Cost-Effectiveness of Remdesivir Plus Supportive Care for Patients with COVID-19 in Iran

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Abstract

Background: Remdesivir is a medication used for moderate to severe Coronavirus disease 2019 (COVID-19) patients with favorable effects. However, it is an expensive medication. Therefore, the present study aimed to assess the cost-effectiveness of remdesivir plus supportive care (SC) for COVID-19 patients in Iran.

Methods: Markov model was used to compare costs and quality-adjusted life-days (QALDs) of remdesivir+SC and SC for patients with COVID-19. The model simulated a cycle length of one day and a 30-day time horizon in TreeAge 2020 software. The costs from the healthcare system perspective were obtained from Afzalipour hospital as a referral hospital for the hospitalization of COVID-19 patients in Kerman, Iran. All the costs were converted to 2018 purchasing power parity (PPP) US dollars. Utility values were derived from published sources. The results were presented as an incremental cost-effectiveness ratio (ICER) at a willingness-to-pay (WTP) threshold of three times the Gross Domestic Product per capita of Iran. Both deterministic and probabilistic sensitivity analyses were performed.

Results: The base-case results showed that the treatment of COVID-19 patients with remdesivir+SC had a cost of 8795 PPP US dollars for 21.13 QALD gained. The SC alone cost 8637 PPP US dollars with a gain of 20.20 QALD. Our findings demonstrated that at a WTP threshold of 159 PPP US dollars per QALD, remdesivir+SC was not cost-effective with an ICER of 168 PPP US dollars per QALD. Deterministic sensitivity analysis indicated ICER to be sensitive to the transition probabilities and costs. Probabilistic sensitivity analysis revealed that remdesivir+SC was cost-effective at a WTP of 159 PPP US dollars per QALD in 47% of iterations.

Conclusions: Our findings demonstrated that remdesivir+SC is not cost-effective, compared to SC alone. Considering the lack of studies on the effectiveness of remdesivir, the findings should be interpreted with caution. Further evaluations are recommended to determine the efficacy and effectiveness of remdesivir in COVID-19 patients.

Background

Coronavirus disease 2019 (COVID-19) has been a serious global socio-economic and public health crisis with more than 115 million cases worldwide and 2.5 million deaths until March 2, 2021. The disease prevalence in Iran has been high with more than 2 million people infected by June 13, 2021, and nearly 65000 died. The World Health Organization reported a median COVID-19 infection fatality rate of 0.27% based on data from 51 locations (1). Although this disease has a low mortality rate, it is extremely contagious (2).

No medicine has been proposed to be completely effective for COVID-19 treatment. Studies have shown that various medications, such as chloroquine (3), hydroxychloroquine (4), remdesivir (5), and favipiravir (6) could be used to treat patients with COVID-19. At the onset of the pandemic, chloroquine and hydroxychloroquine with or without antibiotics, including azithromycin were recommended. Subsequent

investigations demonstrated that these agents do not affect mortality (7–10). Meanwhile, the effect of remdesivir was indicated to be different in variable studies (11, 12). Some systematic reviews showed that remdesivir had a significant effect on the clinical outcomes of patients with COVID-19 (13, 14).

The COVID-19 has affected the healthcare system resulting in serious shortages of resources, such as hospital beds, intensive care unit (ICU) beds, medical equipment, and medical staff. Many patients develop COVID-19 and their disease progresses to severe and critical conditions. As a result, ICUs are overcrowded with critically ill patients that may even create unconventional ICU spaces (15). The ICUs are one of the most expensive wards in hospitals accounting for more than 20% of total hospital costs (16). A large number of patients with COVID-19 require respiratory assistance leading to high demand for ICU services. Therefore, various countries need rapid expansion of ICU infrastructure, capacity, and staffing (17).

There is concern that patients admitted to the ICU with COVID-19 could develop a severe illness or even die. However, research has shown that remdesivir enhances the recovery of patients, prevents disease progress to serious conditions, and shortens the recovery period (18). Health technology assessment and economic evaluation are two strategies used in healthcare decision-making, particularly for allocating limited resources and making good use of budgets (19). These methods assist in selecting the strategy that produces the best benefits at the lowest costs. As a result, the current study aimed to benefit from economic evaluation for determining the optimal therapeutic interventions for the treatment of COVID-19 patients.

Methods

Study design

The present cost-effectiveness analysis was performed on costs extracted from the healthcare system's perspective and quality-adjusted life days (QALDs) in a one-month time horizon.

Model structure

We conducted a Markov model derived from a model of COVID-19 that simulated the natural history of COVID-19 (18) (Fig. 1). The model simulated daily transition cycles over a 30-day time horizon. Figure 1 shows the Markov model, transitions between the health states, and health states, including mild, moderate, severe, critical, recovery, and death. Patients in the mild phase of the disease progress to a moderate state or recover. Patients in the moderate state remain in the same condition, recover, or change to the mild disease (only in people who have taken remdesivir), or their disease progresses to a severe state. Patients in a severe illness either recover, remain in the same condition, change to moderate disease status (only in people who have taken remdesivir), or progress to a critical condition or die. Patients with critical COVID-19 remain in their current state, move to moderate stage, or die.

Strategies

According to the clinical guidelines of COVID-19 treatment in Iran, remdesivir is among the medications used for adult patients with COVID-19. Several pharmaceutical companies in Iran produce remdesivir, which is less expensive than imported ones. In this study, patients received remdesivir manufactured in Iran. Patients receiving remdesivir plus supportive care (SC) for moderate COVID-19 were assumed to receive 200 mg on day one and then 100 mg daily for four additional days. Patients with severe COVID-19 received remdesivir 200 mg on the first day followed by 100 mg on the next days for up to 9 days. Based on the COVID-19 treatment guideline of NIH (20), we did not consider remdesivir for treating patients in the mild and critical conditions of COVID-19. The SC was taken into consideration for patients who received neither therapy as a comparator.

Model inputs

Table 1 shows the model inputs, including costs, health outcomes, efficacy, and transition probabilities.

Table 1
Input parameters, descriptions, and distributions for COVID-19 infection

Parameters	Value	Low	High	SE	Distribution	Source
Transition probabilities						
Remdesivir + SC						
Mild to moderate	0.078	0.062	0.094	0.016	beta	(18)
Moderate to mild	0.155	0	0.155	0.031	beta	(18)
Moderate to severe	0.162	0.130	0.194	0.032	beta	(18)
Severe to moderate	0.048	0.038	0.058	0.010	beta	(18)
Recovery after mild	0.149	0.091	0.207	0.030	beta	(18)
Recovery after moderate	0.005	0.003	0.007	0.001	beta	(18)
Sever to critical	0.008	0.005	0.011	0.002	beta	Expert opinion
Critical to severe	0.005	0.003	0.007	0.001	beta	Expert opinion
Death after severe	0.014	0.009	0.019	0.003	beta	(18)
Death after critical	0.261	0.159	0.363	0.052	beta	(24)
Recovery after severe	0.020	0.012	0.028	0.004	beta	(18)
Supportive care (SC)						
Mild to moderate	0.077	0.047	0.107	0.015	beta	(18)
Moderate to severe	0.147	0.089	0.205	0.029	beta	(18)
Sever to critical	0.008	0.005	0.011	0.002	beta	Expert opinion
Critical to severe	0.005	0.003	0.007	0.001	beta	Expert opinion
Death after severe	0.014	0.009	0.019	0.003	beta	(18)
Death after critical	0.261	0.159	0.363	0.052	beta	(24)
Recovery after mild	0.070	0.043	0.097	0.014	beta	(18)
Recovery after moderate	0.040	0.024	0.056	0.008	beta	(18)
Recovery after severe	0.020	0.012	0.028	0.004	beta	(18)
Utility values						
Mild	0.810	0.780	0.840	0.015	beta	(31)
Moderate	0.562	0.527	0.597	0.018	beta	(32)
Severe	0.230	0.180	0.280	0.026	beta	(31)

Parameters	Value	Low	High	SE	Distribution	Source
Critical	0.230	0.180	0.280	0.026	beta	Assume same utility as Severe state (31)
Recovery	0.930	0.910	0.960	0.013	beta	(31)
Efficacy						
Risk ratio (RR) of death for remdesivir	0.64	0.44	0.94	0.127	beta	(33)
State costs (PPP dollars)						
Remdesivir + SC						
Mild	166	83	249	42	gamma	Study data
Moderate	559	279	838	143	gamma	Study data
Severe	917	459	1,376	234	gamma	Study data
Critical	1,980	990	2,971	505	gamma	Study data
Supportive care (SC)						
Mild	166	83	249	42	gamma	Study data
Moderate	500	250	750	128	gamma	Study data
Severe	900	450	1,350	230	gamma	Study data
Critical	1,257	628	1,885	321	gamma	Study data

Costs

Direct medical and non-medical costs were identified from the Iranian COVID-19 diagnostic and management guidelines. The costs were collected from patient records in Afzalipour Hospital, southeast of Iran, and were converted to US dollars. Costs entailed hospitalization costs, treatment costs, diagnostic costs (e.g., laboratory tests and chest computerized tomography), and overhead costs. In 2021, the average annual exchange rate of Iranian Rials (IR) to one US dollar was 42,000 IR (21). We multiplied the IR exchange rate by the 2018 purchasing power parity (PPP) conversion factor (22) to convert the costs in local currency units to US dollars, which was 146,681 Rials per 1 PPP dollar in 2018.

Health outcome

The consequence of treatment was measured in QALDs. No study has been performed on the impacts of COVID-19 on the quality of life of patients. We used utility values related to influenza because COVID-19 is similar to influenza. The influence of various medicines on the quality of life of patients is uncertain. As a result, we considered the same utility values for all strategies.

Transition probabilities and relative risk

The probability of disease transmission due to the lack of information in Iran has been extracted from an international study. Remdesivir improves the condition of patients causing only patients receiving remdesivir to return from acute to more stable conditions. Moreover, remdesivir reduces the relative risk of death by 0.64 (0.44–0.94). According to infectious disease experts, the number of patients with severe COVID-19 whose disease had progressed to critical condition and patients with critical COVID-19 that recovered to severe state was estimated. The probability of transmission was calculated from the rate using the following formula (23):

$$P = 1 - e^{-rt} \quad (1)$$

Where p is the probability, e represents the base of the natural logarithm, r denotes the rate, and t refers to the period. Furthermore, the probability of death after critical COVID-19 was obtained from the study conducted by Cabore *et al.* (24), which showed a 7-day transition. We converted probability to rate (Eq. 2) and then rate to probability (Eq. 1) to measure one-day transition following formula (23):

$$r = \left(\frac{1}{t}\right) \ln (1 - p) \quad (2)$$

Cost-effectiveness analysis

Data analysis was performed using TreeAge 2020 software. We considered a willingness-to-pay (WTP) threshold of three times Gross Domestic Product (GDP) per capita for Iran, which was 159 PPP dollars per QALD in 2019 (58,148 PPP dollars per QALY) (25). To evaluate the cost-effectiveness of remdesivir + SC strategy, an incremental cost-effectiveness ratio (ICER) was calculated by the following formula:

$$ICER = \frac{Cost_{remdesivir+sc} - Cost_{sc}}{QALD_{remdesivir+sc} - QALD_{sc}}$$

Sensitivity analysis

Deterministic sensitivity analysis (DSA) was performed to test the robustness of the model results. The results of a one-way sensitivity analysis for several uncertain parameters have been presented in the tornado diagram. Key parameters encompassed costs ($\pm 50\%$), utility values, the relative risk of death (confidence interval: 95%), and transition probabilities ($\pm 20\%$). In addition, we performed a probabilistic sensitivity analysis (PSA) by Monte Carlo simulations with 5000 repetitions. We assumed a gamma distribution for costs and a beta distribution for utility values, transition probabilities, and relative risk (23). The assigned probability distributions for the model parameters are reported in Table 1.

Results

Base case

The findings showed that treatment with remdesivir + SC was associated with QALD gains of 21.13 and the average 30-days healthcare costs of 8795 PPP dollars. However, treatment with SC strategy was associated with lower effectiveness (20.2 QALD) and lower costs (8637 PPP dollars). The ICER of remdesivir + SC, compared to SC alone was 168 PPP dollars per QALD and was not cost-effective at a WTP threshold of three times GDP per capita.

Table 2
Base-case results of cost-effectiveness analysis

Strategies	Cost (PPP dollars)	Incremental cost (PPP dollars)	QALD	Incremental QALD	ICER (PPP dollars/QALD)
Remdesivir + SC	8,795	157	21.13	0.94	168
SC	8,637	-	20.20	-	-

Sensitivity analysis

The results of one-way sensitivity analysis for remdesivir + SC, in comparison with SC, summarized in the tornado diagram showed that ten variables had the greatest impact on ICER (Fig. 2). As shown in Fig. 2, changing the costs of SC for severe and moderate COVID-19 patients, costs of remdesivir + SC for moderate and severe COVID-19 patients, the transition probability of moderate to severe in patients receiving SC, the transition probability of mild to moderate in patients receiving SC, the probability of recovery after mild state in patients receiving SC, the transition probability of mild to moderate in patients receiving remdesivir + SC, transition probability from recovery after mild and moderate in patients receiving remdesivir + SC can change the results of the model.

The PSA findings are shown in the incremental cost-effectiveness scatter plot, which is divided into four quadrants. The southeast region is the cost-effectiveness acceptance region and the northwest region is the cost-effectiveness rejection region. The respective strategy of points located in the northeast and southwest is cost-effective if they are below the threshold line. As indicated in Fig. 3, 48%, 46%, 3%, and 1.6% of trial points are in the northeast, southeast, northwest, and southwest over the WTP threshold, respectively. The remaining trial points are in the northeast under the WTP threshold (1%) and the southwest under the WTP threshold (0.4%). The probability of cost-effectiveness of remdesivir + SC at a WTP threshold of three times GDP per capita is 47%.

Discussion

The current study aimed to provide evidence on the cost-effectiveness of remdesivir + SC for patients with COVID-19 in Iran. Remdesivir is not a confirmed therapy for COVID-19 and maybe has little effect on patients. However, this strategy can be used as the best available treatment for COVID-19 until an entirely successful treatment is discovered. Our base case results showed that remdesivir + SC, compared to SC alone was not cost-effective at a WTP threshold of three times GDP per capita. Treating patients with COVID-19 with remdesivir + SC would cost approximately 168 PPP dollars per QALD, compared to SC.

Sensitivity analysis revealed that ICER was sensitive to the alteration in the costs of SC for severe and moderate COVID-19 patients, costs of remdesivir + SC for moderate and severe COVID-19 patients, the transition probability of moderate to severe in patients receiving SC, the transition probability of mild to moderate in patients receiving SC, transition probability from recovery after mild state in patients receiving SC, transition probability from mild to moderate in patients receiving remdesivir + SC, transition probability from recovery after mild and moderate in patients receiving remdesivir + SC. The PSA results showed that remdesivir + SC was cost-effective with a 47% probability at a WTP threshold of three times GDP per capita.

Our results are consistent with a previous cost-utility analysis of treating moderate to severe respiratory COVID-19. In the mentioned study, dexamethasone and remdesivir were compared with SC demonstrating that remdesivir in moderate and severe infections was dominated by SC (26). In contrast, another study conducted in South Africa found that remdesivir for non-ventilated patients and dexamethasone for ventilated patients were associated with 1,111 deaths averted and were cost-saving (27). One of the limitations of the latter investigation was the type of model and the lack of structure explanation. In general, no similar study was found with the Markov model.

Although some researchers have shown that remdesivir affects COVID-19, its impact on other variants such as B.1.1.7 and B.1.351 has not been studied and remains unknown. These new variants have rapidly spread around the United Kingdom, South Africa, and then other countries. A rise in the number of cases will put further strain on healthcare resources resulting in more hospitalizations and more fatalities (28, 29).

It should be taken into consideration that Iran had a difficult time supplying and distributing medications in hospitals due to sanctions. Even though medications and basic medical equipment are exempt from economic sanctions, the direct and indirect consequences of sanctions have limited the banking system of Iran (30), making it impossible to import pharmaceuticals and purchase raw materials. This situation has a significant impact on the cost of drugs and the total cost of the treatment process for patients. As a result, there is a significant difference between the costs in Iran and other countries.

Remdesivir has been removed from the list of medicines prescribed to COVID-19 patients in the most recent version of COVID-19 diagnosis and treatment guidelines in Iran. Previously, this agent was used as the first-line treatment for COVID-19 patients. The findings of the current study confirmed the last version of the COVID-19 diagnosis and treatment guideline in Iran. This study takes the healthcare system's perspective into account and only direct medical costs are collected. The COVID-19 has resulted in significant indirect costs for patients and their families, which have not been addressed in this study. Therefore, further studies from various perspectives, particularly the social perspective are recommended.

The current research similar to all others had some limitations. First, most of the transition probabilities considered in this study are taken from international studies, which may differ from reality due to the new and growing COVID-19. Furthermore, the transition probability between diverse states varies with the prevalence of distinct disease variants. Second, the utility values considered in this study are for

influenza due to the lack of data for COVID-19 patients. Third, the costs vary widely among COVID-19 patients because many of them have underlying diseases, such as cardiovascular disease, diabetes, and hypertension. The costs of different states of COVID-19, regardless of the underlying disease of patients, are considered in this study. Finally, we tried to reduce some of these limitations by performing sensitivity analysis and changing the parameters.

Conclusion

In conclusion, this analysis demonstrated that remdesivir + SC is not cost-effective from the healthcare perspective in patients with COVID-19 in southeast Iran. Although cost-effectiveness results can help in cost management and resource savings, it is necessary to conduct additional research for making decisions in this area due to the limited studies on the effectiveness of remdesivir for COVID-19 patients. The findings of the present study should be interpreted with caution in policymaking and further research is required in this regard.

Abbreviations

ICU: Intensive care unit; QALDs: Quality-adjusted life days; DSA: Deterministic sensitivity analysis; PSA: Probabilistic sensitivity analysis; IR: Iranian Rials; PPP: Purchasing power parity; GDP: Gross domestic product; SC: Supportive care; WTP: Willingness-to-pay; ICER: Incremental cost-effectiveness ratio

Declarations

Acknowledgements

None

Authors' contributions

MTG, RG, VYF, and MY contributed to the conception and design. MHM and MY conducted the data collection and contributed to acquisition. MTG performed the cost-effectiveness analysis. All authors contributed to the interpretation of the results. MTG drafted the manuscript. All authors revisited the manuscript critically. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used during the current study is available from the corresponding author, RG, on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (No. IR.KMU.REC.1399.632)

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Markov model of COVID-19 disease

Figure 2

Tornado diagram for Remdesivir + SC vs. SC, SC=Supportive care, WTP=willingness to pay, PPP=purchasing power parity, QALD=quality-adjusted life-day

Figure 3

Incremental cost-effectiveness scatter plot of remdesivir + SC versus SC