ORIGINAL RESEARCH

Cost-Effectiveness of Combination of Baricitinib and Remdesivir in Hospitalized Patients with COVID-19 in the United States: A Modelling Study

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ABSTRACT

Introduction: Baricitinib–remdesivir (BARI-REM) combination is superior to remdesivir (REM) in reducing recovery time and accelerating clinical improvement among hospitalized patients with coronavirus disease 2019 (COVID-19), specifically those receiving high-flow oxygen/noninvasive ventilation. Here we assessed the cost-effectiveness of BARI-REM versus REM in hospitalized patients with COVID-19 in the USA.

Methods: A three-state model was developed addressing costs and patient utility associated with COVID-19 hospitalization, immediate post hospital care, and subsequent lifetime medical care. Analysis was performed from the perspective of a payer and a hospital. Both perspectives evaluated two subgroups: all patients and patients who required oxygen. The primary measures of benefit in the model were patient quality-adjusted life years (QALYs) accrued during and after hospitalization, cost per life years gained, cost per death avoided, and cost per use of mechanical ventilation avoided.

Results: In the base-case payer perspective with a lifetime horizon, treatment with BARI-REM versus REM resulted in an incremental total cost of $7962, a gain of 0.446 life years and gain of 0.3565 QALYs over REM. The incremental cost-effectiveness ratios of using BARI-REM were estimated as $22,334 per QALY and $17,858 per life year. The base-case and sensitivity analyses showed that the total incremental cost per QALY falls within the reduced willingness-to-pay threshold of $50,000/QALY applied under health emergencies. In all hospitalized patients, treatment with BARI-REM versus REM reduced total hospital expenditures per patient by $1778 and total reimbursement payments by $1526, resulting in a $252 reduction in net costs per patient; it also resulted in a net gain of 0.0018 QALYs and increased survival of COVID-19 hospitalizations by 2.7%.

Conclusion: Our study showed that BARI-REM is cost-effective compared to using REM for hospitalized patients with COVID-19. The base-case results of this cost-effectiveness model were most sensitive to average annual medical costs for recovered patients.

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Key Summary Points

Why carry out this study?

COVID-19 pandemic continues to impose substantial economic and heath care resource burden on payers and hospitals globally and in the USA.

As the treatment landscape continues to evolve, there is a need to assess cost-effectiveness of various therapeutic options available for the treatment of patients hospitalized as a result of COVID-19.

This study assesses the cost-effectiveness of combination of baricitinib and remdesivir versus remdesivir alone in hospitalized patients with COVID-19 in the USA.

What was learned from the study?

Our study showed that the combination of baricitinib and remdesivir is cost-effective compared to using remdesivir alone for patients hospitalized as a result of COVID-19.

INTRODUCTION

Since the first identified case in China, in December 2019, coronavirus disease 2019 (COVID-19) has grown into a global pandemic with 206.9 million confirmed global cases of COVID-19 until August 2021; this number also includes 4.3 million deaths [1, 2]. As of August, 2021, the USA reported 36.3 million confirmed cases of COVID-19 with 615,747 deaths [2]. The Centers for Disease Control and Prevention noted a total of 194,642 laboratory-confirmed hospitalizations in the USA as of August 2021 [3].

Cost impacts and capacity constraints place a large burden on hospitals and health care systems during the global pandemic [4]. Vaccinations are demonstrated to be clinically effective and cost-effective. However, the time taken to vaccinate a sufficient proportion of the population and the uncertainty associated with the emergence of multiple variants of the virus call for more and improved treatment options [5].

Recently, baricitinib (BARI) was granted an emergency use authorization (EUA) by the US Food and Drug Administration (FDA) for the treatment of hospitalized adult and pediatric patients with COVID-19 aged 2 years and more requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [6]. Earlier, BARI was granted an EUA in combination with remdesivir (REM) by the FDA for the treatment of hospitalized adult patients with COVID-19 [7]. Results of the second stage Adaptive COVID-19 Treatment Trial 2 (ACTT-2) showed superiority of BARI-REM over REM alone for reducing recovery time and accelerating clinical improvement in hospitalized patients with COVID-19. This benefit was specifically among patients receiving high-flow oxygen or noninvasive ventilation [8].

The Institute for Clinical and Economic Review (ICER) performed an assessment of REM for hospitalized patients with COVID-19 using clinical efficacy data from ACTT-1 and the report separately evaluated REM plus standard of care in the mild and moderate-to-severe populations on the basis of clinical evidence from several trials [9–14]. However, the ICER model did not consider any COVID-19-specific post hospital care of patients nor the detailed (i.e., diagnostic related group [DRG related]) economics associated with a hospital perspective. For these reasons, we evaluated cost-effectiveness of BARI-REM versus REM using data from the ACTT-2 trial by creating a more detailed version of the cost-effectiveness (CE) model to accommodate these important features of COVID-19 treatment and reimbursement.

METHODS

Model Overview

A pharmacoeconomic model was developed to estimate the cost-effectiveness of BARI-REM as a treatment for hospitalized adults with COVID-19 (aged ≥ 18 years) in the USA. The primary perspective of the analysis used was from the payer or partial societal (Medicare, Medicaid, private payer, uninsured/self-insured patients), where costs to payers were defined as reimbursements paid to hospitals, to post-acute discharge care providers, for long-term post recovery costs, and the indirect costs due to missed work during the inpatient hospital stay to account for the number of working days lost. Inpatient hospital expenditures were based on Medicare Severity DRGs (MS-DRGs) for COVID-19 admissions. 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, where key model parameters were varied. This manuscript does not contain any new studies with human or animal subjects performed by any of the authors.

The measure of benefit in the model was quality-adjusted life years (QALYs) that were accrued during and after discharge of hospitalized patients. QALYs and costs were discounted at 3% per year [15]. Health outcomes represented in the model were based on the ordinal scale (OS) used to measure efficacy in the ACTT-2 trial [11]. Inpatient hospital outcomes in the model included medical care without oxygen (OS 4), supplemental oxygen (OS 5), noninvasive ventilation (OS 6), mechanical ventilation (OS 7), and death (OS 8). Mortality, overall time to recovery, duration of treatment with mechanical ventilation/noninvasive ventilation/supplementary oxygen, proportion of patients who progressed to new use of mechanical ventilation/noninvasive ventilation/supplementary oxygen, and impact of treatment on discharge status of patients were included in the model as treatment effects. For different mortality assumptions, incremental

cost-effectiveness ratio of BARI-REM versus REM was assessed.

In a secondary analysis, we focused on the hospital perspective, whereby the net hospital cost impact (hospital costs less DRG reimbursement) was used with the time horizon set to be within the hospital stay period.

Model Framework

A schematic representation of the model used for this analysis is shown in Fig. 1. The model consists of three functional components addressing inpatient hospitalization, immediate post discharge patient care, and patient life after hospitalization or post discharge care.

The inpatient hospitalization and post discharge portions of the model estimate QALYs and costs for patients based on (treatment-related) hospital survival and disease severity (e.g., use of mechanical ventilation) and the use of acute post hospital discharge care. After a patient left post hospital discharge care (if used), their remaining life medical costs, QALYs, and mortality were based on age-specific inputs (e.g., standard population life tables) adjusted for treated patient comorbidities. The discharge submodel assumed that all patients who were discharged to hospice died at the end of their stay, and all patients discharged to any other type of post-acute care were assumed to survive and proceeded to the recovered submodel.

Patients who entered the recovered submodel were followed until death or the end of the simulation time horizon. The recovered submodel tracked patients surviving hospitalization and immediate post-hospitalization, estimating remaining all-cause mortality over a lifetime horizon. Mortality of patients who recovered from COVID-19 was based on the general population that has not had COVID-19. The model included an upward adjustment to mortality rates to reflect higher rates of comorbidities associated with the hospitalized COVID-19 population as seen in the ACTT-2 trial [8].

In the analysis from hospital perspective, only costs and QALYs incurred during the
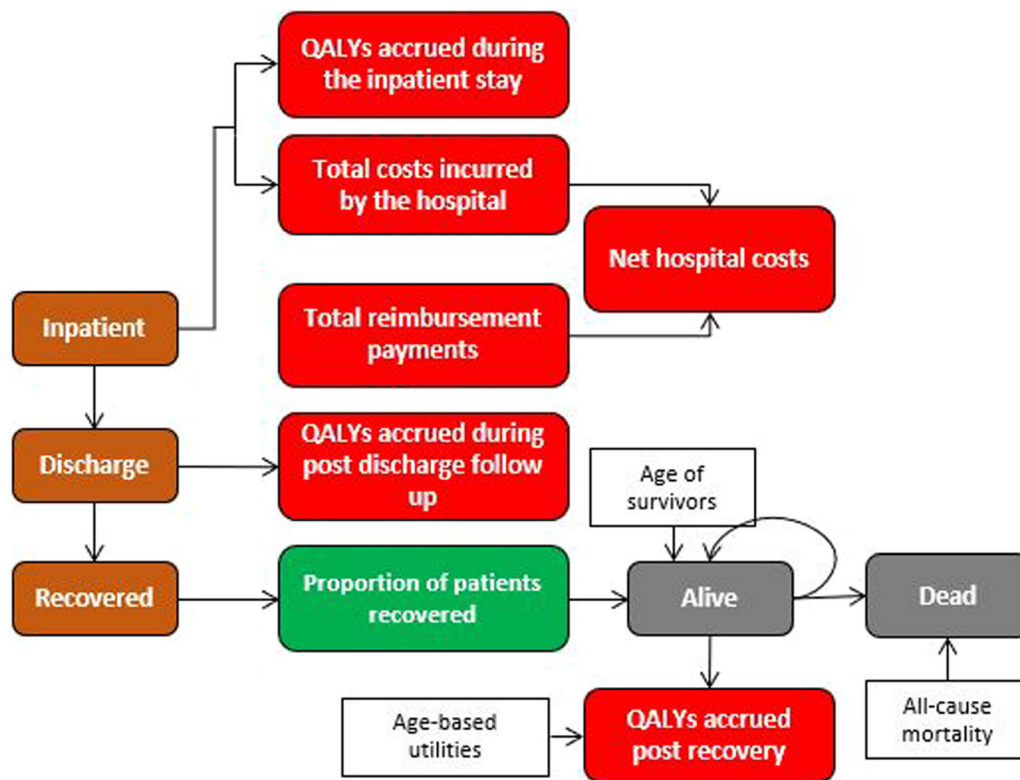
Fig. 1 Model structure. *Patients were tracked after discharge to self-care or custodial care, home health care, inpatient rehab, skilled nursing facility, short-term hospital, long-term acute care hospital, hospice; the color coding is as follows: blue, model stages; gray, health states in the Markov submodel; red, top-line results; green, interim results passed to and from other submodels

inpatient submodel are included, since the costs after discharge are not covered by the hospital.

Model Inputs

Population: The key population variables are demographics, level of care at baseline, severe comorbidities, and distribution of patients by payer type (Table 1). The modeled population consisted of 35.6% female patients with an average age of 58.9 years at hospital admission [11]. The average age of patients who recovered was 57.5 years and was sourced from ICER's REM model report [10]. The level of care required by the cohort at baseline—such as use of mechanical (10.7%) or noninvasive ventilation (20.9%), supplemental oxygen (54.7%), or medical care without oxygen (13.7%) on an OS—was sourced from Kalil et al. [8]. A total of 34.2% patients modeled in the study had severe

comorbidities requiring adjustments to both costs and utilities associated with these patients [8]. The post-discharge cost-multiplier was set at 1.601 [16], the utility multiplier was set at 0.962 [17], and post-discharge mortality multiplier at 1.37 [18] for these patients. The model sourced the distribution of patients by payer type from the Premier Healthcare Database, which is a large and all-payer US hospital database of detailed information on inpatient discharges (henceforth referred to as the Premier cost analysis) [19]. The majority of the modeled population were enrolled in Medicare (52.9%) or had private payer coverage (27.9%) [19].

Treatment efficacy: Clinical efficacy data of BARI-REM and REM were sourced from the ACTT-2 trial, Kalil et al., and Beigel et al. [8, 11, 20] and divided into two overlapping subgroups; (1) all hospitalized patients and (2) patients who required use of oxygen at

Table 1 Population inputs

Parameters	Value	SE	Distribution	Lower–upper	Sources	Reference
Demographics						
Female, %	35.6	5.0	Beta	25.0, 45.0	Beigel 2020	[11]
Average age at hospital admission, years	58.9	5	Normal	55.0–60.0	Beigel 2020	[11]
Average age of patients who recover, years	57.5	5	Normal	55.0–60.0	Campbell 2020	[10]
Level of care at baseline*, %			Dirichlet (N = 1033)	Not varied in OWSA	Kalil 2020	[8]
Mechanical ventilation (OS 7)	10.7					
Noninvasive ventilation (OS 6)	20.9					
Supplemental oxygen (OS 5)	54.7**					
Medical care without oxygen (OS 4)	13.7					
Severe comorbidities						
Patients with severe comorbidities, %	34.2	3.4	Beta	27.5, 40.8	Kalil 2020	[8]
Post-discharge cost multiplier	1.601	0.160	Normal	1.287, 1.914	Boudreau 2009	[16]
Utility multiplier	0.962	0.026	Normal	0.911, 1.014	Vetter 2011 (erratum 2012)	[17]
Post-discharge mortality multiplier	1.37	0.17	Normal	1.09, 1.74	Ford 2005	[18]
Distribution of patients by payer type, %			Dirichlet (N = 105,736)		Premier cost analysis and assumption	[19]
Medicare	52.9					
Medicaid	19.2			45.6, 60.2		
Private payer	27.9			16.5, 21.9		
Uninsured	0.0			17.9, 37.9		

ACTT-2 Adaptive Covid Treatment Trial 2, *ICER* Institute for Clinical and Economic Review, *N* sample size for Dirichlet, *OS* ordinal scale, *OWSA* one-way sensitivity analysis, *SE* standard error

*These values are for the "all patients" subgroup. For patients with oxygen use, ordinal scale 4 was zeroed and all other ordinal scales were renormalized to sum to 100%

**The value was adjusted to ensure that the distribution of patients by baseline ordinal scale summed to 100%

admission for analysis. The efficacy parameters used in the model were incidence of new ventilation or oxygen (after initial hospital admission), duration of care, and probability of recovery (patients that did not die) (Table 2). For all hospitalized patients, there were 10.0%, 20.0%, and 23.0% patients in the BARI-REM group and 15.0%, 24.0%, and 40.0% patients in the REM group who required new mechanical ventilation, new noninvasive ventilation, and new supplemental oxygen, respectively. The time to recovery was 10.6 days in the BARI-REM treatment arm versus 11.2 days in the REM treatment arm. The probability of recovery with mechanical ventilation was 76.8% with BARI-REM versus 77.1% with REM.

Costs: The cost of acquiring 100 mg REM was priced at $390 for Medicaid/Medicare patients and $520 for private payer or uninsured patients [21]. The cost for a 2-mg BARI tablet was $75.50 [22]. The inputs for hospital costs were obtained from Premier cost analysis [19]. The average reimbursement per patient by payer type and highest level of care during the inpatient stay in the base case is presented in Supplementary Table S1. The inpatient cost incurred by payers was based on MS-DRG reimbursement amounts (Supplementary Table S2). For Medicare patients, special additional payments were made by Medicare (a 20% extra payment under the CARES act). BARI and REM were also eligible for potential new COVID-19 treatments add-on payment (NCTAP) (Supplementary Table S3). The indirect costs were estimated by multiplying the percentage of patients employed (32.4%) [23, 24] by missed workdays and cost per workday ($218.63) and were sourced from the Bureau of Labor Statistics [25] (Table 3). The proportion of patients with full-time employment was calculated by weighting the employment percentages for each payer type by the distribution of payers estimated from the Premier cost analysis [19]. The proportion of Medicare patients with full-time employment (11.6%) was assumed to be equal to the proportion of the population aged 65 and older with full-time employment [23]. The proportion of Medicaid patients with full-time

employment (48.0%) was sourced from a report by the Kaiser Family Foundation [24]. The proportion of commercially insured patients with full-time employment was assumed to be the proportion of the US population aged 20–64 years with full-time employment (61%) [23]. The cost per workday missed was based on employer costs for employee compensation from the Bureau of Labor Statistics ($38.26/h) and the assumption of 40 h/week for full-time employment [25]. These indirect costs were only accounted for in the payer perspective.

Health utilities: Health utilities were based on US age-adjusted general population utilities derived from Sullivan et al. [26]. The disutility associated with COVID-19 symptoms and additional disutility associated with each level of oxygen support were based on Campbell et al., Sullivan et al., Barbut et al., and Sackett et al. [10, 26–28] using the assumption that the illnesses in the publications were similar to the corresponding severity of COVID-19. These are presented in Table 4. Our model used the same disutilities as the ICER model for COVID-19 symptoms and levels of care provided during the inpatient stay. The ICER model did not contain a corresponding health state for supplemental oxygen; therefore, the disutility of this health state in our model was interpolated as the midpoint between noninvasive ventilation and medical care without oxygen.

The discount rates for costs and QALY were set to 3% and were sourced from Sanders et al. [29] and the ICER 2020–23 value assessment framework [29, 30]. The life tables were sourced from the Social Security Administration [31].

Base-Case Results and Sensitivity Analyses

Base-case results are presented from both the payer perspective and the hospital perspective. Deterministic sensitivity analysis and probabilistic sensitivity analysis results are presented from the payer perspective. All the analyses in this study were done using Microsoft® Excel® for Microsoft 365 MSO.

Table 2 Treatment effectiveness inputs

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
All hospitalized patients						
Incidence of care post-admission, %			Beta		ACTT-2 results (data on file)	[20]
New mechanical ventilation						
REM	15.0	1.0		12.0, 19.0		
BARI-REM	10.0	1.0		8.0, 13.0		
New noninvasive ventilation						
REM	24.0	1.5		19.0, 28.0		
BARI-REM	20.0	1.5		16.0, 24.0		
New supplemental oxygen						
REM	40.0	3.0		30.0, 52.0		
BARI-REM	23.0	3.0		15.0, 34.0		
Duration of care, days			Normal		ACTT-2 results (data on file)	[20]
Time to recovery						
REM	11.20	0.26		10.69, 11.71		
BARI-REM	10.60	0.24		10.13, 11.07		
Mechanical ventilation days						
REM	4.05	0.38		3.31, 4.79		
BARI-REM	2.79	0.30		2.2, 3.38		
Noninvasive ventilation days						
REM	2.29	0.21		1.87, 2.71		
BARI-REM	2.34	0.23		1.89, 2.78		
Supplemental oxygen days						
REM	4.21	0.13		3.96, 4.46		
BARI-REM	4.40	0.17		4.06, 4.74		
Probability of recovery, %			Beta		Kalil 2020; Biegel 2020	[8, 11]
Mechanical ventilation						
REM	77.1	2.5		70.0, 85.0		
BARI-REM	76.8	2.5		70.0, 85.0		
Noninvasive ventilation						
REM	86.9	2.3		80.0, 94.0		

Table 2 continued

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
BARI-REM	92.6	2.3		85.0, 99.0		
Supplemental oxygen						
REM	95.2	1.7		90.0, 100.0		
BARI-REM	98.1	2.5		95.0, 100.0		
Medical care w/o oxygen						
REM	100.0	0.0		100.0, 100.0		
BARI-REM	100.0	0.0		100.0, 100.0		
Patients with oxygen use at baseline						
Incidence of care post-admission, %			Beta		ACTT-2 results (data on file)	[20]
New mechanical ventilation						
REM	18.0	1.3		14.0, 22.0		
BARI-REM	12.0	1.0		9.0, 15.0		
New noninvasive ventilation						
REM	29.0	1.5		24.0, 35.0		
BARI-REM	24.0	1.7		19.0, 29.0		
New supplemental oxygen						
REM	0.0	0.0		0.0, 0.0		
BARI-REM	0.0	0.0		0.0, 0.0		
Duration of care, days					ACTT-2 results (data on file)	[20]
Time to recovery			Normal			
REM	11.94	0.29		11.37, 12.51		
BARI-REM	10.99	0.26		10.48, 11.51		
Mechanical ventilation days						
REM	4.69	0.43		3.85, 5.54		
BARI-REM	3.23	0.34		2.56, 3.91		
Noninvasive ventilation days						
REM	2.63	0.24		2.16, 3.11		
BARI-REM	2.7	0.26		2.2, 3.21		
Supplemental oxygen days						
REM	4.61	0.01		4.61, 4.62		

Table 2 continued

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
BARI-REM	4.99	0.13		4.73, 5.25		
Probability of recovery, %					Biegel 2020	[11]
Mechanical ventilation			Beta			
REM	77.1	2.5		70.0, 85.0		
BARI-REM	76.8	2.5		70.0, 85.0		
Noninvasive ventilation						
REM	86.9	2.3		80.0, 94.0		
BARI-REM	92.6	2.3		85.0, 99.0		
Supplemental oxygen						
REM	95.2	1.7		90.0, 100.0		
BARI-REM	98.1	2.5		95.0, 100.0		
Medical care without oxygen						
REM	100.0	0.0		100.0, 100.0		
BARI-REM	100.0	0.0		100.0, 100.0		

BARI-REM combination of baricitinib and remdesivir, *REM* remdesivir, *SE* standard error

RESULTS

Payer Perspective

Base-Case Results
The treatment with BARI-REM versus REM for all hospitalized patients resulted in an incremental total cost of $7962, a total life-year gain of 0.446, and a total QALY gain of 0.3565. For all patients, the incremental cost-effectiveness was $22,334 per QALY gained and $17,858 per life year gained (Table 5). In patients with oxygen use at baseline, treatment with BARI-REM versus REM resulted in an incremental total cost of $8960, a total life year gain of 0.513, and a total QALY gain of 0.4107. The incremental cost per QALY gained was $21,818 and cost per life-year gained was $17,458 (Table 5). The disaggregated total costs and QALY results for all hospitalized patients and patients with oxygen use are presented in Supplementary Table S4.

Deterministic (One-Way) Sensitivity Analysis
From the payer perspective, the ten most sensitive inputs identified through one-way sensitivity analysis are shown in Fig. 2. In all hospitalized patients, the incidence of new mechanical ventilation in the REM treatment arm had the greatest effect on the cost-effectiveness ratio, while average annual medical costs for patients that recover from the COVID-19 hospitalization and variations in percentage recovery from supplemental oxygen, non-mechanical and mechanical ventilation in the BARI-REM treatment arms have smaller effects on the cost-effectiveness ratio. The post recovery medical cost multiplier for patients with severe comorbidities was also among the ten inputs that most influenced the output of the model. A similar pattern of the most influential parameters was observed in patients with oxygen use at baseline. The incremental cost-effectiveness ratio lies between $15,000 and

Table 3 Cost inputs

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
Hospital costs, per day (USD)			Normal		Premier cost analysis	[19]
Mechanical ventilation	$3660	$78.64		$3506, $3814		
Noninvasive ventilation	$2450	$124.99		$2205, $2695		
Supplemental oxygen	$1828	$19.05		$1791, $1865		
Medical care without oxygen	$1818	$13.40		$1792, $1844		
Payer costs per patient, by highest level of inpatient care[a]					Tables S2, S3, S5	Refer to supplementary tables for details (reference numbers are in continuation with the main manuscript)
Inpatient hospitalization costs						
REM						
Mechanical ventilation	$89,432					
Noninvasive ventilation	$31,965					
Supplemental oxygen	$31,404					
Medical care without oxygen	$30,876					
BARI-REM						
Mechanical ventilation	$90,553					
Noninvasive ventilation	$33,048					
Supplemental oxygen	$32,494					
Medical care without oxygen	$31,960					

Table 3 continued

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
Post-discharge COVID-19 costs					ACTT-2 results (data on file)	[20]
Mechanical ventilation	$8716					
Noninvasive ventilation	$3527					
Supplemental oxygen	$2388					
Medical care without oxygen	$2165					
Annual all-cause medical costs post recovery among patients without serious comorbidities			Normal		Whittington 2020	[9]
Age 0–18 years	$4432	$100		$3546, $5318		
Age 19–44 years	$5741	$150		$4593, $6889		
Age 45–64 years	$12,073	$200		$9658, $14,488		
Age 65–84 years	$20,071	$250		$16,057, $24,085		
Age 85+ years	$38,900	$300		$31,120, $46,680		
Indirect costs			Normal		Labor force statistics for current population survey 2021; Garfield 2021; Employer Costs for Employee Compensation 2021	[23–25]
Patients employed, %	32.4	5		25.9, 38.9		

Table 3 continued

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
Cost per workday missed	$218.63	$25		$175, $262		

COVID-19 coronavirus disease 2019, *N* sample size, *NA* not applicable, *SE* standard error

[a]Payer costs per patient by highest level of inpatient care reflect scaled DRG payments and NCTAP payments (Medicare) and are calculated in the model based on the inputs shown in Tables S2, S3 and S5; parameters for the sensitivity analyses associated with those parameters are also shown in Tables S2 and S5

$30,000 for all variables, which falls well below the threshold of $50,000 per QALY gained.

Probabilistic Sensitivity Analysis (PSA)

PSA results were generated by jointly varying key model parameters over 5000 replications for the model base case. Depending on the variable, normal, Dirichlet, and Beta distributions were used to generate the variable samples (Tables 1, 2, 3, 4; Supplementary Tables S5, S6). The rationale of the PSA was to understand the robustness of model conclusions when varying all model inputs, given the uncertainty around model input estimates and the assumptions. The payer perspective PSA results for both patient subgroups (all patients and patients with oxygen use on admission) are shown in Fig. 3. The results from the analysis showed that BARI-REM was associated with both increased cost (incremental cost $7962 [95% CI − $14,055 to $23,880]) and benefit (incremental QALY 0.356 [95% CI − 0.416 to 0.952]) versus REM. Similarly, in patients with oxygen use, BARI-REM was associated with both increased cost (incremental cost $8960 [95% CI − $16,637 to $27,276]) and benefit (incremental QALY 0.4107 [95% CI − 0.485 to 1.096]) versus REM. The incremental cost was below the "willingness to pay" threshold for both, all hospitalized patients, and patients with oxygen use.

Treatment Mortality Assumptions

The incremental cost-effectiveness of BARI-REM compared with REM for different mortality assumptions is presented in Table 6. Specifically, two scenarios were evaluated: (a) adding a survival benefit to dexamethasone in the SOC treatment arm, and (b) removing the survival benefit from BARI-REM.

When a survival benefit was added to dexamethasone, the total incremental costs were $6030 and the total incremental QALYs 0.287 in the all-patient group. In the subgroup of patients using oxygen at baseline, the total incremental costs were $6724 and the total incremental QALYs 0.330. When the survival benefit for BARI-REM was removed, the total incremental costs were − $1711 and the total

Table 4 Utility inputs

Parameters	Value	Parameters for sensitivity analyses			Sources	References
		SE	Distribution	Lower–upper		
Age-based utilities among patients without severe comorbidities			Beta		Whittington 2020; Campbell 2020; Sullivan 2006	[9, 10, 26]
18–29 years old	0.922	0.0019		0.918, 0.926		
30–39 years old	0.901	0.0021		0.897, 0.905		
40–49 years old	0.871	0.0024		0.866, 0.876		
50–59 years old	0.842	0.0028		0.836, 0.847		
60–69 years old	0.823	0.0034		0.816, 0.830		
70–79 years old	0.790	0.0036		0.783, 0.797		
80+ years old	0.736	0.0062		0.724, 0.748		
Disutilities of hospitalization for COVID-19			Normal		Campbell 2020; Sullivan 2006; Barbut 2019; Sackett 1978	[10, 26–28]
COVID-19 symptoms	− 0.190	0.022		− 0.233, − 0.147		
Mechanical ventilation	− 0.600	0.045		− 0.688, − 0.512		
Noninvasive ventilation	− 0.500	0.045		− 0.588, − 0.412		
Supplemental oxygen	− 0.400	0.045		− 0.488, − 0.312		
Medical care without oxygen	− 0.300	0.045		− 0.388, − 0.212		

COVID-19 coronavirus disease 2019, *SE* standard error

incremental QALYs 0.009 in the all patient group. In the subgroup of patients using oxygen at baseline, the total incremental costs were − $2237 and the total incremental QALYs 0.008. The detailed results of these scenarios are presented in Supplementary Tables S7, S8, S9, and S10.

Hospital Perspective

Base-Case Results

We also evaluated the use of BARI-REM from a hospital perspective for the base-case scenario. The rationale for the hospital perspective is to examine the effect of US reimbursement policies and how they impact hospital reimbursement and net income. In all hospitalized patients, treatment with BARI-REM versus REM reduced total hospital expenditures by $1778 and total reimbursement payments by $1526,

Table 5 Base-case results: payer perspective

Incremental results	All patients	Oxygen use subgroup
Total costs	$7962	$8960
Total QALYs	0.3565	0.4107
Total LYs	0.446	0.513
Cost-effectiveness		
Cost per QALY gained	$22,334	$21,818
Cost per LY gained	$17,858	$17,458

LY life year, *QALY* quality-adjusted life year

resulting in a $252 reduction in net costs per patient. Treatment with BARI-REM versus REM also resulted in a net gain of 0.0018 QALYs and increased survival by 2.7% (Supplementary Table S11). Similarly, in patients with oxygen use at baseline, treatment with BARI-REM versus REM reduced total hospital expenditures by $2709 and total reimbursement payments reduced by $1961, resulting in a $748 reduction in net costs per patient. Treatment with BARI-REM versus REM also resulted in a net gain of 0.0023 QALYs and increased survival by 3.2% (Supplementary Table S11).

Net Impact on Clinical Outcomes

Net impacts on clinical outcomes are presented in Supplementary Figs. S1 and S2. The net number of patients who progressed to new use of oxygen was lower in BARI-REM versus REM (per 1000 patients, difference: mechanical ventilation, − 45; noninvasive ventilation, − 27; supplemental oxygen, − 23). Similarly, the net impact on total hospital days was lower with BARI-REM versus REM (per 1000 patients, difference: − 600 days), with the difference mainly driven by the mechanically ventilated group (− 1260 days). In patients with oxygen use at baseline, the net number of those who progressed to new use of oxygen was lower in BARI-REM versus REM (per 1000 patients, difference: mechanical ventilation, − 53; noninvasive ventilation, − 32; supplemental oxygen, 0). The net impact on total hospital days was lower with BARI-REM versus REM (per 1000 patients, difference: − 950 days), with the

difference mainly driven by the mechanically ventilated group (− 1460 days) (Supplementary Figs. S1 and S2).

DISCUSSION

We conducted an economic evaluation on the use of BARI-REM versus REM among hospitalized patients with COVID-19 in a US setting. A cost-effectiveness model was developed to capture the costs and QALYs of patients with COVID-19, during the hospital stay, as well as for any post-acute care settings. In the base-case scenario, it was observed that a combination of BARI-REM was cost-effective relative to REM alone for treatment of patients hospitalized as a result of COVID-19. Most of the incremental cost and QALYs were accrued during the recovered time period owing to more patients surviving the hospitalization. A small portion of the incremental QALY gained was due to the greater efficacy of BARI-REM versus REM in reducing time to recovery as well as reducing transitions to worse health states (e.g., fewer patients requiring mechanical ventilation), and thus more QALYs after hospital discharge. The reduction in the number of patients who require mechanical ventilation contributed to reduced inpatient costs, since patients requiring mechanical ventilation are the most resource-intensive and costly to treat. Also, from the payer perspective the savings in inpatient costs are offset by higher costs post discharge because of the higher survival with BARI-REM versus REM. Most of the cost difference and QALY
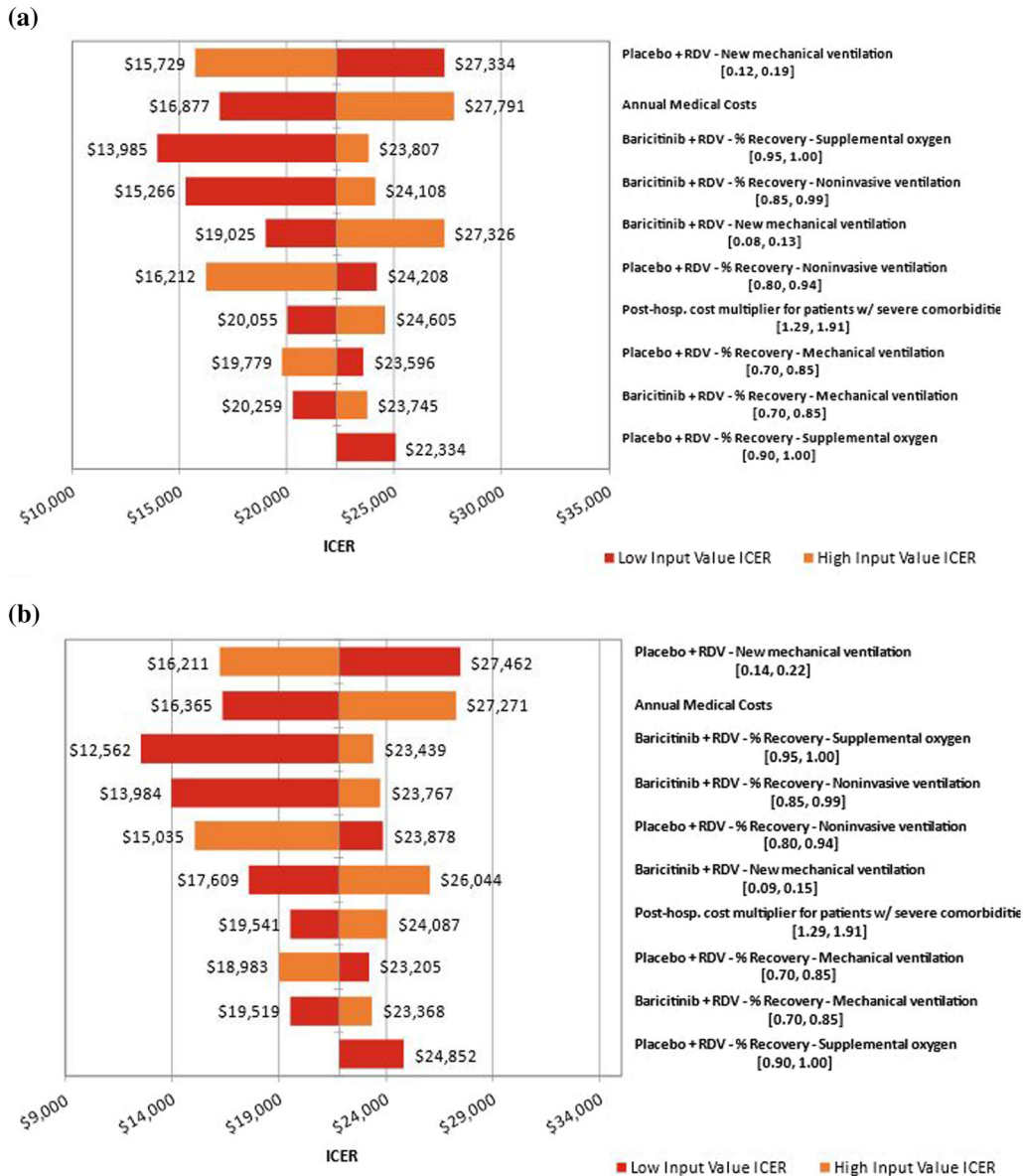
(a)

(b)

Fig. 2 Deterministic sensitivity analysis tornado diagram: payer perspective. **a** One-way sensitivity analysis—10 most sensitive inputs outcome measure: ICER base case = $22,334 —all hospitalized patients. **b** One-way sensitivity analysis—10 most sensitive inputs outcome measure: ICER base case = $21,818—patients with oxygen use at baseline

gains arise from lifetime costs and benefits due to the higher survival. BARI-REM combination remains cost-effective at less than $50,000 per QALY gained despite including lifetime all-cause healthcare costs in the analysis.

Viewing these results in aggregate, we find that treatment with BARI-REM resulted in an incremental cost per QALY gained of $22,334

and cost per life year gained of $17,858. The sensitivity analysis also showed that the total incremental cost per QALY gained falls well below commonly used willingness to pay thresholds, as well as the lowest $50,000/QALY threshold proposed by ICER for public health emergency conditions, and shows the robustness of our model [32].

(a)

(b)
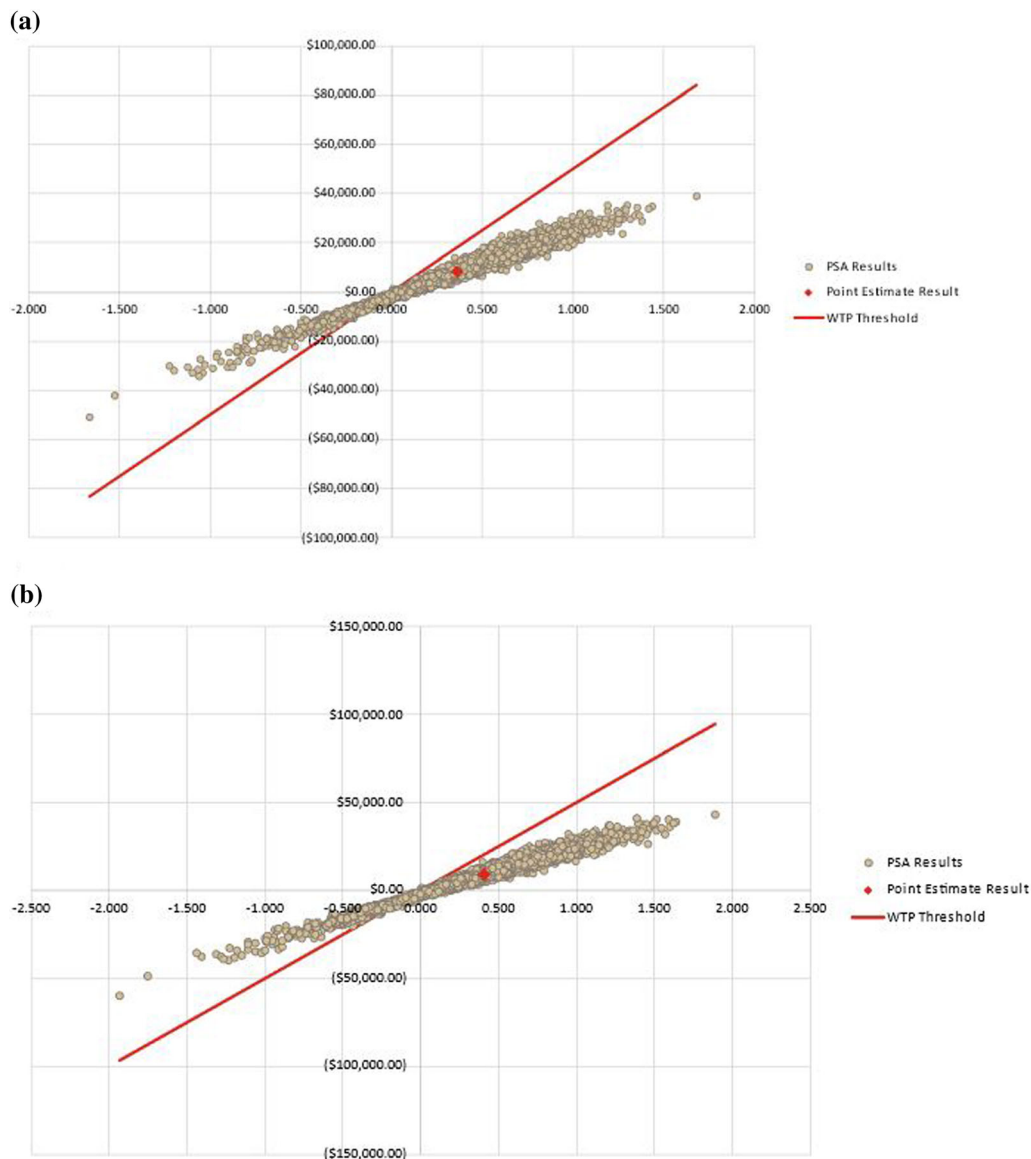
Fig. 3 Probabilistic sensitivity analysis for baricitinib and remdesivir versus remdesivir, payer perspective results for 5000 replications. **a** All-hospitalized patients. **b** Patients with oxygen use at baseline. Costs versus QALYs with a $50,000 WTP threshold for comparison

Our findings from the hospital perspective suggest that treatment with BARI-REM reduces total hospital expenditures versus REM alone, primarily by reducing the proportion of patients who require mechanical ventilation. Since patients requiring mechanical ventilation are reimbursed via more expensive DRGs, corresponding reimbursements are also reduced. Treatment with BARI-REM combination versus REM leads to a reduction in hospital expenses, which is estimated to be larger than the reduction in reimbursements received, yielding net cost savings (reduced expenses minus reduced reimbursement). In addition, the greater number of QALYs accrued to BARI-REM due to increased survival during the hospital stay demonstrates a dominant case of cost-effectiveness (greater benefits and lower costs) for BARI-REM compared to REM in treating patients with COVID-19.

Table 6 Incremental cost-effectiveness of combination of baricitinib and remdesivir compared with remdesivir for different mortality assumptions

Population/scenario	Δ Costs	Δ QALYs	ICER
All hospitalized patients with COVID-19			
Base case (28-day survival in ACTT-2)	$7962	0.356	$22,334
Dexamethasone survival benefit	$6030	0.287	$21,001
No survival benefit with baricitinib	− $1711	0.009	Dominates
Patients with oxygen use at baseline			
Base case (28-day survival in ACTT-2)	$8960	0.411	$21,818
Dexamethasone survival benefit	$6724	0.330	$20,347
No survival benefit with baricitinib	− $2237	0.008	Dominates

COVID-19 coronavirus disease 2019, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year

In the second update by ICER, they investigated the effects of remdesivir on mortality in patients with COVID-19; their report did not support a survival benefit with remdesivir. However, data from the US-based ACTT-1 trial suggested that remdesivir treatment might result in savings on insurer payments for hospital services. In the time since ACTT-1, the label of remdesivir has been expanded to include hospitalized patients with moderate-to-severe disease; ICER's final report suggested a health-benefit price benchmark of $2470 for remdesivir assuming no survival benefit. If a survival benefit was assumed, the updated ICER COVID CE model suggested a CE price range of $3980–4140 for patients hospitalized with moderate-to-severe disease [33]. However, ICER's model did not consider any discharge status or post-acute care of patients, nor did it consider the hospital perspective [33]. Another limitation of the ICER model was simulation of a lifetime horizon using mortality and cost and QALY estimations for the general population, whereas hospitalized patients with COVID-19 tend to have more comorbidities and generally poorer health than the general population.

Our model overcomes those limitations by considering total hospital expenditures, reimbursement payments, and the net costs per QALY gained in the model. Our model also considered the health outcomes and costs by discharge status (self-care or custodial care,

home healthcare, inpatient rehabilitation, skilled nursing facilities, short-term hospitalization, long-term acute care hospitalization, and hospice status) to provide a broader picture of post-acute hospital consequences. Including indirect costs in our model to factor in the costs per workday missed by hospitalized patients gives a holistic view of the payer's perspective. In addition, our model does estimate the potential impact of efficacious therapies that reduce progression to higher levels of oxygen care. Therefore, there is a reduction in the use of hospital days and intensive care unit days. This results in more available resources for hospitals for care of other patients without COVID-19, though these potential benefits are not directly quantified. The adjustment of cost, mortality, and utilities for the higher prevalence of comorbidities makes our analysis more conservative by yielding higher incremental lifetime all-cause costs and lower incremental lifetime QALYs. Also, the mortality calculations in our model accommodated a wide range of age groups. Another major strength of our model is the use of Premier cost analysis, which provides detailed data from real-world COVID-19-affected patients. Using the Premier cost analysis also facilitated the tracking of discharge status of patients and provided highly precise estimates of post-acute care costs in the model. The structure of the model allows for adaptations to other countries using local data inputs.

Data on anticipated long-term burden of COVID-19 have just started surfacing [34, 35]. At present, none of the existing CE models including ours considers long-term consequences of COVID-19 because of lack of data and the very dynamic situation at hand [36]. Further, our model does not factor in any resource constraints that hospitals might experience, such as lack of beds in intensive care units because of more patients with COVID-19 progressing towards requirements for ICU-level care. This might translate to more lives lost as a result of other patients not being able to receive critical care. The data on disutilities is limited in the existing ICER model and our model, which accounts for one of the limitations of this model. Another limitation specific to the secondary analysis from the hospital perspective is that our estimates of hospital expenditures and DRG payments are national averages. Therefore, it may not be representative of the average expenses and reimbursement payments experienced by a specific hospital. Also, the model did not take hospital readmissions into account.

The healthcare situation with COVID-19 is still evolving rapidly and continues to impose substantial burden on the healthcare system. Tocilizumab was also granted an EUA by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients receiving systemic corticosteroids and requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO [37]. Recently, the FDA has issued an EUA to permit the use of BARI for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO [6]. Because of the increasing burden and emerging treatment options, there is an elevated need to assess the value of these treatments to improve patient outcomes and effectively utilize healthcare resources. The assessment of the clinical and economic value of these emerging treatments will help decision-makers to make informed evidence-based pricing and treatment access decisions [38].

CONCLUSION

Our study showed that baricitinib in combination with remdesivir is more cost-effective than using remdesivir alone for patients hospitalized because of COVID-19 in the USA. The sensitivity of this cost-effectiveness model was mainly driven by average annual costs of recovered patients, incidence of new mechanical ventilation after admission, and the mechanical ventilation days on REM and BARI-REM. Effective COVID-19 treatments for hospitalized patients may not only reduce disease burden but also represent good value for the healthcare system.

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