مرکز تحقیقات مدل سازی در سلامت
دانشگاه علوم پزشکی شهرکرد

Modeling and forecasting trend of COVID-19 epidemic in Iran until May 13, 2020

Ali Ahmadi*[1], Yasin Fadaei[2], Majid Shirani[3], Fereydoon Rahmani[4]

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Introduction

Coronaviruses are a large family of viruses that have been identified since 1965; to date, 7 species of them have been reported to affect humans. These viruses have 3 genotypes of alpha, beta, and gamma. The natural reservoirs of these diseases are mammals and birds, and thus they are considered as zoonotic diseases (1, 2). Severe acute respiratory syndrome (SARS) is caused by a species of coronavirus that infects humans, bats, and certain other mammals which has led to epidemics in 2002 and 2003 (2-4); Middle East respiratory syndrome (MERS) caused an epidemic in Saudi Arabia in 2012 (5); and more recently their newest variant Coronavirus Disease-2019 (**COVID-19**) has led to the recent pandemic in China, Iran, Italy, and across the world (6-8). COVID-19 causes a direct and indirect transmission of respiratory diseases with a wide range of symptoms, including cold symptoms, respiratory/fever symptoms, cough, shortness of breath, kidney failure, and even death (9).

Introduction

The complete clinical manifestation of COVID-19 is not clear yet and its transmission risk is not completely understood (10). However, the virus is believed to be transmitted mostly via contact, droplets, aspirates, feces. Generally, everyone is prone to this viral disease. The mean incubation period of COVID-19 was 5.2 days (4.1–7 days) and the basic reproductive number (R_0) was reported 2.2 (95% CI: 1.4 to 3.9) (11). In another study, the incubation period ranged from 0-24 days, with the mean of 6.4 days. The R_0 of COVID-19 at the early phase, regardless of different prediction models, was higher than SARS and MERS, and the majority of patients (80.9%) were considered asymptomatic or mild pneumonia (12). The case fatality ratio was 2% (12), 2.3% (8), 3.46% (13), and elderly men with underlying diseases were at a higher risk of death (13).

Introduction

As of March 29, 2020, COVID-19 pandemic was declared by the World Health Organization (WHO) in more than 100 countries (most prevalent in the United States, Italy, China, Spain, Germany, Iran, and France) (14).

In Iran, the first case of COVID-19 was February 19, 2020 in Qom, and we used the reported data until March 29, 2020 in Iran. Until March 29, 2020 (The date when this manuscript was being conducted), according to the daily reports, 38 309 cases of Covid-19 and 2640 related deaths were reported in Iran (15, 16). As of February 29, 2020, all schools and universities and as of March 7, 2020 almost all public places and shrines have been closed. On March 2, 2020, a team of WHO experts landed in Tehran, Iran, to support the ongoing response to the COVID-19 outbreak in the country (17).

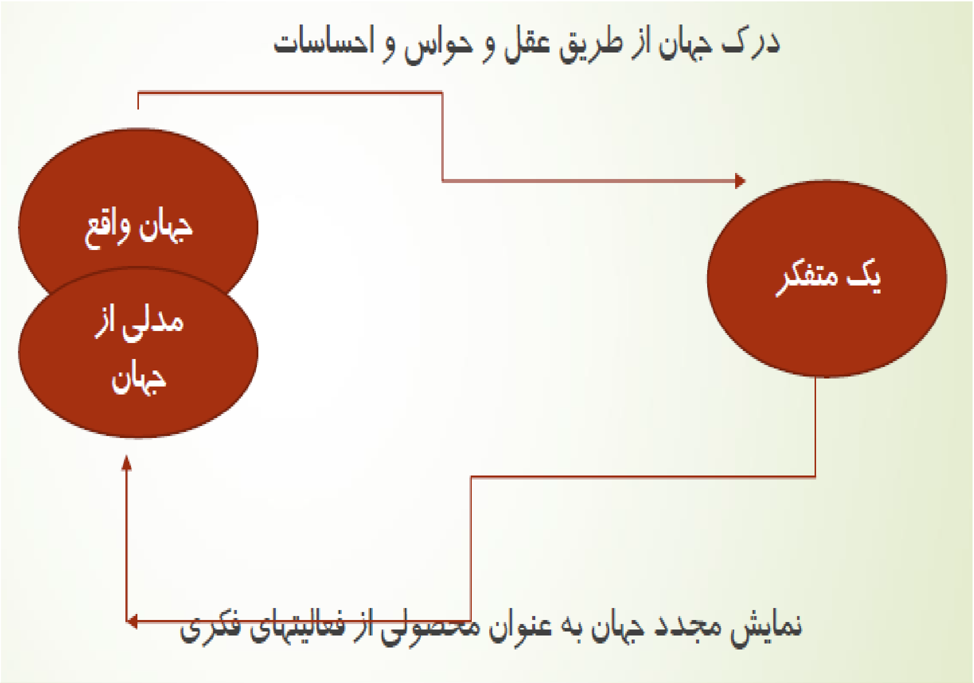
Introduction

Currently, people are referring to health centers and hospitals, and the public is almost alarmed by the epidemic of panic and inaccurate reporting in cyberspace. **Important questions in people's mind are as follow:**

How many people have COVID-19 in Iran? What is the status of COVID-19 epidemic curve in Iran? **When will the epidemic will go and how it ends**?

We cannot answer these questions with certainty, but they will be investigated in terms of pathogenic agents (coronavirus), host conditions, behavior (human), and environmental factors of coronavirus transmission, daily reports of definitive COVID-19 patients released by Iran Ministry of Health and Medical Education, and the **use of modeling given the assumptions and the percentage of error**. Although the **models** are different, multiple and changeable in nature and **do not insist on** the correctness of the forecasts, the decision-making conditions for health policymakers and authorities are more transparent and helpful (18).

- This study aimed to model and determine the **epidemic trend** and **predict the number of patients hospitalized** due to COVID-19 in Iran using mathematical and statistical modeling.



تفسیر جهان بر اساس درک ما و مدل سازی:

۱- واقعیتی از طریق عقل و حواس به فرد منتقل می شود.

۲- شخص بر اساس تفکرات خود اطلاعات را تحلیل و تفسیر می کند.

۳- فرد، تفسیر (درک) خود را بعنوان واقعیت ارایه می دهد.

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مفاهیم مدل سازی

- مدل سازی یک مفهوم انتزاعی انتخابی از واقعیت است.
- بیانگر تمام واقعیت نیست.
- فقط جنبه های خاصی از واقعیت را به انتخاب و هنر مدل ساز ارایه می دهد.

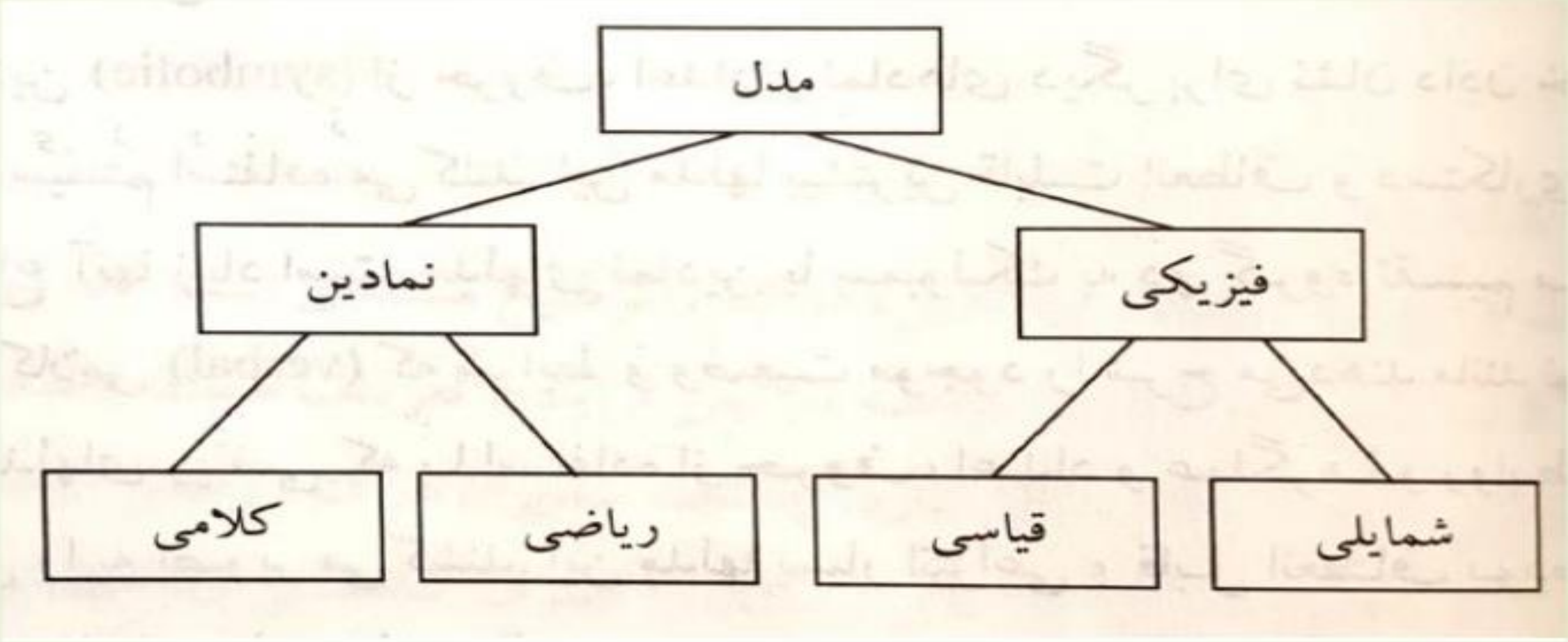
مثال: در علم اقتصاد یک مدل ساز برای نشان دادن تعادل «مقدار کالا» و « قیمت» از دو منحنی عرضه و تقاضا استفاده می کند.

این مدل بسیاری از امور واقعی موثر بر تعادل بازار را در نظر نمی گیرد و فقط سه فاکتور» قیمت، تقاضا و عرضه« را در نظر دارد.

- درک جهان خارج از طریق حواس و تعقل است.

- مدل ها نمایشی مجدد از واقعیت ها هستند که می توانند به طور دقیق واقعیت ها را بیان دارند و یا به علل اشتباهات مدل ساز پاسخ های غیردقیق یا دور از واقع ارایه نمایند.
- اعتبار یک مدل بستگی به میزان واقع گرایی آن دارد.

طبقه بندی مدل ها



اقتباس از کتاب مدل سازی ریاضی- دکتر محمدرضا مهرگان

مدل سازی در سلامت

- وقتی آگاهانه ویژگی ها و خصوصیات بعضی متغیرهای مهم برای نشان دادن یک ساختار بکار رود در واقع نوعی مدل سازی است. مانند ساخت یک مدل نمادین از یک هواپیما

- **واژه مدل در سه نقش: اسم، صفت و فعل**

- اسم: بیانگر یک مفهوم ذهنی و یا شکل ذهنی است.

مثال: مدلی که یک معمار از یک ساختمان بیمارستانی در مقیاس کوچکتر یا یک فیزیک دان از یک اتم یا یک میکروبشناس از یک میکروب، مدلی در اندازه بزرگتر می سازد.

- صفت: به صفات عالیه و مطلوب و نمونه ای شاخص و الگو اشاره دارد.

مثال: خانه بهداشت مدل، دانشجوی مدل، بیانگر الگوی کامل و شاخصی برای ساختن یک خانه بهداشت ایده ال و یا آموزش و ساختن یک دانشجوی نمونه

یا یک انسان سالم و یا یک بیمار واجد شاخصهای خاص.

- فعل: نمایش دادن بخشی از واقعیت.

مثال: مدل آماری عوامل تعیین کننده سکته قلبی در ایران یا مدل ریاضی سیر پیشرفت سرطان در یک بیمار مبتلا به سرطان معده یا مدل عوامل تعیین کننده طغیان آنفلوانزا یا اسهال خونی در یک شهر

ضرورت مدل سازی

۱ – آشکار نمودن روابط بین اجزای سازنده مدل

۲– درک بیشتر از اجزای مدل و متغیرها

۳– امکان تجزیه و تحلیل ریاضی آن

٤– امکان پذیر نمودن آزمایشات

٥– قابلیت استفاده در آموزش و پیشگیری

٦– قابلیت استفاده در تصمیم سازی و تصمیم گیری

فرایند مدل سازی در سلامت

مدل سازی در یک فرایند ۷ مرحله ای قابل انجام است:

۱- **تعریف مسئله یا مشکل مرتبط با سلامتی:** تعیین سوال پژوهش، درک ، توضیح، تبیین، تعیین وضعیت موجود، تشریح و شناخت واقعی و درک مسئله، انجام یک بررسی متون و مرور سیستماتیک درباره مشکل مرتبط با سلامتی

۲- **جمع آوری داده ها:** انجام یک پژوهش اولیه یا ثانویه و جمع اوری پارامترها و فاکتورهایی که بر مسئله مورد بررسی تاثیر گذار هستند. انجام مطالعات اپیدمیولوژیک و استفاده از مشاهده، مصاحبه، پرسشنامه، نمونه گیری و به طور کلی اجرای گام های یک پژوهش اکادمیک و تحلیل های تک متغیره

۳- **ساخت مدل:** نیاز به مهارت و فنون اپیدمیولوژی، آمار زیستی، ریاضی و آمیخته نمودن آنها با تخیل، هنر و هنرمندی و تجربه، تعیین روابط متقابل بین متغیرها. دیدگاهها و راههای مختلفی برای ساخت مدل ها وجود دارد. در جهان واقعی تنها یک راه صحیح برای ساخت یک مدل وجود ندارد.

- فرموله کردن مدل: تعیین اجزا متشکله یک مدل، ورودی ها و خروجی ها، متغیرهای تصمیم و قابل کنترل، متغیرهای غیرقابل کنترل و پارامتر، اندازه های عملکرد، متغیرهای نتیجه، متغیرهای مستقل و وابسته، مخدوش کننده ها ، متغیرهای برهمکنش کننده، متغیرهای کولایدر، متغیرهای ترکیبی.

٤- **بررسی صحت عملکرد مدل:** این مرحله از مدل سازی و به ویژه در بکارگیری در سلامت و جهان واقعی بسیار مهم است. مشاوره با متخصصین علوم بالینی مرتبط با موضوع مدل سازی در سلامت و همچنین متخصصین علوم پایه مرتبط، احتمال پذیرش مدل ساخته شده را افزایش می دهد. بنابراین ارزیابی پیش فرض های مدل سازی و ممیزی و صحت عملکرد نیاز به تایید دارد. بازنگری داده ها، محاسبه شاخصهای ارزیابی مدل، صحت، دقت، روایی و پایایی، بازنگری پیچیدگی های مدل، ساده بودن مدل و تعداد کمتر متغیر، نیاز به زمان کمتر برای اجرا و استفاده.

٥- **حل مدل:** پیاده سازی تصمیمات یا استراتژی ها توصیه شده توسط مدل در این گام مورد توجه است. بهینه کردن مدل، استفاده از نرم افزارهای مورد نیاز و گزارش الگوریتم ها و دستورات بکار رفته، تحلیل حساسیت و تعیین پارامترهای حساس و در صورت نیاز اصلاح و تغییر در مدل و نهایی کردن مدل سازی. گزارش شاخص های حساسیت، ویژگی، نسبت درستنمایی مثبت و منفی و کارایی مدل.

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ادامه فرایند مدل سازی در سلامت

۶- ارایه نتایج مطالعه: در اختیار قرار دادن نتایج مدل سازی برای کاربران و سفارش دهندگان. با توجه به اینکه کاربران با مفاهیم مدل سازی آشنایی دقیقی ندارند و ممکن است به سختی مدل را متوجه یا قبول کنند توصیه میشود از ابتدا درگیر مراحل مدل سازی گردند. ارایه نتایج بر اساس سطوح پیشگیری در نظام سلامت بسیار کمک کننده است. کدام یک از متغیرهای تعیین کننده مدل را می توان در آموزش به مردم، غربالگری، پیش آگهی، تشخیص، درمان بیماری بکار بست؟

۷- اجرا و بکارگیری مدل: بکارگیری مدل در عمل با انجام شش مرحله گذشته بسیار مهم است.

Methods

This was a secondary data analysis and mathematical modeling study based on a research proposal approved by Shahrekord University of Medical Sciences (Code of Ethics Committee on Biological Research: IR.SKUMS.REC 1398.254) (19).

For the statistical analysis of definitive COVID-19 patients in Iran, daily reports of the Ministry of Health and Medical Education were used (15). The definitive diagnosis of COVID-19 was made using virus isolates from patients' biological samples in hospitals. When **real time polymerase chain reaction (PCR) test** turned positive for COVID-19 in **patients with respiratory symptoms and confirmed by the reference laboratory** in School of Public Health, Tehran University Medical of Sciences and Pasteur Institute of Iran (20), they were used for analysis. **Patient population growth**, epidemic curves, and recovered, and deceased individuals were used to form a **conceptual framework** of an epidemic and predict the COVID-19 epidemic trend. Quasi classical infectious disease (Susceptible→Exposed→Infected→Removed: SEIR) model was used (21). Different **scenarios** were designed and implemented for modeling and **forecasting**. First, based on a search for reliable sources of disease trends and epidemic curves across the world, the curve of Iran was drawn (10, 18, 22).

Focused and **scientific group** discussion sessions were held with experts on epidemiology, biostatistics, and mathematics, infectious diseases specialists, and health care managers on the topic.

Different scenarios were discussed and agreement was reached on the application of final scenarios. To predic**In the first scenario**t the growth of this epidemic, different models were used., the most optimistic estimation and control of the epidemic was during an incubation period (von model, the most ideal model). In this scenario, traced contacts are isolated immediately on symptom onset (and not before) and isolation prevents disease transmission. In **the second scenario**, an intermediate and fit-to-data model (Gompertz) was used. **In the third scenario**, the use of the growth rate is greater than the first and second models, and it is the opposite of the first scenario (LSE).

To select the scenarios, fit the data with the models and growth rate of the cases were used. The Gompertz growth, von Bertalanffy growth equation, and curve fitting by LSE method with cubic polynomial for Epidemic forecasts were run in **MATLAB software**. Models are presented as the following differential equations:

Gompertz Differential Equation:

$$\frac{d}{dt}P(t) = aP\,ln(1/bP)$$

Von Bertalanffy's differential growth equation:

$$\frac{d}{dt}P(t) = aP\,((bP)^c - 1)$$

Cubic polynomial polynomials:

$$P(t) = at^3 + bt^2 + ct + e.$$

Where p represents the number of individuals in each population, a, b, c, and e represent unknown parameters and t time. *d/dt* is a derivative of time (23,24).

The assumptions of the model are as follow:

- Models are based on official reported data and recruitment testing from hospitalized cases.
- Any manipulation and misinformation will affect the model.
- The method for finding patients is fixed.

Table 1. Estimated Parameters (values of the inputs used) for modeling

Model / Parameter	Infected cases			Recovered cases			Death cases		
	a	*B*	*c*	*a*	*B*	*c*	*a*	*B*	*c*
Gompertz	0.1	2.9939e+04	-	0.1	1.8107e+04	-	0.0660	2.6710e+04	-
VonBertalanffy	0.8702	2.7109e-05	0.2109	0.5564	7.5133e-05	0.3708	0.7321	2.2840e-05	0.1239

The unknown parameters were estimated by running the fminsearch, a MATLAB function, which is a least squares algorithm. The parameters were estimated based on the official reported data of infected, cured, and dead cases. The estimated values of the parameters for different scenarios are reported in Table 1.

the percentage of the root mean square error (RMSE) was used to **validate the models and 95% confidence interval** (CI) was utilized to calculate the coefCI MATLAB function.

- All estimations and detections of COVID-19 were made based on the current conditions of **laboratory sampling from critically ill** and hospitalized patients (**tip of the iceberg spread of the disease**).
- In this modeling, asymptomatic patients and those with moderate symptoms from whom no samples were taken were **not included**. Also, the data of **patients diagnosed based on CT scans were not included** in this study.
- The forecast dates were selected based on the **end of New Year** (April 3, 2020) holidays in Iran and the **onset of epidemic curve flattening** (May 13, 2020).
-

Results

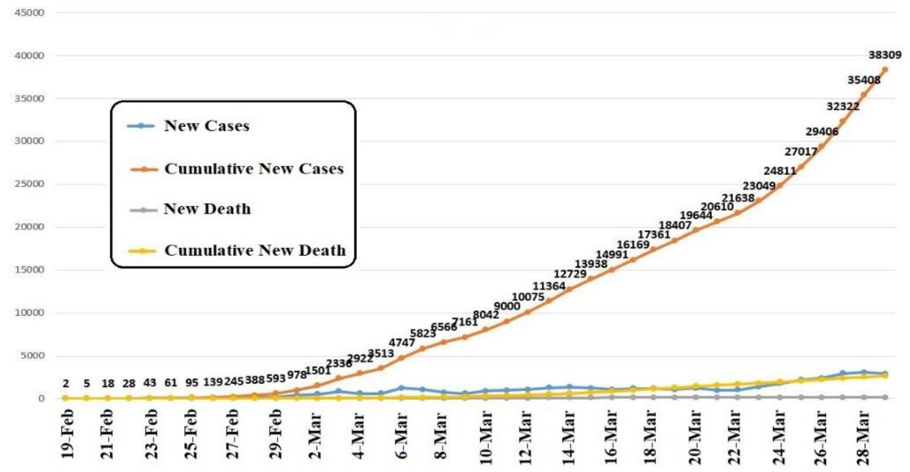


Table 2. The frequency of COVID-19 new cases, cumulative cases, and deceased cases in Iran

Date	New cases	Cumulative number cases	New deceased	Cumulative deceased	Cumulative recovered ca
19-Feb-20	2	2	2	2	0
20-Feb-20	3	5	0	2	0
21-Feb-20	13	18	2	4	0
22-Feb-20	10	28	1	5	0
23-Feb-20	15	43	3	8	0
24-Feb-20	18	61	4	12	0
25-Feb-20	34	95	4	16	0
26-Feb-20	44	139	3	19	0
27-Feb-20	106	245	7	26	0
28-Feb-20	143	388	8	34	73
29-Feb-20	205	593	9	43	123
1-Mar-20	385	978	11	54	175
2-Mar-20	523	1501	12	66	291
3-Mar-20	835	2336	11	77	435
4-Mar-20	586	2922	15	92	552
5-Mar-20	591	3513	15	107	739
6-Mar-20	1234	4747	17	124	913
7-Mar-20	1076	5823	21	145	1669
8-Mar-20	743	6566	49	194	2134
9-Mar-20	595	7161	43	237	2394
10-Mar-20	881	8042	54	291	2731
11-Mar-20	958	9000	63	354	2959
12-Mar-20	1075	10075	75	429	3276
13-Mar-20	1289	11364	85	514	3529
14-Mar-20	1365	12729	97	611	4339
15-Mar-20	1209	13938	113	724	4790
16-Mar-20	1053	14991	129	853	4996
17-Mar-20	1178	16169	135	988	5389
18-Mar-20	1192	17361	147	1135	5710
19-Mar-20	1046	18407	149	1284	5979
20-Mar-20	1237	19644	149	1433	6745
21-Mar-20	966	20610	123	1556	7635
22-Mar-20	1028	21638	129	1685	7913
23-Mar-20	1411	23049	127	1812	8376
24-Mar-20	1762	24811	122	1934	8913
25-Mar-20	2206	27017	143	2077	9625
26-Mar-20	2389	29406	157	2234	10457
27-Mar-20	2926	32322	144	2378	11133
28-Mar-20	3076	35408	139	2517	11679
29-Mar-20	2901	38309	123	2640	12391

Fig. 1. The trend of new and cumulative cases of COVID-19 in Iran

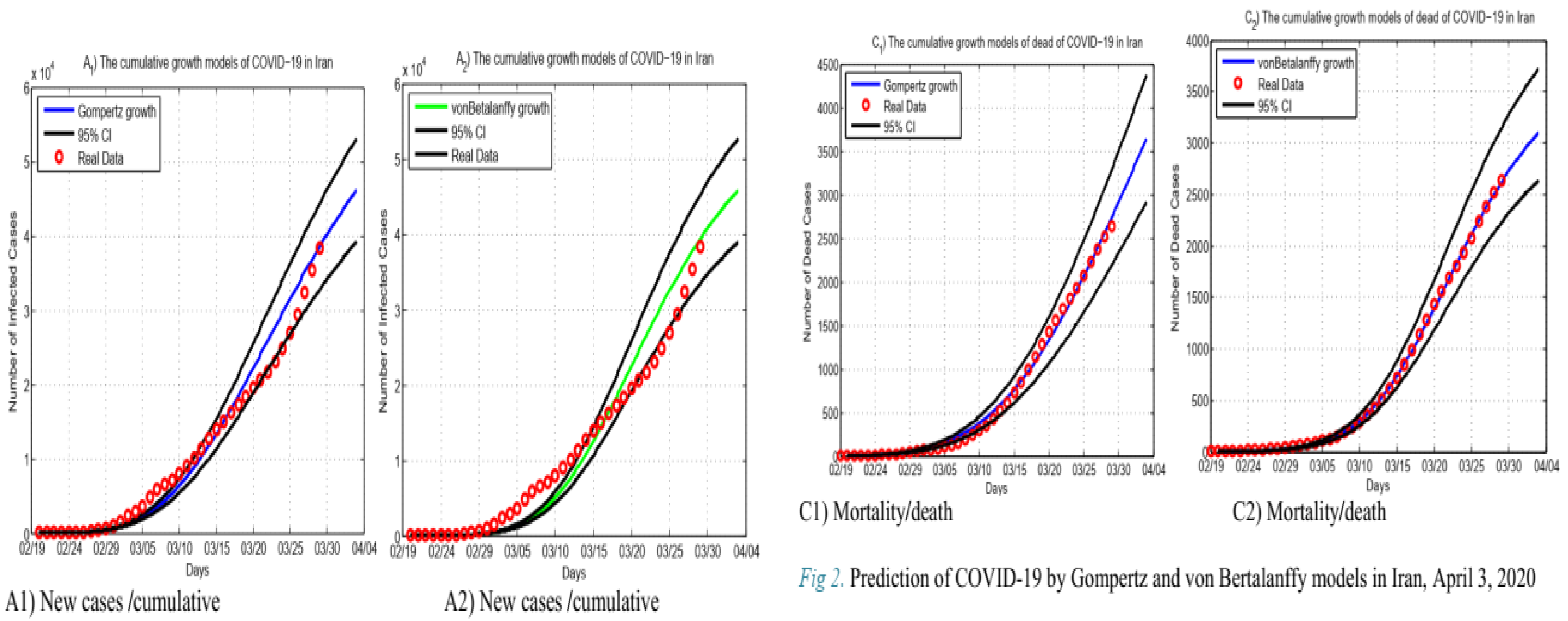
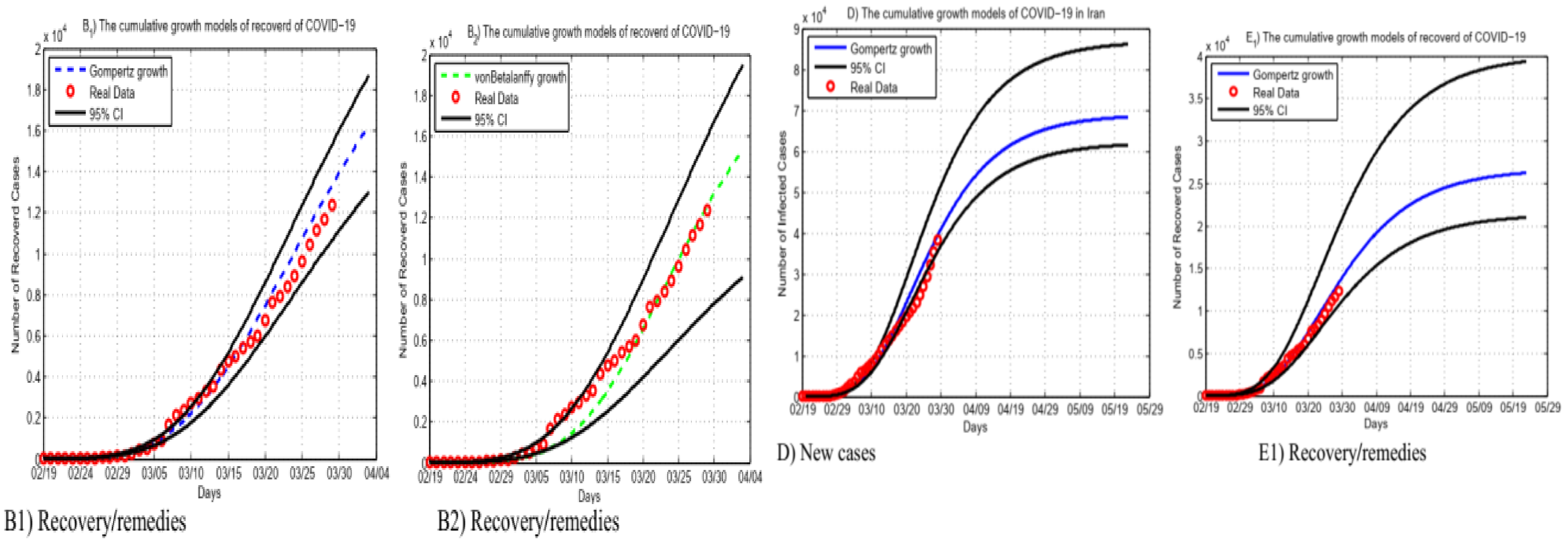
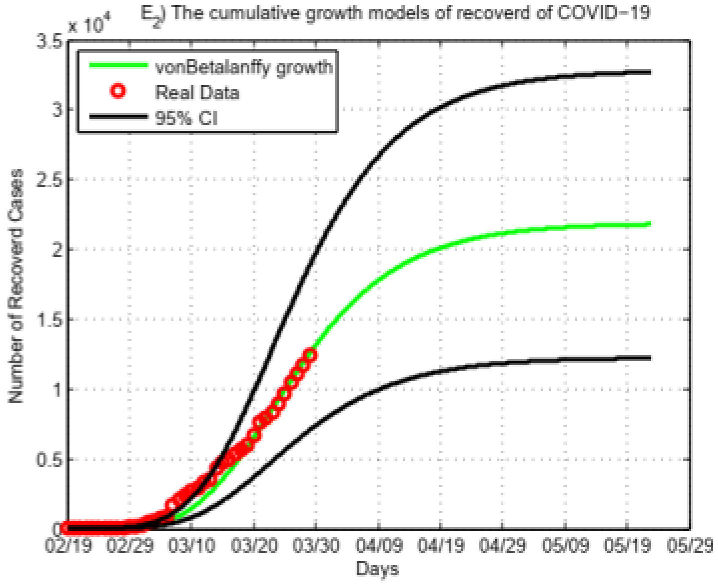


Fig 2. Prediction of COVID-19 by Gompertz and von Bertalanffy models in Iran, April 3, 2020

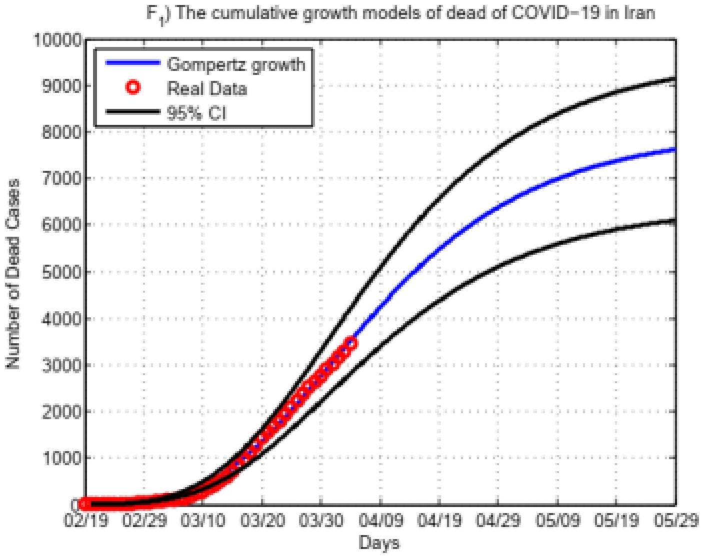


3-Apr-20: case:2715 total: 53183 death: 134, total death: 3294 recovery: 17935

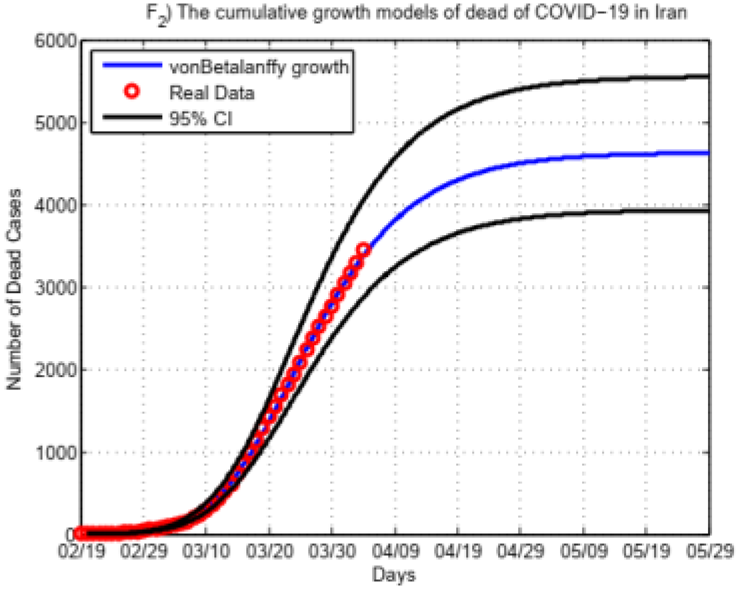
According to the Gompertz model, in the most optimistic perspective, the maximum number of infected people until April 3, 2020 is 47 500, with 95% confidence interval (**CI: 38907- 52640**) (Fig. 2 A1). The percentage of the root mean square error **(RMSE) for Gompertz model is 12%.** Based on von Bertalanffy's growth model (the most ideal model with high isolation of patients and others intervention such as China experience), the maximum number of COVID-19 patients is 44 200, with 95% confidence interval (**CI: 39208-53809**), (Fig. 2 A2) and 17% RMSE. According to the method of the least squared error, this value was estimated to be 48 000 (**CI: 40000 - 57560), with 19%** RMSE (Fig. 4 H).



E2) Recovery/remedies



F1) The cumulative mortality



F2) The cumulative mortality

Fig. 3. Prediction of the flat of epidemic curve of COVID-19 in Iran, May 13, 2020

To make prediMay 13, 2020, when the epidemic curve will be flatctions for, 3 models of growth with 95% confidence interval were used. Based on Gompertz model, the epidemic curve will be flattened on May 13, 2020 with about 67 000 patients (CI: 61500- 87000), with 10% RMSE (Fig. 3 D). Based on von and Gompertz models, the number of cured cases will be 22 000 (CI: (12500 -32000), with 3.1% MSRE, and 26 000 (CI: 21700-39500), with 3.7% MSRE, respectively (Fig. 3 E2, E1). To predict the number of deaths due to COVID-19 when the epidemic curve is flat based on Gompertz and von models, there will be 7900 deaths (CI: 6200-9300), with 10% MSRE, and 4620 deaths (CI: 3930-5550), with 9.1% MSRE, until May 13 and June 1, 2020, respectively. (Fig. 3 F1, F2).

Discussion

In this study, the trend of COVID-19 epidemic prediction and estimation of the number of patients, R_0, deaths, and recovered individuals were performed and reported based on mathematical and statistical models **There are 3 important and debatable points of view about this epidemic in Iran**:

First, to avoid tension in the society; second, to properly interpret the COVID-19 case fatality ratio (CFR) in Iran and calculate CFR tactfully; and **third**, to recommend personal hygiene, including hand washing and avoiding contact with suspected patients, social distancing, discovering unknown cases of infection and early detection, tracing direct contact and isolation of patients, all of which have been emphasized by the health care officials to overcome this disease.

CFR

- in interpreting this index, since the denominator of the fraction is only positive cases in hospital beds and the numerator is the number of patients who died of COVID-19. This index should also be calculated until the end of the epidemic period, and if it is until the end of the epidemic and their outcome (death/recovery) is determined, this indicator will approach the real number. The estimated case fatality ratio among medically attended patients was reported to be approximately 2% (12) and the true ratio may not be known for some time (27). The underreporting estimation is very sensitive to the baseline CFR, meaning that small errors lead to large errors in the estimate for underreporting (28).

CFR

Underreporting of COVID-19 patients (**1.38% / cCFR**) and modification of disease mortality had previously been estimated by the **Center for Mathematical Modeling of Infectious Diseases, London School of Health and Tropical** (28).

If a country has a higher adjusted CFR (eg, 20.02%), it means that only a fraction of cases have been reported (in this case, 1.38 /20.02 = 6.89% cases reported approximately).

This formula can accurately estimate the statistics of all patients with COVID-19 (from asymptomatic and mild to severe cases and death).

One article reported that up to 70% of the supply chain could be cut off and the epidemic could be controlled if contact and isolation, quarantine and isolation were appropriately accomplished (18).

- We recommend using the WHO guideline to properly manage patients (29). Up-to-date and accurate data on definitions related to suspected, probable, and definitive people with Coronavirus should be collected at all provincial levels in the health care system.
- Percentage of completion and accuracy of assessments and data should be monitored precisely and the epidemic curve should be drawn based on district, province, rural, and urban divisions and be provided to provincial and academic headquarters in an updated dashboard format.
- Data should be carefully recorded and analyzed regarding the pathology, time of onset of symptoms, natural course of the disease, and the outcome of the disease to determine effective strategies to prevent and determine the necessity of intervention to control the spread of the disease at different levels.

Limitations

Given the urgency of the need for valid and transparent models to informed interventions and policies, some further considerations like the no consideration or account of systematic cases, testing coverage and time delay to the test results **availability, seasonality, and comorbidities** have not been included in this study. However, it may be feasible to consider them in revisions of the models or future studies. Moreover, the progression of disease epidemic across space-time has not been seen in Iran, as we used the parameters of Chinese models in modeling estimates in Iran to calculated R_0.

In this study, no attempt was made to detect and report cases and deaths in Iran. Although this could have been performed, given that the study has already been designed, conducted, and being reported, and given the exceptional mortality and morbidity situation, it was not feasible to go back and report the cases and deaths due to COVD-19. However, it can be done for the future similar studies. **There is no fixed page in Ministry of Health and Medical Education web site for reference of daily reports and they are scattered on various pages of this site**. If **screening** is done in the **community** along with biological sampling to diagnose COVID-19, the **number of cases** will certainly be higher and the **results of modeling will change.**

The actual trend of detecting COVID-19 cases in Iran, which has been based on people's health behaviors and government interventions, has been increasing. In this study, estimates were based on current trends, social distancing, sampling of severe cases, hospitalization, and tip of iceberg spread disease, and thus asymptomatic, mild, and moderate cases could not be calculated. We used the reports of positive COVID-19 cases in hospitals; thus, the prediction model in this study can be used for patients hospitalized due to COVID-19. Complete reliance on any type of model will lead to systematic and random error, unless modeling provides a prediction with precise and clear assumptions and inputs and outputs.

Conclusion

- This study suggests that government interventions and people's behaviors determine the persistence of the epidemic, and thus they should be addressed with greater responsibility, accountability, rigor, and quality.

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Conflict of Interests

The authors declare that they have no competing interests.

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