



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.jfma-online.com](http://www.jfma-online.com)



Original Article

# Assessing efficacy of antiviral therapy for COVID-19 patients: A case study on remdesivir with bayesian synthesis design and multistate analysis



Sih-Han Liao <sup>a,b,c</sup>, Chien-Ching Hung <sup>d,e</sup>, Chiung-Nien Chen <sup>f,g</sup>,  
Jui-Yi Yen <sup>h</sup>, Chen-Yang Hsu <sup>a,i</sup>, Amy Ming-Fang Yen <sup>j</sup>,  
Chi-Ling Chen <sup>a,g,k,\*</sup>

<sup>a</sup> Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

<sup>b</sup> Section of Gastroenterology, Department of Medicine, National Taiwan University Cancer Center, Taipei, Taiwan

<sup>c</sup> Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

<sup>d</sup> Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

<sup>e</sup> Department of Tropical Medicine and Parasitology, National Taiwan University College of Medicine, Taipei, Taiwan

<sup>f</sup> Center for Functional Image and Interventional Therapy, National Taiwan University, Taipei, Taiwan

<sup>g</sup> Department of Surgery, National Taiwan University Hospital, Taipei, Taiwan

<sup>h</sup> Department of Anesthesiology, Taipei Veterans General Hospital, Taipei, Taiwan

<sup>i</sup> Dachung Hospital, Miaoli, Taiwan

<sup>j</sup> School of Oral Hygiene, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan

<sup>k</sup> Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan

Received 6 April 2021; received in revised form 18 April 2021; accepted 21 April 2021

## KEYWORDS

Antiviral therapy;  
COVID-19;  
Remdesivir;  
Clinical efficacy;

**Background/purpose:** A synthesis design and multistate analysis is required for assessing the clinical efficacy of antiviral therapy on dynamics of multistate disease progression and in reducing the mortality and enhancing the recovery of patients with COVID-19. A case study on remdesivir was illustrated for the clinical application of such a novel design and analysis. **Methods:** A Bayesian synthesis design was applied to integrating the empirical evidence on the one-arm compassion study and the two-arm ACTT-1 trial for COVID-19 patients treated with

\* Corresponding author. Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, 7 Chung-Shan South Road, Taipei, 100, Taiwan. Fax: +886 2 23709820.

E-mail address: [chlnchen@ntu.edu.tw](mailto:chlnchen@ntu.edu.tw) (C.-L. Chen).

Bayesian synthesis  
sequential design

remdesivir. A multistate model was developed to model the dynamics of hospitalized COVID-19 patients from three transient states of low, medium-, and high-risk until the two outcomes of recovery and death. The outcome measures for clinical efficacy comprised high-risk state, death, and discharge.

**Results:** The efficacy of remdesivir in reducing the risk of death and enhancing the odds of recovery were estimated as 31% (95% CI, 18–44%) and 10% (95% CI, 1–18%), respectively. Remdesivir therapy for patients with low-risk state showed the efficacy in reducing subsequent progression to high-risk state and death by 26% (relative rate (RR), 0.74; 95% CI, 0.55–0.93) and 62% (RR, 0.38; 95% CI, 0.29–0.48), respectively. Less but still statistically significant efficacy in mortality reduction was noted for the medium- and high-risk patients. Remdesivir treated patients had a significantly shorter period of hospitalization (9.9 days) compared with standard care group (12.9 days).

**Conclusion:** The clinical efficacy of remdesivir therapy in reducing mortality and accelerating discharge has been proved by the Bayesian synthesis design and multistate analysis.

Copyright © 2021, Formosan Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

The clustered cases of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were first reported in Wuhan in December, 2019,<sup>1,2</sup> which has resulted in COVID-19 pandemic from March, 2020 until April, 2021, which has led to more than 140 million cases and claimed more than 3 million deaths.<sup>3</sup>

This soaring number of COVID-19 cases, in spite of great efforts made to put on non-pharmaceutical interventions (NPIs) in most of countries and regions, has stressed medical care systems and compromised the critical care capacity around the world.<sup>4–7</sup> Although several vaccines have been developed and showed promising effects to prevent SARS-CoV-2 infection,<sup>8–12</sup> antiviral therapy has been shown to play the key role for the hospitalized patients to reduce the risk of disease progression to its severe form such as acute respiratory distress syndrome (ARDS) and to shorten the length of hospital stay.<sup>13–17</sup>

To prove evidence-based efficacy, several randomized controlled trials (RCTs) have been conducted to investigate the effects of selected compounds such as chloroquine, hydroxychloroquine, lopinavir/ritonavir, ivermectin, interferon, steroids, and remdesivir since the identification of SARS-CoV-2 in 2020.<sup>12–26</sup> While there is a strong recommendation supporting the systematic use of steroids in patients with severe and critical COVID-19, there are uncertainties regarding the suggestions for the clinical use of other therapeutic compounds. Among the candidate compounds for COVID-19, hydroxychloroquine, chloroquine, and lopinavir/ritonavir have been excluded from the recommendation lists of the treatment guidelines of the World Health Organization (WHO) and National Institutes of Health (NIH) due to the lack of clinical efficacy in reducing mortality and severe disease requiring invasive ventilation and in accelerating recovery and discharge from COVID-19.<sup>27–30</sup> Currently, ivermectin and antibody therapies are also not recommended due to insufficient evidence supporting the beneficial effect of their clinical use.<sup>16,17,31,32</sup>

Remdesivir is another promising compound for treating COVID-19 patients and have been approved by the US FDA for such a purpose.<sup>33</sup> Remdesivir is a monophosphoramidate adenosine analogue prodrug which could be metabolized to active tri-phosphate form to inhibit the synthesis of viral RNA.<sup>16,34–36</sup> Several clinical trials and observational studies have been conducted to evaluate the clinical efficacy in treating COVID-19 patients with various disease severities.<sup>18–22</sup> However, discrepancies in the efficacy exist for different studies. The clinical use of this antiviral therapy thus remains controversial. More importantly, current evidence on its clinical efficacy in reducing mortality for COVID-19 patients still remains inconclusive even after several one-arm studies and two-arm RCTs.<sup>18–22</sup> Based on the inconsistent evidence, the current WHO guideline suggests against the administration of remdesivir in addition to usual care for treating hospitalized COVID-19 patients.<sup>16,32</sup> However, remdesivir has been recommended by the NIH guideline for the hospitalized COVID-19 patients requiring supplementary oxygen without the necessity for oxygen delivery through a high-flow device, non-invasive or invasive ventilation, or extracorporeal membrane oxygenation (ECMO).<sup>17</sup>

To prove an evidence-based clinical efficacy, the best way is to conduct a RCT. However, the conduction of an RCT for assessing a new or a variant of the existing antiviral therapy can be very challenging in the era of COVID-19 pandemic. Moreover, even a two-arm RCT may be underpowered and may also have ethical and feasibility concerns.<sup>33,37–40</sup> While waiting for a well-powered RCT trial for validating the efficacy of any new antiviral therapy, it is worthwhile to elucidate how antiviral therapy alters the mechanism of COVID-19 disease progression from mild to severe stage and until death based on available information from one-arm study without the control group and also from the two-arm RCT.

The aim of this study was to estimate the clinical efficacy of remdesivir by using a novel synthesis sequential design and analysis to integrate the empirical information

provided by the one-arm compassionate study and two-arm RCT with the consideration of the dynamic of COVID-19.

## Materials and methods

### Bayesian synthesis sequential design

The antiviral therapy of remdesivir has been proposed as a candidate and been provided to hospitalized COVID-19 patients in the early stage of first pandemic period. Although the early results suggested the possible benefit of remdesivir therapy, the lack of comparator makes it difficult to quantify the clinical efficacy. The use of RCT design in the latter studies provide the ground of evidence-based evaluation for remdesivir. However, the heterogeneity in the clinical evolution of COVID-19 patients render the results controversial.

Given these scenario, we thus used the Bayesian synthesis sequential design to integrate the information from two studies on the use of remdesivir taking into account the temporal sequence. Specifically, the period of enrollment for the one-arm compassionate between January 25 and March 7, 2020 was taken as the prior study before the RCT. Following the conduction of one-arm compassionate use for remdesivir, the two-arm ACTT-1 trial was performed with the enrollment of study participants between February 12 and April 19, 2020.

The information on the clinical evolution of COVID-19 patients with remdesivir was first obtained on the basis of the empirical data provided by the one-arm compassionate use study.<sup>18</sup> The aggregated data listed in the report of ACTT-1<sup>19</sup> was then used as the main study to update the information derived from the prior study sequentially. Namely, prior information on the daily progression of COVID-19 disease states were first estimated from the data of one-arm study, which was then updated by using the data derived from the two-arm ACTT-1 trial.<sup>19</sup>

### Empirical data on the evolution of hospitalized COVID-19 patients

As indicated in the synthesis design, two empirical data sets, the one-arm compassionate remdesivir use study<sup>18</sup> and the two-arm ACTT-1 trial,<sup>19,20</sup> on the evolution of hospitalized COVID-19 patients across the risk states defined by the WHO R&D Blueprint Group<sup>41</sup> were used for assessing the clinical efficacy of remdesivir. The ordinal scale of COVID-19 severity was classified into three transient states, namely low- (no and low oxygen supplement), medium- (non-invasive ventilator and high oxygen supplement), and high- (ECMO and invasive ventilator) risk states, and the two events of discharge and death. Based on the information provided in the published article, the distribution on the baseline COVID-19 risk states and the transitions across the risk states during the study period were collected for the following analysis.

For the one-arm compassionate remdesivir use study, data on the transitions for COVID-19 patients were abstracted, which provides the empirical information on the daily change of the COVID-19 risk states for 53 patients. This detailed patient-level information recorded on a daily

basis through the 28-day period gives a clear profile of disease evolution across the risk states of COVID-19 from the date of the initiation of remdesivir therapy until discharge, death, or the end of study.<sup>18</sup>

Regarding the two-arm ACTT-1 trial, the original article provides the baseline distribution of COVID-19 risk states by the two treatment groups of remdesivir and standard care and the aggregated information on the transition of COVID-19 states from each of the baseline risk state during the 14-day study period.<sup>19</sup> The aforementioned data with the information on transition from baseline risk states to that observed in the 14-day period were used as the basis for multistate analysis.<sup>42</sup>

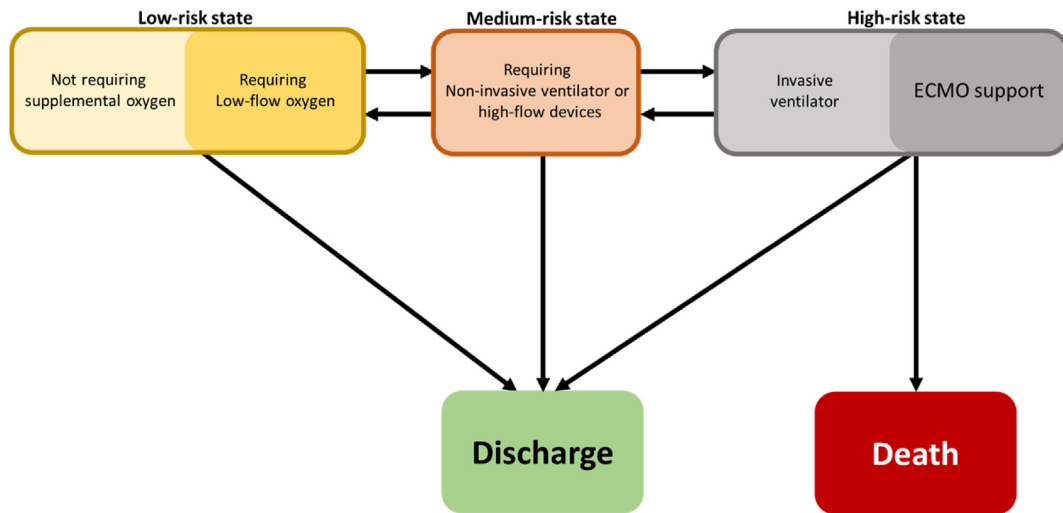
### Statistical analysis

To depict the evolution of COVID-19 through the three transient risk states (low-, medium-, and high-risk state) to the two events of discharge and death, we applied a five-state Markov model (Fig. 1) that have been proposed to assess the efficacy of antiviral therapy.<sup>42</sup> In brief, the hospitalized COVID-19 patients can progress and regress between each of the low-, medium-, and high-risk states (low-risk  $\leftrightarrow$  medium-risk  $\leftrightarrow$  high-risk transitions, Fig. 1). Patients at each of the risk state are possible to recover and discharge at a higher rate from low-risk state followed by that of medium- and high-risk state. For patients with unfavorable outcome, the COVID-19 disease state may progress to the high-risk state followed by the terminal outcome of death, which is also captured by a daily event rate. The kernel consisting of eight transition rates is thus required for the full specification of the five-state Markov model for COVID-19 evolution.

The proposed COVID-19 transition model not only models forward progression but also allows for backward regression from medium- to low-risk and from high- to medium-risk. The mechanisms in the benefit of interventions such as antiviral therapy can thus be captured by both the acceleration in the regression between risk states and the enhancement of the discharge from different risk states.

The continuous-time five-state Markov models were applied to estimate the daily transition rates of movements between risk states, discharge, and death regarding the disease evolution of COVID-19 patients with the remdesivir-treated group and the standard-care group.<sup>41–43</sup> Bayesian Markov Chain Monte Carlo (MCMC) simulation was used to estimate these daily transition rates in light of likelihood functions based on aggregated data on the remdesivir-treated and the standard care groups abstracted from the original articles.<sup>18,19,42</sup>

The dynamic curve depicting the evolution of COVID-19 across three risk states and two events of discharge and death in 28-day period was derived from the transition probability matrix for the five defined states given the estimated results on eight daily transitions rates for the five-state Markov model (Fig. 1). Based on the predicted 28-day probabilities to the outcomes of discharge and death for the remdesivir-treated and the standard care groups, we were able to assess the efficacy of remdesivir therapy in accelerating discharge and in decreasing subsequent risk of death for hospitalized COVID-19 patients. We further



**Figure 1** Five-state model for the clinical evolution of hospitalized COVID-19 patients.

evaluated the clinical efficacy of remdesivir in reducing the risk of high-risk state and the composite outcome of death and high-risk state. The effect of remdesivir on the prognosis of hospitalized COVID-19 patients was evaluated by using relative risk derived by comparing the probability distributions of patients receiving remdesivir with that of patients with standard care.

## Results

### Empirical data on COVID-19 dynamic abstracted from published article

Table 1 shows the total of 53 patients on repeated data featuring the change of risk states of COVID-19 after receiving remdesivir.<sup>18</sup> Table 1 also shows the transition of 53 patients across three risk states and the final destination of discharge during a one-month study period. The data of Table 1 are used for deriving the rate of COVID-19 evolution in the light of the five-state disease transition models.

### Daily transition rates of COVID-19 evolution

Fig. 2 and Table 2 show the estimated results on the daily transition rates of progression and regression, discharge, and death for three risk states by treatment groups of remdesivir versus standard care based on the five-state COVID-19 progression model. Both groups show significant higher discharge rates for the low-risk state compared with those of medium- and high-risk patients. Fig. 2 shows that the discharge was mainly from the low-risk state of COVID-19 patients with the orders of 0.1678 (95% CI, 0.1456–0.1917, Table 2) and 0.1396 (95% CI, 0.1178–0.1618, Table 2) for the remdesivir-treated group and the standard care group, respectively.

Fig. 2 also shows the side-by-side comparisons for the daily transition rates of progression by treatment groups. Compared with remdesivir-treated group, the standard care group shows a higher rate of progression, especially for the low-risk patients. The daily progression rates from

low- to medium-risk (Fig. 2, the row in green; 0.0747; 95% CI, 0.0572–0.0959, Table 2), from medium- to high-risk state (Fig. 2, the row in yellow; 0.2054; 95% CI, 0.1537–0.2650, Table 2), and from high-risk state to death (Fig. 2, the row in pink; 0.0270; 95% CI, 0.0195–0.0355) were lower for the remdesivir-treated group compared with the corresponding figures, 0.1394 (95% CI, 0.0764–0.2310, Table 2), 0.2744 (95% CI, 0.1710–0.4189, Table 2), and 0.0370 (95% CI, 0.0275–0.0476, Table 2), for the standard care group.

Considering the dynamics between the progression and regression for patients at medium risk by using the net force of regression (regression rate - progression rate, Fig. 2, the row in orange), remdesivir-treated group shows a largely positive net regression with certainty. The minus

**Table 1** Empirical data on the transitions of COVID-19 in the study of compassionate remdesivir use.

Transition mode		Frequency <sup>a</sup>
Preceding state	Succeeding state	
Low <sup>b</sup>	Low	197
	Medium	4
	Discharge	23
Medium <sup>b</sup>	Low	12
	Medium	113
	High	5
	Discharge	1
	Death	1
High <sup>b</sup>	Low	11
	Medium	11
	High	403
	Discharge	1
	Death	6

<sup>a</sup> The total patient numbers of the low-, medium-, and high-risk states at baseline were 12, 7, and 34, respectively.

<sup>b</sup> Low-risk state: no and low oxygen supplement; medium-risk state: non-invasive ventilator and high-flow oxygen supplement; high-risk state: ECMO and invasive ventilator.

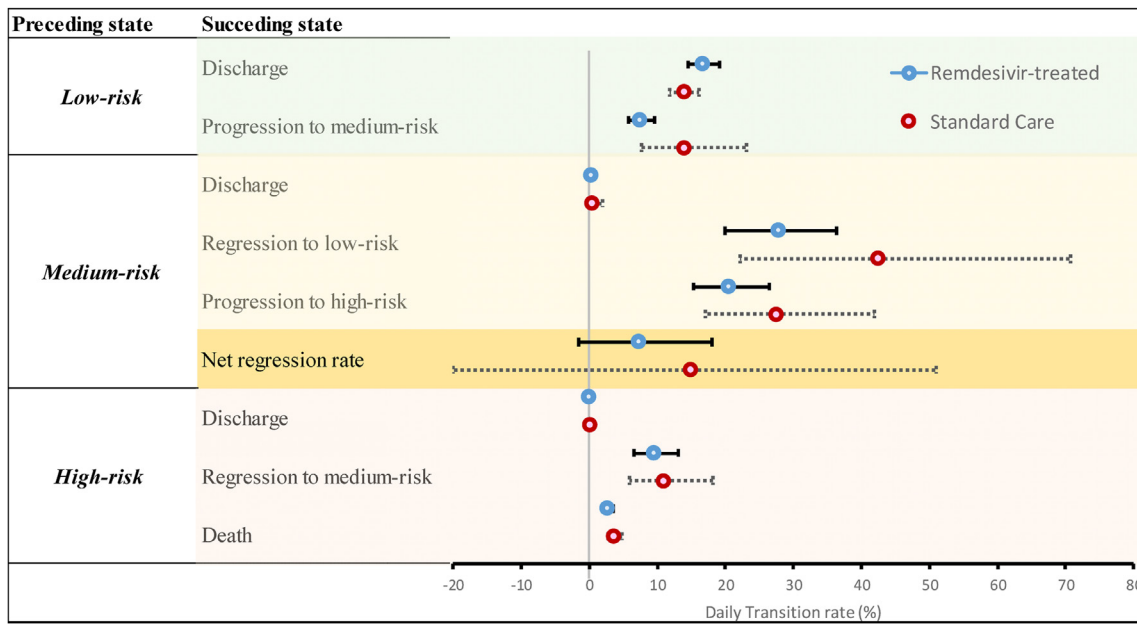


Figure 2 Estimated results by synthesis the information on compassionate remdesivir use study and ACTT-1 trial.

Table 2 Estimated results on the daily transition rates between risk states by the two treatment groups.

Transitions		Remdesivir	Standard care
Preceding state	Succeeding state	Daily transition rate (95% CI)	Daily transition rate (95% CI)
Low	Medium	0.0747 (0.0572, 0.0959)	0.1394 (0.0764, 0.2310)
	Discharge	0.1678 (0.1456, 0.1917)	0.1396 (0.1178, 0.1618)
Medium	Low	0.2797 (0.1997, 0.3637)	0.4244 (0.2212, 0.7075)
	High	0.2054 (0.1537, 0.2650)	0.2744 (0.1710, 0.4189)
High	Discharge	0.0036 (0.0005, 0.0088)	0.0041 (0.0001, 0.0191)
	Medium	0.0955 (0.0660, 0.1306)	0.1101 (0.0592, 0.1824)
	Discharge	0.0008 (0.0002, 0.0015)	0.0008 (0.0003, 0.0013)
	Death	0.0270 (0.0195, 0.0355)	0.0370 (0.0275, 0.0476)

net regression rate for COVID-19 patients receiving standard care exhibited the risk of deterioration in the absence of antiviral therapy.

### Comparisons of the dynamic of COVID-19 risk states by two groups

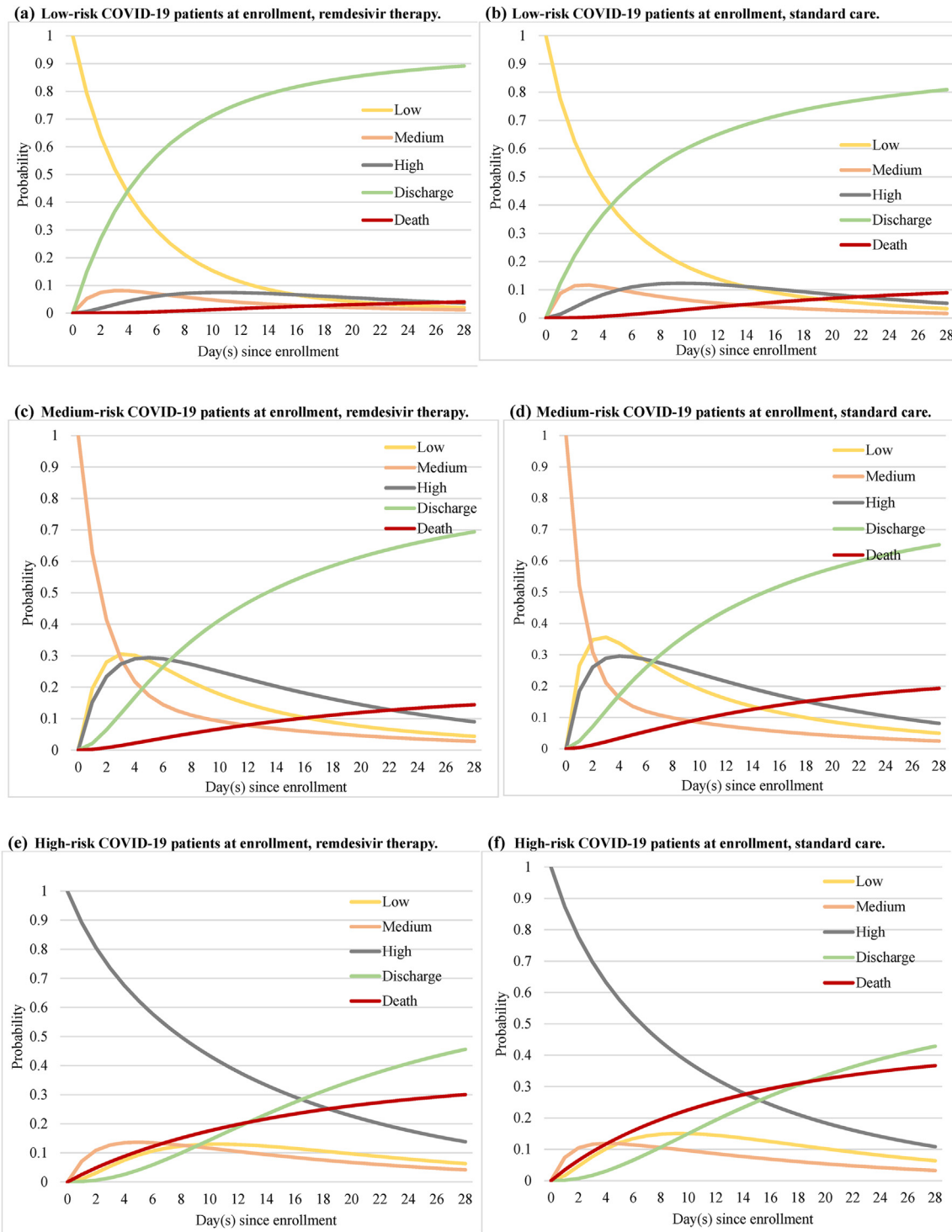
The efficacy of remdesivir therapy was further elucidated by the dynamics of COVID-19 across three risk states and the outcomes of discharge and death based on the estimated results on daily transition rates with the application of the two disease transition modes to detailed empirical data. Fig. 3 (a) shows the daily progression on the dynamic of COVID-19 for the hospitalized patients with low-risk state at baseline who received remdesivir and those who received standard care. In line with the estimated results listed in Table 2, the discharge rate for COVID-19 patients were accelerated by remdesivir therapy. The probability of discharge (green line) was uniformly higher compared with that of the control group. For the medium- and high-risk state, the benefit of regression to a lower risk states

resulting from remdesivir therapy (Fig. 3 (a)) was demonstrated by the uniformly lower probability for medium- (orange line) and high-risk (gray line) compared with the control group (Fig. 3 (b)). The risk of death (red line) after one-month follow-up period was also lower for COVID-19 patients receiving remdesivir compared with those receiving standard care.

Similar trends regarding the probabilities of discharge, death, and high-risk state can be observed in Fig. 3 (c) vs (d) and Fig. 3 (e) vs (f), showing the dynamic of COVID-19 by two treatments for patients at medium- and high-risk state at enrollment, respectively.

### Efficacy of remdesivir therapy

Based on the estimated results on the daily rates for clinical evolution of COVID-19 patients by using the Bayesian synthesis sequential design and analysis, we further assessed the efficacy of remdesivir therapy in reducing the risk of death and increasing the odds of recovery and discharge. Table 3 lists the estimated results on the clinical efficacy in



**Figure 3** The dynamic of COVID-19 states for remdesivir-treated group (a, c, e) and standard care group (b, d, f) by risk-state at enrollment.

terms of discharge, high-risk states, and death given the 28-day period of follow-up derived by comparing the 28-day probability for each of the defined outcome for two groups (S-Table 1). Regarding the outcome of COVID-19 death, remdesivir therapy can significantly reduce the risk by 31% (RR, 0.69; 95% CI, 0.56–0.82). For the outcome of discharge, remdesivir therapy results in significantly higher

odds by 10% (RR, 1.10; 95% CI, 1.01–1.18). Given the observation of the significant efficacy of remdesivir treatment in terms of both death and discharge, we further elucidated its benefit for COVID-19 patients of three risk states at baseline.

In all three risk states of COVID-19 patients, the use of remdesivir gave statistically significant higher odds of

**Table 3** Estimated results on the clinical efficacy for outcomes of discharge, high-risk state, and death by baseline risks of COVID-19 patients.

Baseline risk state	Outcomes	Relative risk	95% CI
Low	(1) Discharge	1.11	(1.07, 1.14)
	(2) High-risk	0.74	(0.55, 0.93)
	(3) Death	0.38	(0.29, 0.48)
	(2)+(3)	0.52	(0.39, 0.64)
Medium	(1) Discharge	1.11	(1.07, 1.16)
	(2) High-risk	1.12	(0.96, 1.27)
	(3) Death	0.61	(0.56, 0.67)
	(2)+(3)	0.76	(0.69, 0.84)
High	Discharge	1.25	(1.18, 1.32)
	Death	0.65	(0.62, 0.69)
Overall	Discharge	1.10	(1.01, 1.18)
	Death	0.69	(0.56, 0.82)

discharge and lower risks of death. The efficacy of remdesivir in accelerating discharge of COVID-19 patients was most prominent for the high-risk group (RR, 1.25; 95% CI, 1.18–1.32, Table 3) followed by the medium-risk group (RR, 1.11; 95% CI, 1.07–1.16) and the low-risk group (RR, 1.11; 95% CI, 1.07–1.14). For low-risk patients at baseline, remdesivir therapy led to the reduction of subsequent progression to high-risk state by 26% (RR, 0.74; 95% CI, 0.55–0.93) and to final death by 62% (RR, 0.38; 95% CI, 0.29–0.48). For the medium-risk patients, less but still statistically significant efficacy results were noted in reducing progression to death by 39% (RR, 0.61; 95% CI, 0.56–0.67). Patients at high-risk state treated with remdesivir also led to a 35% reduction in death from COVID-19 (RR, 0.65; 95% CI, 0.62–0.69).

The median days to discharge for hospitalized COVID-19 patients at low-, medium-, and high-risk receiving remdesivir treatment was estimated as 4.8 days (interquartile range [IQR], 4.7–5.0), 13.2 days (IQR, 12.8–13.6), and 31.3 days (IQR, 29.7–32.8), respectively. The corresponding results for COVID-19 receiving standard care were estimated as 6.8 days (IQR, 6.5–6.9), 14.6 days (IQR, 13.0–15.7), and 38.8 days (IQR, 33.0–44.7), respectively. The remdesivir therapy (9.9 days, IQR, 9.5–10.2) resulted in significantly reduced time to discharge compared with COVID-19 patients receiving standard care (12.9 days, IQR, 12.3–13.0).

## Discussion

Based on the empirical information abstracted from the one-arm compassionate use study and the two-arm ACTT-1 trial, we demonstrated the clinical efficacy of remdesivir in the statistically significant reduction of mortality by 31% (95% CI, 18–44%) and acceleration of discharge by 10% (95% CI, 1–18%) taking into consideration of the dynamic of COVID-19 evolution among hospitalized patients. While the remdesivir therapy for the low-risk patients at baseline shows the highest benefit in mortality reduction by 62% (95% CI, 52–71%), the therapy shows the highest benefit in increasing the odds of discharge by 25% (95% CI, 18–32%)

when it was administrated to COVID-19 patients at high-risk state at baseline.

We further explored the mechanism of remdesivir therapy based on the dynamic of hospitalized COVID-19 patients receiving standard care and those receiving remdesivir. By using the daily transitions of COVID-19 patients across three risk-states and two outcomes of discharge and death, we showed that the beneficial effect of remdesivir therapy was attributed mainly to reductions of the progression rate in low-risk patients and increases of the net regression for medium-risk patients. Our results not only have strengthened the evidence for the clinical use of remdesivir for hospitalized COVID-19 patients, the proposed synthesis sequential design and analysis with the backbone of five-state COVID-19 progression model also provides a framework for an efficient assessment of novel compounds to inform their clinical use at the earliest and optimal timing.

While a substantial proportion of COVID-19 cases have occurred from a cascade of outbreaks in five continental countries since January 2020, the global disease burden resulted from an enormous number of deaths from COVID-19 as well as slow recovery after the ascertainment of COVID-19 diagnosis. The slow recovery may increase the possibility of transmission and infectious period so as to spur the subsequent outbreaks among the susceptible people. Although effective vaccines have been available since the end of 2020, the virial variants, the implementation and scale-up of vaccination, and the global vaccination distribution remain great concerns.<sup>44–47</sup> The resurgence of COVID-19 outbreaks in India and countries in Europe, South America, and Africa in March, 2021 further shows the persistent threat of COVID-19 global pandemic and the urgent need for effective antiviral therapies with evidence-based support.<sup>3,48</sup>

Reported from the one-arm study, remdesivir has been proposed for compassionate use in 53 patients and demonstrated 68% clinical improvement.<sup>18</sup> However, the one-arm study has been argued with a lacking of control group. It requires a two-arm RCT to demonstrate its evidence-based efficacy.<sup>19–22</sup> However, in the era of COVID-19 pandemic, identifying a new potential antiviral therapy with a RCT design is fraught with the difficulty of logistics in implementation and ethical concerns. An underpowered RCT without consideration of the dynamic of COVID-19 further results in the controversial evidence. Alternative methods for evaluating evidence-based antiviral therapy with efficiency is therefore urgently needed.

The proposed synthesis sequential design analysis can be a solution to this dilemma. By making use of the information derived from two studies, we were able to derive precise estimates on the daily rate of COVID-19 evolution altered by remdesivir therapy. This approach not only takes into account the temporal sequence on the clinical use of remdesivir for COVID-19 patients but also provides a framework for the evaluation of the clinical efficacy of remdesivir treatment by incorporating the standard care group as the comparator.

Compared with the empirical results on marginally statistically significant reduction in the risk for death (HR, 0.73; 95% CI, 0.52–1.03) derived from the two-arm RCT of remdesivir,<sup>19,20</sup> the point estimate was consistent but our proposed approach was more precise due to the



incorporation of information sources derived from both the one-arm study and the two-arm trial. The dynamics of COVID-19 evolution depicted by the five-state progression model further makes use of full information on the transition across risk states reported on a daily basis by the one-arm compassionate use study. Our estimated results are also consistent with that reported by Jen et al. with the mortality reduction by 30.5% (95% CI, 6.6–50.9).<sup>42</sup>

The additional advantages of our synthesis sequential design and analysis of the empirical data from the one-arm compassionate study<sup>18</sup> and two-arm ACTT-1 trial<sup>19</sup> on the use of remdesivir are three-fold. Firstly, we improved the weakness of lacking a control group in the original one-arm study as a proportion of COVID-19 patients may be discharged in recovery dispensing with the use of remdesivir. Second, incorporating the information from two-arm ACTT-1 trial with the consideration of the baseline risk state enables us to evaluate the efficacy of remdesivir with clear primary endpoints including death and discharge rather than only based on the clinical improvement before and after the use of remdesivir. Third, the results on the clinical dynamic of COVID-19 evolution derived from such a synthesis sequential design and analysis can support the clinical decision on the administration of therapies based on the risk states of COVID-19 patients.

The results of finding an effective antiviral therapy like remdesivir in reducing death and length of hospital stay from COVID-19 have also two significant implications for containing COVID-19 pandemic. First, it reduces the sequelae of COVID-19 and also accelerates its recovery. Besides, the administration of antiviral therapy may also reduce transmission probability and infectious duration in contact with the susceptible people. Such an efficacy of antiviral therapy in the prophylaxis and treatment has been demonstrated in the management of influenza.<sup>49,50</sup>

In conclusion, we propose a Bayesian synthesis sequential design with multi-state analysis to evaluate evidence-based antiviral therapy with efficiency. The illustrated results based on the proposed approach not only provide an even precise estimate of efficacy in reducing death and time-to-discharge of COVID-19 patients but also shed light on the underlying mechanism for the potential benefit of antiviral therapy, which can enlighten the clinical management of COVID-19 patients with precision and timeliness.

## Funding support

This work was supported by Ministry of Science and Technology, Taiwan (MOST 108-2118-M-038-001-MY3, MOST 109-2327-B-002 -009).

## Role of funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jfma.2021.04.026>.

## References

- Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;**382**(13):1199–207.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**(10223):497–506.
- Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020;**20**(5):533–4.
- Peters AW, Chawla KS, Turnbull ZA. Transforming ORs into ICUs. *N Engl J Med* 2020;**382**(19):e52.
- Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med* 2020;**8**(5):506–17.
- Ranney ML, Griffeth V, Jha AK. Critical supply shortages - the need for ventilators and personal protective equipment during the covid-19 pandemic. *N Engl J Med* 2020 Apr 30;**382**(18):e41.
- Truog RD, Mitchell C, Daley GQ. The toughest triage - allocating ventilators in a pandemic. *N Engl J Med* 2020 May 21;**382**(21):1973–5.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020;**383**(27):2603–15.
- Baden LR, ElSahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;**384**(5):403–16.
- Sadoff J, LeGars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S covid-19 vaccine. *N Engl J Med* 2021;**384**(19):1824–35.
- Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;**397**(10269):99–111.
- Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;**384**(15):1412–23.
- Liu W, Zhou P, Chen K, Ye Z, Liu F, Li X, et al. Efficacy and safety of antiviral treatment for COVID-19 from evidence in studies of SARS-CoV-2 and other acute viral infections: a systematic review and meta-analysis. *CMAJ (Can Med Assoc J)* 2020;**192**(27):E734–44.
- Abdelrahman Z, Liu Q, Jiang S, Li M, Sun Q, Zhang Y, et al. Evaluation of the current therapeutic approaches for COVID-19: a systematic review and a meta-analysis. *Front Pharmacol* 2021;**12**:607408.
- Gandhi RT, Lynch JB, Del Rio C. Mild or moderate covid-19. *N Engl J Med* 2020;**383**(18):1757–66.
- World Health Organization. *Therapeutics and COVID-19: living guideline, 20 November 2020*. Geneva, Switzerland: World Health Organization; 2020. Available from: <https://www.who>.

- int/publications/i/item/therapeutics-and-covid-19-living-guideline. [Accessed 6 December 2020].
17. National Institute of Health. *COVID-19 Treatment guidelines*. National Institute of Health; November 3, 2020. p. 2020. Available from: <https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/>. [Accessed 6 December 2020].
  18. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe covid-19. *N Engl J Med* 2020;**382**(24):2327–36.
  19. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19—preliminary report. *N Engl J Med* 2020;**383**(10):993–4.
  20. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 - final report. *N Engl J Med* 2020;**383**(19):1813–26.
  21. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with covid-19. *N Engl J Med* 2021;**384**(9):795–807.
  22. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;**395**(10236):1569–78.
  23. Abd-El Salam S, Esmail ES, Khalaf M, Abdo EF, Medhat MA, Abd El Ghafar MS, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. *Am J Trop Med Hyg* 2020;**103**(4):1635–9.
  24. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med* 2020;**382**(19):1787–99.
  25. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate covid-19. *N Engl J Med* 2020;**383**(21):2041–52.
  26. Chen C-P, Lin Y-C, Chen T-C, Tseng T-Y, Wong H-L, Kuo C-Y, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). *PLoS One* 2020;**15**(12):e0242763.
  27. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of hydroxychloroquine in hospitalized patients with covid-19. *N Engl J Med* 2020 Nov 19;**383**(21):2030–40.
  28. Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for early treatment of adults with mild covid-19: a randomized-controlled trial. *Clin Infect Dis* 2020:ciaa1009.
  29. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. *EclinicalMedicine* 2020 Dec;**29**:100645.
  30. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020 Oct 5;**396**(10259):1345–52.
  31. Lamontagne F, Agoritsas T, Siemieniuk R, Rochweg B, Bartoszko J, Askie L, et al. A living WHO guideline on drugs to prevent covid-19. *BMJ* 2021 Mar 1;**372**:n526.
  32. Siemieniuk R, Rochweg B, Agoritsas T, Lamontagne F, Leo Y-S, Macdonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020 Sep 4;**370**:m3379.
  33. Rubin D, Chan-Tack K, Farley J, Sherwat A. FDA approval of remdesivir - a step in the right direction. *N Engl J Med* 2020 Dec 31;**383**(27):2598–600.
  34. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science* 2020;**368**(6492):779–82.
  35. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem* 2020 Apr;**295**(15):4773–9.
  36. Jorgensen SCJ, Kebriaei R, Dresser LD. Remdesivir: review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19. *Pharmacotherapy* 2020;**40**(7):659–71.
  37. Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. *Lancet* 2020;**395**(10236):1525–7.
  38. McCreary EK, Angus DC. Efficacy of remdesivir in COVID-19. *J Am Med Assoc* 2020;**324**(11):1041–2.
  39. Cohen J, Kupferschmidt K. “A very, very bad look” for remdesivir. *Science* 2020;**370**(6517):642–3.
  40. Dyer O. Covid-19: remdesivir has little or no impact on survival, WHO trial shows. *BMJ* 2020 Oct 19;**371**:m4057.
  41. World Health Organization. *WHO R&D Blueprint novel coronavirus: COVID-19 therapeutic trial synopsis*. Geneva, Switzerland: World Health Organization; 2020. Available from: <https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis>.
  42. Jen H-H, Chang W-J, Lin T-Y, Hsu C-Y, Yen AM-F, Lai C-C, et al. Evaluating clinical efficacy of antiviral therapy for COVID-19: a surrogate endpoint Approach. *Infect Dis Ther* 2021 Mar 18: 1–11.
  43. Wu Y-Y, Yen M-F, Yu C-P, Chen H-H. Risk assessment of multistate progression of breast tumor with state-dependent genetic and environmental covariates. *Risk Anal* 2014 Feb;**34**(2):367–79.
  44. Nachega JB, Sam-Agudu NA, Masekela R, van der Zalm MM, Nsanzimana S, Condo J, et al. Addressing challenges to rolling out COVID-19 vaccines in African countries. *Lancet Glob Heal* 2021;**9**(6):e746–8.
  45. Vergara RJD, Sarmiento PJD, Lagman JDN. Building public trust: a response to COVID-19 vaccine hesitancy predicament. *J Public Health* 2021:fdaa282.
  46. Schaffer DeRoo S, Pudalov NJ, FuL Y. Planning for a COVID-19 vaccination program. *J Am Med Assoc* 2020 Jun 23;**323**(24):2458–9.
  47. Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrahi M, Zigran A, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. *Eur J Epidemiol* 2020 Aug;**35**(8):775–9.
  48. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. *Lancet* 2021;**397**(10273):452–5.
  49. Ferguson NM, Cummings DAT, Cauchemez S, Fraser C, Riley S, Meeyai A, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 2005 Sep 8;**437**(7056):209–14.
  50. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005 Sep 29;**353**(13):1363–73.