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COVID Original Research

Cost-Effectiveness of Baricitinib Compared With Standard of Care: A Modeling Study in Hospitalized Patients With COVID-19 in the United States

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ABSTRACT

Purpose: In the Phase III COV-BARRIER (Efficacy and Safety of Baricitinib for the Treatment of Hospitalised Adults With COVID-19) trial, treatment with baricitinib, an oral selective Janus kinase 1/2 inhibitor, in addition to standard of care (SOC), was associated with significantly reduced mortality over 28 days in hospitalized patients with coronavirus disease–2019 (COVID-19), with a safety profile similar to that of SOC alone. This study assessed the cost-effectiveness of baricitinib + SOC versus SOC alone (which included systemic corticosteroids and remdesivir) in hospitalized patients with COVID-19 in the United States.

Methods: An economic model was developed to simulate inpatients' stay, discharge to postacute care, and recovery. Costs modeled included payor costs, hospital costs, and indirect costs. Benefits modeled included life-years (LYs) gained, quality-adjusted life-years (QALYs) gained, deaths avoided, and use of mechanical ventilation avoided. The primary analysis was performed from a payor perspective over a lifetime horizon; a secondary analysis was performed from a hospital perspective. The base-case analysis modeled the numeric differences in treatment effectiveness observed in the COV-BARRIER trial. Scenario analyses were also performed in which the clinical benefit of baricitinib was limited to the statistically significant reduction in mortality demonstrated in the trial.

Findings: In the base-case payor perspective model, an incremental total cost of 17,276 US dollars (USD), total QALYs gained of 0.6703, and total LYs gained of 0.837 were found with baricitinib + SOC compared with SOC alone. With the addition of baricitinib, survival was increased by 5.1% and the use of mechanical ventilation was reduced by 1.6%. The base-case incremental cost-effectiveness ratios were 25,774 USD/QALY gained and 20,638 USD/LY gained; a "mortality-only" scenario analysis yielded similar results of 26,862 USD/QALY gained and 21,433 USD/LY gained. From the hospital perspective, combination treatment with baricitinib + SOC was more effective and less costly than was SOC alone in the base case, with an incremental cost of 38,964 USD per death avoided in the mortality-only scenario.

Implications: In hospitalized patients with COVID-19 in the United States, the addition of baricitinib to SOC was cost-effective. Cost-effectiveness was demonstrated from both the payor and the hospital perspectives. These findings were robust to sensitivity analysis and to conservative assumptions limiting the clinical benefits of baricitinib to the statistically significant reduction in mortality demonstrated in the COV-BARRIER trial. (*Clin Ther.* 2021;43:1877–1893.)

Keywords: baricitinib, cost-effectiveness, COVID-19, hospital, mechanical ventilation, mortality.

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INTRODUCTION

Coronavirus disease–2019 (COVID-19), caused by the novel severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, and reported to the World Health Organization at the end of 2019.[1] By March 2020, a global pandemic was declared by the World Health Organization.[2] The cumulative number of confirmed global cases of COVID-19 by June 2021 was 178.8 million, with 3.9 million deaths.[1,3] Also as of June 2021, the United States reported 33.2 million confirmed cases of COVID-19, with 597,037 deaths.[3]

Cost impacts and capacity-related constraints have proved to be large burdens to hospitals and health care systems during the global pandemic.[4] As of June 2021 in the United States, 65% of the population aged 18+ years had received at least one dose of a COVID-19 vaccine, 150.8 million were fully vaccinated, and hospitalizations had decreased from a peak 7-day mean of 16,492 in January to just 1824 in June.[5] However, vaccine availability and current vaccination levels do not diminish the need for effective and cost-effective treatments for hospitalized patients with COVID-19, which can reduce the severity of the disease and the resultant resource and cost burdens on hospitals.[6] Although vaccines have been demonstrated to be clinically effective, they are not 100% effective, and not everyone can receive them (eg, those taking immunosuppressant drugs). Also, considering the time it takes to vaccinate the population and the uncertainty with the emergence of multiple variants,[6] even with increased vaccination rates, COVID-19 will continue to consume important in-hospital health care resources.

Combination treatment with the immunomodulator baricitinib and the antiviral remdesivir was approved by the US Food and Drug Administration under emergency use authorization for the treatment of hospitalized patients with COVID-19 requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[7] The second stage of the Phase III Adaptive COVID-19 Treatment Trial (ACTT-2)[61] demonstrated the effectiveness of baricitinib + remdesivir over remdesivir alone in reducing recovery time and accelerating improvement in clinical status in hospitalized patients with COVID-19, specifically among those receiving high-flow oxygen or noninvasive ventilation. The subsequent Phase III COV-BARRIER (Efficacy and Safety of Baricitinib for the Treatment of Hospitalised Adults With COVID-19) trial, which evaluated combination treatment with baricitinib + standard of care (SOC), demonstrated statistically significant reductions in 28- and 60-day all-cause mortality compared with SOC alone (including large percentages of patients receiving dexamethasone and remdesivir). The study demonstrated numerically but statistically nonsignificantly lesser rates of progression to noninvasive ventilation and to mechanical ventilation.[8]

Clinical and economic outcomes with the use of remdesivir in hospitalized patients with COVID-19 were assessed by the Institute for Clinical and Economic Review. That assessment was based on clinical data on the efficacy of remdesivir versus SOC from ACTT-1. The Institute for Clinical and Economic Review later published an updated evaluation of remdesivir + SOC in the populations with mild disease and moderate to severe disease, separately, based on clinical evidence from several trials.[9–14] The model by the Institute for Clinical and Economic Review did not account for the discharge status of patients requiring postacute care, or the prevalence of comorbidities among hospitalized patients with COVID-19, nor did it consider the hospital perspective.

To address these limitations, the present cost-effectiveness analysis (CEA) used a model that reflected the patient's in-hospital experience and postacute hospital consequences. The overall cost burden on payors and the impact of resource utilization on hospitals are large; therefore, more evidence is needed to guide the efficient utilization of resources. This CEA of baricitinib + SOC versus placebo + SOC used data from the COV-BARRIER trial by replicating and extending the cost-effectiveness model (CEM) developed by the Institute for Clinical and Economic Review .

PARTICIPANTS AND METHODS

Population and Perspective

A pharmacoeconomic model was developed to estimate the cost-effectiveness of baricitinib + SOC treatment in hospitalized patients aged ≥18 years with COVID-19 in the United States. Although eligible patients did not require invasive mechanical ventilation at admission, a percentage had various other severe comorbidities. The model was constructed to analyze cost-effectiveness from the perspective of a third-party payor or from the narrow perspective of a hospital. The primary analysis was performed from the payor

perspective, in which costs to payors were defined as payments made to hospitals, postacute discharge care providers, long-term post-recovery costs, and indirect costs due to missed work during the inpatient hospital stay. To capture benefits with regard to long-term all-cause health care costs and mortality, a lifetime horizon was used in the base-case analysis. The robustness of the base-case results was evaluated using one-way and probabilistic sensitivity analyses (PSAs), in which key model parameters were varied. In a secondary analysis, we focused on the hospital perspective, whereby the net cost impact (calculated as hospital costs minus Medicare Severity–Diagnosis-Related Groups [MS-DRG] reimbursement) was used with the time horizon set to the hospital length of stay (LOS).

Modeled Economic and Health Outcomes

The measures of benefit in the model were quality-adjusted life-years (QALYs) gained, life-years (LYs) gained, number of deaths avoided, and use of mechanical ventilation, accrued during hospitalization and after discharge of patients to quantify the impact of reducing progression to greater oxygen support level of care, duration of mechanical ventilation, and COVID-19–related mortality, due to therapy intervention. Health outcomes represented in the model were based on the National Institute of Allergy and Infectious Disease–Ordinal Scale (OS) score, used to measure efficacy in the COV-BARRIER trial[8,11]; inpatients' hospital-related outcomes in the CEM included medical care without oxygen, supplemental oxygen, noninvasive ventilation, mechanical ventilation, and death. Mortality, overall time to recovery, duration of mechanical ventilation/noninvasive ventilation/supplemental oxygen, percentage of patients who progressed to new use of mechanical ventilation/noninvasive ventilation/supplemental oxygen, and the effects of treatment on the discharge status of patients were simulated in the model as treatment effects and were derived from the COV-BARRIER results (data on file, Eli Lilly and Company, 2021).[8,15]

Model Framework

The CEM was structured as a sequence of three submodels: inpatient, discharged, and recovered (Figure 1). Descriptions of the three submodels are presented here; additional details of the model structure are provided in the **Appendix**. The inpatient submodel simulates treatment effects on new use of oxygen support, the total LOS, the number of days (duration of care) at each level of oxygen support, and the probabilities of survival and recovery. Inpatient hospital expenditures were based on MS-DRGs for COVID-19 admissions. It was assumed that the highest level of oxygen support received determined the DRG for the purposes of estimating payments to hospitals. For analysis from the hospital perspective, hospital expenditures were calculated as the number of days at each level of oxygen support multiplied by the unit-cost per day, based on estimates from a large, all-payor US hospital database with detailed cost information on inpatient discharges.[17] QALYs were calculated as disutilities for COVID-19 symptoms and for each level of oxygen support subtracted from the patients' age-based utilities. It was assumed that treatment effects on mortality had no impact on inpatient costs or health utilities directly but had downstream effects on the costs, QALYs, and LYs gained accrued in the discharged and recovered submodels.

The discharged submodel simulated postacute care related to COVID-19. Patients could be discharged to one of the following types of discharge care: self-care or custodial care, home health care, inpatient rehabilitation, skilled nursing facility, short-term hospital, long-term acute care hospital, or hospice. In the Premier Healthcare Database (PHD)-based cost analysis, the percentage of patients with each type of discharge care was calculated in patients grouped by the highest level of oxygen support received during the inpatient stay (see **Supplemental Table S1**). Payor costs of postacute care were calculated as the duration of care multiplied by the unit-cost per day of each type of care. QALYs were calculated as the relative utility of each type of care multiplied by the age-based utilities for the duration of postacute care. The base-case analysis assumed that all patients discharged to hospice died at the end of their stays, and that patients discharged to any status other than self-care or custodial care were unable to work while receiving postacute care.

The recovered submodel simulated all-cause health care costs and all-cause mortality for a lifetime horizon. This submodel assumed that patients recovered from COVID-19 incurred all-cause health care costs, health utilities, and all-cause mortality based on the general non–COVID-19 infected population, adjusted to reflect greater rates of comorbidities in the modeled COVID population.

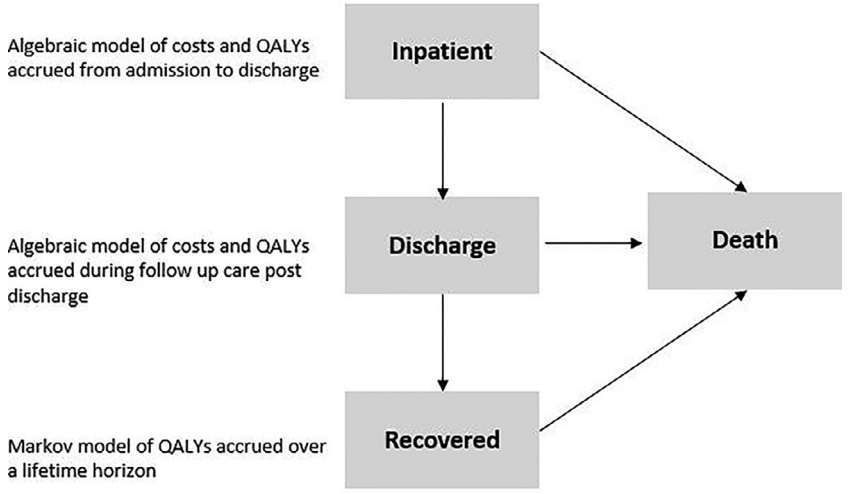

Figure 1. Structure of the cost-effectiveness model. QALY = quality-adjusted life-year.

In the secondary analysis (hospital perspective), only costs and benefits incurred during the inpatient submodel were included, given that the costs after discharge were not covered by the hospital.

Model Inputs

Population

The key population variables were demographic characteristics, level of care at baseline, and severe comorbidities (Table I). Demographic inputs were based on the intent-to-treat population in COV-BARRIER.[8] The mean age of the recovered subgroup in the model was imputed by the assumption that the relative age of survivors compared with the age of all patients in COV-BARRIER was identical to the relative age of survivors compared with all modeled patients in the Institute for Clinical and Economic Review's CEA of remdesivir.[10] The percentage of patients with severe comorbidities was used only in the calculation of posthospitalization costs, utilities, and posthospitalization mortality to reflect the greater prevalence of comorbidities among hospitalized patients with COVID-19 compared with the general US population.

The distribution of patients by level of care at baseline (medical care without oxygen, supplemental oxygen, and noninvasive ventilation) was derived from the ordinal scores at baseline in the trial. Patients on mechanical ventilation at study entry were excluded from the trial and from the modeled population.[8]

In the analysis, adjustments were applied to the all-cause health care costs, health utilities, and all-cause mortality in the general population for more representative modeling of the greater prevalence of comorbidities among hospitalized patients with COVID-19. The estimated percentage of patients with severe comorbidities (32.1%) was derived from the prevalence of comorbidities (obesity, diabetes, chronic respiratory disease, and hypertension) in the COV-BARRIER trial population relative to the prevalence of comorbidities in the general population.[8] Multipliers were derived from the research literature to estimate greater all-cause health care costs, reduced quality of life, and greater all-cause mortality associated with metabolic syndrome, which has comorbidity risk factors similar to those of COVID-19 infection and severity (Table I). The postdischarge cost and utility multipliers for severe comorbidities were based on the ratios of per-annum health care costs[18] and EuroQual–Five Dimension utility scores,[19] respectively, in patients with and without metabolic syndrome. The comorbid mortality multiplier was assumed to be the same as the fixed-effects estimate of the relative risk for all-cause mortality (1.37; 95% CI, 1.09–1.74) in a meta-analysis of data from studies that used the most exact definition of metabolic syndrome derived from the World Health Organization.[20]

Table I. Population inputs.

Parameter	Parameters for Sensitivity Analysis			Study
	Value (SE)	Distribution	Range	
Demographic characteristics				
Female, %	36.9 (1.2)	β	34.4–39.3	Marconi et al[8]
Age at hospital admission, mean, y	57.6 (0.36)	Normal	56.9–58.3	Marconi et al,[8] and ACTT-2[15]
Age of patients who recovered,* mean, y	56.2 (0.36)	Normal	55.5–56.9	Di Fusco et al,[4] US Bureau of Labor Statistics[17]
Level of care at baseline, %		Dirichlet (N = 1525)	Not varied in OWSA	Marconi et al[8]
Mechanical ventilation (OS 7)	0	–	–	
Noninvasive ventilation (OS 6)	24.4	–	–	
Supplemental oxygen (OS 5)	63.4	–	–	
Medical care w/o oxygen (OS 4)	12.3	–	–	
Severe comorbidities, %	32.1 (1.2)	β	29.7–34.4	Data on file, Eli Lilly and Company, 2021
Postdischarge cost multiplier	1.601 (0.160)	Normal	1.287–1.914	Boudreau et al[18]
Utility multiplier	0.962 (0.026)	Normal	0.911–1.014	Vetter et al[19]
Postdischarge mortality multiplier	1.37 (0.17)	Normal	1.09–1.74	Ford[20]

OS = ordinal scale; OWSA = one-way sensitivity analysis.

*The mean age of patients who recovered in the model was imputed with the assumption that the relative age of survivors compared with the age of all patients in COV-BARRIER was identical to the relative age of survivors compared with all modeled patients in the cost-effectiveness analysis of the remdesivir Institute for clinical and economic review. The SE was assumed to be the same as the SE of the mean age at baseline in all patients in the trial.

Treatment Effectiveness

Estimates of treatment effectiveness with baricitinib + SOC and placebo + SOC (Table II) were derived from the intent-to-treat population in COV-BARRIER.[8] SOC was similar in both study arms and included systemic corticosteroids (79.3%) and/or remdesivir (18.9%); 91.6% of patients who received remdesivir also received a corticosteroid.[8]

The prevalences of new use of mechanical ventilation and of noninvasive ventilation within each treatment arm were sourced from the corresponding end points in COV-BARRIER (data on file, Eli Lilly and Company, 2021). New use of supplemental oxygen was not reported as an end point and thus was not modeled in the analysis (ie, it was specified as 0% in both comparator arms). The overall time to recovery within each treatment arm was also sourced from the corresponding end point in COV-BARRIER (data on file, Eli Lilly and Company, 2021). The duration of care at each level of oxygen support was imputed by rescaling of the number of days at each level of oxygen support in ACTT-2[15] to match the total time to recovery within each treatment arm in COV-BARRIER (data on file, Eli Lilly and Company, 2021).[8,15] The probabilities of recovery were calculated as the complements of the Kaplan-Meier estimates of all-cause mortality at day 28 in COV-BARRIER.[8]

Costs

Estimates of inpatient costs were primarily sourced from an analysis of data from patients with a diagnosis of COVID-19 in the PHD, a large-scale and all-payor US hospital database of detailed information on

Table II. Treatment effectiveness inputs.

Parameter	Parameters for Sensitivity Analysis				Source
	Value (SE)		Distribution	Range	
Prevalence of care postadmission, %			β		Marconi et al[8]
New mechanical ventilation					
Placebo + SOC	18.0	1.4		15.3–20.8	
Baricitinib + SOC	16.4	1.3		13.9–19.1	
New noninvasive ventilation					
Placebo + SOC	13.0	1.4		10.4–15.9	
Baricitinib + SOC	12.1	1.4		9.6–14.9	
New supplemental oxygen					
Placebo + SOC	0	0		0	
Baricitinib + SOC	0	0		0	
Duration of care, d			Normal		ACTT-2,[15] data on file, Eli Lilly and Company, 2021
Time to recovery					
Placebo + SOC	13.10	0.32		12.47–13.73	
Baricitinib + SOC	12.30	0.32		11.67–12.93	
Mechanical ventilation days					
Placebo + SOC	3.46	0.46		2.56–4.37	
Baricitinib + SOC	1.88	0.40		1.1–2.67	
Noninvasive ventilation days					
Placebo + SOC	3.44	0.26		2.93–3.95	
Baricitinib + SOC	3.55	0.30		2.96–4.15	
Supplemental oxygen days					
Placebo + SOC	5.45	0.15		5.14–5.75	
Baricitinib + SOC	5.67	0.23		5.22–6.12	
Probability of recovery, %			β		Marconi et al[8]
Noninvasive ventilation					
Placebo + SOC	69.2	4.2		60.1–76.6	
Baricitinib + SOC	81.5	3.6		74.0–87.9	
Supplemental oxygen					
Placebo + SOC	91.1	1.6		87.5–93.6	
Baricitinib + SOC	93.8	1.3		90.9–96.1	
Medical care w/o oxygen					
Placebo + SOC	95.8	3.0		87.6–98.6	
Baricitinib + SOC	98.8	1.1		95.7–100	

SOC = standard of care; w/o = without.

inpatient discharges (henceforth referred to as the *PHD cost analysis*).[16] The data covered inpatient admissions from April 1, 2020, to September 15, 2020. The modeled population represents a mix of Medicare (52.9%), Medicaid (19.2%), and commercially insured (27.9%) patients (Table III) (data on file, Eli Lilly and Company, 2020). The data from uninsured patients were excluded from the analysis due to the unavailability of data regarding out-of-pocket costs in uninsured and self-insured patients.

From the payor perspective, direct costs included DRG payments to hospitals for the inpatient stay, costs of postacute care immediately following discharge, and lifetime all-cause health care costs among recovered patients. It was assumed that hospitals were reimbursed for the costs of care for patients with COVID-19 through DRG payments, and that drug-acquisition costs were borne by the hospital. Therefore, drug-acquisition costs were excluded from the payor perspective.

The analysis assumed that the primary determinant of the DRG used for reimbursement was the highest level of oxygen support provided during the inpatient stay. Each patient record in the PHD was assigned an MS-DRG, and the PHD cost analysis classified each patient by the highest level of oxygen support received based on the charge codes in each patient's record (data on file, Eli Lilly and Company, 2020). These data were used to construct frequency distributions of MS-DRGs, stratified by payor type (Medicare, Medicaid, or commercial) and by highest level of inpatient care (mechanical ventilation, noninvasive ventilation, supplemental oxygen, or no oxygen). The pooled frequency distributions of Medicare, Medicaid, and commercially insured patients at each level of care were used as proxies for the MS-DRG frequency distributions of uninsured patients (see **Supplemental Table S2**).

Medicare payments for each MS-DRG (see **Supplemental Table S3**) were sourced from the Center for Medicare and Medicaid Services (CMS) public-use file of inpatient charge data by MS-DRG for fiscal year 2017.[27] MS-DRG payments for Medicare-insured patients were increased by 20% to represent greater payments authorized by the Coronavirus Aid, Relief, and Economic Security (CARES) Act (see **Supplemental Table S3**).[28] MS-DRG costs to Medicaid and commercial payors were calculated by multiplying the standard Medicare payments by reimbursement ratios sourced from the research literature (see **Supplemental Table S4**).[29,30]

Payor costs of postacute care in the discharged submodel were specified by the duration of care and the unit-cost per day of care (Table III and see **Supplemental Table S1**). It was assumed that patients discharged to self-care or custodial care incurred no additional payor costs of postacute care. The duration of postacute care in each other discharge-status group was sourced from the CMS postacute care public-use file for calendar year 2017 except for short-term hospitals, which were not reported in the CMS public-use file.[31] In the subgroup discharged to a short-term hospital, the mean inpatient hospital LOS reported in the Agency for Healthcare Research and Quality 2016 National Inpatient Sample was used as a proxy estimate for the duration of postacute care.[32]

The unit-cost per day of home health care was derived from the CMS national, standardized 30-day period payment rate for the 2021 calendar year.[33] Unit-costs per day of inpatient rehabilitation, skilled nursing facilities, and short-term hospitals were sourced from a longitudinal cohort study in mechanically ventilated survivors of acute respiratory distress syndrome[34] and inflated from 2014 USD by the method described in the 2020 Institute for Clinical and Economic Review Reference Case[35]: costs were inflated to the most recent year available (2019) using the CMS personal health care expenditure deflator,[36] and further inflated to 2020 USD using the Bureau of Economic Analysis personal consumption expenditure price index.[37] The unit-cost per day of long-term acute care hospitals was sourced from the March 2020 Medicare Payment Advisory Commission Report.[38] The cost per day of hospice care was derived from CMS hospice payment rates for the 2021 fiscal year,[39] including the service intensity add-on (0.099 h/d)[40] for the last 7 days of life.[41]

In the recovered submodel, payor costs consisted of all-cause health care costs of surviving patients with COVID-19. The analysis used the same age-based future health care costs reported in the Institute for Clinical and Economic Review's CEA of remdesivir,[42] derived from CMS National Health Expenditure Data for 2014[43] and inflated to 2020 USD.

For the hospital perspective, direct costs were limited to drug-acquisition costs and the medical costs of treating inpatients with COVID-19. Hospital revenues were based on DRG reimbursements received

Table III. Cost and utility inputs.

Parameter	Parameters for Sensitivity Analysis			Source
	Value	Distribution	Range	
Distribution of patients by payor type, %		Dirichlet (N = 105,736)		Data on file, Eli Lilly and Company, 2020
Medicare	52.9		45.6–60.2	
Medicaid	19.2		16.5–21.9	
Private payor	27.9		17.9–37.9	
Uninsured	0		0	
Hospital costs per day, mean (SE), USD		Normal		Data on file, Eli Lilly and Company, 2020
Mechanical ventilation	3660 (78.64)		3506–3814	
Noninvasive ventilation	2450 (124.99)		2205–2695	
Supplemental oxygen	1828 (19.05)		1791–1865	
Medical care w/o oxygen	1818 (13.40)		1792–1844	
Payor costs per patient, by highest level of inpatient care,* USD				
Inpatient hospitalization costs				Supplemental Table S3†
Mechanical ventilation	48,884			
Noninvasive ventilation	17,468			
Supplemental oxygen	17,241			
Medical care w/o oxygen	16,946			
Post-discharge COVID-19 costs, USD				Supplemental Table S4†
Mechanical ventilation	8716			
Noninvasive ventilation	3527			
Supplemental oxygen	2388			
Medical care w/o oxygen	2165			
Per-annum all-cause medical costs post recovery among patients without serious comorbidities, USD		Normal		Whittington[9]
Age 19–44 y	5741 (150)		4593–6889	
Age 45–64 y	12,073 (200)		9658–14,488	
Age 65–84 y	20,071 (250)		16,057–24,085	
Age 85+ y	38,900 (300)		31,120–46,680	
Indirect costs		Normal		
Percent of patients employed, %	32.4 (5)		25.9–38.9	US Bureau of Labor Statistics,[17,22] Garfield et al[21]

(*continued on next page*)

Table III. (*continued*)

Parameter	Parameters for Sensitivity Analysis			Source
	Value	Distribution	Range	
Cost per workday missed, USD	218.63 (25)		175–262	US Bureau of Labor Statistics,[17,22] Garfield et al[21]
Age-based utilities among patients without severe comorbidities		β		Whittington,[9] Campbell et al,[10] Sullivan and Ghushchyan[23]
Age 18–29 y	0.922 (0.0019)		0.918–0.926	
Age 30–39 y	0.901 (0.0021)		0.897–0.905	
Age 40–49 y	0.871 (0.0024)		0.866–0.876	
Age 50–59 y	0.842 (0.0028)		0.836–0.847	
Age 60–69 y	0.823 (0.0034)		0.816–0.830	
Age 70–79 y	0.790 (0.0036)		0.783–0.797	
Age 80+ y	0.736 (0.0062)		0.724–0.748	
Disutilities of hospitalization for COVID-19		Normal		Campbell et al,[10] Sullivan and Ghushchyan,[23] Smith and Roberts,[24] Barbut et al,[25] Sackett and Torrance[26]
COVID-19 symptoms	−0.190 (0.022)		−0.233 to −0.147	
Mechanical ventilation	−0.600 (0.045)		−0.688 to −0.512	
Noninvasive ventilation	−0.500 (0.045)		−0.588 to −0.412	
Supplemental oxygen	−0.400 (0.045)		−0.488 to −0.312	
Medical care w/o oxygen	−0.300 (0.045)		−0.388 to −0.212	

USD = US dollars; w/o = without.

* Payor costs per patient by highest level of inpatient care were calculated in the model based on the inputs shown in **Supplemental Tables S4 and S5**; parameters for the sensitivity analyses associated with those parameters are also shown in **Supplemental Tables S4 and S5**.

† See the online version at doi:10.1016/j.clinthera.2021.09.016.

from payors. The cost of acquiring remdesivir 100 mg was sourced from publicly disclosed pricing for governmental payors (390 USD) and nongovernmental payors (520 USD),[44] and was prorated by the percentage of patients (18.9%) receiving concurrent remdesivir as SOC in the COV-BARRIER trial.[8] The cost per baricitinib 2-mg tablet (75.50 USD) was calculated by prorating the wholesale acquisition cost of a 30-day supply.[45] Unit-costs per day of treatment at each level of oxygen support (Table III) were sourced from the PHD cost analysis (data on file, Eli Lilly and Company, 2020), and reimbursement payments were based on the same inputs and methods used to calculate DRG payments in the payor perspective.

Indirect costs were included only in the payor perspective and did not factor into the CEA in the hospital perspective. Indirect costs were estimated by multiplying the percentage of patients employed

full-time (32.4%) by the hospital LOS and cost per workday (218.63 USD) (Table III).[17,21] The percentage of patients with full-time employment was calculated by weighting the percentages of employed patients in each subgroup of payor type by the distribution of payors estimated from the PHD cost analysis (Table I) (data on file, Eli Lilly and Company, 2020). The percentage of Medicare-insured patients with full-time employment was assumed to be equal to the percentage of the population aged ≥65 years with full-time employment (11.6%).[17] The percentage of Medicaid-insured patients with full-time employment (48.0%) was sourced from a report by the Kaiser Family Foundation.[21] The percentage of commercially insured patients with full-time employment was assumed to be the percentage of the US population aged 20 to 64 years with full-time employment (61%).[17] The cost per workday missed was based on employer costs of employee compensation from the Bureau of Labor Statistics (38.26 USD) and the assumption of 40 hours per week for full-time employment.[22]

Health Utilities

Health utilities (Table III) were modeled by extending the approach used in the Institute for Clinical and Economic Review's evaluation of remdesivir.[10] Age-adjusted health utilities for the US general population were used to represent overall quality of life absent the effects of COVID-19.[10,23] These utilities were adjusted to account for the greater prevalence of comorbidities in the modeled population (Table I).

In the inpatient submodel, the disutility associated with influenza in prior economic modeling[24] was used as a proxy estimate of the disutility associated with COVID-19 symptoms,[10] and disutilities associated with hospitalization and ventilation were derived from a quality-of-life study from France in patients hospitalized for the treatment of *Clostridium difficile* infection.[10,25] The Institute for Clinical and Economic Review model did not contain a corresponding health state for supplemental oxygen, and so the disutility of this state in the CEM was interpolated as the midpoint between noninvasive ventilation and medical care without oxygen (Table III).

In the discharged submodel, reduced quality of life among patients requiring postacute care was simulated by relative utility multipliers sourced from the literature (see **Supplemental Table S1**). Relative utilities associated with inpatient rehabilitation and skilled nursing facility care were estimated by replicating the approaches used in a published CEM of severe chronic obstructive pulmonary disease.[46] The relative utility of inpatient rehabilitation was derived from a quality-of-life study in patients with myocardial infarction who underwent 8-week inpatient rehabilitation,[47,48] while the relative utility associated with a skilled nursing facility was derived from a CEA of osteoporosis.[48,49] A derived estimate of the relative utility of hospice care was calculated as the quotient of the utility of hospice divided by the utility of progression-free survival in a published CEA of ovarian cancer.[50] In the absence of available evidence, the relative utility of home health care was assumed to be identical to the relative utility of inpatient rehabilitation, and the relative utilities of a short-term hospital and a long-term acute care hospital were assumed to be the same as the relative utility of a skilled nursing facility.

In the recovered submodel, the health utilities of patients recovered from COVID-19 were assumed to be the same as the age-adjusted health utilities of the general US population, adjusted to account for the greater prevalence of comorbidities among hospitalized patients with COVID-19 (see the earlier discussion of comorbidities in the population subsection).[23]

Other Inputs

Treatment dosing and administration inputs assumed that remdesivir was administered by infusion as a single loading dose of 200 mg on day 1, followed by daily doses of 100 mg during hospitalization for up to 10 days,[51] and that baricitinib was administered orally as a daily dose of 4 mg during hospitalization for up to 14 days.[8] Age- and sex-adjusted all-cause mortality rates were sourced from the Social Security Administration Period Life Table of 2017.[52] The discounted rates for costs and QALY were set to 3% per annum.[53–55]

Model Base-Case, Scenarios, and Sensitivity Analyses

For the base case, we evaluated the cost-effectiveness of baricitinib + SOC versus placebo + SOC in hospitalized patients with COVID-19 using efficacy data from the COV-BARRIER trial, from a health payor perspective over a lifetime horizon, which accounted for long-

Table IV. Cost-effectiveness results for baricitinib + SOC versus placebo + SOC, from the payor's perspective.

Scenario and arm	Total Costs, USD	Total QALYs Gained	Total LYs Gained	Cost per QALY Gained, USD	Cost per LY Gained, USD
Base case					
Placebo + SOC	329,268	11.3879	14.300		
Baricitinib + SOC	346,544	12.0582	15.137		
Incremental, baricitinib vs placebo	17,276	0.6703	0.837	25,774	20,638
Mortality only					
Placebo + SOC	329,268	11.3879	14.300		
Baricitinib + SOC	347,170	12.0544	15.136		
Incremental, baricitinib vs placebo	17,902	0.6664	0.835	26,862	21,433

LY = life-years; QALY = quality-adjusted life-years; SOC = standard of care; USD = US dollars.

term direct medical costs. In a secondary "mortality-only" analysis, we examined the cost-effectiveness of baricitinib + SOC versus placebo + SOC, assuming that the statistically significant reduction in mortality demonstrated in COV-BARRIER was the only benefit with baricitinib treatment. We tested the impact of parameter uncertainty on the results of the primary analysis through deterministic sensitivity analysis and PSA. We also examined the cost-effectiveness of baricitinib + SOC from the hospital perspective.

RESULTS

Payor Perspective

Base-Case and Scenario Results

With baricitinib + SOC versus placebo + SOC, the incremental total cost was 17,276 USD, total QALY gained was 0.6703, and total LY gained was 0.837 (Table IV). The primary components of the incremental results were the greater lifetime all-cause medical costs (17,673 USD) and lifetime QALYs (0.6669) accrued by patients who survived and recovered from COVID-19 (see **Supplemental Table S5**). In the base-case analysis, the incremental cost-effectiveness ratios (ICERs) of adjunctive treatment with baricitinib were 25,774 USD/QALY gained and 20,638 USD/LY gained (Table IV). When the only difference in treatment effects between baricitinib + SOC and placebo + SOC was the probability of recovery (ie, the mortality-only scenario), the ICERs were 26,862 USD/QALY gained and 21,433 USD/LY gained—only slightly greater than the base case (Table IV).

Deterministic (One-Way) Sensitivity Analysis

The 10 most sensitive inputs identified through one-way sensitivity analysis in the base-case analysis from the payor perspective are shown in Figure 2. The base-case results were most sensitive to uncertainty regarding the lifetime all-cause health care costs among recovered patients, followed by progression to mechanical ventilation during the inpatient stay. The ICER was between 20,000 and 32,000 USD for all variables explored in the one-way sensitivity analysis, which fell well within the threshold of 50,000 USD/QALY gained recommended by the Institute for Clinical and Economic Review.

Probabilistic Sensitivity Analysis

A PSA of the base-case analysis was implemented in Excel software (Microsoft, Redmond, Washington) with 5000 replications (Figure 3). Compared with SOC alone, adjunctive treatment with baricitinib was associated with a cost increase of 17,373 USD (95% CI, –3300 to 38,306) and a clinical effect increase of 0.674 QALYs (95% CI, –0.096 to 1.441). The cost-effectiveness acceptability curve indicated that adjunctive treatment with baricitinib was cost-effective at a willingness-to-pay threshold

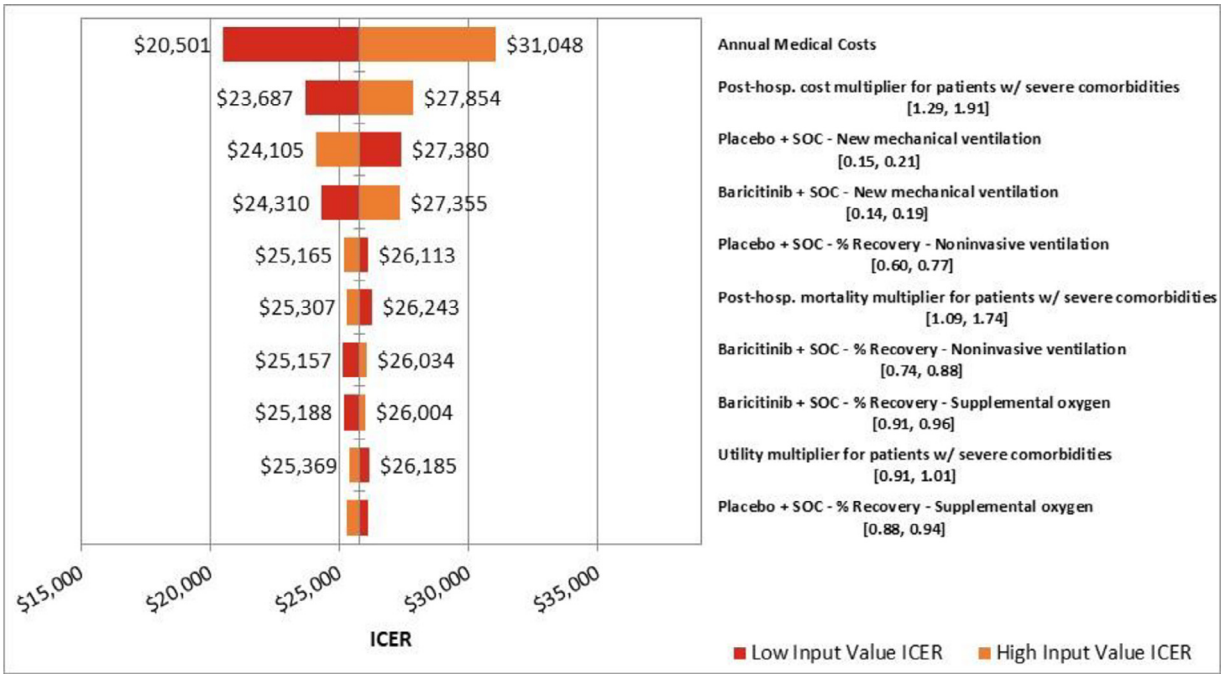

Figure 2. Deterministic sensitivity analysis tornado diagram with 10 most sensitive inputs for base case (payor perspective) with an incremental cost-effectiveness ratio (ICER) = 25,774 US dollars.

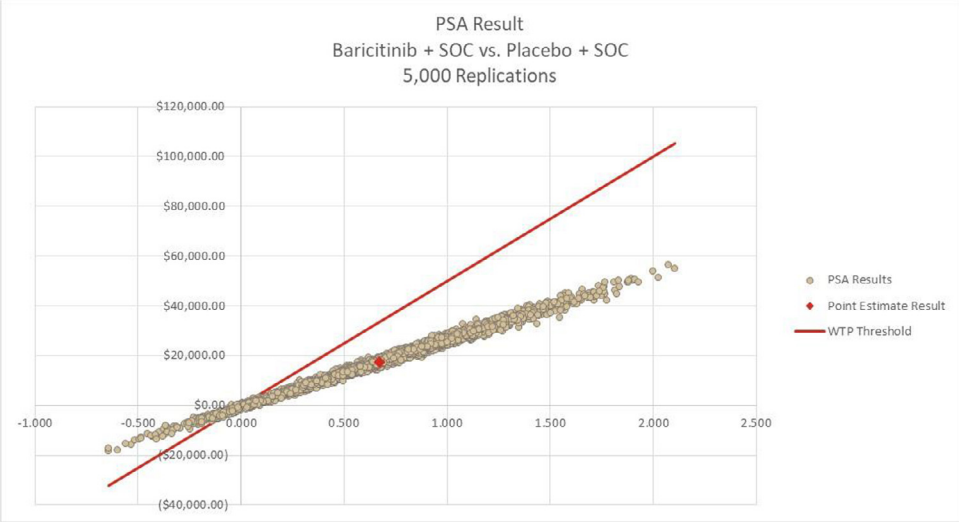

Figure 3. Probabilistic sensitivity analysis cost-effectiveness plane for baricitinib + standard of care (SOC) vs placebo + SOC, with 5000 replications for the base case from private payor perspective. Costs versus quality-adjusted life-years (QALYs), with a 50,000 US dollars willingness-to-pay (WTP) threshold for comparison.

of 50,000 USD/QALY gained in 96.5% of the PSA replications.

Hospital Perspective

We also ran secondary analyses from a hospital perspective. In the base-case hospital perspective analysis, treatment with baricitinib + SOC was both more effective and less costly than treatment with placebo + SOC. Adding baricitinib to SOC reduced total hospital expenditures by 2436 USD and reduced total reimbursement payments by 503 USD, resulting in a 1932 USD reduction in net costs. It also resulted in a net gain of 0.0023 QALYs, reduced the use of mechanical ventilation by 1.6%, and increased survival by 5.1% (see **Supplemental Table S6**). In the mortality-only scenario analysis, the addition of baricitinib to SOC increased hospital expenditures by 1978 USD and increased survival by 5.1%, resulting in an incremental cost of 38,964 USD per death avoided (see **Supplemental Table S6**).

Net Impact on Clinical Outcomes

Net impacts on clinical outcomes are presented in the **Appendix**. Compared with placebo + SOC, treatment with baricitinib + SOC reduced the use of mechanical ventilation by 16 patients per 1000 treated and reduced the use of noninvasive ventilation by 7 patients per 1000 treated. Similarly, treatment with baricitinib + SOC reduced the total hospital LOS by 800 days per 1000 patients treated, with the decrease mainly driven by a decrease of 1580 days of mechanical ventilation per 1000 patients treated.

DISCUSSION

We conducted an economic evaluation on the use of baricitinib + SOC versus placebo + SOC among hospitalized patients with COVID-19 in a US setting, based on the outcomes from the Phase III COV-BARRIER trial. A *de novo* CEM was developed by extending the methods used in the Institute for Clinical and Economic Review's evaluation of remdesivir to support a hospital perspective and to account for discharge status, postacute care, and the greater prevalence of comorbidities among hospitalized patients with COVID-19.

In the base-case analysis from the payor perspective, with baricitinib + SOC, the incremental cost per QALY gained was 25,774 USD, and the cost per LY gained was 20,638 USD. In the mortality-only scenario analysis, which limited the treatment benefit of baricitinib to the statistically significant reduction in mortality demonstrated in COV-BARRIER, the ICERs were 26,862 USD/QALY gained and 21,433 USD/LY gained—only slightly greater than the base case. The principal drivers of the incremental results with baricitinib were the greater lifetime all-cause medical costs and greater lifetime QALYs accrued by recovered patients due to the greater survival rate. The robustness of the results in the mortality-only scenario analysis, deterministic sensitivity analysis, and the PSA provides further evidence that baricitinib + SOC is cost-effective versus SOC alone at the conservative willingness-to-pay threshold of 50,000 USD/QALY gained recommended by the Institute for Clinical and Economic Review, even when lifetime all-cause medical costs were factored into the analysis.

The base-case analysis from the hospital perspective indicated that adjunctive treatment with baricitinib reduces total hospital expenditures, primarily by reducing the number of patients who require mechanical ventilation. Given that patients requiring mechanical ventilation were reimbursed via more expensive DRGs, reimbursement payments were also reduced. However, the reduction in hospital expenditures was greater than the reduction in reimbursement payments, producing an overall savings in net costs (expenses minus reimbursement). With baricitinib + SOC, QALYs were also greater; therefore, baricitinib + SOC was a dominant strategy (lesser costs and greater effectiveness) compared with SOC alone. In the mortality-only scenario analysis from the hospital perspective, with adjunctive treatment with baricitinib, the incremental cost was 38,964 USD per death avoided.

The COVID-19 pandemic continues, and new variant strains are emerging, despite the increasing percentage of vaccinated population. Thus, decision makers will continue to rely on CEAs to assess the relative value of emerging treatments.[56] Evidence on the CEA of COVID-19 treatments in the United States is limited. Remdesivir, the first treatment approved by the US Food and Drug Administration for use in patients with COVID-19, was evaluated by the Institute for Clinical and Economic Review using a CEM, without consideration of discharge status or postacute care outcomes of patients, nor was the hospital perspective evaluated.[57] While the Institute

for Clinical and Economic Review's model simulated a lifetime horizon using mortality and cost and QALY estimations from the general population, the poorer health of hospitalized patients with COVID-19 due to more comorbidities *vis-à-vis* the general population was not addressed.

Our model overcame those key limitations by considering total hospital expenditures, reimbursement payments, and net costs per QALY gained. Our model explicitly considered the health outcomes and costs by discharge status (self-care or custodial care, home health care, inpatient rehabilitation, skilled nursing facility care, short-term hospitalization, long-term acute care hospitalization, and hospice status) to provide an overall picture of postacute hospital consequences. Also, the mortality-related calculations in our model accommodated a wide range of age groups, and the long-term all-cause health care costs reflected the impact of comorbidities in this population. Another major strength of our model was the use of detailed data on inpatient and discharge status from patients with COVID-19 in clinical practice in the United States from the PHD. The flexible and realistic features of the model allowed for adaptations for use outside the United States.

Data on the possible long-term burden of COVID-19 have only recently emerged.[58,59] Thus, our model, as well as other existing CEMs, did not consider the long-term consequences of COVID-19 due to a lack of data.[60] Although our model estimated the potential impact of efficacious therapies that can reduce progression to greater levels oxygen care, and therefore reductions in hospital and intensive care unit LOSs, these potential benefits to hospitals in terms of alternative, non COVID-19–related care were not directly quantified. Another limitation specific to our hospital data inputs was the potential lack of generalizability of these national estimates to individual hospitals. Also, our hospital costs did not include COVID-19–related hospital readmissions. Finally, the model assumed that recovered patients incurred all-cause health care costs, health utilities, and all-cause mortality based on the general non–COVID-19 infected population, adjusted to reflect greater rates of comorbidities in the modeled COVID-19 population, but not reflective of currently indeterminant long-term COVID-19 sequalae.

CONCLUSIONS

In the present analysis, baricitinib in combination with SOC in patients hospitalized due to COVID-19 infection in the United States was cost-effective. These results were robust across multiple sensitivity analyses and scenarios in the model and were driven by the reduced risk for mortality with baricitinib treatment.

AUTHOR CONTRIBUTIONS

R.O.: design of the work and interpretation of the data; T.S. and M.B.: concept and design of the work, interpretation of data; P.M.: concept and design of the work, acquisition and interpretation of data; K.K. and T.K.: concept and design of the work, acquisition, analysis, and interpretation of data; R.B.: concept of the work, acquisition and interpretation of the data; N.A.: interpretation of the data.

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DISCLOSURE

K.K. and T.K. are employees of Medical Decision Modeling Inc and received funding from Eli Lilly and Company to conduct the study. P.L.M., T.S., R.B., and M.B. are employees of Eli Lilly and Company. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2021.09.016.

SUPPLEMENTARY APPENDIX 1. DETAILS OF THE MODEL STRUCTURE

The model is structured as three submodels (Figure A1):

1. **Inpatient:** Algebraic model of the inpatient stay from admission to discharge. This phase accounts for the effects of treatment on health outcomes, which in turn determine the costs expended by the hospital, reimbursement payments received from insurers, and patient quality of life while hospitalized.
2. **Discharge:** Algebraic model of the potential for follow-up care, such as discharge to a rehabilitation facility, skilled nursing facility, long-term acute care hospital, hospice, or self-care. This phase accounts for the impact of prolonged care on costs and the patient's quality of life immediately following discharge.
3. **Recovered:** Markov model of the remaining life years after the patient recovers from COVID-19. This phase accounts for the costs and benefits of reducing mortality associated with COVID-19.

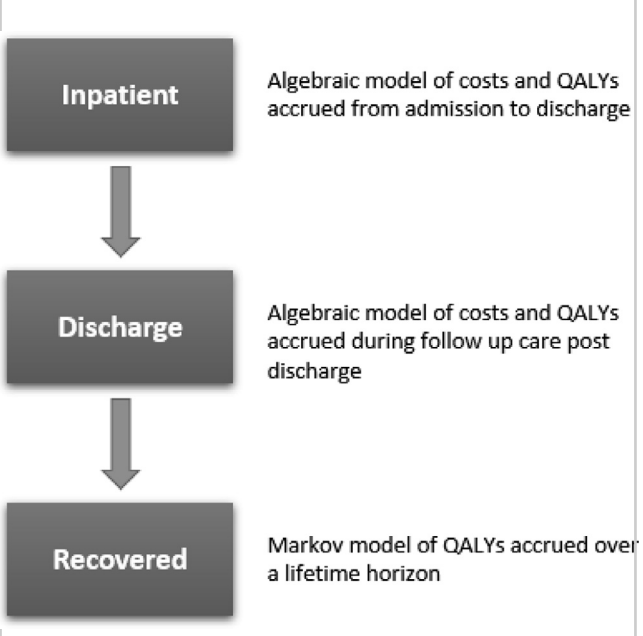


Figure A1. Top-level structure of the cost-effectiveness model. Abbreviations: QALY, quality-adjusted life year.

1.1 Inpatient Submodel

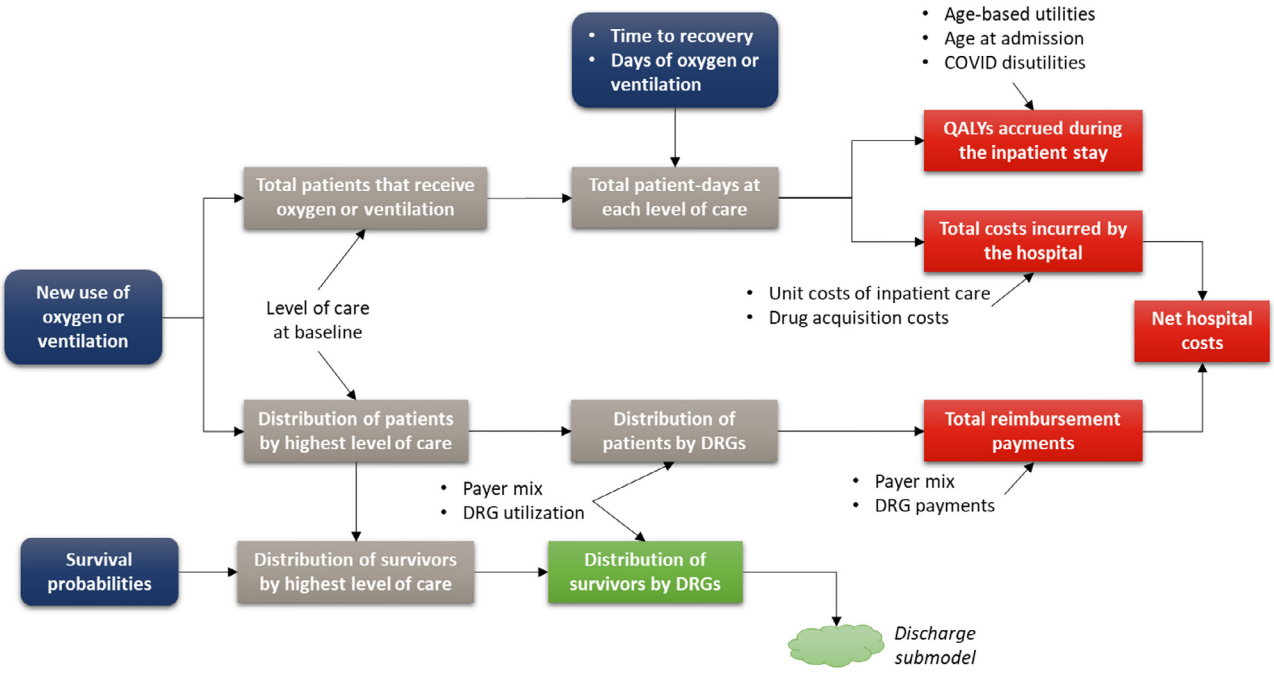
The inpatient submodel is an algebraic model that calculates the costs and QALYs accrued during the inpatient stay through a sequence of matrix operations (Figure A2). The key drivers of cost effectiveness during the inpatient stay are the total patient-days at each level of care (expenses and QALYs) and the distribution of patients by highest level of care (DRGs and reimbursements). Treatment effects on mortality do not directly affect inpatient costs and QALYs but have downstream effects in the discharge and recovered submodels.

1.2 Discharge Submodel

The discharge submodel is an algebraic model that calculates the costs and QALYs accrued during the post-discharge follow-up period through a sequence of matrix operations (Figure A3). The submodel assumes that patients discharged to hospice die at the end of their hospice stay, and patients discharged to any other status enter the recovered submodel at the end of the follow-up period.

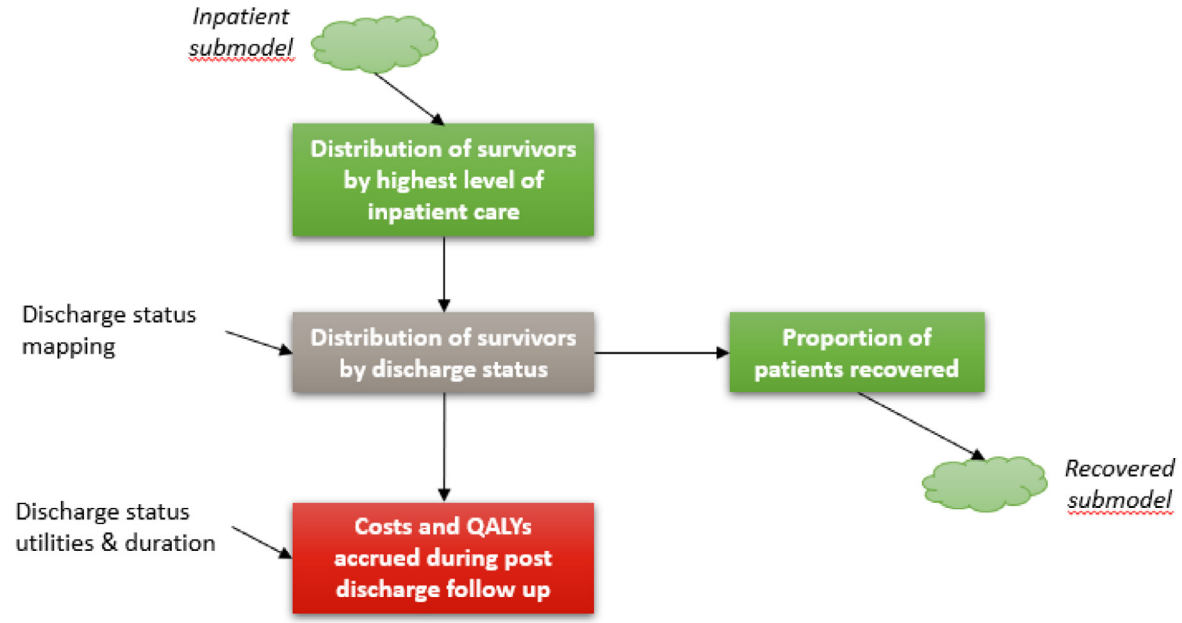
1.3 Recovered Submodel

The recovered submodel is a Markov model that simulates patients after they have recovered and completed any required post-discharge follow-up care (Figure A4). The purpose of this submodel is to account for the costs and QALY benefits of treatment effects on COVID-related mortality. It is a simple Markov model with two states, alive or dead, that simulates all-cause mortality over a lifetime horizon. Costs incurred during this phase may be excluded from the analysis by the user if they are considered beyond the scope of the payer (hospital, Medicare, Medicaid, private insurer, or the patient). The assumption is that recovered COVID-19 patients incur all-cause healthcare costs, health utilities, and all-cause mortality based on the general non-COVID-19 infected population, adjusted to reflect higher rates of comorbidities in the modeled COVID population.



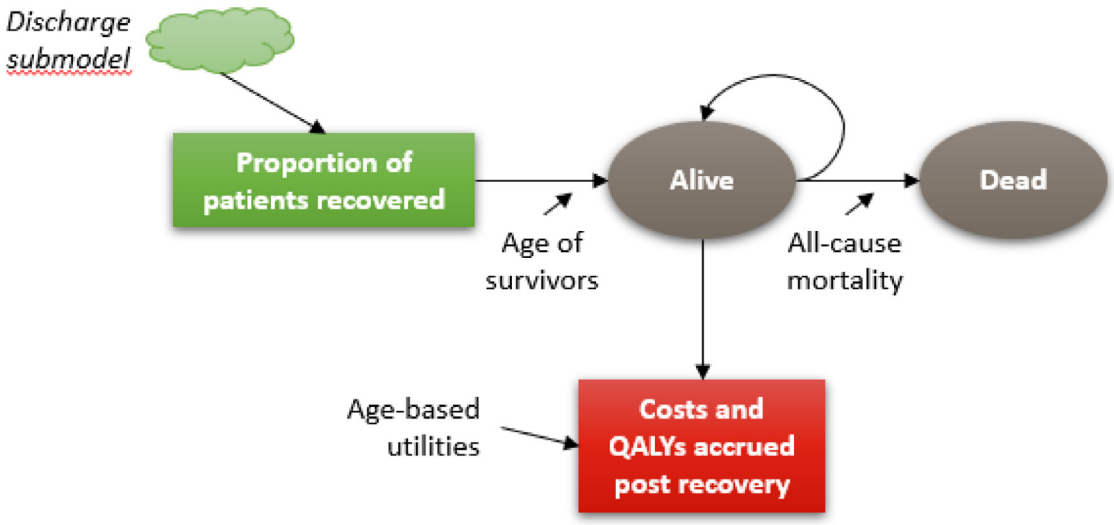
Note: The color coding is as follows: dark blue, treatment-specific user inputs; no fill, non-treatment-specific user inputs; grey, interim calculations in the inpatient submodel; red, top-line results; green, interim results passed to the discharge submodel.
Abbreviations: COVID, coronavirus disease; DRG, diagnosis-related group; QALY, quality-adjusted life year.

Figure A2. Flow of calculations in the inpatient submodel.



Note: The color coding is as follows: no fill, non-treatment-specific user inputs; grey, interim calculations in the discharge submodel; red, top-line results; green, interim results passed to and from other submodels.
Abbreviations: QALY, quality-adjusted life year.

Figure A3. Flow of calculations in the discharge submodel.



Note: The color coding is as follows: no fill, non-treatment-specific user inputs; grey, health states in the Markov submodel; red, top-line results; green, interim results passed to and from other submodels.
Abbreviations: QALY, quality-adjusted life year.

Figure A4. Flow of calculations in the recovered submodel