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SYSTEMATIC REVIEW

Value of Emerging and Existing Pre-prophylaxis and Therapeutic Options for COVID-19 in Transplant Recipients: A Systematic Review of Economic Evaluations

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Abstract

Background High-risk populations, including transplant recipients, are at increased risk of severe Coronavirus disease 2019 (COVID-19) outcomes. Certain treatments and pre-exposure prophylaxis (PrEP) have been approved to reduce the risk of severe illness. However, data on the cost effectiveness of currently approved COVID-19 therapeutics and preventative treatments are limited for those at high-risk of severe disease.

Objective The aim of this study was to systematically review the cost effectiveness of COVID-19 treatments and PrEP in high-risk, immunocompromised, and transplant populations.

Methods Electronic databases were searched from inception to September 2025 for studies comparing costs and effectiveness of monoclonal antibodies PrEP or COVID-19 therapeutics in high-risk, immunocompromised or transplant populations. Two reviewers independently screened studies, extracted data, and critically appraised them using the Joanna Briggs Institute checklist for economic evaluations. Cost data are presented in 2025 US dollars.

Results Of 8905 studies identified, 60 met inclusion criteria, with seven focused on or including transplant populations. Most studies were cost-utility analyses published between 2020 and 2025. Nirmatrelvir-ritonavir, tixagevimab-cilgavimab, casirivimab-imdevimab, sotrovimab, remdesivir, molnupiravir, and fluvoxamine were compared with no prophylaxis or standard of care. Among transplant populations, the incremental cost-effectiveness ratio (ICER) for tixagevimab-cilgavimab PrEP following vaccination was US$76,024 per quality-adjusted life year (QALY), while ICERs for COVID-19 therapeutics ranged from US$440 to US$126,676 per QALY.

Conclusion Cost effectiveness varied widely across studies due to differences in variant periods, population risk profiles, model assumptions, and healthcare systems. Future research should integrate variant-specific effectiveness, real-world vaccine responsiveness, long-term COVID-19 outcomes, and adverse events to better inform resource allocation for transplant and other high-risk populations.

1 Introduction

The Coronavirus Disease-19 (COVID-19) pandemic has placed an immense burden on global health systems and economies, driving substantial increases in healthcare expenditures and reductions in workforce productivity [1]. Since its emergence in December 2019 to October 2025, more than 778 million confirmed COVID-19 cases and 7.1 million COVID-19 deaths have been reported [2]. Certain populations, particularly older adults, males, and individuals with pre-existing comorbidities face a heightened risk of severe COVID-19 outcomes [3, 4]. Severe COVID-19 infections contribute to higher direct medical costs, including costs from hospitalizations, intensive care unit (ICU) admissions, and ventilation support, while also causing substantial indirect costs due to productivity losses associated with premature mortality [5–8].

Transplant recipients are at a significantly heightened risk of severe outcomes and mortality from COVID-19 due to their prolonged severe immune dysfunction or suppression

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Key Points for Decision Makers

Economic evidence for COVID-19 interventions in transplant populations remains limited but suggests that broad-acting antivirals (e.g., nirmatrelvir–ritonavir) may offer good value in high-risk or immunocompromised groups, with incremental cost-effectiveness ratios (ICERs) ranging from $440 to $126,676 per QALY gained. The ICER for Tixagevimab–cilgavimab PrEP was estimated at roughly $76,024 per QALY gained in transplant recipients, based on pre-Omicron data.

Cost-effectiveness is highly context-dependent and varies with variant susceptibility, population risk profiles, model assumptions, and jurisdiction-specific healthcare costs. Results should therefore be interpreted and adapted within local epidemiologic and policy settings.

and associated comorbidities [9–13]. For example, solid organ transplant (SOT) recipients exhibited higher risks of hospitalization, ICU admission, acute kidney injury, and mortality from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection compared with non-transplant populations [14, 15].

While COVID-19 vaccines have proven highly effective in preventing SARS-CoV-2 infection, certain populations face challenges with vaccination, including low response rates, limited uptake, or vaccine intolerance [16]. Notably, solid organ transplant recipients—regardless of vaccination status—remain at elevated risk for severe COVID-19 outcomes due to their immunocompromised state [17, 18]. As such, additional preventive and therapeutic strategies, such as monoclonal antibodies (mAbs) for treatment and pre-exposure prophylaxis (PrEP), have been introduced to protect these vulnerable populations. Despite the availability and clinical use of these interventions, there is a significant evidence gap regarding their economic value. Current literature provides limited insight into the cost effectiveness of COVID-19 therapeutics and PrEP in immunocompromised populations, particularly those with SOTs. This lack of economic evidence hinders informed decision making by payers, clinicians, and policymakers who must balance clinical benefit with resource allocation. This study aims to fill this critical gap by systematically synthesizing available evidence on the cost effectiveness of COVID-19 treatments and PrEP strategies in solid organ and hematopoietic stem cell transplant (HSCT) populations. By doing so, it seeks to inform value-based healthcare decisions, guide resource prioritization, and support the development of future economic evaluations tailored to these populations.

2 Methods

This systematic review was conducted in accordance with the process and methods recommended by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [19] (Supplemental Appendix 1, see electronic supplementary material [ESM]).

2.1 Protocol and Registration

The study protocol was pre-registered on the Open Science Framework (https://doi.org/10.17605/OSF.IO/PD2XW).

2.2 Eligibility Criteria

We included economic evaluation studies published in peer-reviewed journals or grey literature that provided cost-effectiveness measures of COVID-19 therapeutics or mAbs PrEP. The inclusion criteria for this review were as follows: studies reporting on high-risk or immunocompromised populations, including transplant recipients; studies providing clinical efficacy and cost data for COVID-19 therapeutics or prophylaxis; studies involving either adult or pediatric populations, as specified in the individual studies; and studies published in any language. The exclusion criteria included studies lacking relevant efficacy or cost data, animal or in-vitro studies, and duplicates or conference abstracts without full-text availability.

2.3 Information Sources

An experienced medical information specialist (BS) developed and tested the search strategies in consultation with the review team. Another senior information specialist peer-reviewed the MEDLINE strategy prior to execution using the PRESS Checklist [20].

We searched Ovid MEDLINE® ALL and Embase Classic + Embase, both of which include extensive preprint records, together encompassing more than 250,000 preprints at the time of our search, including over 44,000 from medRxiv. As many of these preprints were retrieved in our initial search, pilot testing demonstrated that a separate search of medRxiv identified no additional eligible studies. Because Cochrane Database of Systematic Reviews content is indexed in both MEDLINE and Embase, and CENTRAL aggregates records largely from these databases and trial registries, our chosen databases provided comprehensive coverage of relevant material while avoiding unnecessary duplication. We also searched EconLit (Ebsco) and the Web of Science (core collection). The initial searches were performed on February 4, 2024. An updated search using the same databases was carried out on September 4, 2025.

The strategies utilized a combination of controlled vocabulary and keywords (Supplemental Appendix 2, ESM). We initially conducted a transplant-focused search; however, because very few economic evaluations were identified, we performed an additional broader search that included studies of low-risk, high-risk, and immunocompromised individuals. This two-stage approach ensured that we did not miss economic evaluations reporting transplant-specific results embedded within larger mixed populations, a common feature of COVID-19 studies. There were no language or date restrictions on any of the searches.

We performed a targeted grey literature search to complement published studies and capture economic evaluations and reimbursement assessments that are often not indexed in bibliographic databases. Following the sources listed in Canada's Drug Agency (CDA-AMC)'s Grey Matters [21], we searched major health technology assessment (HTA) and economic evaluation repositories, including CDA-AMC, National Institute for Health and Care Excellence, and other national HTA agencies. We also searched Google Scholar and COVID-END [22] to identify publicly available reports with sufficient methodological detail for extraction.

2.4 Data Management

Covidence was used to manage and screen records. Data extraction was performed using Microsoft Excel, while Endnote was used for deduplication and bibliography management.

2.5 Article Selection Process

Two reviewers (AG, YP) independently screened the titles and abstracts to assess study eligibility based on the prespecified inclusion criteria. Articles deemed potentially eligible were considered in a full-text review. Discrepancies during either the title and abstract screening or the full-text review were resolved through discussion between the reviewers until a consensus was reached.

2.6 Data Extraction Process

Two reviewers (AG, AV, MB, TS, JR, CT, or MX) independently extracted data using a standardized data extraction form. Any discrepancies were discussed between the reviewers until a consensus was reached.

The extracted data included publication information, study design, study location and currency, perspective of economic evaluation, economic modeling methods, sensitivity analyses conducted, willingness-to-pay (WTP) threshold, and specifics of the therapeutics or preventative treatments (including type and dosage). We also collected data on COVID-19 severity, comparators, population characteristics, key model parameters (such as efficacy and cost), and results (total cost, total effectiveness, incremental cost-effectiveness ratios [ICERs], incremental net benefits [INBs]). Where available, information on SARS-Cov-2 variant and vaccination status were also recorded. Populations were categorized as high risk if they included older adults (60+ years), individuals who had not received all COVID-19 vaccine doses, or those living with obesity or chronic medical conditions [23]. Populations were classified as immunocompromised if they included individuals undergoing chemotherapy or radical radiotherapy, those with a history of hematological malignancy, receiving immunosuppressive or immunomodulating therapy, or individuals with a human immunodeficiency virus infection or genetic disorders affecting the immune system [24]. Studies that specifically identified transplant recipients were categorized separately, while recognizing that transplant recipients are, by definition, a subset of immunocompromised patients.

2.7 Assessment of Methodological Aspects of the Study

The methodological quality of the included studies was independently assessed by the two reviewers using the Joanna Briggs Institute (JBI) systematic review checklist for economic evaluations [25]. This tool examines key elements of study design, data sources, model structure, assumptions, and generalizability. Discrepancies between reviewers were resolved through discussion, and a third reviewer (KT) was consulted if consensus could not be reached.

2.8 Data Synthesis

We performed a narrative synthesis and presented data in tabulated form, as substantial heterogeneity in study designs, populations, interventions, comparators, and outcome measures precluded a meaningful meta-analysis. Cost estimates were converted to 2025 US dollars (US$) to allow for comparison between studies, using Internal Revenue Service yearly average exchange rates for currency conversion and the US Consumer Price Index for inflation adjustment [26, 27]. Studies were grouped by treatment type and/or population subgroup to reflect differences in clinical use and target populations. Because several included studies evaluated interventions that were relevant early in the pandemic but are no longer recommended, these were therefore grouped and discussed separately to avoid conflating historical evidence with current clinical practice. The primary outcome of interest was cost-effectiveness measures of COVID-19

therapeutics or mAbs PrEP. Total costs, total effectiveness, ICERs, and INB estimates were reported.

3 Results

3.1 Study Selection

A study flow diagram, presented in Fig. 1, outlines the review process. The initial and updated searches yielded 8905 unique articles. Screening narrowed the selection to 95 articles for full-text review. After inclusion criteria were applied and consensus was reached, 60 articles were included in the final review. Of these, seven studies specifically focused on or included the transplant population.

3.2 Study Characteristics

Table 1 summarizes the characteristics of the included studies, all of which were published between 2020 and 2025. Among studies explicitly including or focusing on transplant populations, five performed cost-utility analyses (CUA) [28–32], one performed a cost-effectiveness analysis (CEA) [33] and one performed a cost-consequence analysis (CCA) [34]. Among these studies, two were performed in the United Kingdom [30, 31], three in the Netherlands [28, 32, 33], one in Thailand [29] and one in the United States [34]. Among the studies examining populations including high-risk and immunocompromised patients, 36 were CUAs [31, 35–70], and 17 studies were CEAs [71–87]. The geographic distribution of the studies included 19 studies conducted in the United States [35–43, 47, 49, 62, 65, 67, 69, 70, 75, 77, 80], 10 in Europe [45, 48, 50, 58–60, 66, 71, 83, 84], 14 in Asia [46, 54, 56, 57, 61, 63, 64, 73, 76, 79, 82, 85–87], four in Russia [52, 53, 74, 81], two in Africa [55, 72], one in Brazil [44], two in Canada [68, 78], and one in Turkey [51] (Supplementary Figure 1, ESM).

Five studies [28, 29, 52–54] examined mAbs COVID-19 PrEP, specifically focusing on tixagevimab-cilgavimab (TIX-CIL). In contrast, 55 studies [30–51, 55–87] assessed the cost effectiveness of COVID-19 therapeutics. Among the treatments evaluated, the most studied were dexamethasone, remdesivir, baricitinib, casirivimab-imdevimab, molnupiravir, and nirmatrelvir-ritonavir. Additional COVID-19 treatments examined included tocilizumab, sotrovimab, favipiravir, lenzilumab, olokizumab, azvudine, vilobelimab, convalescent plasma, and levilimab. Details on study efficacy inputs, including prevalent COVID-19 strain at the time of each study, are presented in Supplementary Table 1 (ESM).

Among studies assessing mAbs COVID PrEP, four [28, 52–54] considered no prophylaxis as a comparator and one study [29] compared TIX-CIL with COVID-19 vaccination versus COVID-19 vaccination alone. For studies evaluating COVID-19 therapeutics, most ($n = 44$) [30–35, 37–46, 48–51, 55–57, 59, 61, 62, 64–73, 75–78, 80, 81, 83, 84] considered standard of care (SOC; best treatment available according to local guidelines and/or systemic corticosteroids) as a comparator, seven studies [36, 47, 63, 74, 79, 82, 87] compared two or more COVID-19 therapeutics, while five studies used no specific treatment [33, 58, 60, 85] or only symptomatic treatment [86] as a comparator.

Studies employed various modeling approaches to compare the costs and health outcomes of COVID-19 PrEP or treatment relative to their comparators. Twenty-two studies adopted hybrid modelling techniques [31, 32, 35, 37, 41–43, 46, 48, 52, 53, 58, 59, 61–67, 79, 83]. Fourteen studies used a decision tree model [28, 33, 34, 39, 40, 45, 47, 51, 55, 60, 68, 77, 82, 86], ten studies used a Markov model [29, 36, 38, 49, 56, 69–71, 80, 81], and three studies used compartmental models [54, 72, 76]. Eleven studies performed person-level economic evaluations without modeling [30, 57, 75, 78, 85, 87], or used other [44, 50, 73, 84] or unspecified [74, 84] modelling techniques.

In terms of study perspective, 26 studies adopted a public or private health payer perspective [28, 30, 31, 33, 35–37, 39, 41, 42, 47, 48, 51, 55, 57, 60, 62–64, 68, 73, 78, 80, 83, 85], 26 took a health system or healthcare sector perspective[29, 34, 38, 40, 43–46, 49, 50, 52–54, 58, 59, 61, 66, 69–72, 76, 77, 79, 81, 86], and two studies took a healthcare provider perspective [82, 87]. Five studies considered a societal or modified societal perspective [32, 41, 56, 65, 67], one study used a hospital perspective [75], one study considered a consumer's point of view [74], and one study did not specify a study perspective [84]. Notably, 25 studies [32, 35–37, 41–43, 47–49, 51, 58–63, 65–67, 71, 75, 79, 81, 83] (42%) were fully or partially funded by industry sponsors. Key cost-effectiveness measures from the included studies are summarized in Table 2.

3.3 Cost-Effectiveness Results of Individual Studies

Cost-effectiveness results of the included studies summarized by population groups and COVID-19 treatment types are presented in Table 2 and Supplementary Figures 2–6 (see ESM).

3.3.1 Pre-exposure Prophylaxis and Therapeutic Options in Transplant Recipients

Two studies examined the cost effectiveness of mAbs PrEP in SOT or HSCT recipients, using efficacy inputs from studies conducted during periods of Alpha, Beta, Epsilon, Gamma, and Omicron variant dominance [28, 29]. One study from Thailand reported an ICER of US$76,024/

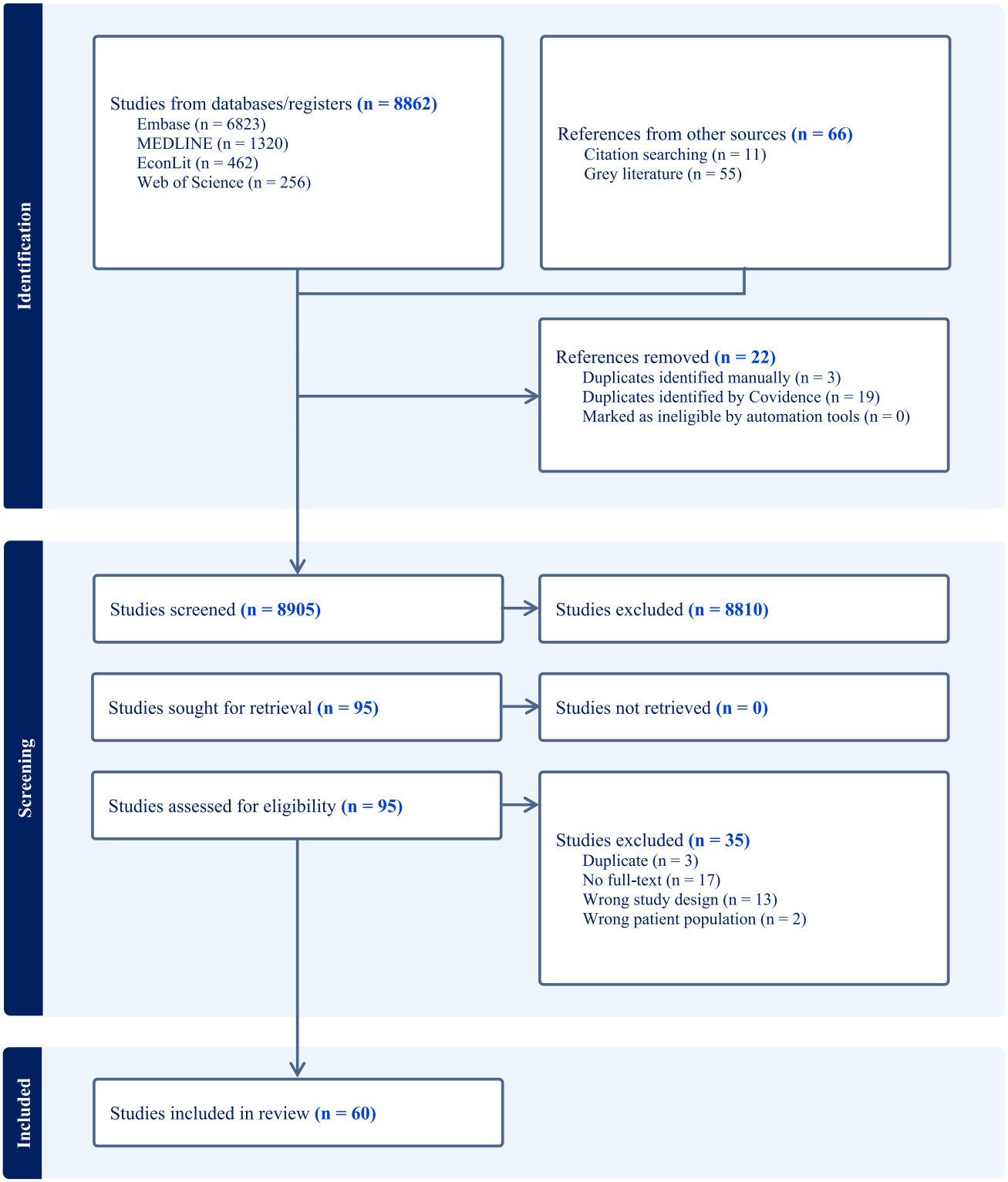

Fig. 1 PRISMA study flow diagram

Table 1 Overview of included studies

Study	Location	Type of model (time horizon)	Type of analysis	Population	Covid severity	Intervention	Comparator	Industry sponsored
Pre-exposure prophylaxis and COVID-19 therapeutics in transplant populations								
Arteaga Duarte et al. (2025) [32]	Netherlands	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised and transplant patients	Mild-moderate	NMV/r	BSC	Yes
Birnie et al. (2025) [33]	Netherlands	Decision tree (90 days)	CEA	High-risk and immunocompromised and transplant patients	Mild-moderate	NMV/r	No NMV/r	No
Metry et al. (2023) [31]	United Kingdom	Partitioned survival/area under the curve approach for hospitalised patients and decision tree for non-hospitalised patients (Lifetime)	CUA	High-risk, immunocompromised and transplants patients included	Mild-severe	TCZ NMV/r REM Sotrovimab BARI BARI/REM	SOC	No
Mills et al. (2023) [34]	USA	Decision tree (28 days)	CCA	High-risk and immunocompromised patients and transplant patients	Mild-moderate	Fluvoxamine	SOC	No
Png et al. (2024) [30]	United Kingdom	No model: within trial CUA (6 months)	CUA	High-risk, immunocompromised and transplant patients	Mild-moderate	Molnupiravir + SOC	SOC	No
Popping et al. (2023) [28]	Netherlands	Decision tree (90 days)	CUA	High-risk, immunocompromised and transplant patients	Mild-severe	CAS/IMD Sotrovimab	No prophylaxis	No
Rattanavipapong et al. (2023) [29]	Thailand	Markov (Lifetime)	CUA	Immunocompromised and transplant patients	Mild-severe	TIX/CIL + COVID-19 vaccines	COVID-19 vaccines alone	No
Pre-exposure prophylaxis in high-risk and immunocompromised populations								
Jo et al. (2023) [54]	South Korea	Age-specific, deterministic compartment epidemic (1 year)	CUA	High risk and Immunocompromised	Mild-severe	TIX/CIL	No prophylaxis	No
Zhuravleva et al. (2023) [53]	Russia	Decision tree (active phase) and Markov (long-term) (24.5 years)	CUA	High risk and immunocompromised	Mild-severe	TIX/CIL	No prophylaxis	No

Table 1 (continued)

Study	Location	Type of model (time horizon)	Type of analysis	Population	Covid severity	Intervention	Comparator	Industry sponsored
Zhuravleva et al. (2023) [52]	Russia	Decision tree (active phase) and Markov (long-term) (24.5 years)	CUA	High risk and immunocompromised	Mild-severe	TIX/CIL	No prophylaxis	No
COVID-19 therapeutics in high-risk and immunocompromised populations								
Alamer et al. (2023) [73]	Saudi Arabia	Patient simulation (5 months)	CEA	High-risk patients included	Moderate-severe	Favipiravir	SOC	No
Athanasakis et al. (2023) [48]	Greece	Decision tree and Markov (50 years)	CUA	High-risk included	Moderate-severe	REM + SOC	SOC	Yes
Azanza et al. (2025) [58]	Spain	Decision tree and Markov (Lifetime)	CUA	High-risk patients	Mild-moderate	NMV/r	No treatment	Yes
Campbell et al. (2020) [70]	USA	Markov (Lifetime)	CUA	High-risk patients included	Mild-severe	REM + SOC	SOC	Not reported
Carlson et al. (2024) [43]	USA	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised patients	Mild-moderate	NMV/r	SOC	Yes
Carta and Conversano (2021) [39]	USA	Decision tree (1 year)	CUA	High-risk patients included	Mild-moderate	DEX REM DEX/REM	SOC	No
Chow et al. (2022) [80]	USA	Markov (4 weeks)	CEA	High-risk patients included	Mild-moderate	Statin use	No statin use	No
Congly et al. (2021) [47]	USA	Decision tree (1 year)	CUA	High-risk and immunocompromised patients included	Moderate-severe	REM DEX	SOC	Yes
Dijk et al. (2022) [38]	USA	Markov (Lifetime)	CUA	High-risk and immunocompromised included	Moderate-severe	Hydroxychloroquine REM CAS/IMD DEX BARI/REM TCZ Lopinavir + ritonavir Interferon beta-1a	SOC	No
Edoka et al. (2025) [55]	Ghana, Rwanda, Zambia	Decision tree (30 days)	CUA	High-risk and immunocompromised patients and all adult patients, separately	Mild-moderate	NMV/r Molnupiravir	SOC	No

Table 1 (continued)

Study	Location	Type of model (time horizon)	Type of analysis	Population	Covid severity	Intervention	Comparator	Industry sponsored
Fernandes et al. (2023) [44]	Brazil	Individual-based state-transition microsimulation (1 year)	CUA	High risk and immunocompromised patients included	Mild-severe	NMV/r	SOC	No
Frolov et al. (2020) [81]	Russia	Markov (20 days)	CEA	High-risk patients and immunocompromised included	Moderate-severe	Tocilizumab Olokizumab Levilimumab (+ glucocorticosteroids + SOC)	SOC	Yes
Goswami et al. (2022) [42]	USA	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised patients	Mild-severe	Molnupiravir	SOC	Yes
Goswami et al. (2025) [61]	Japan	Decision tree and Markov (Lifetime)	CUA	High-risk patients	Mild-moderate	Molnupiravir	BSC	Yes
Jiang et al. (2021) [46]	China	Dynamic transmission & Markov (55 days)	CUA	High-risk patients included	Severe	REM	SOC	No
Jo et al. (2021) [72]	South Africa	Stochastic compartmental transmission (6 months)	CEA	High-risk and immunocompromised included	Mild-severe (primarily severe)	DEX/REM DEX REM	SOC	No
Jo et al. (2022) [76]	Korea	Age-specific, deterministic compartmental model (1 year)	CEA	High-risk patients and immunocompromised included (all adults) and high-risk and immunocompromised focused (adults with underlying disease and elderly)	Mild-severe	Molnupiravir NMV/r	SOC	No
Jovanoski et al. (2022) [37]	USA	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised patients included	Mild-moderate	CAS/IMD	SOC	Yes
Kelton et al. (2022) [36]	USA	Three-state pharmacoeconomic model including Markov (Lifetime)	CUA	High risk and immunocompromised included	Mild-severe	BARI/REM	Remdesivir	Yes
Kilcoyne et al. (2022) [75]	USA	No model: patient level analysis (28 days)	CEA	High-risk patients included	Severe	Lenzilumab + SOC	SOC	Yes

Table 1 (continued)

Study	Location	Type of model (time horizon)	Type of analysis	Population	Covid severity	Intervention	Comparator	Industry sponsored
Korwiwattanakan et al. (2025) [82]	Thailand	Decision tree (6 months)	CEA	High-risk and immunocompromised patients	Mild-moderate	NMV/r REM	Molnupiravir	No
Kowal and Rosettie (2025) [62]	USA	Decision tree and Markov (Lifetime)	CUA	General population	Not reported?	TCZ	SOC	Yes
Krylova et al. (2021) [74]	Russia	Model structure & time horizon not specified	CEA	High-risk patients included	Mild-severe	Favipiravir	Mild form: Umifenovir + SOC Severe form: Remdesivir	No
Lau et al. (2022) [78]	Canada	No model: patient-level data analysis Time horizon: from participant randomization to hospital discharge or death	CEA	High risk and immunocompromised patients included	Mild-severe	REM + SOC	SOC	No
Low et al. (2024) [85]	Malaysia	Real-world data (30 days)	CEA	High-risk and immunocompromised included	Mild-moderate	NMV/r	No NMV/r	No
Malone et al. (2025) [65]	USA	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised patients included	Severe	Vilobelimab + SOC	SOC	Yes
Malone et al. (2025) [67]	USA	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised patients included	Severe	Vilobelimab + SOC	SOC	Yes
Marbaix et al. (2024) [60]	Belgium	Decision tree (1 year)	CUA	High-risk patients	Mild-moderate	NMV/r REM	No specific antiSARS-CoV-2 treatment	Yes

Table 1 (continued)

Study	Location	Type of model (time horizon)	Type of analysis	Population	Covid severity	Intervention	Comparator	Industry sponsored
Rusdi et al. (2023) [87]	Indonesia	No model (April 1 to June 30, 2021)	CEA	High-risk patients included	Moderate-severe	Favipiravir + levofloxacin + azithromycin + N-acetylcysteine Favipiravir + azithromycin + N-acetylcysteine Favipiravir + levofloxacin + N-acetylcysteine Remdesivir + favipiravir + levofloxacin + azithromycin + N-acetylcysteine Remdesivir + favipiravir + levofloxacin + N-acetylcysteine	Each regimen served as an active comparator to the others in a multi-arm comparative design	No
Mizuno et al. (2024) [64]	Japan	Decision tree and Markov (Lifetime)	CUA	High-risk patients included	Mild-moderate	NMV/r	BSC	No
Moreno et al. (2025) [66]	Italy	Decision tree and Markov (Lifetime)	CUA	High-risk patients included	Mild-moderate	NMV/r	SOC	Yes
Nilsson et al. (2025) [59]	Sweden	Decision tree and Markov (Lifetime)	CUA	High-risk and immunocompromised patients	Mild-moderate	NMV/r	BSC	Yes
Ohsfeldt et al. (2021) [35]	USA	Algebraic and Markov (Lifetime)	CUA	High-risk patients included	Mild-severe	BARI + SOC	SOC	Yes
Oksuz et al. (2021) [51]	Turkey	Decision tree (COVID-19 episode)	CUA	High-risk and immunocompromised included	Mild-severe	REM + SOC	SOC	Yes
Park et al. (2022) [57]	Singapore	No model Time horizon: N/A	CUA	High-risk and immunocompromised patients included	Mild-severe	CAS/IMD	SOC	No
Pietrantonio et al. (2024) [84]	Italy	Model: not described (1 year)	CEA	High-risk and immunocompromised patients	Mild-moderate	Molnupiravir	SOC	No
Rafia et al. (2022) [50]	England and Wales	Partitioned survival (Lifetime)	CUA	High-risk patients included	Moderate-severe	REM + SOC	SOC	No
Ruggeri et al. (2023) [71]	Italy	Markov (20 weeks)	CEA	High-risk patients included	Mild-moderate	CAS/IMD	SOC	Yes

Table 1 (continued)

Study	Location	Type of model (time horizon)	Type of analysis	Population	Covid severity	Intervention	Comparator	Industry sponsored
Savinkina et al. (2022) [77]	USA	Decision tree (30 days)	CEA	High-risk and immunocompromised patients included	Mild-moderate	NMV/r	SOC	No
Schmalhofer et al. (2025) [83]	Germany	Decision tree and Markov (Lifetime)	CEA	High-risk and immunocompromised patients	Mild-moderate	NMV/r	BSC	Yes
Sheinson et al. (2021) [41]	USA	Decision tree and Markov model (Lifetime)	CUA	High-risk and immunocompromised patients included	Mild-severe	DEX/REM	SOC	Yes
Sinha and Linas (2021) [40]	USA	Decision tree (Lifetime)	CUA	High-risk and immunocompromised patients included	Severe	DEX DEX/TCZ	SOC	No
Subhi et al. (2023) [79]	United Arab Emirates	Decision tree and Markov (1 year)	CEA	High-risk patients included	Mild-severe	REM + SOC	Favipiravir + SOC SOC alone	Yes
Tse et al. (2024) [68]	Canada, USA, Brazil	Decision tree (30 days)	CUA	High-risk and immunocompromised patients	Moderate-severe	Convalescent plasma	SOC	No
Whittington et al. (2022) [49]	USA	Markov (Lifetime)	CUA	High-risk patients included	Mild-severe	REM + SOC	SOC	Yes
Wikman-Jorgensen et al. (2023) [45]	Spain	Decision tree (Lifetime)	CUA	High-risk patients	Mild-moderate	NMV/r	SOC	No
Yang et al. (2024) [86]	China	Decision tree (28 days)	CEA	High-risk and immunocompromised patients	Mild-moderate	Azvudine	Only symptomatic treatment	No
Yeung et al. (2022) [69]	USA	Markov (Lifetime)	CUA	High-risk patients included	Mild-Moderate	Sotrovimab Molnupiravir Paxlovid Fluvoxamine	SOC	No
Yuasa et al. (2025) [63]	Japan	Decision tree and Markov (Lifetime)	CUA	High-risk patients	Mild-moderate	NMV/r	Molnupiravir	Yes
Zhang et al. (2023) [56]	China	Markov (5 months)	CUA	High-risk and immunocompromised patients included	Mild-Moderate	NMV/r	SOC	No

BARI baricitinib, *BARI/REM* baricitinib + remdesivir, *BSC* best supportive care, *CAS/IMD* casirivimab + imdevimab, *CCA* cost-consequence analysis, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *DEX* dexamethasone, *NMV/r* nirmatrelvir + ritonavir, *REM* remdesivir, *SOC* standard of care, *TCZ* tocilizumab, *TIX/CIL* tixagevimab + cilgavimab

Table 2 Summary of cost-effectiveness results

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Pre-exposure prophylaxis and COVID-19 therapeutics in transplant populations								
Arteaga Duarte et al. (2025) [32]	NMV/r	BSC	Dutch societal perspective	Immunocompromised: $55 Aged 60+ with comorbidity: $530 Aged 70+: $771	Immunocompromised: 0.125 Aged 60+ with comorbidity: 0.054 Aged 70+: 0.053	Immunocompromised: $440/QALY Aged 60+ with comorbidity: $9815/QALY Aged 70+: $14,547/QALY	**Key drivers:** Baseline hospitalization risk, treatment effectiveness on reducing the risk of hospitalization, treatment acquisition cost **Scenario analyses:** Considering a health care perspective only also yielded favorable cost-effectiveness results for NMV/r compared with BSC alone across all groups analyzed, although ICER values were higher than in the base-case analysis	**WTP**: €20,000 Immunocompromised: 100% Aged 60+ with comorbidity: 94% Aged 70+: 85%
Metry et al. (2023) [31]	REM	SOC	NHS and Personal Social Services	People who require supplemental oxygen on admission to hospital: $7707 People who do not require supplemental oxygen on admission to hospital: $3763 People at high risk of hospitalisation: $4555	People who require supplemental oxygen on admission to hospital: 0.47 People who do not require supplemental oxygen on admission to hospital: 0.28 People at high risk of hospitalisation: 0.04	People who require supplemental oxygen on admission to hospital: $16,398/QALY People who do not require supplemental oxygen on admission to hospital: 13,439/QALY People at high risk of hospitalisation: $113,875/QALY	**Key drivers:** Efficacy of intervention, proportion of high-risk patients in the community that needed hospitalisation **Scenario analyses:** In the mean and high efficacy scenarios using data from Solidarity trial, remdesivir had a positive NMB regardless of the WTP and oxygen status assumed. In the low efficacy scenario, remdesivir had a positive NMB regardless of the WTP and oxygen status assumed if Solidarity trial data and the HR for time to discharge from ACTT-1 were used	Not reported
Png et al. (2024) [30]	Molnupiravir + SOC	SOC	UK NHS and Personal Social Services	$719.43	0.0055	$130,805/QALY	**Key drivers:** Admitted patient care, critical care, accident & emergency **Scenario analyses:** Finding was robust to all sensitivity and subgroup analyses, except for those aged ≥ 75 y that had a 55% probability of being cost effective	**WTP:** £15,000, 20,000, and 30,000, <0.001%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Rattanavipapong et al. (2023) [29]	TIX/CIL + COVID-19 vaccines	COVID-19 vaccines alone	Thailand healthcare system	Renal dialysis patients: $1,048,818 Organ transplant patients: $6,081,928 Autoimmune disease patients: $259,279,911	Renal dialysis patients: 753 Organ transplant patients: 80 Autoimmune disease patients: 558	Renal dialysis patients: $1393/QALY Organ transplant patients: $76,024/QALY Autoimmune disease patients: $464,659/QALY	**Key drivers:** Renal dialysis patients: Probability of COVID-19 infection, cost of Evusheld, proportion of patients with inadequate anti-S titres Organ transplant patients: Probability of death from severe COVID-19 infection, probability of progression to severe infection, probability of COVID-19 infection Autoimmune disease patients: Probability of COVID-19 infection, cost of Evusheld, probability of death from severe COVID-19 infection **Scenario analyses:** None	**WTP**: 160,000 THB/QALY: 0–48% (renal dialysis patients), 0–15% (organ transplant patients), 0% (autoimmune disease patients)
Pre-exposure prophylaxis in high-risk and immunocompromised populations								
Jo et al. (2023) [54]	TIX/CIL	No prophylaxis	Korean healthcare system	Vaccinated-immunocompromised: $7,252,235,156 Unvaccinated-immunocompromised: $34,169,258 Severe allergic reaction: $60,745,347 Unvaccinated high-risk elderly: $3,271,136,954	Vaccinated-immunocompromised: 118,843 Unvaccinated-immunocompromised: 1365 Severe allergic reaction: 994 Unvaccinated high-risk elderly: 103,916	Vaccinated-immunocompromised: $61,024/QALY Unvaccinated-immunocompromised: $25,032/QALY Severe allergic reaction: $61,112/QALY Unvaccinated high-risk elderly: $31,479/QALY	**Key drivers:** Vaccinated-immunocompromised: Remaining life years due to COVID-19 premature death, case fatality from COVID-19 infection, Evusheld efficacy to reduce symptomatic disease Unvaccinated-immunocompromised: Remaining life years due to COVID-19 premature death, case fatality from COVID-19 infection, Evusheld efficacy to reduce symptomatic disease Severe allergic: Evusheld efficacy to reduce symptomatic disease, percentage of severe symptomatic COVID-19 patients, Evusheld intervention cost Unvaccinated high-risk elderly: Evusheld efficacy to reduce symptomatic disease, disability weight with existing risk conditions, percentage of severe symptomatic COVID-19 patients **Scenario analyses:** Epidemic scenarios with low and high intervention efficacy estimates increased and decreased ICER estimates, respectively	**WTP:** $100,000/QALY, 67% for vaccinated immunocompromised patients, ~87% for unvaccinated immunocompromised patients, and ~99% for severe allergic reaction and unvaccinated high-risk elderly patients

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Zhuravleva et al. (2023) [53]	TIX/CIL	No prophylaxis	Russian healthcare system	$898	0.2255	$3982/QALY	None performed	Not reported
Zhuravleva et al. (2023) [52]	TIX/CIL	No prophylaxis	Russian healthcare system	$474	0.0247	$19,190/QALY	None performed	Not reported
COVID-19 therapeutics in high-risk and immunocompromised populations								
Athanasakis et al. (2023) [48]	REM + SOC	SOC	Greek third-party payer	− $5437	1.11	Dominant	**Key drivers:** Percentage of patients in both scenarios who were initially hospitalized in a general ward and at day 15 they were discharged, the number of REM vials per treatment course **Scenario analyses:** None	**WTP:** €30,000/QALY, 95.4%
Azanza et al. (2025) [58]	NMV/r	No treatment	Spanish National Health System	− $189.46	0.05	Dominant	**Key drivers:** Variations in the parameters analyzed in the OWSA did not influence the dominance results **Scenario analyses:** Assessed (1) the robustness of results using real-world effectiveness data for NMV/r from Lewnard et al., reflecting Omicron infections and vaccinated populations, and (2) the impact of varying the age-based high-risk proxy from ≥ 70 to ≥ 60 years on outcomes. In both scenarios, NMV/r remained dominant compared with no treatment	**WTP**: €25,000, 100%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Campbell et al. (2020) [70]	REM + SOC	SOC	Health system	Moderate-severe Covid-19: $2291 Mild Covid-19: $3442	Moderate-severe Covid-19: 0.006 Mild Covid-19: 0.001	Moderate-severe Covid-19: $381,833/QALY Mild Covid-19: $3,442,000/QALY	**Key drivers:** Not reported **Scenario analyses:** 1. Remdesivir effect based on SOLIDARITY trial: - Assumes no benefit of remdesivir on mortality, time to recovery, or length of stay - Zero value in both mild and moderate-to-severe populations 2. Hospitalization reimbursed per diem: - Assumes hospital payments are calculated per day rather than as a bundled per-stay cost - Allows estimation of the average daily hospital price required to offset remdesivir's cost - Moderate-to-severe: hospital day cost ≥ $800 needed to offset price; Mild: no cost offsets expected	Not reported
Carlson et al. (2024) [43]	NMV/r	SOC	US health sector	$358	0.030	$11,933/QALY	**Key drivers:** NMV/R reduction in hospitalization, baseline risk of hospitalization, proportion of hospitalizations that result in ICU **Scenarios analyses:** NMV/r treatment was cost effective under several alternative assumptions including post-COVID-19 conditions, outpatient healthcare resource use, different utility values, and societal perspective costs. When including the effects of all 3 scenarios, NMV/r treatment was dominant to SOC	**WTP:** $50,000/QALY, 98%; $100,000/QALY, 99%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Carta and Conversano (2021) [39]	DEX REM DEX/REM	SOC	US healthcare payer	DEX: $225 REM: − $1229 DEX/REM: − $1003	DEX: 0.0357 REM: 0.0061 DEX/REM: 0.00417	DEX: $6303/QALY REM: Dominant DEX/REM: Dominant	**Key drivers:** Dexamethasone: Follow up costs, hazard mortality ratio (HMR) for ventilated patients, HMR for non-ventilated patients Remdesivir: Rate ratio for time to recovery, cost of remdesivir, total cost of being in ECMO Dexamethasone + remdesivir: Rate ratio for time to recovery, cost of remdesivir, total cost of being in ECMO **Scenario analyses:** ICERs were dominant in scenarios assuming a mortality benefit for remdesivir and where hospital costs were the only cost per day	**WTP:** $50,000, ~83% (DEX/REM), ~14% (DEX), 0% (REM)
Congly et al. (2021) [47]	REM DEX	SOC	US healthcare payer	All: DEX: $24 REM: $3184 Severe: DEX: $4 REM: $778	All: DEX: 0.0196 REM: 0.0035 Severe: DEX: 0.0101 REM: 0.0055	All: DEX: $1224/QALY REM: $909,714/QALY Severe: DEX: $375/QALY REM: $141,455/QALY	**Key drivers:** Risk reduction of dexamethasone for moderate COVID-19 infection, risk reduction of remdesivir for moderate COVID-19 infection **Scenario analyses:** ICER findings were unchanged in scenarios where all patients were assumed to be admitted to the ICU, and in which hospital costs were reduced by 60% to try and extrapolate these findings outside of the USA	**WTP:** $100,000, 98.3% (DEX for all patients), 0.007% (DEX for severe only), 1.7% (REM in moderate and DEX in severe), 0.001% (REM for moderate)
Dijk et al. (2022) [38]	Hydroxychloroquine REM CAS/IMD DEX BARI/REM TCZ Lopinavir + ritonavir Interferon β−1a	SOC	US healthcare sector	CAS/IMD: $842 REM: − $6 DEX: $8292 BARI/REM: $12,909 TCZ: $43,358 Interferon-β1a: − $3070 Lopinavir-ritonavir: − $1698 Hydroxychloroquine: − $20,126	CAS/IMD: 0.171 REM: 0.252 DEX: 0.614 BARI/REM: 0.775 TCZ: 0.882 Interferon-β1a: − 0.472 Lopinavir-ritonavir: − 0.091 Hydroxychloroquine: − 0.263	CAS/IMD: $4924/QALY REM: Dominant DEX: $13,505/QALY BARI/REM: $16,657/QALY TCZ: $49,159/QALY Interferon-β1a: $6504/QALY Lopinavir-ritonavir: $18,659/QALY Hydroxychloroquine: $76,525/QALY	**Key drivers:** Treatment costs, healthcare costs, decreased survival **Scenario analyses:** None	**WTP:** $100,000/QALY, ~99% (BARI/REM), ~77% (CAS/IMD), ~99% (DEX), ~25% (hydroxychloroquine), 0% (Interferon-β1a), ~37% (Lopinavir-ritonavir), ~85% (REM), ~80% (TCZ)

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Fernandes et al. (2023) [44]	NMV/r	SOC	Brazilian public health system	$257	0.009	$28,552/QALY	**Key drivers:** RR of the vaccinated population, cost of NMV-r, baseline utility **Scenario analyses:** In the scenario considering the population aged >60 y or immunocompromised, 100% of simulations were less than the WTP, indicating that NMV/r treatment could be considered cost effective for this subpopulation	**WTP:** $24,000/QALY, 4%
Goswami et al. (2022) [42]	Molnupiravir	SOC	US healthcare payer	− $978	0.21	Dominant	**Key drivers:** Treatment effect of hospitalization reduction by molnupiravir, treatment effect of molnupiravir relative risk of mechanical ventilation, mortality rate in the highest hospital setting (among patients not treated with molnupiravir) **Scenario analyses:** ICERs remained dominant in all scenarios, including subgroups; alternative health state utility values; exclusion of long-term sequelae and readmissions; alternative patient characteristics and baseline risks; alternative patient characteristics, baseline risks, and cost; inclusion of productivity loss among inpatients or symptomatic outpatients	**WTP:** $100,000/QALY, 100%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Goswami et al. 2025 [61]	Molnupiravir	BSC	Japanese healthcare sector	$690	0.018	$38,333/QALY	**Key drivers:** Baseline hospitalization rate, mortality benefit of molnupiravir, mortality rate in general ward **Scenario analyses:** Molnupiravir remained cost effective vs best supportive care across scenario analyses excluding long-term sequelae and readmissions, applying 5-, 10-, and 15-year time horizons, adopting a societal perspective, and using alternative quality-of-life parameters from published sources, confirming the robustness of the findings within the predefined WTP threshold	**WTP** ¥5,000,000, 80%
Jiang et al. (2021) [46]	REM	SOC	Chinese healthcare system	$14,455,748	6947	$2081/QALY	**Key drivers:** RR of clinical improvement, remdesivir 5-day regimen costs, r: fraction practicing strict physical distancing **Scenario analyses:** ICER results were robust in alternative epidemic scenarios where r (fraction moving into social distancing) was changed to 20% and 5 times of its original values	**WTP:** CN¥ 70,892/QALY, 98%
Kelton et al. (2022) [36]	BARI/REM	REM	US healthcare payer perspective	All hospitalized patients: $8260 Oxygen use subgroup: $9295	All hospitalized patients: 0.3565 Oxygen use subgroup: 0.4107	All hospitalized patients: $23,170/QALY Oxygen use subgroup: $22,632/QALY	**Key drivers:** Incidence of new mechanical ventilation in the REM treatment arm, average annual medical costs for patients that recover from COVID-19 hospitalization, variations in percentage recovery from supplemental oxygen, non-mechanical and mechanical ventilation in the BARI-REM treatment arms **Scenario analyses:** ICERs were robust in scenarios adding a survival benefit to dexamethasone in the SOC treatment arm. Dominance occurred when there was no survival benefit with BARI-REM	Not reported

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Kowal and Rosettie (2025) [62]	TCZ	SOC	US health payer (Medicare)	$11,386	0.22	$51,755	**Key drivers:** Not reported **Scenario analyses:** Tested alternative opportunity cost thresholds and assumptions about how opportunity costs and social vulnerability risks were distributed, as well as varying tocilizumab use among high-risk subgroups, showing that net health and social welfare gains remained robust across all scenarios, with the greatest improvements observed when higher social vulnerability index-related risks and targeted increases in tocilizumab use for the least healthy populations were assumed	Not reported
Malone et al. (2025) [65]	Vilobelimab + SOC	SOC	Modified societal perspective	$30,657	1.29	$23,765/QALY	**Key drivers:** Survival probability at day 60 with SOC, survival probability at day 60 with vilobelimab + SOC, age **Scenario analyses:** Compared with the base-case ICER of $22,287/QALY, the worst-case scenario (lower survival bound) increased the ICER to $66,058/QALY, whereas the best-case scenario (upper survival bound) reduced it to $12,641/QALY, demonstrating sensitivity of cost effectiveness to survival assumptions	**WTP:** $50,000/QALY, 81%
Malone et al. (2025) [67]	Vilobelimab + SOC	SOC	Modified societal perspective	$30,657	3.65	$8300/QALY	**Key drivers:** Survival probability at day 60 with vilobelimab, age, survival probability at day 60 with SOC **Scenario analyses:** Varied survival probabilities for vilobelimab and SOC. When vilobelimab's survival benefit was reduced (worst case), the ICER increased to by 129%, while when SoC survival was lower (best case), the ICER decreased by 36%	**WTP:** $50,000, 98%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Marbaix et al. (2024) [60]	NMV/r REM	No specific anti-SARS-CoV-2 treatment	Belgian healthcare payer perspective	NMV/r: − $95 REM: $1237	NMV/r: 0.097 REM: 0.083	NMV/r: Dominant REM: $14,899/QALY	**Key drivers:** Treatment effectiveness on reducing the risk of hospitalizations, general ward cost per day, general ward length of stay **Scenario analyses:** Scenario analyses showed that even when excluding long covid benefits, nirmatrelvir/ritonavir remained cost-saving, and that lower vaccination rates among older adults further increased both cost savings and QALY gains	**WTP:** €2000, 100% (NMV/r)
Metry et al. (2023) [31]	TCZ NMV/r Sotrovimab BARI BARI/REM	SOC or placebo	NHS and Personal Social Services	People who require supplemental oxygen on admission to hospital: TCZ: $4674 BARI: $11,051 BARI/REM: $11,450 People who do not require supplemental oxygen on admission to hospital: BARI: $3763 BARI/REM: $5724 People at high risk of hospitalisation: NMV/r: $1026 Sotrovimab: $3449	People who require supplemental oxygen on admission to hospital: TCZ: 0.51 BARI: 0.85 BARI/REM: 0.71 People who do not require supplemental oxygen on admission to hospital: BARI: 0.5 BARI/REM: 0.42 People at high risk of hospitalisation: NMV/r: 0.12 Sotrovimab: 0.07	People who require supplemental oxygen on admission to hospital: TCZ: $9165/QALY BARI: $13,001/QALY BARI/REM: $16,128/QALY People who do not require supplemental oxygen on admission to hospital: BARI: $7526/QALY BARI/REM: $13,629/QALY People at high risk of hospitalisation: NMV/r: $8550/QALY Sotrovimab: $49,271/QALY	**Key drivers:** Efficacy of intervention, proportion of high-risk patients in the community that needed hospitalisation **Scenario analyses:** The use of 5-day outcome measures for TIX/CIL increased total discounted QALYs in all efficacy scenarios	Not reported
Mizuno et al. (2024) [64]	NMV/r	BSC	Japanese public healthcare payer	Age 40: $624 Age 50: $653 Age 60: $719 Age 70: $977 Age 80: $1916	Age 40: 0.005 Age 50: 0.01 Age 60: 0.019 Age 70: 0.049 Age 80: 0.157	Age 40: $124,800/QALY Age 50: $65,300/QALY Age 60: $37,842/QALY Age 70: $19,939/QALY Age 80: $13,204/QALY	**Key drivers:** Mortality risk during the treatment phase, relative mortality risk with NMV/r **Scenario analyses:** Including a reduction in long-COVID risk in the scenario analysis lowered ICERs for all age groups compared with the base case, indicating improved cost effectiveness of NMV/r, with the greatest absolute impact seen in younger patients	**WTP:** 5 million JPY/QALY: Age 40: 0% Age 50: 0.2% Age 60: 45.4% Age 70: 99.9% Age 80: 100%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Moreno et al. (2025) [66]	NMV/r	SOC	Italian National Health Service perspective	$1152	0.46	$2503/QALY	**Key drivers:** Paxlovid reduction in hospitalizations, proportion of high-risk hospital patients (vaccinated), baseline utility **Scenario analyses:** None	**WTP:** €33,004, 100%
Nilsson et al. (2025) [59]	NMV/r	BSC	Healthcare perspective	$687	0.023	$29,870/QALY	**Key drivers:** Treatment effectiveness on reducing the risk of hospitalizations, general ward cost per day, general ward length of stay **Scenario analyses:** Ran scenarios for different subgroups based on age and vaccination status. The ICERs for different patient profiles show significant variation. Treatment with NMV/r was generally cost effective across most subgroups, except for recently vaccinated patients aged 70–79 y without comorbidities and those <40 y regardless of vaccination or comorbidity status, with cost effectiveness varying by age, vaccination status, and comorbidity burden	Not reported
Ohsfeldt et al. (2021) [35]	BARI + SOC	SOC	US healthcare payer perspective	$20,892	0.6703	$31,168/QALY	**Key drivers:** Annual medical costs, post-hospitalization cost multiplier for patients with severe comorbidities, progression to mechanical ventilation during the inpatient stay **Scenario analyses:** When the only difference in treatment effects between baricitinib + SOC and SOC was the probability of recovery (mortality-only scenario), the ICER increased	**WTP:** $50,000, 96.5%
Oksuz et al. (2021) [51]	REM + SOC	SOC	Turkey healthcare payer	− $93	0.174	Dominant	None conducted	**WTP:** (3x GDP/capita for Turkey) $25,797/QALY, 90%

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Rafia et al. (2022) [50]	REM + SOC	SOC	Health service	$4593	0.27	$17,011/QALY	**Key drivers:** Additional decrement in utility associated with comorbidities included in this analysis, age, odds ratio of invasive ventilation **Scenario analyses:** ICERs were affected the most by the treatment effect for OS, list price for REM, the model time horizon, the baseline curve for SoC, and inclusion of unrelated costs	**WTP:** £20,000/QALY, 74%
Sheinson et al. (2021) [41]	DEX/REM	SOC	US health payer, societal, and fee-for-service (FFS)	Bundled payment: $12,127 FFS payment: $15,228	0.433	Bundled payment: $28,007/QALY FFS: $35,169/QALY	**Key drivers:** Exact reimbursement values for bundled care, impact of provider-level practice patterns on LOS and other key hospital outcomes, change in total market and nonmarket productivity over time **Scenario analyses:** Removing the LOS benefit led to marginal increases in the ICER from the health payer perspective, whereas the ICER from the FFS perspective increased by about $10,000 dollars. Removing both LOS and reduced use of mechanical ventilation from the treatment profile results in marginal increases in ICERs across all perspectives	**WTP**: $100,000 and $150,000/QALY, 99%
Sinha and Linas (2021) [40]	DEX DEX/TCZ	SOC	US healthcare system	DEX: $2109 DEX/TCZ: $12,568	DEX: 0.23 DEX/TCZ: 0.7	DEX: $9170/QALY DEX/TCZ: $17,954/QALY	**Key drivers:** Age, mortality associated with DEX, cost of TCZ **Scenario analyses:** ICER results robust to use of lower relative risks for death in supportive care group	**WTP:** $100,000/QALY, >98% (DEX/TCZ)

Table 2 (continued)

Study	Treatment	Comparator	Perspective of analysis	Incremental costs (USD, 2025)	Incremental QALYs	ICER (2025 USD/QALY)	Results of uncertainty analysis	Probability cost effective
Whittington et al. (2022) [49]	REM + SOC	SOC	US healthcare sector	Moderate-severe: $4824 Mild: $3321	Moderate-severe: 0.006 Mild: 0.001	Moderate-severe: $804,000/QALY Mild: $3,321,000	**Key drivers:** Survival benefit associated with remdesivir, probability of death among SOC-treated patients, amount paid for COVID-19 hospitalization **Scenario analyses:** Cost-effectiveness findings were sensitive to changes in the risk of death among SOC-treated patients, incorporating a survival benefit associated with remdesivir, and assuming a per-diem reimbursement structure in lieu of the bundled payment approach	Not reported
Wikman-Jorgensen et al. (2023) [45]	NMV/r	SOC	Spanish health system service provider	$100,239,734	620.89	$161,445/QALY	**Key drivers:** Probability of death, probability of hospitalization, price **Scenario analyses**: None	**WTP:** one time the GDP per capita of Spain in 2022/QALY, 0%
Yeung et al. (2022) [69]	Sotrovimab Molnupiravir NMV/r Fluvoxamine	SOC	Healthcare sector	Sotrovimab: $3467 Molnupiravir: $956 NMV/r: $836 Fluvoxamine: $120	Sotrovimab: 0.0432 Molnupiravir: 0.0143 NMV/r: 0.042 Fluvoxamine: 0.0153	Sotrovimab: $80,255/QALY Molnupiravir: $66,853/QALY NMV/r: $19,905/QALY Fluvoxamine: $7843/QALY	**Key drivers:** Relative risk of hospitalization, probability of hospitalization among usual care, cost of hospitalization **Scenario analyses:** 1. Modified societal perspective (productivity gains/losses and ICU capacity). Threshold prices were higher in the societal perspective as compared to the health care perspective 2. Unvaccinated population only: cost-effectiveness estimates were slightly more favorable than the base-case estimates that included vaccinated individuals 3. Lower probability of hospitalization: cost-effectiveness estimates were less favorable for the base-case estimates, but remained lower than $100,000/QALY	**WTP:** $100,000/QALY Sotrovimab: 72% Molnupiravir: 73% NMV/r: 100% Fluvoxamine: 100%

BARI baricitinib, *BARI/REM* baricitinib + remdesivir, *BSC* best supportive care, *CAS/IMD* casirivimab + imdevimab, *DEX* dexamethasone, *ECMO* extracorporeal membrane oxygenation, *FFS* fee-for-service, *GDP* gross domestic product, *HR* hazard ratio, *ICER* incremental cost-effectiveness ratio, *ICU* intensive care unit, *LOS* length of stay, *NHS* National Health Service, *NMB* net monetary benefit, *NMV/r* nirmatrelvir + ritonavir, *OS* overall survival, *QALY* quality-adjusted life year, *REM* remdesivir, *RR* relative risk, *SOC* standard of care, *TCZ* tocilizumab, *THB* Thai Baht, *TIX/CIL* tixagevimab + cilgavimab, *USD* US dollars, *WTP* willingness to pay

QALY over a lifetime horizon for TIX-CIL PrEP following COVID-19 vaccination compared with vaccination alone in organ transplant recipients [29]. In this study, the probability that TIX-CIL following COVID-19 vaccination was cost effective was 0–15% at a WTP of US$5028/QALY. Another study from the Netherlands, using a 90-day time horizon, found that TIX-CIL could be cost effective for high-risk, immunocompromised individuals, including SOT and HSCT recipients, who have a high probability of SARS-CoV-2 infection. This cost effectiveness was observed at a drug price of US$285 and a minimum effectiveness of 75% in reducing hospital (ward and ICU) admissions and death [28]. Five studies examined the cost effectiveness of antiviral therapies for COVID-19 in transplant populations (Fig. 2). A UK study reported ICERs for remdesivir compared with SOC over a lifetime horizon, ranging from US$13,439/QALY for patients who were admitted to the hospital but did not require supplemental oxygen to US$113,875/QALY for those at high risk of hospitalization [31]. Another UK study with a 6-month time horizon evaluated the cost effectiveness of molnupiravir combined with SOC for high-risk, immunocompromised, and transplant patients during the Delta and Omicron variant dominance. The study reported an ICER of US$130,805/QALY [30]; however, the probabilities of this treatment being cost effective was <0.001% at WTP thresholds ranging from US$24,034 to US$48,068/QALY. In the US, treating high-risk, immunocompromised and transplant patients with fluvoxamine was shown to reduce costs and avoid hospital days over a 28-day time horizon as compared with SOC, using efficacy inputs from the Gamma, Delta, and Omicron variant periods [34]. The cost effectiveness of nirmatrelvir/ritonavir (NMV/r) in transplant and immunocompromised populations was assessed during the Delta and Omicron variant dominance. One study conducted in the Netherlands reported an ICER of US$440/QALY for NMV/r versus best supportive care among an immunocompromised subgroup, including patients with serious immune disorders, many of whom were solid organ or stem cell transplantation recipients [32]. In a Dutch evaluation of high-risk individuals, 17% of whom were SOT or HSCT recipients, NMV/r was unlikely to be cost effective during periods of low variant severity [33]. Key drivers of the cost effectiveness of mAbs PrEP and therapeutic options in transplant recipients include intervention efficacy, the probabilities of COVID-19 infection, hospitalization, progression to severe infection and death from severe infection, treatment acquisition costs, and the costs of inpatient and critical care.

3.3.2 Pre-exposure Prophylaxis in High-Risk and Immunocompromised Populations

Four studies assessed the cost effectiveness of TIX-CIL as PrEP, either alone or administered within weeks of a COVID-19 vaccine booster. While more effective, TIX-CIL was also more costly compared with no prophylaxis or vaccines alone [29, 52–54], with ICERs ranging widely based on population, time horizon, and context. In Thailand, ICERs for vaccinated populations ranged from US$1393/QALY in renal dialysis to US$464,659/QALY in autoimmune patients [29]. Comparisons with no prophylaxis were associated with ICERs of US$3982/QALY [53] to US$61,112/QALY [54] in high-risk and immunocompromised populations in Russia and South Korea. Cost-effectiveness estimates of mAbs PrEP in high-risk and immunocompromised populations depended on the prevalence of COVID-19 variants, with lower ICERs observed during delta variant prevalence. Key drivers of cost-effectiveness results included infection risk, severe COVID-19 mortality rates, cost, and mAbs efficacy.

3.3.3 Antiviral Therapeutics in High-Risk and Immunocompromised Populations

The cost effectiveness of antiviral therapeutics for high-risk and immunocompromised populations varied across studies, with results influenced by treatment efficacy, disease severity, and healthcare costs.

Remdesivir showed a wide range of cost-effectiveness findings. It was dominant compared with SOC over 1-year and lifetime horizons in US studies [38, 39]. ICERs ranged from dominant [82] to US$3,442,000/QALY [70], depending on the population, study location, time horizon, comparator, and COVID-19 severity. Remdesivir in combination with SOC was also dominant to SOC in two studies conducted in Greece and Turkey examining the active disease phase [48, 51]. Other studies reported ICERs of US$17,012 [50] to US$2,312,043/QALY [49] over lifetime horizons. Higher ICERs were reported in high-risk populations with mild COVID-19. Studies also demonstrated the cost effectiveness of remdesivir compared with SOC [72, 78, 79, 82]. In CEA studies, remdesivir was dominant in hospitalized and non-ventilated patients, leading to reduced costs and better outcomes than SOC and favipiravir in South Africa, Canada, and the United Arab Emirates (UAE) [72, 78, 79]. Prevalent SARS-CoV-2 variants varied between studies but were primarily wild type and Alpha. Cost effectiveness was demonstrated across wild-type, Alpha, and Omicron-dominant periods. ICERs of NMV/r ranged from dominant in Africa and Spain [55, 58] to US$161,445/QALY [45] in another Spanish study, compared with SOC over a lifetime horizon. It was cost effective for adults aged 80+ years and unvaccinated individuals but not cost effective for those aged 18–79 years over a 5-month time horizon in China, regardless of vaccination status [56]. In unvaccinated African populations with mild-moderate COVID-19, ICERs ranged from dominant to US$28,901/disability-adjusted life year (DALY) averted over 30 days, varying by country

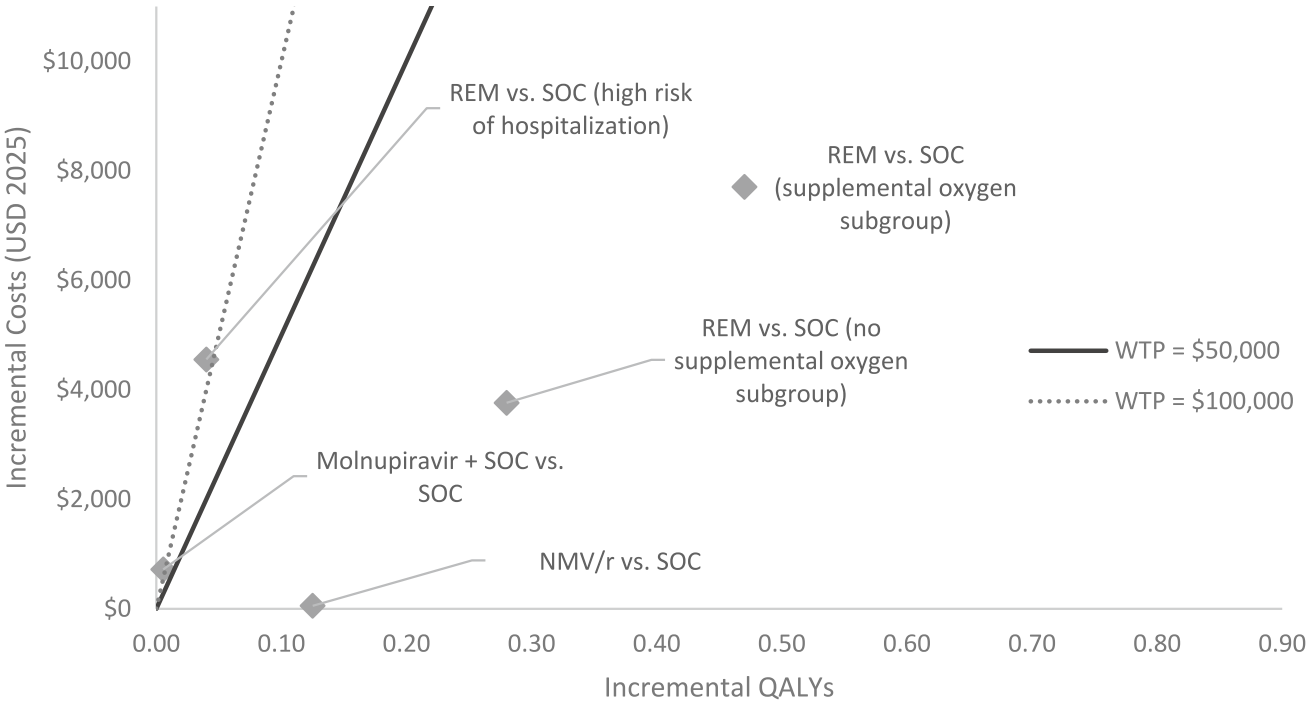

Fig. 2 Cost effectiveness of COVID-19 therapeutics among transplant populations. *NMV/r* nirmatrelvir/ritonavir, *QALY* quality-adjusted life year, *REM* remdesivir, *SOC* standard of care, *WTP* willingness to pay

and hospitalization risk [55]. A Thai cost-effectiveness study reported that ICERs for preventing one unfavorable clinical outcome with NMV/r were US$448 compared with remdesivir and US$9356 compared with molnupiravir [82]. Korean and US CEAs showed increased costs of US$1587 to US$9790 per severe case averted in adults with underlying diseases or elderly patients [76, 77]. In the US, four allocation strategies for NMV/r showed ICERs ranging from dominance in unvaccinated high-risk patients to US$1,642,640 per hospitalization avoided for all patients [77]. In another US CEA, treatment of high-risk patients reduced costs and increased hospital days avoided compared with SOC [34]. In a German study, NMV/r compared with best supportive care reduced hospitalizations, ICU admissions, and deaths while increasing life years, yielding ICERs of US$12,128 per hospitalization avoided and US$10,929 per life-year gained [83]. During the Omicron period in Malaysia, NMV/r added US$397 per patient and reduced hospitalization risk by 0.17%, resulting in an ICER of US$231,375 per hospitalization averted [85]. NMV/r cost effectiveness was mainly demonstrated during Omicron dominance.

Molnupiravir was dominant to SOC in one US study involving high-risk and immunocompromised individuals over a lifetime horizon [42]. In another US study, including high-risk individuals, molnupiravir had an ICER of US$66,853/QALY [69]. In Japanese patients at high risk of progression to severe Covid-19, molnupiravir had an ICER of US$38,333/QALY versus best supportive care [61]. In a Korean CEA, it increased costs by US$8646 to US$32,306 per severe case averted over 1 year when targeting adults with underlying conditions or elderly patients [76]. In Ghana, Rwanda, or Zambia, ICERs ranged from dominant to US$86,476/DALY averted over 30 days [55]. During the Omicron period in Italy, molnupiravir was dominant to SOC [84]. Studies conducted during Omicron predominance showed higher cost effectiveness than during Delta, Mu, or Gamma periods.

Baricitinib demonstrated ICERs ranging between US$7526 [31] to US$31,168/QALY [35], depending on treatment combinations and population characteristics, with cost effectiveness driven by efficacy and mechanical ventilation rates. Dexamethasone was examined alone and in combination with remdesivir and tocilizumab [38–41, 47]. In US studies, ICERs ranged from US$375 [47] to US$35,169/QALY [41], with lower ICERs observed in severe infections. In South Africa, combinations with remdesivir were dominant in high-risk populations [72]. Baricitinib and dexamethasone demonstrated cost effectiveness during the wild-type, D614G, and Alpha-predominant periods; however, their cost effectiveness has not been evaluated for later-emerging variants.

Casirivimab-imdevimab was found to be cost effective or cost saving across multiple studies conducted during periods of wild-type, D614G, and Alpha predominance. A US

CUA reported an ICER of US$4924/QALY [38] compared with SOC over a lifetime horizon, while another US study found it cost effective for patients aged 40+ years with ≥ 2% hospitalization risk or aged 20+ years with ≥ 4% risk [37]. Two CEAs also evaluated casirivimab-imdevimab versus SOC among individuals at high risk of progression to severe COVID-19 [57, 71]. Among Italian outpatients with mild–moderate SARS-CoV-2, it was cost saving, reducing hospitalizations, ICU admissions, and deaths over a 20-week period [71]. In Singapore, casirivimab-imdevimab was cost effective in all scenarios, with costs per DALY averted ranging from − US$2229 to $14,121 [57].

Cost-effectiveness analyses of other COVID-19 therapeutics showed mixed results. Tocilizumab had ICERs ranging from US$9165/QALY in the UK to US$51,755/QALY in the US for patients requiring oxygen support [31, 62]. Sotrovimab was cost effective at US$49,271/QALY in the UK among high-risk hospitalized patients [31] but had an ICER of US$80,255/QALY [69] in US outpatients over a lifetime horizon. The cost effectiveness of favipiravir was primarily assessed during the predominance of earlier COVID-19 variants, including the wild type, D614G, Alpha, and Delta. Compared with SOC, favipiravir was cost saving over a 5-month horizon in Saudi Arabia for patients with moderate–severe COVID-19 [73] but associated with an ICER of US$36,103/death averted over 1 year among hospitalized COVID-19 patients in the UAE [79]. The cost per frequency of complete elimination of the virus was higher for favipiravir compared with umifenovir in mild infections and was lower than remdesivir for moderate–severe infections in Russia [74]. In an Indonesian CEA, favipiravir + levofloxacin + N-acetylcysteine was dominant over four alternative regimens for moderate-to-severe COVID-19 inpatients, including combinations with azithromycin and/or remdesivir [87]. In a US study, lenzilumab reduced costs and increased resource availability, including ICU and hospital bed days over a horizon of 28 days [75]. For Russian patients with cytokine storm symptoms, tocilizumab, olokizumab, and levilimab combined with glucocorticosteroids had incremental costs per life saved ranging from US$3045 to US$4564 over 20 days [81]. Vilobelimab in combination with SOC resulted in ICERs ranging from US$8300 [67] to US$23,765/QALY [65] versus SOC alone in treatment of patients with severe Covid-19 in the US during the predominance of D614G, B.1.177, Alpha and Delta variants. The ICER of azvudine for treating mild–moderate COVID-19 among high-risk outpatients in China during the Omicron period was US$17,913 per patient [86]. Key cost-effectiveness drivers included treatment efficacy, time to recovery, treatment and healthcare costs, probabilities of death, ICU admission and hospitalization, and patient characteristics such as age and comorbidities.

Interferon-B1a, lopinavir-ritonavir, and hydroxychloroquine demonstrated negative QALY increments (dominated by their comparators) in the US, with cost per QALY lost ranging from US$6504 to US$76,525 [38]. Fluvoxamine was cost effective in 100% of PSA iterations (ICER US$7843/QALY) [69] among high-risk US outpatients over a lifetime horizon during periods of Gamma, Zeta, and Delta variant predominance. Statins also reduced costs while improving efficacy in hospitalized patients over a 4-week horizon in a US study [80]. These therapeutics were evaluated during the early phases of the COVID-19 pandemic; however, based on subsequent clinical evidence and updated guideline recommendations, they are now either no longer authorized, no longer recommended, or considered clinically irrelevant in current practice.

3.4 Risk of Bias in Individual Studies

The methodological quality of the included economic evaluation studies is presented in Supplementary Table 2 (ESM). The studies demonstrated varying levels of methodological rigour. All included studies (n = 60/60) included a well-defined research question, and most studies accurately valued costs and outcomes (n = 47/60) and conducted incremental analyses (n = 58/60) and sensitivity analyses (n = 51/60). However, several limitations were identified. Many studies did not clearly describe the SOC options (n = 29/60) and lacked completeness in identifying relevant costs and consequences (n = 31/60). Uncertainty in clinical effectiveness and cost measurements was also evident (n = 16/60), with important resource categories, such as readmissions and rehabilitation, often overlooked. Additionally, the generalizability of results was limited, as efficacy inputs were frequently derived from controlled trial conditions with variant-specific susceptibility that may not reflect real-world practice (n = 44/60).

4 Discussion

Our systematic review identified very few economic evaluations conducted specifically in transplant populations, including SOT and HSCT recipients. Two studies examined the cost effectiveness of mAb PrEP in transplant recipients, with results differing by the study location, efficacy and cost estimates utilized in models, and population group examined, including their vaccination status. For antiviral therapies, remdesivir demonstrated ICERs ranging from US$14,866/QALY to US$109,513/QALY across studies, while molnupiravir combined with SOC was not cost effective in a UK study that included transplant and other high-risk populations. Studies performed

in the Netherlands found that NMV/r was not cost effective over a 90-day time horizon during the period of low disease severity; however, using a lifetime horizon, it showed a very low ICER (approximately US$440/QALY) among immunocompromised patients, including transplant recipients. These findings illustrate the substantial heterogeneity across studies in terms of target population, baseline risk, variant period, and local cost structures, which should be considered when interpreting their relevance for current clinical practice.

The ICERs of COVID-19 therapies varied widely due to differences in country-specific healthcare costs, population risk profiles, treatment combinations, comparators, model structures/assumptions, and analytical perspectives. These differences make direct comparison challenging and limit the generalizability of individual studies across jurisdictions. Variation in treatment efficacy estimates further contributes to this heterogeneity. Many evaluations drew on clinical trials conducted during earlier variant periods, such as Alpha, Beta, Epsilon, Gamma, Delta, or wild-type SARS-CoV-2, while others incorporated data from later waves dominated by Omicron. For example, most mAb PrEP evaluations relied on efficacy estimates from pre-Omicron trials; the subsequent emergence of Omicron subvariants resistant to TIX-CIL led to its withdrawal in the United States [88]. Similarly, evaluations of baricitinib, dexamethasone, and casirivimab-imdevimab were based on efficacy observed during earlier, more severe variant waves, while trials informing molnupiravir and NMV/r were conducted during the Gamma, Mu, Delta, and early Omicron circulation. As a result, cost-effectiveness findings anchored in variant-specific efficacy are not readily transferable to scenarios involving newer or rapidly evolving strains.

In addition, treatments with broad antiviral activity, such as NMV/r, may demonstrate more stable cost effectiveness across variant periods, whereas monoclonal antibodies and other variant-sensitive strategies require continual reassessment as viral susceptibility changes. Furthermore, the widespread rollout of vaccination campaigns has substantially reduced baseline risks of hospitalization and death in the general population, lowering the incremental benefit of both therapeutics and PrEP in many settings. However, this effect is less predictable in immunocompromised or under-vaccinated groups, such as transplant recipients, where vaccine response remains attenuated and the absolute benefit of additional interventions may still be considerable. These considerations underscore the need for cost-effectiveness analyses that incorporate evolving viral epidemiology, variant susceptibility, and population-level immunity, and underscore the importance of context-specific interpretation when applying these findings to policy decisions.

Moreover, cost inputs varied substantially across studies due to differences in healthcare financing systems, healthcare delivery, analytical perspectives, and data availability. Hospitalization probabilities also fluctuated across jurisdictions, depending on local variant-specific risks and population vaccination status. These contextual factors are particularly consequential for transplant recipients, whose baseline risks of hospitalization, invasive mechanical ventilation, and death remain elevated due to underlying immunosuppression and comorbidities. Country-specific factors, such as drug acquisition costs, hospitalization and ICU costs, and assumptions regarding baseline risk and variant-specific treatment efficacy, further shape cost-effectiveness outcomes. Differences in WTP thresholds and health utility estimates across settings can also lead to different conclusions about whether an intervention is considered cost effective. Together, these factors highlight the need for local adaptation when interpreting cost-effectiveness evidence. Scenario analyses that incorporate jurisdiction-specific costs, risk profiles, variant epidemiology, and decision thresholds are essential to support policymakers in applying these findings within their own healthcare systems.

At the time of this review, three systematic reviews had assessed the costs and cost effectiveness of COVID-19 prevention and treatment strategies. Rezapour et al. demonstrated that remdesivir was cost effective compared with SOC in high- and middle-income countries, including China, Turkey, and South Africa, while studies in the United States yielded mixed results [89]. They also found that combining remdesivir with baricitinib was cost effective compared with remdesivir alone. Murton et al. showed that remdesivir could reduce hospital bed occupancy by 6% to 21.3% and it was cost effective in three out of four economic evaluations. Their findings highlighted the importance of context-specific evaluations, particularly in lower-income settings where data remain sparse [90]. Additionally, Elvidge et al. conducted an updated systematic review identifying 18 studies evaluating antivirals, immunotherapies, and corticosteroids. They identified key gaps, including a lack of head-to-head comparisons, limited disease-specific utility values, and few analyses incorporating the impact of viral variants [91].

Our review builds upon these prior studies by focusing specifically on high-risk, immunocompromised, and transplant populations—groups that were underrepresented in earlier reviews. We also incorporate recent evidence up to September 2025, capturing updated insights into both mAb PrEP and COVID-19 treatments. This review is the first to evaluate the cost effectiveness of these interventions in the context of population-specific factors, such as vaccination status and variant-specific risks. By doing so, we provide timely and relevant evidence to guide resource allocation for vulnerable populations. We also assessed the methodological quality of the included studies. Most studies clearly defined

research questions, valued costs and outcomes appropriately, and conducted sensitivity analyses. However, many lacked adequate descriptions of standard-of-care comparators and omitted key costs such as readmissions and rehabilitation. These gaps may underestimate the true economic burden of COVID-19 and reduce the relevance of findings for policymakers and payers.

Uncertainty in clinical effectiveness and cost measurements further weakens the reliability of results. Many studies rely on efficacy data from controlled trials, which may not reflect real-world conditions. These trials often do not account for factors such as limited healthcare resources or differences in care delivery. As a result, their findings may not apply well to routine clinical settings. Most studies also exclude long-term health outcomes and societal perspectives. This limits the ability to fully assess the broader economic impact of interventions, such as productivity losses or long-term disability. Many studies use variant-specific effectiveness data and country-specific cost inputs. While necessary for local relevance, this makes it difficult to apply findings to other countries or future scenarios involving new COVID-19 variants. Despite these challenges, this review has several strengths. It includes recent evidence covering a broad range of therapies and preventive treatments, as well as diverse patient populations, including transplant recipients. By including studies from both high- and low-income countries, our findings contribute to a broader understanding of the economic value of COVID-19 mAb PrEP and treatments. The use of comprehensive search strategies across multiple electronic databases and grey literature, without language restrictions, further enhances the overall rigor and inclusiveness of this review.

However, significant limitations should be acknowledged. Sponsorship bias is a potential concern, as over 40% of the included studies were at least partially funded by pharmaceutical companies [92]. This level of industry involvement is common in health technology assessment of emerging therapeutics, where early economic evidence is often generated by manufacturers as part of reimbursement submissions. Although we did not observe clear or systematic differences in the direction or magnitude of results between industry-sponsored and independent studies, the potential for subtle influences, such as selective comparator choice, optimistic efficacy assumptions, or favorable scenario analyses, cannot be excluded. Given these possibilities, and the inherent difficulty of quantifying their impact within a heterogeneous evidence base, the results presented in this review should be interpreted with appropriate caution, particularly when considering policy decisions. Furthermore, many studies had methodological limitations that may affect the validity and generalizability of their findings. Incomplete identification of relevant costs and outcomes, limited transparency in model structure, and insufficient reporting of key assumptions can lead to ICERs that appear favorable but do not fully capture the economic and clinical burden of COVID-19—particularly for high-risk or immunocompromised populations. Such issues underscore the importance of careful appraisal when using economic evidence to inform reimbursement or policy decisions. In addition, several evaluations were conducted early in the pandemic and relied on clinical efficacy data from variants that are no longer circulating or from interventions that have since lost relevance. While these studies have limited applicability to current policy decisions, they remain informative for understanding how economic evidence evolved over time. Finally, because few studies reported outcomes specifically for transplant recipients, we were unable to distinguish between solid organ and hematopoietic stem cell transplant populations. As a result, we grouped all transplant types together, which may obscure clinically meaningful differences in baseline risk, treatment response, and cost effectiveness between these subgroups.

To improve the quality, transparency, and policy relevance of future economic evaluations, researchers should follow established best practice guidelines [93, 94]. This includes clearly describing comparators, comprehensively identifying all relevant costs and consequences, and incorporating real-world data where possible. Studies should also transparently describe funding sources and potential conflicts of interest. These improvements will be essential for generating robust, generalizable evidence that can meaningfully inform reimbursement and resource-allocation decisions for high-risk and immunocompromised populations, including SOT and HCST recipients, whose risk profiles and clinical needs continue to evolve as the pandemic landscape changes.

5 Conclusion

Our systematic review demonstrates that the cost effectiveness of COVID-19 treatments and prevention strategies in transplant populations remains limited, heterogeneous, and context dependent. Variation in geographic settings, population vaccination levels, circulating variants, hospitalization risks, patient demographics, comparators, and model assumptions contributes to wide differences in cost-effectiveness estimates. These inconsistencies highlight the need for more rigorous, transparent, and context-specific economic evaluations tailored to the clinical realities of transplant recipients. Nonetheless, several clinical and policy implications emerge. Broad-acting antivirals tend to provide consistent value across epidemiologic contexts, whereas monoclonal antibody PrEP is highly sensitive to variant susceptibility and requires ongoing reassessment. Although declining hospitalization rates in the general population may reduce the cost effectiveness of additional interventions, transplant recipients and other

immunocompromised patients, who remain at elevated risk, may continue to benefit clinically and economically.

Cost effectiveness is strongly influenced by local healthcare costs, baseline risk, vaccination status, variant-specific efficacy, and jurisdictional willingness-to-pay thresholds; therefore, findings should be adapted to local contexts. Future economic evaluations should incorporate variant-specific effectiveness, real-world vaccine response, long-term COVID-19 outcomes, and societal impacts to better inform resource allocation and support decision making for transplant and other high-risk populations.

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Declarations

Author Contributions AG and KT conceptualized the study, led the project administration, conducted a narrative synthesis of the study findings, and drafted the initial manuscript. BS performed the literature search. AG and AV performed data extraction and risk-of-bias assessment. All authors contributed to the interpretation of findings, reviewed and approved the final manuscript, and agree to be accountable for all aspects of the work.

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Data Availability Data extracted are available in the cited studies.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication (from patients/participants) Not applicable.

Code Availability Not applicable.

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