Modeling the Potential Impact of Remdesivir Treatment for Hospitalized Patients with COVID-19 in Saudi Arabia on Healthcare Resource Use and Direct Hospital Costs: A Hypothetical Study

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Abstract

Background and Objectives Coronavirus disease 2019 (COVID-19) has spread rapidly worldwide. Saudi Arabia was significantly impacted by COVID-19. In March 2021, 381,000 cases were reported with 6539 deaths. This study attempts to quantify the impact of remdesivir on healthcare costs in Saudi Arabia, in terms of intensive care unit admissions, mechanical ventilation, and death prevention.

Methods A forecasting model was designed to estimate the impact of remdesivir on the capacity of intensive care units and healthcare costs with patients requiring low flow oxygen therapy. The forecasting model was applied in the Saudi context with a 20-week projection between 1 February and 14 June, 2021. Model inputs were collected from published global and Saudi literature, available forecasting resources, and expert opinions. Three scenarios were assumed: the effective pandemic infection rate (Rt) remains at 1, the Rt increases up to 1.2, and the Rt declines from 1 to 0.8 over the study period.

Results The model estimated that the use of remdesivir in hospitalized patients, in the optimistic and pessimistic scenarios, could prevent between 1520 and 3549 patient transfers to intensive care units and mechanical ventilation, prevent between 815 and 1582 deaths, and make potential cost savings between $US154 million and $US377 million owing to the reduction in intensive care unit capacity, respectively.

Conclusions The treatment with remdesivir may improve patient outcomes and reduce the burden on healthcare resources during this pandemic.

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Key Points

Remdesivir-based treatment in patients requiring low-flow oxygen can reduce the burden on healthcare facilities.

The introduction of remdesivir for the treatment of coronavirus disease 2019, in patients requiring low-flow oxygen, can generate important cost savings for hospitals.

1 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) causes the respiratory illness designated as coronavirus disease 2019 (COVID-19). The worldwide COVID-19 pandemic put significant pressure on national healthcare systems resulting in a high social and economic impact [1, 2]. As of 16 May, 2022, Saudi Arabia has recorded 759,856 cases and 9118 deaths due to COVID-19 [3]. With an estimated 13% of all cases resulting in hospitalizations, this has placed a substantial additional burden on the Saudi Arabian healthcare system [4] despite the early and active prevention measures adopted by the Saudi Arabian government [5].

A substantial number of patients who are hospitalized for COVID-19 require resource-intensive and expensive treatment in intensive care units (ICUs) with or without the support of mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) [6]. Given that ICUs have limited capacity and are required to treat numerous severe pathologies, effective therapies for COVID-19 offer the opportunities to free up ICU capacity for the treatment of other diseases and improve the management of emergency units in hospitals.

Remdesivir (Veklury®) is an antiviral drug developed by Gilead Sciences, Inc. and has been conditionally or fully approved for use in hospitalized patients with COVID-19 in more than 50 countries, including by the US Food and Drug Administration (full approval granted October 2020 [7]), and conditional approval in the European Medicines Agency in June 2020 [8]. Typically, remdesivir is indicated for hospitalized patients with COVID-19 with pneumonia, though there is variation by agency on whether patients must also be receiving oxygen support. The Ministry of Health of Saudi Arabia issued guidelines that state that severe or critical patients with COVID-19 are eligible for treatment with remdesivir [6]. On 1 September, 2021, the Saudi Food and Drug Administration approved remdesivir by granting it marketing authorization [9].

The pivotal, randomized, double-blind, placebo-controlled clinical trial, ACTT-1, enrolled 1062 patients [10]. The results of the trial demonstrated that treatment with remdesivir significantly reduced the time to recovery in adults who were hospitalized with COVID-19 by a median of 5 days, with a rate ratio of 1.29 (95% confidence interval 1.12–1.49; $p < 0.001$) [10]. In addition, patients treated with remdesivir showed a reduced need for new oxygen support and a 43% reduction in the incidence of MV or ECMO use. In a sub-group analysis, patients requiring low-flow oxygen had a statistically significant 70% reduction in mortality compared with placebo (95% confidence interval 0.14–0.64) [10]. The objective of this study was to investigate the potential impact of treating hospitalized patients with COVID-19 on low-flow oxygen with remdesivir on healthcare resource use and costs in Saudi Arabia by using an epidemiologic and health economic model.

2 Materials and Methods

2.1 Study Design and Model Structure

This study utilizes a previously published epidemiologic model [11, 12] to estimate the potential impact of remdesivir administration on hospital resource use and costs in Saudi Arabia. A targeted literature review for Saudi Arabia-specific data as well as the elicitation of local clinical opinion was conducted to ensure the model reflected the local healthcare context.

The model (Fig. 1) has two stages:

1. A weekly epidemiological estimation of the infection rate (Rt) in Saudi Arabia, including the estimated number of:

    (a) patients infected with COVID-19 requiring hospitalization; and

    (b) those requiring a stay in the ICU.

2. An economic model that estimates the subsequent direct costs to the health system because of hospitalization from COVID-19, comparing a cohort of patients on low-flow oxygen who receive remdesivir plus standard of care to a cohort of patients who receive standard of care alone.

2.2 Epidemiological Model

The first stage of the model estimates the development of the COVID-19 epidemic and is modeled over a 20-week period in order to allow comparison to previously published studies [11, 12]. The model utilizes published data

Fig. 1 Model structure. *Rt* infection rate. Graphic adapted from Ruggeri et al. [11, 12]
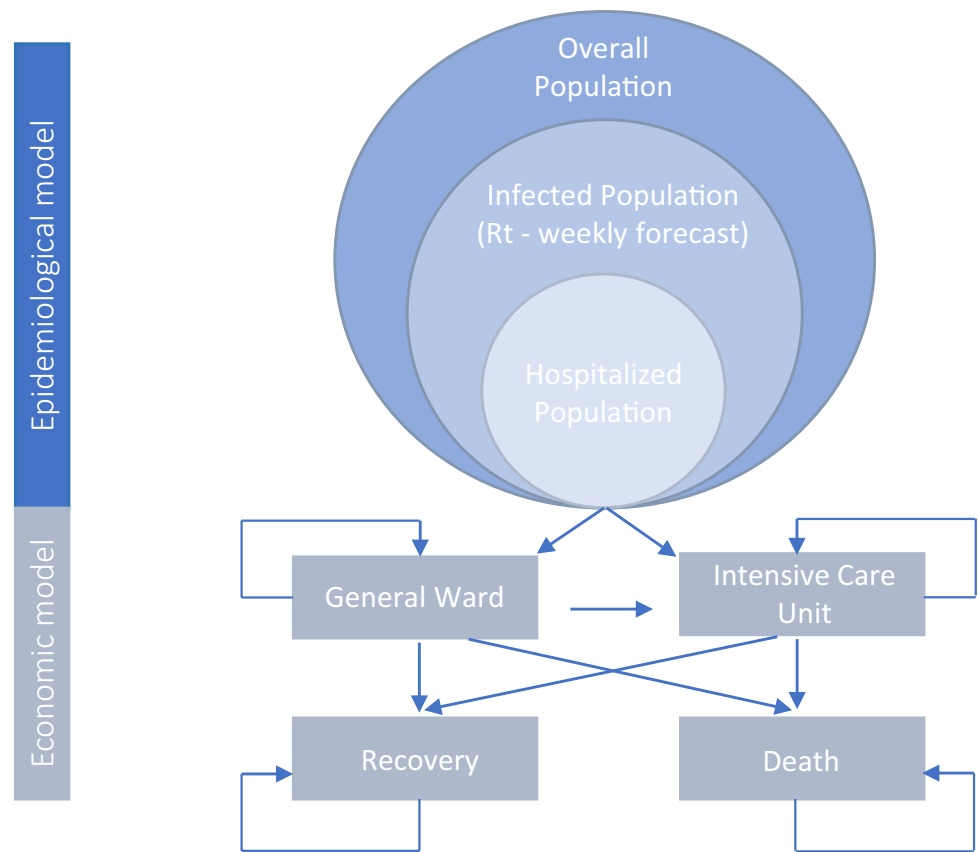
on Rt based on real observations between 1 February and 22 March, 2021, [13] and subsequently we modeled three potential scenarios (see Table 1):

- A base case, where the Rt remains at 1.
- Scenario 1: an 'optimistic' scenario where the weekly Rt decreases to 0.8 over the 20-week period.
- Scenario 2: a 'pessimistic' scenario where the weekly Rt increases to 1.2.

These scenarios were developed alongside clinical experts from Saudi Arabia (see Expert Validation for details on the selection of experts and opinion elicitation) to take into account specific Saudi Arabia epidemic circumstances (e.g., Ramadan festivities from April to May 2021 in the pessimistic scenario and government vaccination campaigns in the optimistic scenario). The estimation of COVID-19 hospitalization rate was taken from published data [13]. The model also estimated the mortality rate in the non-hospitalized infected population using data from the literature [14–19].

Table 1 Infection rate (Rt) over 20 weeks

| Week | Starting date | Rt | | Source |
		Scenario 1	Scenario 2	
1	1 February	1	1	[13]
2	8 February	0.9	0.9	[13]
3	15 February	1	1	[13]
4	22 February	1.05	1.05	[13]
5	1 March	1.1	1.1	[13]
6	8 March	1	1	[13]
7	15 March	1.1	1.1	[13]
8	22 March	1.15	1.15	[13]
9	29 March	1.15	1.15	[13]
10	5 April	1.15	1.15	[13]
11	12 April	1.2	1	Experts' opinion
12	19 April	1.2	0.97	Experts' opinion
13	26 April	1.2	0.96	Experts' opinion
14	3 May	1.2	0.95	Experts' opinion
15	10 May	1.2	0.93	Experts' opinion
16	17 May	1.2	0.91	Experts' opinion
17	24 May	1.2	0.87	Experts' opinion
18	31 May	1.2	0.85	Experts' opinion
19	7 June	1.2	0.83	Experts' opinion
20	14 June	1.2	0.8	Experts' opinion

2.3 Economic Model

The second stage of the model uses a Markov dynamic-cohort cost-effectiveness model [11, 12] with a 1-week cycle and a 20-week time horizon. New individuals are added to the model for each cycle based on the Rt for that cycle. The model is made up of four mutually exclusive health states: hospitalized (general ward, with or without non-invasive oxygen support), ICU (with MV or ECMO), recovery (discharge), and death. Hospitalized individuals can stay hospitalized, move into the ICU, recover, or die. For individuals admitted directly into the ICU, they can stay in the ICU, recover, or die. No discount rate was applied given the short time horizon.

The model compares patients on low-flow oxygen who are treated with remdesivir plus standard of care versus those on low-flow oxygen on standard of care alone. The outcomes of interest included the number of days in hospital (ward and ICU), deaths, and associated hospital costs. Estimates of the number of ICU patients requiring MV or ECMO as well as the length of hospital/ICU stay were provided by the experts. Estimates of the mortality rate for hospitalized patients were derived from the literature [14–19]. To estimate the comparative impact of remdesivir on patients who receive low-flow oxygen, efficacy data from the pivotal phase III trial [10] were used to model the potential reduction in time to recovery, disease progression, and mortality (see Table 2).

Data on the use of healthcare resources, specifically on general ward stay, were sourced from the local literature [17, 18]. The ICU length of stay (stratified by the need for MV/ECMO or not) was provided by clinical expert opinion. For patients requiring an ICU stay, it was assumed that they would spend at least some time on a general ward. This length of stay estimate was provided by clinical expert opinion. For the remdesivir arm, it was assumed that 5 days of therapy was provided in line with the guidelines. Direct medical costs for the cost per day of the hospital ward and the ICU (for non-MV and MV) were taken from Khan et al. [15] and are based on the year of 2020. The cost of remdesivir was set to be $US390 per vial [20]. Table 2 provides an overview of the model inputs.

2.4 Sensitivity Analysis

To investigate uncertainty around the parameter estimates, both one-way and probabilistic sensitivity analyses were conducted for both stages of the model. When possible, the standard deviation of the estimates from the literature was used. If this was not possible, values were adjusted by ± 30%. Table 1 in the Electronic Supplementary Material (ESM) provides an overview of the variables included in the probabilistic sensitivity analysis as well as the distributions utilized.

2.5 Expert Input Validation

In order to ensure that the models fit the Saudi Arabia context, an expert panel of local physicians was formed to

Table 2 Parameter model input

Parameter	Base case	Distribution	Source
Mortality rate, general infected	3.5%	Beta	Mathematical average [17, 18]
Mortality rate, hospitalized population	10%	Beta	Mathematical average [17, 18]
Percent starting in ward	96%	Beta	[13]
Percent starting in ICU	4%	Beta	[13]
Percent of patients requiring low-flow O_2	55%	Beta	[13]
Percent of patients requiring MV/ECMO	23%	Beta	[10]
Hazard ratio, time to recovery (low-flow patients)	1.32	Beta	[10]
Relative reduction in progression to ICU	30%	Beta	[10]
Hazard ratio, mortality (low-flow patients)	0.30	Beta	[10]
Remdesivir treatment	5 days (6 vials)	Gamma	Assumption: from clinical practice
Hospital ward stay	12 days	Gamma	[17, 18]
ICU stay, non MV/ECMO	5 days	Gamma	Expert opinion
ICU stay, MV/ECMO	13 days	Gamma	Expert opinion
Hospital stay, patients who die	24.7 days	Gamma	[15, 17, 18]
Hospital ward per day	$US1666	Deterministic	[15]
ICU non-MV per day	$US2536	Deterministic	[15]
ICU MV per day	$US2990	Deterministic	[15]
Remdesivir (per vial)	$US390	Deterministic	Gilead Sciences, Inc.

ECMO extra corporeal membrane oxygenation, *ICU* intensive care unit, *MV* mechanical ventilation

validate the model structure and local information. Three experts were selected according to their real-world clinical experience caring for patients with COVID-19 as well as their expertise with the Saudi Arabia health system and hospital management. Once chosen, the experts participated in a one-to-one structured interview to elicit views on the model structure and inputs, as well as potential variations specific to the Saudi Arabia context. The second phase involved a joint interview where the results from a targeted literature review were provided for their validation as well as reaching a consensus on the Rt evolution scenarios. This research employed structured interviews [21, 22], where participants were provided with clear objectives at the beginning of the interview. The structured questions allowed the elicitation of information on specific issues and themes surrounding key model inputs and assumptions. Standard methods of synthesizing the interview data were used [21].

3 Results

3.1 Population

In the base case, the model estimated that there was a total of 178,405 people who were infected with COVID-19 in the time period. Of those, 27,438 were people admitted to hospital with 10,027 requiring the ICU. Table 3 presents the findings of the epidemiological model, which provided the population for the economic model.

Table 3 Results of the epidemiological model

Population	Overall
Number of infected	
Base case	178,405
Scenario 1	109,087
Scenario 2	247,724
Number requiring hospitalization	
Base case	27,438
Scenario 1	16,942
Scenario 2	37,934
Number requiring ICU at baseline	
Base case	10,027
Scenario 1	5966
Scenario 2	14,088
Number of deaths, without RDV	
Base case	1712
Scenario1	1164
Scenario2	2260

ICU intensive care unit, *RDV* remdesivir

3.2 Comparative Outcomes

When investigating the impact of treating patients requiring low-flow oxygen with remdesivir, the model estimated substantially lower ICU use across all three scenarios when patients were treated with remdesivir. Table 4 summarizes the overall admissions to ICU for the three scenarios and by treatment arm. Figure 2 presents the weekly ICU admissions, over 20 weeks, for the base case, Scenario 1, and Scenario 2. In the base case, there were a total of 7491 ICU admissions over the modeled period for the group treated with remdesivir, compared with 10,027 in the standard of care group, a difference of 2535. For Scenario 1, there was a difference of 1520 and for Scenario 2, there was a difference of 3549 admissions. In terms of mortality, the use of remdesivir in the low-flow oxygen population resulted in 1199 fewer deaths than standard of care alone.

3.3 Cost Effectiveness

The use of remdesivir resulted in both a reduction in the number of ICU admissions and in the rates of mortality and was less costly, resulting in remdesivir plus standard of care being dominant over standard of care regardless of the scenario. Table 5 provides a summary of the deterministic cost results.

3.4 Sensitivity Analysis

One-way deterministic sensitivity analyses indicated that the model was most sensitive to Rt values, the subsequent number of ICU admissions, mortality rates, overall hospitalization rate, and the relative risk of mortality when treated with remdesivir. Despite being sensitive to these factors, the model results consistently demonstrated substantial cost savings (see Figs. 1–3 of the ESM). The results of the probabilistic sensitivity analysis show that over 93% of simulations result in remdesivir plus standard of care being dominant

Table 4 Outcomes by treatment arm

Outcome	SoC	SoC + RDV	Difference
Total admissions to ICU			
Base case	10,027	7491	−2535
Scenario 1	5966	4445	−1520
Scenario 2	14,088	10,538	−3549
Total number of deaths			
Base case	1712	513	−1199
Scenario 1	1164	349	−815
Scenario 2	2260	678	−1582

ICU intensive care unit, *RDV* remdesivir, *SoC* standard of care

Fig. 2 Predicted weekly intensive care unit (ICU) admissions for the three scenarios in the 20-week time horizon: the base case (**A**), Scenario 1 (**B**), and Scenario 2 (**C**). Yellow bars representing standard of care (SoC); orange bars representing SoC plus remdesivir (RDV)
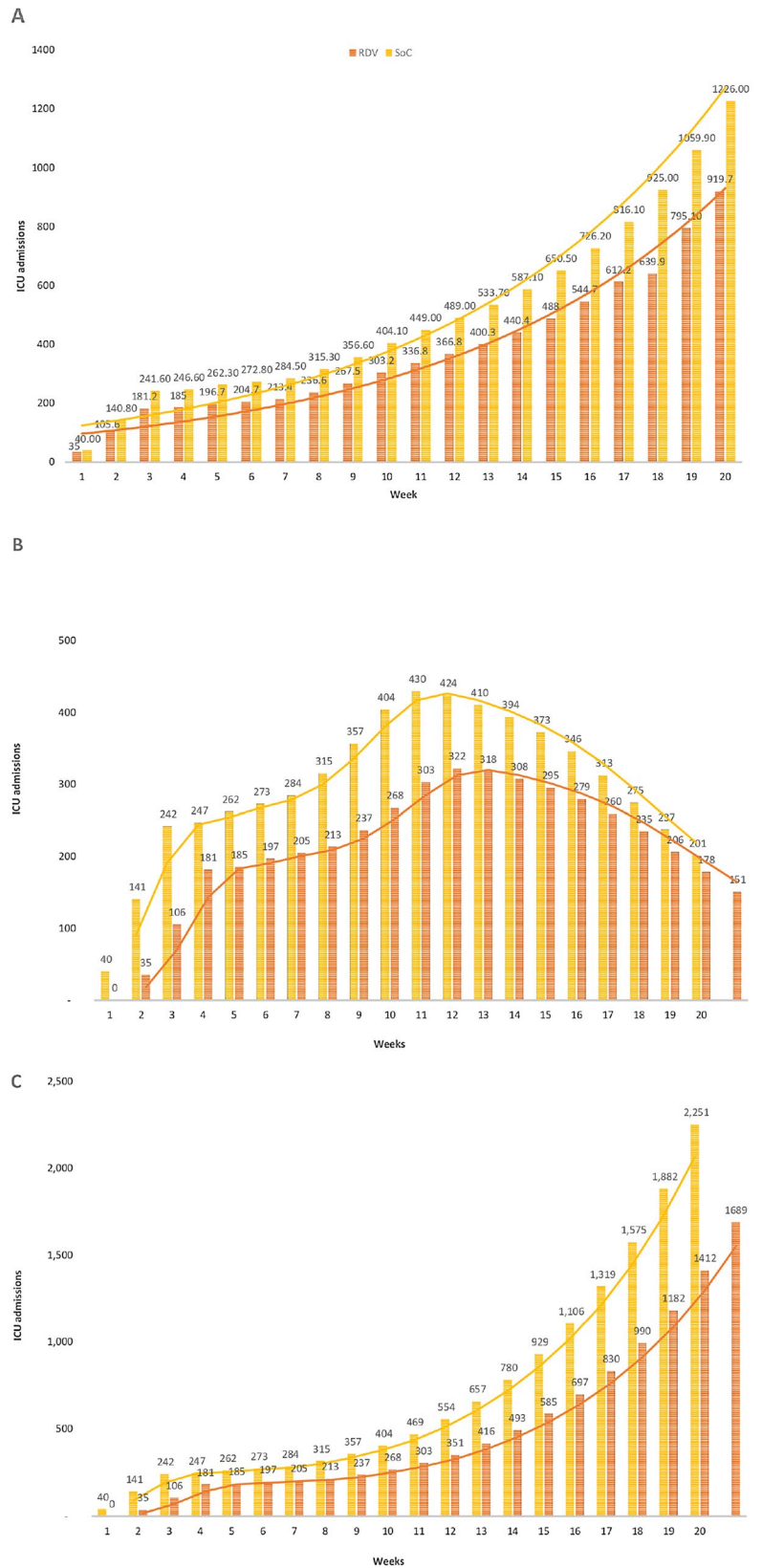
Table 5 Cost-effectiveness outcomes

Outcome	SoC	SoC + remdesivir	Difference
Total cost for hospital ward patients, $US			
Base case	252,578,717	203,964,078	−48,614,639
Scenario 1	288,505,171	232,944,906	−5560,265
Scenario 2	645,976,423	523,403,092	−122,573,331
Total cost for ICU, $US			
Base case	202,803,340	150,967,278	−51,836,061
Scenario 1	231,932,306	172,818,955	−59,113,351
Scenario 2	547,620,706	409,638,921	−37,981,784
Total cost for patients who died, $US			
Base case	77,517,030	23,255,109	−54,261,921
Scenario 1	85,905,704	25,771,711	−60,133,992
Scenario 2	166,729,155	50,018,746	−116,710,408
Total costs, $US			
Base case	532,899,088	378,186,466	−154,712,622
Scenario 1	606,343,182	431,535,572	−174,807,610
Scenario 2	1,360,326,285	983,060,760	−377,265,524

ICU intensive care unit, *SoC* standard of care

over standard of care alone, regardless of the outcome (see Figs. 3, 4).

4 Discussion

This analysis has shown that in Saudi Arabia, remdesivir plus standard of care has the potential to reduce healthcare resource use, mortality, and costs when compared with standard of care alone across a range of plausible local epidemiological scenarios. The Markov dynamic-cohort model is a simplification of the reality, and it allows an estimate of the epidemiologic situation on a 20-week time horizon. The model hypothesizes four health states (general ward, ICU, recovery, and death) where patients can move from one state to another (except for death) with a certain transition probability defined for each state, obtaining the weekly number of admissions to each state. The modeled cost savings arise primarily because of the data from Beigel et al. [10], which reported a reduction in the number of patients needing to move into the ICU as well as a statistically significant reduction in mortality in patients receiving low-flow oxygen support. Similar to other countries around the world, the costs of stay in the ICU are substantially higher than standard hospitalization (45% higher in the case of Saudi Arabia) and therefore any therapies, which can potentially reduce the need and/or the length of stay in an ICU, can result in substantial cost savings.

Fig. 3 Cost-effectiveness plane: relationship between incremental costs and avoided deaths
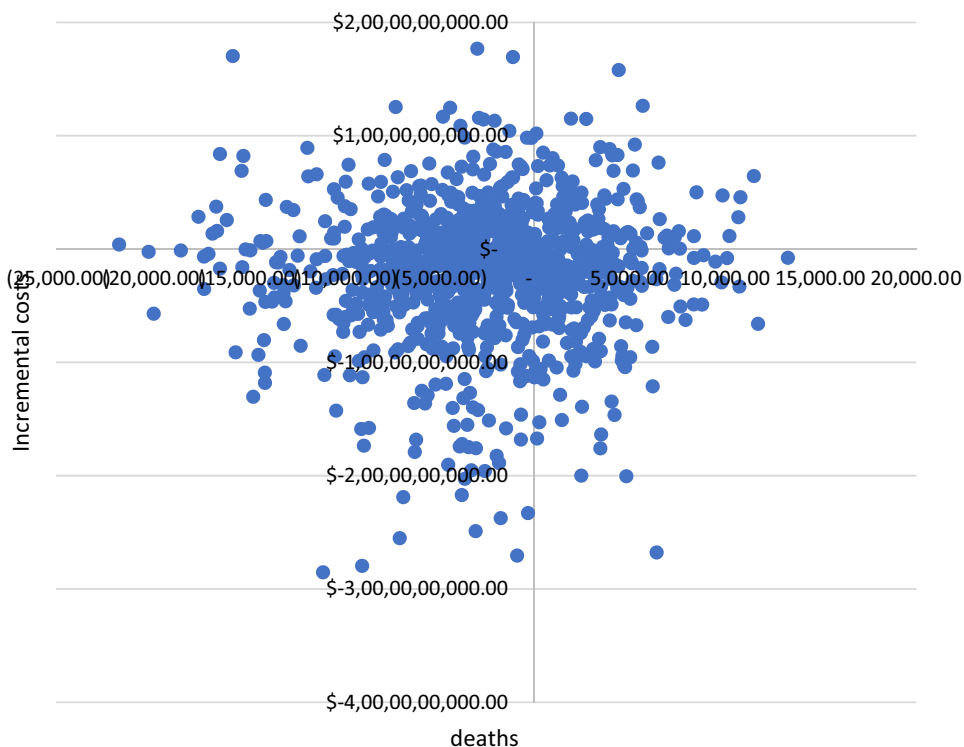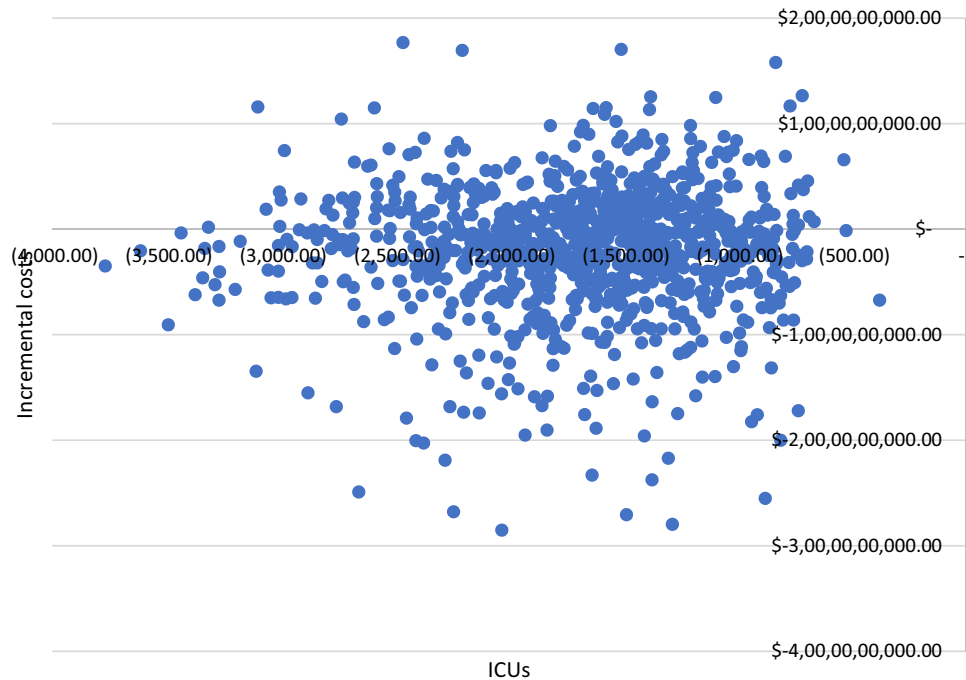
Fig. 4 Cost-effectiveness plane: relationship between incremental costs and incremental intensive care units (ICUs) [mechanical ventilation]

This study is subject to some limitations. The model scenarios were based on forecasting derived from expert clinical opinion that took into account the situation in Saudi Arabia, but uncertainty in these assumptions remain. Additionally, we recognize that the use of the Rt index does have some limitations [23], it is a firmly established methodology and allows for generalizability and comparability across studies. In addition, the information on many of the inputs was taken from a targeted literature review, which may mean that relevant data were missed. The model could potentially benefit from testing the clinical inputs using data from other studies as the model currently relies on clinical effectiveness data for remdesivir from one phase III trial, ACTT-1 [10]. While this was a pivotal trial upon which regulatory approval was granted, additional sources of data such as trial meta-analyses or real-world data may strengthen this analysis. A recently published meta-analysis and findings of the SOLIDARITY trial show that in those patients who were receiving oxygen support (the modeled population in this study) at admission saw a decrease in mortality and were at a lower risk of progressing to needing MV [24]. Finally, the model does not take into account adverse events for either treatment (remdesivir nor standard of care) arm. This is because of the relatively low rates of serious treatment-related adverse events reported in Beigel et al. [10] but the exclusion of adverse events may result in a small impact on both the costs and benefits. Despite these limitations, the sensitivity analyses conducted demonstrated that the results were robust overall. In conclusion, a strength of this model is that it can be easily adjusted to a narrower context, for instance regional, and can be continuously updated with the most recent data available. Hence, the model can be a useful decision-making tool in times of crisis, such as the COVID-19 pandemic.

This model was originally built as part of a wider project to estimate the impact of potential changes in epidemiology on the cost effectiveness of alternative treatments for different pathologies, testing its ability to adapt to different realities. The model was originally developed for the Italian context [11] and was later adapted for the Portuguese context, reporting similar findings to this study. Although this paper has the limitation of using a methodology that was already published, it provides an overview of how the model could work in contexts with different economic structures, emergency management protocols, and epidemiological courses (e.g., Middle East vs Europe).

In addition, several other countries have used similar models to estimate the impact of treating patients with remdesivir on healthcare resource use and overall costs to the healthcare system [25–28]. The findings from the Italian and Portuguese studies are similar to what was found with this model, indicating that these results can be generalizable across geographies experiencing similar infection and hospitalization rates.

5 Conclusions

This study indicates that the use of remdesivir in patients requiring low-flow oxygen reduces the burden on healthcare facilities and provides important cost savings for Saudi Arabia hospitals.

Declarations

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