 2 (0.7) • Placebo (n = 283): 5 (1.8)	"Among nonhospitalized patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo."(page 305)

CI = confidence interval; HR = hazard ratio; MD = mean difference; RR = risk ratio; SAE = serious adverse event.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] No patients in either group died by day 28; therefore, the results for the composite outcome could be used for our single outcome of interest (COVID-19–related hospitalization).

[c] Cox proportional hazards model with the baseline stratification factors as covariates (i.e., residence in a skilled nursing facility [yes or no], age [< 60 years or ≥ 60 years], and country [inside or outside US]) was used to estimate HR and 95% CI.

[d] Only 2 patients in the remdesivir arm were considered to have been hospitalized because of COVID-19 (2 and 3 days, respectively). Non-COVID-19–related causes were atrial fibrillation, cardiac failure congestive, and angina pectoris.

[e] Authors provided the outcome (transfer, discharged, or death) for all hospitalized patients; only 1 patient in the placebo group died as of day 59.

[f] Severity grades were defined according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

In Table 20 the reported results on the outcomes of interest from the cohort studies are presented as in Table 12. In addition, concluding comments by the study investigators are provided as reported in the cohort studies. This provides a summary of the perspective of the investigators on the results of their study. However, even though the cohort study reports have been peer-reviewed, caution in reading these comments must be exercised since investigators may have overinterpreted the associations and causality of their results.

Table 20

Reported Results on Outcomes of Interest for Cohort Studies With Study Authors' Conclusion

Reported results on outcomes of interest	Study authors' conclusion
Emergency department visit without hospitalization	
Piccicacco et al. (2022)[13]	
COVID-19–related 29 day ED visit, within 29 days from symptom onset (initial COVID-19 diagnosis made in the ED did not count as an ED visit), n (%) • 14 days ◦ Remdesivir (n = 82): 1 (1.2) ◦ No treatment control (n = 90): 6 (6.7) ◦ P = 0.05[c] • 29 days ◦ Remdesivir (n = 82): 2 (2.4) ◦ No treatment control (n = 90): 10 (11.1) ◦ P = 0.04 ◦ Unadjusted OR = 0.2 (95% CI, 0.04 to 0.94) ◦ Absolute risk reduction: 8.7% ◦ Number needed to treat: n = 12 (95% CI, 6.3 to 72.9)	"Patients treated with **remdesivir** or sotrovimab were significantly less likely to visit the ED within 29 days from symptom onset (2.4% versus 1.2%, respectively) in comparison with control patients (11.1%)" (page 2693)
Hospitalization	
Piccicacco et al. (2022)[13]	
Hospitalization, n (%) • 14 days ◦ Remdesivir (n = 82): 4 (5) ◦ No treatment) control (n = 90): 8 (8.9) ◦ P = 0.27[c] • 29 days ◦ Remdesivir (n = 82): 7 (8.5) ◦ No treatment control (n = 90): 11 (12.2) ◦ P = 0.58[c]	"Patients treated with remdesivir were significantly less likely to be hospitalized or visit the ED within 29 days from symptom onset compared with control patients" (page 2693)
Manciulli et al. (2023)[17]	
Hospitalization due to COVID-19 progression by day 28, n (%) • Remdesivir (n = 142): 7 (4.9) • Molnupiravir (n = 205): 4 (1.9) • Nirmatrelvir-ritonavir (n = 120): 3 (2.5)	"No significant differences of outcome were observed in preventing 28-day hospitalization and death among patients treated with RMD [remdesivir], MOL [molnupiravir], and NRM/r [nirmatrelvir/ritonavir]."(page 1)

Reported results on outcomes of interest	Study authors' conclusion
Tiseo et al. (2023)[10]	
Hospitalization due to COVID-19 by day 30, n (%) • Remdesivir (n = 196): 10 (5.1) • Molnupiravir (n = 114): 1 (0.9) • Nirmatrelvir-ritonavir (n = 252): 1 (0.4) • P = 0.002 (test for multiple comparisons)	No interpretation for this. For the composite end point of death or hospitalization "The composite endpoint occurred in 2.5% of patients and was more frequent in patients treated with remdesivir (5.1%) compared with molnupiravir (1.8%) or nirmatrelvir/ ritonavir (0.8%, analysis of variance among groups p = 0.012). (page 1)
Pinargote-Celorio et al. (2022)[14]	
All-cause hospitalization by day 30 post treatment, n (%) • Remdesivir (n = 124): 8 (6.5) • Nirmatrelvir-ritonavir (n = 94): 3 (3.2) **Hospitalization due to COVID-19 progression by day 30 post treatment**, n (%) • Remdesivir (n = 124): 5 (4) • Nirmatrelvir-ritonavir (n = 94): 2 (2.1)	No interpretation for this. The relevant general conclusion is "Regarding the effectiveness of the treatment, although we do not have a comparator group that allows for its proper evaluation, the absence of mortality, a 6% overall hospital admission rate and 3.8% due to progression of COVID-19, seem to point towards the effectiveness of the treatments, particularly given the very high-risk population" (page 5)
Mazzitelli et al. (2023)[12]	
Progression to hospitalization, unclear follow-up,[d] n (%) • Remdesivir (n = 316): 3 (0.9) • Control-no antiviral treatment (n = 365): 56 (15.3) **Adjusted result**[e] • Early remdesivir vs. control (reference): • Adjusted OR = 0.049 (95% CI, 0.015 to 0.163, P < 0.001)	"Univariate analysis identified the same factors as associated with both the risk of oxygen requirement and hospitalization …previous SARS-CoV-2 immunization (either by vaccine or natural infection) and ER (early remdesivir) independently associated with lower risk of progression to oxygen and hospitalization" (page 5)
Colaneri et al. (2022)[16]	
28-day hospital admission • **Adjusted result**[f] ◦ Number of patients: remdesivir (n = 15); not treated (n = 33) ◦ Remdesivir vs. nontreated (reference): HR = 1.16 (SE = 0.71; P = 0.83)	"…the multivariable Cox proportional-hazard regression model showed that none of the early treatments did significantly reduce the hospitalization at day 28 compared with no treatment" (page 6)
Solera et al. (2023)[11]	
Covid-related hospitalization by day 30, n (%) • Remdesivir (n = 86): 2 (2.3%) • No remdesivir (n = 106): 13 (12.3%) • P = 0.013 **Adjusted result**[g] • Remdesivir vs. without remdesivir (reference) • HR = 0.12 (95% CI, 0.03 to 0.57; P = 0.007) • NNT to prevent admission = 15.2 (95% CI, 13.6 to 31.4)	"Using this adjustment, remdesivir use was protective of hospitalization with a hazard ratio (HR) of 0.12 (95% CI, 0.03–0.57) and an adjusted number needed to treat (NNT) to prevent 1 admission of 15.2 (95% CI, 13.6–31.4)" (page 82)

Reported results on outcomes of interest	Study authors' conclusion
Length of hospitalization (days)	
Mazzitelli et al. (2023)[12]	
Length of hospitalization (days), median (IQR)[h] • Remdesivir (n = 3): 3 (8 to 12) • No remdesivir (n = 56): 14 (10 to 29) • P = 0.299	"The study was not designed to detect statistical differences in hospitalization length; nevertheless, of the 3 hospital admissions in the ER group, two ended by death, and 1 lasted 4 days, whereas the median length of hospitalization in surviving controls (n = 48) was 14 (10–29) days." (page 5)
Solera et al. (2023)[11]	
Duration of hospitalization (days), median (IQR) • Remdesivir (n = 2): 11 (8 to 14) • No remdesivir (n = 13): 6 (4 to 15)	"There were no differences in the duration of hospitalization in the remdesivir (median 11 days [IQR 8–14]) and no remdesivir (median 6 days [IQR 4–15]) groups." (page 82)
ICU admission	
Mazzitelli et al. (2023)[12]	
ICU admission, unclear follow-up, n (%) • Remdesivir (n = 316): 0 (0) • No antiviral treatment control (n = 365): 4 (1.1)[i]	"The rare occurrence of ICU admission and death did not allow for enough power to consider these two relevant clinical outcomes among those evaluated in our study."(page 9)
Pinargote-Celorio et al. (2022)[14]	
Patients required admission to the critical care unit by day 30, n (%) • Remdesivir (n = 124): 0 (0) • Nirmatrelvir-ritonavir (n = 94): 0 (0)	"No patients required non-invasive ventilation or admission to the critical care unit, and none of them died." (page 4)
Solera et al. (2023)[11]	
ICU admission at day 30, n (%) • Remdesivir (n = 86): 0 (0) • No remdesivir (n = 106): 3 (2.8)	"No patient in the early remdesivir group was admitted to the ICU, required mechanical ventilation, or died by day 30 of follow-up." (page 82)
Need for supplemental oxygen	
Mazzitelli et al. (2023)[12]	
Progression to oxygen requirement, unclear follow-up, n (%) • Remdesivir (n = 316): 2 (0.6) • no antiviral treatment control (n = 365): 56 (15.3) • Remdesivir vs. control (reference) • OR = 0.035 (95% CI, 0.009 to 0.145 (unadjusted), P < 0.001) **Adjusted result**[e] • Early remdesivir vs. control (reference) • Adjusted OR = 0.034 (95% CI, 0.008 to 0.144; P < 0.001)	"According to the number needed to treat, on average 6.8 and 6.9 participants would have to receive ER (instead of no treatment) for 1 additional patient to not require oxygen support and hospitalization, respectively."(page 5) "Univariate analysis identified the same factors as associated with both the risk of oxygen requirement and hospitalization …previous SARS-CoV-2 immunization (either by vaccine or natural infection) and ER independently associated with lower risk of progression to oxygen and hospitalization" (page 5)

Reported results on outcomes of interest	Study authors' conclusion
Pinargote-Celorio et al. (2022)[14]	
Patients required noninvasive ventilation, n (%) • Remdesivir (n = 124): 0 (0) • Nirmatrelvir-ritonavir (n = 94): 0 (0)	"No patients required non-invasive ventilation or admission to the critical care unit, and none of them died." (page 4)
Solera et al. (2023)[11]	
Need for supplemental oxygen (including both patients who needed to start oxygen therapy and those with oxygen at baseline whose requirement increased), n (%) • Remdesivir (n = 86): 1 (1.2) • No remdesivir (n = 106): 4 (1.8) • HR = 0.21 (95% CI, 0.02 to 2.03; P = 0.38) • (unclear if unadjusted or adjusted) **Mechanical ventilation**, n (%) • Remdesivir (n = 86): 0 (0) • No remdesivir (n = 106): 2 (1.9)	"There was a non-significant (p=0.38) reduction in oxygen requirement for patients treated with outpatient remdesivir" (page 82) "No patient in the early remdesivir group was admitted to the ICU, required mechanical ventilation, or died by day 30 of follow-up." (page 82)

Reported results on outcomes of interest	Study authors' conclusion
Post–COVID-19 condition	
Mazzitelli et al. (2023)[12]	
COVID-19-related sequelae, 1 month after, n (%) • Remdesivir (n = 314): 27 (8.6) • No antiviral treatment control (n = 365): 155 (43.4) • P = 0.001 **Adjusted result**[j] • Among 671 survivors, early remdesivir vs. control (reference) • Adjusted OR = 0.147 (95% CI, 0.089 to 0.242) • P = 0.001 **Number of sequelae per patient**, 1 month after, median (IQR)[k] • Remdesivir (n = 27):1 (1 to 2) • No antiviral treatment control (n = 155): 1 (1 to 2) • P = 0.525 **COVID-19-related sequelae**, 3 months after, n (%) • Remdesivir (n = 314): 21 (6.7) • No antiviral treatment control (n = 365): 108 (30.3) • P < 0.001 **Adjusted result**[l] • Among 671 survivors, early remdesivir vs. control (reference): • Adjusted OR = 0.181 (95% CI, 0.105 to 0.312) • P < 0.001 **Number of sequelae per patient**, 3 months after, median (IQR)** • Remdesivir (n = 21): 1 (1 to 2) • No antiviral treatment control (n = 108): 1 (1 to 2) • P = 0.754	"At both 1- and 3-month follow up, participants in early remdesivir group (n = 314) reported reduced prevalence of COVID-19 related sequelae" (page 5) "In terms of number of complaints and clinical issues per patient, no difference was observed in the severity of sequelae between those who developed any in both groups at both time points. On average, 2.9 and 4.2 participants would have to receive ER (instead of no treatment) for one additional patient to not develop sequelae at 1 and 3 months from infection, respectively." (page 6)
Del Borgo et al. (2023)[9]	
Persistence of symptoms at 30 days (e.g., dyspnea, arthromyalgia, fever, cough, rhinitis, gastrointestinal problems, asthenia) • Number of patients: remdesivir (n = 230), molnupiravir (n = 499), nirmatrelvir-ritonavir (n = 389) **Adjusted result** • Molnupiravir vs. remdesivir (reference): OR = 0.46 (95% CI, 0.30 to 0.71, P = 0.001) • Nirmatrelvir-ritonavir vs. remdesivir (reference): OR (95% CI): OR = 0.56 (95% CI, 0.37 to 0.85, P = 0.006)	"Furthermore, patients treated with MP [molnupiravir] and NMV/r [nirmatrelvir/ritonavir] showed a significantly lower persistence of symptoms at 30 days compared to the group treated with RDV [remdesivir], as the univariate analysis pointed out" (page 7)

Reported results on outcomes of interest	Study authors' conclusion
Rebound COVID-19 (at 7 days and at 30 days)	
Tiseo et al. (2023)[10]	
Rebound of symptoms after antiviral discontinuation, 30 days, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 109): 2 (1.8) • Nirmatrelvir-ritonavir (n = 236): 5 (2.1) • P = 0.130 (test for multiple comparison)	"Finally, we found that about 2% of patients treated with nirmatrelvir/ritonavir and molnupiravir experienced a rebound of symptoms after the antiviral discontinuation…However, it is not known if rebound may occur in the general population of infected patients or whether is unique to nirmatrelvir/ritonavir."
Mazzitelli et al. (2023)[12]	
SARS-CoV-2 reinfection within 3 months, n (%) • Remdesivir (n = 316): 5 (1.6) • No antiviral treatment control (n = 365): 22 (6.2) • P = 0.003	"Five participants in the ER group (1.6%) while 22 (6.2%) among controls (p = 0.003). No further adjustment or analysis were performed to assess re-infection rates between groups considering that the study was not designed for this outcome and only symptomatic participants underwent testing on a self-base initiative." (page 6)
Death	
Manciulli et al. (2023)[17]	
Death due to COVID-19 progression, by day 28, n (%) • Remdesivir (n = 142): 2 (1.4) • Molnupiravir (n = 205): 0 (0) • Nirmatrelvir-ritonavir (n = 120): 0 (0)	"All drugs showed low rates of hospitalization and/or death due to COVID-19 progression, in line with results from previous studies"(page 7)
Tiseo et al. (2023)[10]	
30-day mortality due to COVID-19, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 114): 1 (0.9) • Nirmatrelvir-ritonavir (n = 252): 1 (0.4) • P = 0.453 (test for multiple comparison)	No interpretation for this. For the composite end point of death or hospitalization "The composite endpoint occurred in 2.5% of patients and was more frequently in patients treated with remdesivir (5.1%) compared with molnupiravir (1.8%) or nirmatrelvir/ ritonavir (0.8%, ANOVA [analysis of variance] among groups p = 0.012)." (page 1)

Reported results on outcomes of interest	Study authors' conclusion
Del Borgo et al. (2023)[9]	
All-cause mortality (COVID-19 and no COVID-19) by day 30, n (%) • Remdesivir (n = 230): 2 (0.9%) • Molnupiravir (n = 499): 7(1.4%) • Nirmatrelvir-ritonavir (n = 389): 4 (1%) • P = 0.785 • • COVID-19 mortality by day 30, n (%) • Remdesivir (n = 230): 1 (0.4%) • Molnupiravir (n = 499): 3 (0.6%) • Nirmatrelvir-ritonavir (n = 389): 0 (0%) • P = 0.261	No interpretation for these specific outcome. Generally "The three antivirals showed a similar effectiveness in containing the progression of the infection to severe COVID-19 and a good tolerability in the absence of serious adverse effects" (page 1) "From the univariate analysis among the immunocompromised subgroup, no statistically significant difference was found between the three groups of treatment in terms of clinical progression of SARS-CoV-2 infection to severe patterns of disease and in terms of all-cause mortality (COVID-19 and non-COVID-19), as shown in ..." (page 6)
Pinargote-Celorio et al. (2022)[14]	
All-cause 30-day mortality, n (%) • Remdesivir (n = 124): 0 (0) • Nirmatrelvir-ritonavir (n = 94): 0 (0)	No interpretation. Zero events for both groups.
Mazzitelli et al. (2023)[12]	
Covid-related death, unclear follow-up, n (%) • Remdesivir (n = 316): 2 (0.6) • No antiviral treatment control (n = 365): 8 (2.2) • P = 0.092	"... despite the study was not designed and thereby not powered enough to properly assess any difference in mortality or in in-hospital complications, raw unadjusted disbalance in the prevalence of in-hospital death and complications was observed." (page 5)
Piccicacco et al. (2022)[13]	
29 day all-cause mortality, n (%) • Remdesivir (n = 82): 0 (0) • No treatment control (n = 90): 1 (1.1) • P = 0.39[c]	"Incidence of 29 day all-cause mortality was low in all arms, with only one death occurring in the control group." (page 2697)
Solera et al. (2023)[11]	
All-cause mortality by day 30, n (%) • Remdesivir (n = 86): 0 (0) • No remdesivir (n = 106): 2 (1.9)	"No patient in the early remdesivir group was admitted to the ICU, required mechanical ventilation, or died by day 30 of follow-up." (page 82)

Reported results on outcomes of interest	Study authors' conclusion
Any serious adverse event	
Piccicacco et al. (2022)[13]	
Serious adverse event requiring intervention, n (%) • Remdesivir (n = 82): 1 (1.2) • No treatment control (n = 90): NR	"The remdesivir adverse drug event occurred in a myasthenia gravis patient who experienced transient subjective confusion, left lower extremity numbness and right upper extremity numbness after their second infusion. This event resulted in an ED visit and was classified as a possible myasthenia gravis exacerbation secondary to remdesivir by the ED provider. This patient was instructed not to receive their third remdesivir dose." (page 2697)
Del Borgo et al. (2023)[9]	
Severe adverse effects according to European Medicines Agency definition, n (%) • Remdesivir (n = 230): 0 (0) • Molnupiravir (n = 499): 0 (0) • Nirmatrelvir-ritonavir (n = 389): 0 (0)	Generally "the three antivirals showed a similar effectiveness in containing the progression of the infection to severe COVID-19 and a good tolerability in the absence of serious adverse effects" (page 1)
Drug discontinuation	
Manciulli et al. (2023)[17]	
Discontinuation by drug intolerance, n (%) • Remdesivir (n = 142): 3 (2.1) • Molnupiravir (n = 205): 5 (2.5) • Nirmatrelvir-ritonavir (n = 120): 0 (0)	No interpretation for this.
Tiseo et al. (2023)[10]	
Discontinuation, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 109): 4 (3.7) • Nirmatrelvir-ritonavir (n = 236): 5 (2.1) • P = 0.043)	"Discontinuation because of an AE was uncommon in the three study groups" (page 10)
Del Borgo et al. (2023)[9]	
Voluntarily interrupted early treatment with antiviral drugs, n (%) • Remdesivir (n = 230): 0 (0) • Molnupiravir (n = 499): 5 (1) • Nirmatrelvir-ritonavir (n = 389): 6 (2)	"Only 13 patients voluntarily interrupted early treatment with antiviral drugs: five patients treated with MP, for diarrhea and urticarial rash onset, six with NMV/r [nirmatrelvir/ritonavir], complaining of nausea and vomiting, and two with RDV [remdesivir]. However, it must be pointed out that these latter were not for the onset of adverse effects but rather because one patient decided on his own to not continue the treatment and the other one was converted to a 5-day scheme therapy with RDV [remdesivir] after a thorax CT scan documented COVID-19-related bilateral interstitial pneumonia." (page 8-9)

Reported results on outcomes of interest	Study authors' conclusion
Mazzitelli et al. (2023)[12]	
AE-related discontinuation, unclear follow-up, n (%) • Remdesivir (n = 316): 5 (1.6%) • No antiviral treatment Control (n = 365): NR	"…16 (5.1%) patients did not complete the treatment schedule: 5 developed to ER [early remdesivir] associated adverse events (all grade 1 abdominal discomfort and nausea in 5 patients), while 11 patients decided not to have the third remdesivir infusion due to rapid clinical improvement." (page 5)
Acute liver injury	
Tiseo et al. (2023)[10]	
AST and ALT increase (2 × ULN) by day 30, n (%) • Remdesivir (n = 196): 0 (0) • Molnupiravir (n = 109): 1 (0.9) • Nirmatrelvir-ritonavir (n = 236): 0 (0) • P = 0.137	No interpretation for this.
Treatment failure	
Mikulska et al. (2023)[15]	
Treatment failure defined as progression to severe COVID-19 requiring oxygen supplementation, corresponding to grade 4 or higher on the WHO COVID Outcomes Scale, or COVID-19–related death. Categories of the WHO 7-point ordinal scale are: (1) not hospitalized, no limitations on activities; (2) not hospitalized, limitation on activities; (3) hospitalized, not requiring supplemental oxygen; (4) hospitalized, requiring supplemental oxygen; (5) hospitalized, on noninvasive ventilation or high flow oxygen devices; (6) hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygen (ECMO); (7) death. Secondary outcomes were the length of SARS-CoV-2 positivity, COVID-19–associated mortality, and overall 90-day mortality, n (%) • Remdesivir (n = 59): 2 (3.4) • Molnupiravir (n = 33): 4 (12.1) • Nirmatrelvir-ritonavir (n = 116): 6 (5.2) This outcome is not listed in the PICOS statement, but this is the only outcome reported in this study that was related to the outcomes of interest.	No interpretation regarding comparison of these treatment. Only "Failure developed in 31 patients (9.5%). Its independent predictors were older age, fewer vaccine doses, and treatment with MABs." (page 628)

AE = adverse event; ALT = alanine transaminase; ARR = absolute risk reduction; AST = aspartate aminotransferase: CI = confidence interval; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; mAB = monoclonal antibody; MD = mean difference; M-H = Mantel Haenszel; NC = no calculation; NNT = number needed to treat; NR = not reported; OR = odds ratio; RR = relative risk; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SE = standard error; ULN = upper limit of normal.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Since these additional calculations are based on unadjusted data, the resulting effect estimates will be unadjusted and interpretation must be made with caution.

[c] Not adjusted; this P value corresponds to a comparison of the 3 treatment groups remdesivir, sotrovimab and control; sotrovimab is not eligible.

[d] Although the follow-up was not clearly reported, author stated that all hospitalizations occurred within the first 10 days from COVID-19 symptom onset. As this study had 1 month and 3 month follow-up, 1 month was used for comparisons with other studies.

[e] Multivariable analyses were used to compute univariate significant variables (P < 0.05) plus biological relevant variables by linear and binary regressions (entry method). Factors adjusted: sex, immunodeficiency, number of comorbidities per patient, time from COVID-19 onset to diagnosis.

[f] Multivariable Cox proportional hazards regression model for 28-day hospital admission considering the impact of each treatment and adjusting for sex, age, number of underlying comorbidities, and number of anti-SARS-CoV-2 vaccinations performed.

[g] Cox proportional hazards regression model. Due to the low rate of events for hospitalization, proportional hazards models were adjusted solely for lung transplant status.

[h] These data are only for hospitalized patients (early remdesivir (n = 3) versus no early remdesivir (n = 56)). For the 3 hospital admissions in the remdesivir group, 2 ended with death and 1 was hospitalized for 4 days.

[i] Reported percentage of ICU admission was only from hospitalized patients; P = 0.858 reported for the comparison among hospitalized patients.

[j] Multivariable analyses were used to compute univariate significant variables (P < 0.05) plus biological relevant variables by linear and binary regressions. Factors adjusted: age, any previous SARS-CoV-2 immunity, chronic renal disease, immunodeficiency, time from COVID-19 onset to diagnosis, and number of comorbidities per patient.

[k] In patients with sequelae only (month 1: early remdesivir [n = 27] vs. no early remdesivir [n = 155]; month 3: early remdesivir [n = 21] vs. no early remdesivir [n = 108]).

[l] Multivariable analyses with factors adjusted: age, any previous SARS-CoV-2 immunity, cardiovascular disease, chronic renal disease, immunodeficiency, time from COVID-19 onset to diagnosis, and number of comorbidities per patient.