Original Article

# The real-time reproduction number, impact of interventions and prediction of the epidemic size of COVID-19 in the center of Iran

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**Background:** The monitoring of reproduction number over time provides feedback on the effectiveness of interventions and on the need to intensify control efforts. Hence, we aimed to compute basic ($R_0$) and real-time (Rt) reproduction number and predict the trend and the size of the coronavirus disease 2019 (COVID-19) outbreak in the center of Iran. **Materials and Methods:** We used the 887 confirmed cases of COVID-19 from February 20, 2020, to April 17, 2020 in the center of Iran. We considered three scenarios for serial intervals (SIs) with gamma distribution. $R_t$ was calculated by the sequential Bayesian and time-dependent methods. Based on a branching process using the Poisson distributed number of new cases per day, the daily incidence and cumulative incidence for the next 30 days were predicted. The analysis was applied in R packages 3.6.3 and STATA 12.0. **Results:** The model shows that the $R_t$ of COVID-19 has been decreasing since the onset of the epidemic. According to three scenarios based on different distributions of SIs in the past 58 days from the epidemic, $R_t$ has been 1.03 (0.94, 1.14), 1.05 (0.96, 1.15), and 1.08 (0.98, 1.18) and the cumulative incidence cases will be 360 (180, 603), 388 (238, 573), and 444 (249, 707) for the next 30 days, respectively. **Conclusion:** Based on the real-time data extracted from the center of Iran, $R_t$ has been decreasing substantially since the beginning of the epidemic, and it is expected to remain almost constant or continue to decline slightly in the next 30 days, which is consequence of the schools and universities shutting down, reduction of working hours, mass screening, and social distancing.

**Key words:** Coronavirus disease 2019, coronavirus, reproduction number, predict, Iran

**How to cite this article:** Moradzadeh R, Jamalian M, Nazari J, Hosseinkhani Z, Zamanian M. The real-time reproduction number, impact of interventions and prediction of the epidemic size of COVID-19 in the center of Iran. J Res Med Sci 2021;26:87.

## INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, China, in December 2019 developed into a pandemic and has been threatening human health almost all over the world.[1,2] Coronaviruses are a diverse group of viruses which have been identified since 1965 and caused serious large-scale outbreaks and considerable global health consternation in the past two decades worldwide, such as severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus, and their newest variant COVID-19.[3]

The people infected or killed by the new virus around the world are much more than the people from its two predecessors.[2,4] The $R_0$ of this virus was estimated between 2 and 3.5 that means each patient on average could transmit the COVID-19 to two up to three people. The average age of patients is about 55 years, and the most prevalent symptoms in patients are dry cough, fever, and shortness of breath; the case fatality rate of COVID-19 has been estimated to be around 2%.[2,4-6] There is still much to know about the viral characteristics, pathogenicity, and the ways COVID-19 spreads, but droplets, contact, aspirates, feces, and aerosols are the most important identified modes of its transmission.[7]

**Access this article online**

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_480_20



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**Submitted:** 06-May-2020; **Revised:** 09-Jun-2020; **Accepted:** 30-Jun-2020; **Published:** 30-Sep-2021

COVID-19 pandemic has now reached most of countries and has resulted in around 7.1 million cases and more than 400,000 of deaths at the time of writing this article (11 June 2020).[2,8] The first confirmed cases of COVID-19 in Iran were reported on February 19, 2020, in Qom,[2] and in total, 180,176 confirmed cases and 8,584 deaths of COVID-19 at the time of writing this article have been reported in Iran (11 June 2020).[8]

Despite the uncertainty associated with forecasting, modeling and estimating the daily number of confirmed cases are still crucial for the treatment system and health-care policymakers to provide the optimal intervention strategies and the required services for the new patients. This issue could be dependent on host conditions, pathogenic behavior, and environmental and behavioral factors.[7,9] Throughout the epidemic, the government and health authorities should constantly monitor the epidemic curve and effect of interventions on it to control the epidemic and manage the condition. A key parameter in modeling studies to evaluate the potential transmissibility of COVID-19 and to estimate the probable size of the outbreak is the real-time reproductive number ($R_{t)}$).[10] In this study, we aimed to forecast $R_t$, the trend of the epidemic and the probable size of COVID-19 outbreak in the next 30 days in Arak University of Medical Sciences (AUMS) in the center of Iran based on the data gathered from the past 2 months.

## MATERIALS AND METHODS

This study was approved by Ethics Committee of AUMS (Project number: 3675). The present study was a mathematical modeling based on daily confirmed cases of COVID-19 from February 20 to April 17, 2020 ($n$ = 887), in AUMS. AUMS is covering 974,000 population in nine cities in the center of Iran.[11] The main city of the AUMS is Arak. The population of the study area has many communications with other provinces of the country. This area has a lot of immigration from other parts of the country. All confirmed cases on the positive RT-PCR were reported to the COVID-19 registry system of AUMS. For confirmed cases, residence in Markazi Province was the basic inclusion criteria of the study. The date of laboratory sampling was considered as the date of confirmed cases. It is better to enter the date of the onset of symptoms in the analysis, but the date of symptoms was potentially susceptible to missing and recall bias.[12,13] The included variables were age (year), sex (female/male), daily incidence, and death by COVID-19.

### Data analysis

As Rothman was expressed, "A key concept in assessing whether an outbreak that is spread by person to person transmission will ignite or die out is the basic reproductive number, usually written as $R_0$. $R_0$ is the average number of secondary cases that occur from a single index case in a susceptible population in which no interventions are being taken. If the $R_0$ is <1, each case will on average lead to <1 additional case, and the outbreak will die out, unless fueled by external re-infections. The rate at which disease disappears from the population depends on how much below 1 the basic reproductive number is and on the interval between successive generations of infection. If the basic reproductive number is above 1, each case in the early stage of an outbreak produces more than one new secondary case, and the epidemic grows. The speed at which it grows depends on the magnitude of the basic reproductive number for that disease and the time between successive infections."[14] Moreover, the real-time reproductive number, $R_t$, is the reproductive number that was included the mix of immunity and social interaction at any point in time that the epidemic was progresses.[14]

The daily incidence data were used for the estimation of reproduction numbers for the COVID-19 epidemic. Serial interval (SI) is defined as the time between the onset of symptoms in a primary case and the onset of symptoms in secondary cases.[15] We considered three scenarios for SI. According to Hwang *et al.*,[16] we used gamma distribution with mean ± standard deviations (SD) for SI distributions (6 ± 3 and 4 ± 2).

In this study, we estimated $R_0$ and $R_t$ along with 95% confidence intervals (CIs). Moreover, the outputs have been shown by graphs. $R_0$ estimations were shown the epidemic curve and an adjusted model, and $R_t$ was calculated by the sequential Bayesian and time-dependent method to present the R (t) variations throughout the COVID-19 epidemic period. To evaluate the impact of different SI, the sensitivity analysis was done based on different SIs and $R_0$ values.[17,18]

In sequential Bayesian method, incidence at time t + 1, $N(t+1)$, is approximately Poisson distributed with mean $N(t)\, e^{(\gamma[R-1])}$, where $\frac{1}{\gamma}$ the average duration of the infectious period. The distribution of the $R_t$ is updated as new data using posterior distribution as:

$P(R_t \mid N_0, \ldots, N_{t+1}) = P(N_{t+1} \mid R_t, N_0, \ldots, N_t)\, P(R_t \mid N_0, \ldots, N_t) / P(N_0, \ldots, N_{t+1})$.[17]

$R_t$ in time-dependent method calculates $R_t$ by averaging over all transmission networks compatible with observations. The probability $p_{ij}$ that case i with onset at time $t_i$ was infected by case j with onset at time $t_j$ was obtained by $p_{ij} = N_i w(t_i - t_j) / \sum_{i \neq k} N_i w(t_i - t_k)$. The R for case j is therefore $R_j = \sum_i p_{ij}$ and is averaged as $R_t = \frac{1}{N_t} \sum^{[17]} R_j$ over all cases with the same date of onset. Moreover, the CI for $R_t$ was obtained by simulation.[17]

Furthermore, to provide the prediction of daily incidence and cumulative incidence for the next 30 days, we used past incidence and the estimates of the SIs and reproduction numbers. This approach is based on a branching process using a Poisson distributed number of new cases per day,[19] computed as: $\lambda_t = \sum_{s=1}^{t-1} y_s w(t-s)$, where w $(t-s)$ is the probability mass function of the SI distribution, and $y_s$ is the incidence at time $s$. The prediction of daily incidence for the next 30 days was calculated by a bootstrap resampling method with 10,000 times.[6,20]

The analysis was conducted in R packages 3.6.3 (R Core Team) and STATA 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX, USA: StataCorp LP). Applied R libraries were incidence, earlyR, R0, and projections packages.[8,15]

## RESULTS

### Descriptive

A total of 887 COVID-19 cases were confirmed with the RT-PCR test in this study. The epidemic curve of infections is shown in Figure 1. Among identified cases, 51% were female. The mean age of confirmed cases was 56 (standard deviation: 19, range: 1–99). Until now, the case fatality rate of COVID-19 was 11.7% among confirmed cases. Based on the linear regression analysis, there were not any statistically significant changes in the reported COVID-19 cases in this study (regression coefficient: 0.009 and $P$ = 0.3) [Figure 1 in Appendix].

### Real-time reproduction number

The real-time reproduction number ($R_t$) in the sequential Bayesian model in A, B, and C scenario indicated a

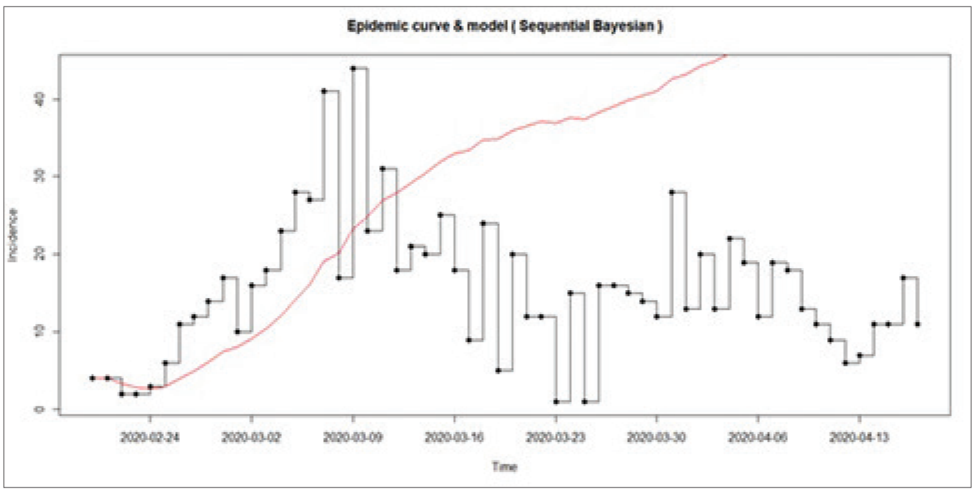


**Figure 1:** Epidemic curve of COVID-19 in the study area

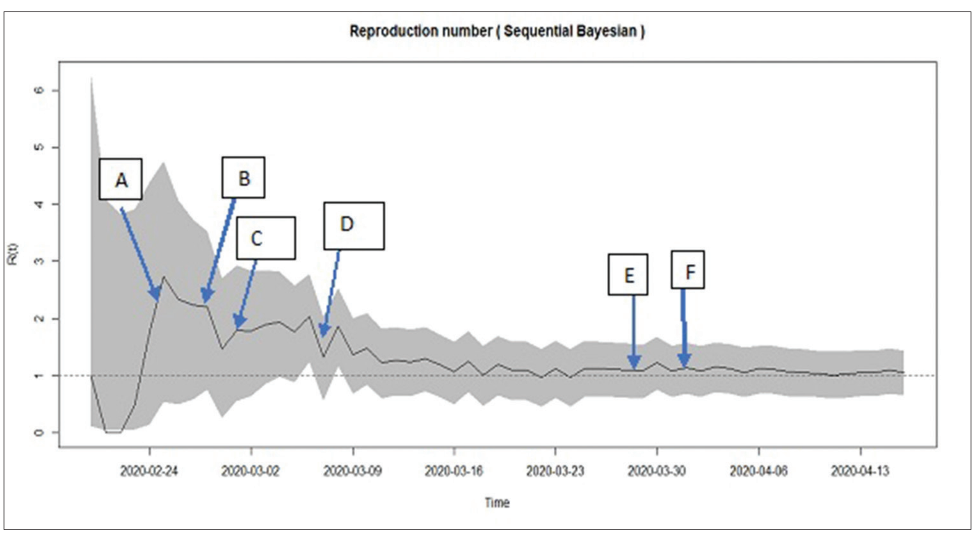


**Figure 2:** Sequential Bayesian method for evaluating the time-dependent reproduction number ($R_t$) in serial interval with gamma distribution and mean 6 ± 3. (a) Onset of closing all schools and universities, (b) onset of closing mosques and reducing working hours. (c) Onset of the evaluation of infection symptoms of passengers at the entrances and exits of cities. (d) Mass screening. (e) Onset of social distancing. F: Onset of restrictions on vehicle traffic

decrease in the $R_t$ of COVID-19 in the 58-day period of the study. These changes were considerably tended to move the curve to $R_t$ one. As seen in Figure 2, approximately from March 16 to April 17, this proximity to $R_t$ one has continued [the figures of other related scenario are in Figure 2 in the Appendix].

Moreover, the time-dependent model showed that the trend of $R_t$ has decreased, but the changes of the curve have been a little different. From the onset of the epidemic to March 17, a decrease in $R_t$ has been observed, dropping to <1 by the end of the study. This situation has occurred in all three scenarios. The differences between the draw curves in different scenarios are due to the amounts of $R_t$ at different times as eventually, at about a similar time, they approached $R_t$ one. However, the shape and direction of the curves in all three scenarios have been similar [the figures of other related scenario are in Figure 3 in Appendix].

### Ecologic interventions in epidemic

$R_t$ depends on intervention efficacy and the intervention coverage of the population.[14] Therefore, in time that the epidemic was progresses, increase in the intervention efficacy and the intervention coverage of the population

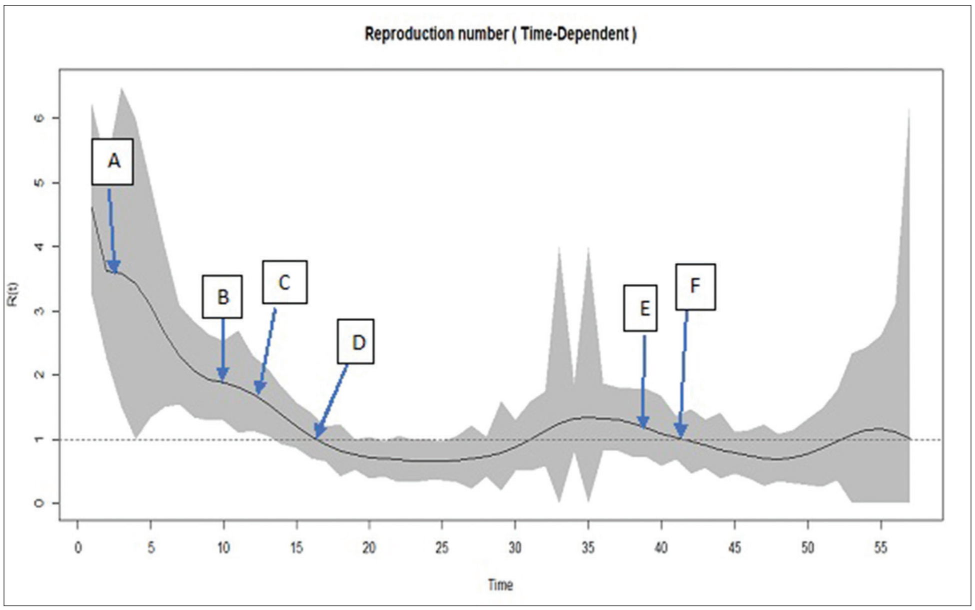


Figure 3: Time-dependent method for evaluating time-dependent reproduction number ($R_t$) in serial interval with gamma distribution and mean 6 ± 3. (a) Onset of closing all schools and universities. (b) Onset of closing mosques and reducing working hours. (c) Onset of evaluation of infection symptoms of passengers at the entrances and exits of cities. (d) Mass screening. (e) Onset of social distancing. (f) Onset of restrictions on vehicle traffic

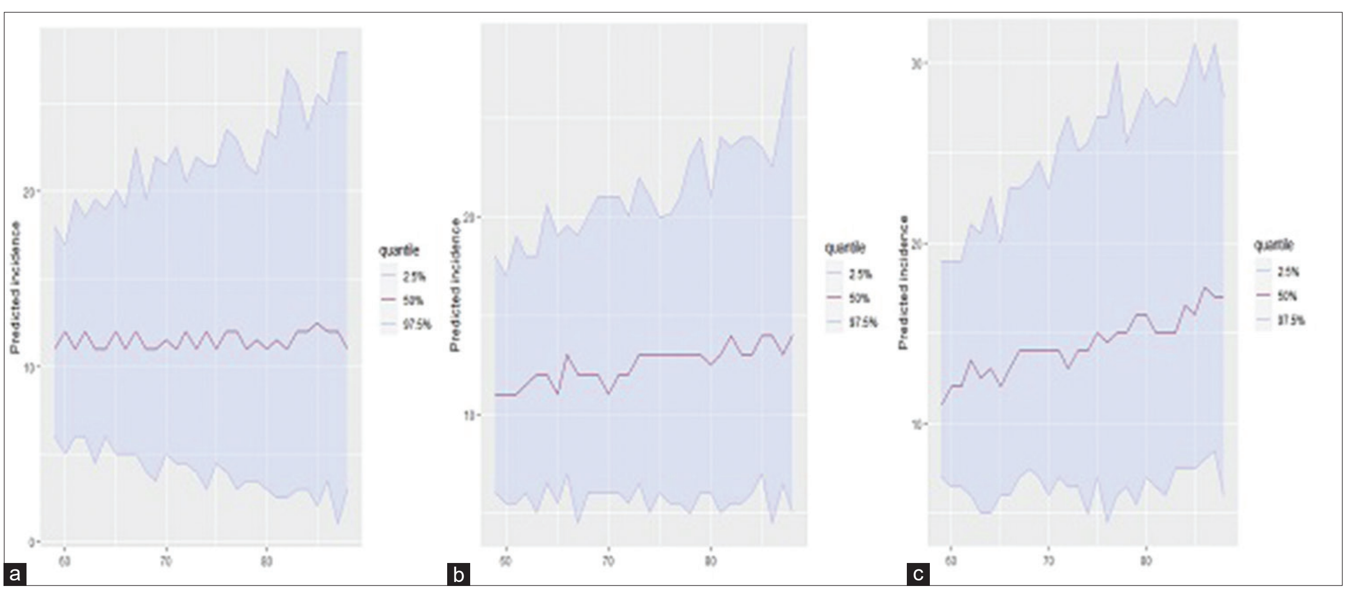


Figure 4: Predicted incidence cases and 95% confidence intervals in next 30 days with assumption of (a) $R_t$ = 1.03, SI = 4 ± 2, (b) $R_t$ = 1.05, SI = 6 ± 3, and (c) $R_t$ = 1.08, SI = 6 ± 3. SI = Serial interval

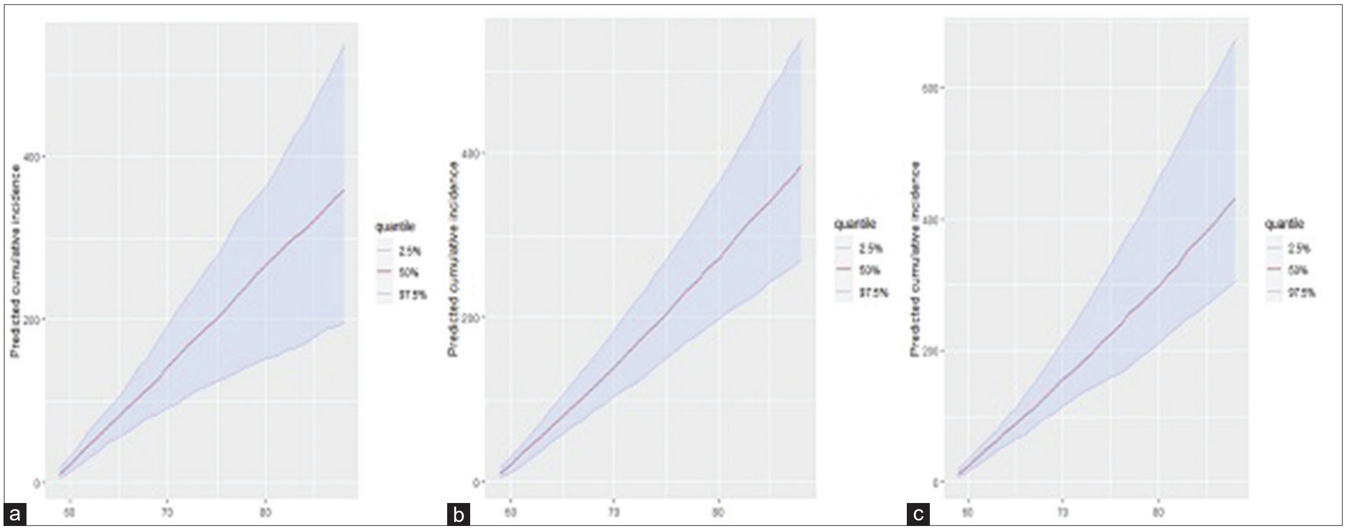


**Figure 5:** Predicted cumulative incidence cases and 95% confidence intervals in next 30 days with assumption of (a) $R_t$ = 1.03, SI = 4 ± 2, (b) $R_t$ = 1.05, SI = 6 ± 3, and (c) $R_t$ = 1.08, SI = 6 ± 3. SI = Serial interval

leads to a decrease in $R_t$. As observed in Figure 3, the conducted interventions during the epidemic are demonstrated in Figure 2. It is highly probable that the decrease in $R_0$ has been a consequence of the schools and universities shutting down and the reduction of working hours.

### Predicted epidemic size

According to three scenarios in the past 58 days, $R_t$ estimates were measured as 1.03 (0.94, 1.14), 1.05 (0.96, 1.15), and 1.08 (0.98, 1.18). With these $R_t$ amounts, the new daily cases of infection for the next 30 days will be 11–12, 11–14, and 11–17 cases, respectively [Figure 4]. Moreover, cumulative incidence cases will be 360 (95% CI: 180, 603), 388 (95% CI: 238, 573), and 444 (95% CI: 249, 707) for the next 30 days [Figure 5], respectively.

According to the maximum likelihood value of $R_0$ in C scenario and with the assumption of 100%, 70%, and 50% effectiveness of conducted interventions, at least 5%, 7%, and 10% of the people are predicted to be needed to get infected or immunized to achieve $R_0 < 1$, respectively. Furthermore, the R estimate in the next 30 days was predicted as 1.05 (95% CI: 0.99, 1.11).

## DISCUSSION

The speed of epidemic growth depends on the value of $R_0$ and time intervals between successive infections. In COVID-19 infection, time intervals between successive infections could be from 4 to 6 days, what seems to be important is the $R_0$. $R_0$ indicates the biologic potential of COVID-19 that leads to transmissibility of infection. $R_0$ reflects the potential for spread of epidemic in a susceptible population. In following, in order to monitoring of immunity and social interaction and effectiveness of the strategies to diminish transmissibility of infection, including isolation of infected people, social distancing, quarantine and others, the $R_t$ was calculated. $R_0$ could be different from population to population. In addition, it varies by subpopulations among the population.[14]

The epidemic curve of COVID-19 has been steep, the spread of the virus has exponentially increased, and the total number of COVID-19 patients has raised steeply within a few weeks. Governments and health authorities have tried to flatten the curve by necessary interventions to decrease the stress on the health-care system, but on the other hand, a flatter curve will have a longer duration as well.[21] In Iran, the first confirmed cases of COVID-19 were reported on February 19, 2020, and the number of confirmed cases has grown exponentially and reached its peak in the late march, experiencing a decline afterward till now. A study conducted by Zhou *et al*. based on the logistic model had already predicted 40 days for Iran to reach its peak consistent with the findings of this study.[10]

In the present study, we predicted the future number of COVID-19 cases, $R_t$, and the trend of the epidemic through statistical models and based on the previous data of COVID-19 with the assumption of the current condition of Iran. We have prepared the predictions to our local health authorities and the government at the regional level to inform them about the epidemic extent in the upcoming weeks so that better planning is provided for the required hospital beds and staff resources. We were obtained the $R_t$ to be from 1.03, 1.05, and 1.08 in AUMS area. These findings were indicated that averagely, 103, 104, and 108 infectious persons resulting from contact with 100 infected persons given that not everyone is susceptible. Therefore, the epidemic was still uncontrolled.

Based on the real data accumulated in Iran, $R_t$ has decreased substantially since the beginning of the epidemic, and it is expected to remain almost constant or continue to decline slightly in the next 30 days. The primary significant decrease of $R_0$ is believed to be due to some interventions such as the closing of all schools and universities, public places, and shrines nationwide, the large-scale screening of population and social distancing.[2,7] Other interventions were reducing working hours, evaluating infection symptoms among passengers at the entrances and exits of cities and vehicle traffic restrictions within cities in some days.

According to the results of this study, three scenarios including the worst, the intermediate, and the best possible scenario for AUMS can be considered. The best scenario predicts a stationary condition, yet the worst scenario predicts a slowly increasing trend of new cases for the next 30 days. Align with our estimates, using the Gompertz model, Ahmadi *et al*. predicted a stationary condition in May for Iran.[7]

According to the maximum likelihood value of $R_0$ in C scenario and with the assumption of 100%, 70%, and 50% effectiveness of conducted interventions, at least 5%, 7%, and 10% of the people will be needed to be infected or get immunized to achieve $R_0 <1$, respectively. Therefore, policymakers should try to implement more effective interventions in order to achieve $R_0 <1$ as soon as possible.[2]

One of the strongest points of this study is the epidemic mathematic model based on the Poisson distribution of the incidence of infection. In addition to some random errors which are associated with forecasting, the new policy of the government to allow more people to go back to work or possible changes in the behavior of the population and the spread of the virus could affect the epidemic extent in the next weeks. Still, executing optimal government strategies against COVID-19 appears to be very necessary to continue to come out of this pandemic. However, each policy that countries execute against COVID-19 has some limitations, and it seems that there will be transmission chains until an effective vaccine is developed or population immunity or seasonal changes are observed.[12,22,23] Therefore, the most important issue for controlling the COVID-19 epidemic is finding all transmission events because each undetected case of COVID-19 could be a source of a new epidemic. Moreover, people should take personal protective measures during the upcoming weeks.[2,10] Additional limitation for this and other studies in these settings was about the asymptomatic infections inevitably did not included in this study. It should be emphasized that the CIs for the last days of prediction were wider than beginning of prediction.

It is recommended that this presented information will be updated for the future time. Furthermore, it is recommended to conduct seroepidemiology surveys in the subgroups of studied population to clarify the distribution of population immunity.

## Conclusion

Based on the real-time data extracted from the center of Iran, Rt has been decreasing substantially since the beginning of the epidemic, and it is expected to remain almost constant or continue to decline slightly in the next 30 days, which is consequence of the schools and universities shutting down, reduction of working hours, and social distancing.

## Acknowledgments

This study has been funded by Arak University of Medical Sciences and approved by the Arak Medical University's Ethics Committee.

## Financial support and sponsorship

Arak University of Medical Sciences, Arak, Iran.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. El Zowalaty ME, Järhult JD. From SARS to COVID-19: A previously unknown SARS-CoV-2 virus of pandemic potential infecting humans – Call for a one health approach. One Health 2020;9:100124
2. Moradzadeh R. The challenges and considerations of community-based preparedness at the onset of COVID-19 outbreak in Iran, 2020. Epidemiol Infect 2020;148:e82.
3. Lau SK, Chan JF. Coronaviruses: Emerging and Re-Emerging Pathogens in Humans and Animals. Virol J 2015;12:209
4. Mahase E. Coronavirus: COVID-19 has Killed more People than SARS and MERS Combined, Despite Lower Case Fatality Rate. BMJ 2020;368:m641.
5. Guarner J. Three Emerging Coronaviruses in Two Decades: The Story of SARS, MERS, and Now COVID-19. USA: Oxford University Press; 2020.
6. Zhang S, Diao M, Yu W, Pei L, Lin Z, Chen D. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis. Int J Infect Dis 2020;93:201-4.
7. Ahmadi A, Fadaei Y, Shirani M, Rahmani F. Modeling and forecasting trend of COVID-19 epidemic in Iran until May 13, 2020. Med J Islam Repub Iran 2020;34:27.
8. Available from: https://CRAN.R-project.org/package=R0. [Last accessed on 2020 Apr 10].
9. Sriwijitalai W, Wiwanitkit V. Herbs that might be effective for the management of COVID-19: A bioinformatics analysis on anti-tyrosine kinase property. J Res Med Sci 2020;25:44.
10. Zhou X, Ma X, Hong N, Su L, Ma Y, He J, *et al*. Forecasting the Worldwide Spread of COVID-19 Based on Logistic Model and SEIR Model. medRxiv; 2020.

11. Moradzadeh R, Anoushirvani AA. Trend of gastric cancer incidence in an area located in the center of Iran: 2009-2014. J Gastrointest Cancer 2020;51:159-64.
12. Moradzadeh R, Mansournia MA, Baghfalaki T, Nadrian H, Gustafson P, McCandless LC. The impact of maternal smoking during pregnancy on childhood asthma: Adjusted for exposure misclassification; results from the National Health and Nutrition Examination Survey, 2011-2012. Ann Epidemiol 2018;28:697-703.
13. Moradzadeh R, Mansournia MA, Ghiasvand R, Baghfalaki T, Nadrian H, Holakouie-Naieni K. Impact of Age at Menarche on Breast Cancer: The Assessment of Recall Bias. Arch Iran Med 2019;22:65-70.
14. Rothman KJ. Epidemiology: An Introduction. 2nd ed. New York: Oxford University Press, Inc.; 2012.
15. Cori A, Ferguson NM, Fraser C, Cauchemez S. A new framework and software to estimate time-varying reproduction numbers during epidemics. Am J Epidemiol 2013;178:1505-12.
16. Hwang J, Park H, Kim SH, Jung J, Kim N. Basic and effective reproduction numbers of COVID-19 cases in South Korea excluding Sincheonji cases. medRxiv 2020, 20039347; doi: 10.1101/2020.03.19.20039347.
17. Obadia T, Haneef R, Boëlle PY. The R0 package: A toolbox to estimate reproduction numbers for epidemic outbreaks. BMC Med Inform Decis Mak 2012;12:147.
18. Available from: https://cran.r-project.org/web/packages/earlyR/index.html. [Last accessed on 2020 Apr 24].
19. Available from: https://CRAN.R-project.org/package=projections. [Last accessed on 2020 Apr 24].
20. Thibaut J, Pierre N, Sangeeta B, Kamvar Zhian N. Projections: Project future case incidence; 2018. Available from: https://CRAN.R-project.org/package=projections. [Last accesse on 2020 Jun 17].
21. Mahmud A, Lim PY. Applying the SEIR Model in Forecasting the COVID-19 Trend in Malaysia: A Preliminary Study. medRxiv; 2020. Doi: 10.1101/2020.04.14.20065607.
22. Ferguson N, Laydon D, Nedjati Gilani G, Imai N, Ainslie K, Baguelin M, *et al*. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Imperial College London (16-03-2020), doi: https://doi.org/10.25561/77482.
23. Javanmard SH, Nasirian M, Ataei B, Vaseghi G, Vaezi A, Changiz T. Isfahan COvid-19 REgistry (I-CORE): Design and methodology. J Res Med Sci 2020;25:32.