

# Coronavirus disease-19 spread in the Eastern Mediterranean Region, updates and prediction of disease progression in Kingdom of Saudi Arabia, Iran, and Pakistan

Asmaa Fady Sharif<sup>1,2</sup>,  
Sara Kamal Mattout<sup>3</sup>,  
Noha Adel Mitwally<sup>4</sup>

<sup>1</sup>Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Tanta University, Egypt, <sup>2</sup>Department of Basic Medical Sciences, College of medicine Dar Al Uloom University, Riyadh, Kingdom of Saudi Arabia, <sup>3</sup>Department of Diagnostic Radiology, Zagazig Infectious Diseases Hospital, Ministry of Health and Population, Egypt; Department of Clinical Medical Sciences, College of Medicine Dar Al Uloom University, Riyadh, Kingdom of Saudi Arabia, <sup>4</sup>Department of Basic Medical Sciences, College of medicine Dar Al Uloom University, Riyadh, Kingdom of Saudi Arabia

#### Address for correspondence:

Noha Mitwally, Al Mizan Street, Al Falah District, Exit 7, Riyadh, KSA.  
Phone: 00966564006777.  
E-mail: nmtwally@dau.edu.sa

WEBSITE: ijhs.org.sa

ISSN: 1658-3639

PUBLISHER: Qassim University

## Introduction

Recently and by the end of 2019, Wuhan city, a developing business hub of China, experienced an outbreak of a novel coronavirus (nCoV) that killed more than eighteen hundred and infected more than seventy thousand individuals within the first 45 days of the epidemic.<sup>[1]</sup> The earliest documentation for the initial cluster of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, was reported in December 2019, with clinical presentations greatly resembling viral pneumonia.<sup>[2]</sup>

The International Committee on Taxonomy of Viruses called the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the sickness as coronavirus disease (COVID)-19. This virus was reported to be a member of the  $\beta$  group of coronaviruses. The novel virus was termed as Wuhan coronavirus or 2019 nCoV by the Chinese scholars.<sup>[1]</sup>

## ABSTRACT

**Objectives:** The present study is considered the first study that aims to estimate the spread of coronavirus disease (COVID)-19 pandemic in the Eastern Mediterranean Region and to predict the pattern of spread among Kingdom of Saudi Arabia (KSA) in comparison to Iran and Pakistan.

**Methods:** Data during the period from January 29, 2020, till April 14, 2020, were extracted from 76 WHO situational reports and from the Worldometer website. Numbers of populations in each country were considered during data analysis. Susceptible, infectious, recovered, and deaths (SIRD) model and smoothing spline regression model were used to predict the number of cases in each country.

**Results:** SIRD model in KSA yielded  $\beta = 2e-0.6$ ,  $\gamma = 0.006$ , and  $\mu = 0.00038$  and  $R^0 = 0.00029$ . It is expected that by the 1<sup>st</sup> of May 2020, that number of cumulative infected cases would rise to 16848 in KSA and to 11,825 in Pakistan while in Iran, it is expected that the number mostly will be 100485. Moreover, the basic reproduction number  $R^0$  is expected to decrease by time progression.

**Conclusion:** The cumulative infected cases are expected to grow exponentially. Although  $R^0$  is expected to be decreased, the quarantine measures should be maintained or even enhanced.

**Keywords:** Eastern Mediterranean region, Kingdom of Saudi Arabia, prediction, severe acute respiratory syndrome coronavirus 2, smoothing spline regression model, susceptible, infectious, recovered, and deaths model

SARS-CoV-2 is the seventh coronavirus known to infect humans. Previous studies declared that SARS-CoV-2 is not a laboratory construct virus. However, it is currently impossible to attest or controvert the other theories of its origin.<sup>[3]</sup> Although most human coronavirus infections are unremarkable, within the last 20 years two significant epidemics of two beta coronaviruses took place, SARS-CoV and The Middle East Respiratory Syndrome coronavirus (MERS-CoV), with more than 10,000 amassed cases, and mortality rates of 10% for SARS-CoV and almost 37% for MERS-CoV.<sup>[4]</sup>

The early studies suggested a link between a specific fish and wild animal market in Wuhan, indicated the possible animal-to-human transmission.<sup>[5]</sup> Meanwhile, Genomic analysis revealed that SARS-CoV-2 is phylogenetically linked to SARS-like bat viruses, this fact strongly suggests that bats could be the primary reservoir, while the intermediate source of origin and transmission to humans is still not known.<sup>[1]</sup> Chan

*et al.* concluded that the existing epidemic has been driven entirely by a human to human transmission through droplets or direct contact.<sup>[3]</sup> Within a few weeks, the virus spread rapidly throughout China and within 1 month disseminated to several other countries, including the Eastern Mediterranean Region.<sup>[6]</sup>

Under the electron microscope, the new strain SARS-CoV-2 is an enveloped single-stranded positive-sense RNA virus-like all known coronaviruses. Its genome consists of around 29,900 nucleotides. SARS-CoV-2 is considered as a SARS related coronavirus.<sup>[7]</sup> This is evidenced by the phylogenetic analysis done by Zhu *et al.* According to their analysis, SARS-CoV-2 belongs to the harmful genus  $\beta$  coronavirus, which includes SARS-CoV and MERS-CoV and infects humans, bats, and wild animals.<sup>[8,9]</sup> Upon comparing the nucleotide sequences, SARS-CoV-2 is 80% identical to SARS-CoV and 50% to MERS-CoV.<sup>[10,11]</sup>

SARS-CoV-2 genome organization contains four main structural genes, which encode for spike protein (S), envelope (E), nucleocapsid protein (N), and membrane (M); in addition to other accessory membrane glycoproteins on the S called receptor binding domains (RBD), these proteins interfere with the host innate immunity and defense mechanism.<sup>[12]</sup> In all coronaviruses, the RBD is the most variable part of the genome structure.<sup>[13,14]</sup> Through the RBD of the S protein, SARS-CoV-2, similarly to SARS-CoV, targets Angiotensin-Converting Enzyme 2 (ACE2) of the human body as a receptor. This clarifies the pathogenesis of SARS-CoV and links its genetic composition to its harmful effect; moreover, it opens the way to the therapeutic solution of the infection.<sup>[14]</sup>

On January 30, 2020, the WHO stated the COVID-19 outbreak as the sixth public health emergency of international concern, following H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016), and Ebola as well in the Democratic Republic of Congo (2019). Consequently, health workers, governments, and the public need to cooperate globally to prevent its dissemination.<sup>[15]</sup>

Upon penetration of the SARS-COV-2 virus to the larynx and nasal mucous membrane, it may reach the human lower respiratory tract, then it would cause viremia by escaping from the lung to the blood.<sup>[16]</sup> The spike glycoprotein (S) of the virus binds initially to the cellular receptor angiotensin-converting enzyme 2 (ACE2). Consequently, ACE2 is considered as a target of SARS-CoV.<sup>[12]</sup> The virus attaches all tissues expressing ACE2 such as the lungs, heart, renal, and gastrointestinal tract.<sup>[17,18]</sup> This is called the Viremia phase; then, a significant gradual decrease in the lymphocytes in patients with COVID-19 is noticed as the disease progresses, but the mechanism is unknown. Moreover, the inflammatory markers and the cytokines such as IL-6 are increased, contributing to the worsening of the disease, which will take the patient to the pneumonia phase.<sup>[16,19]</sup> According to Lin *et al.* the pneumonia phase of the disease is very critical if the patient is elderly or his immune system is impaired or with

the presence of comorbidities such as chronic diseases such as hypertension and diabetes, the patient will not be able to enter the (Recovery phase) and will become critically ill. Since there is no specific treatment of COVID-19 until now, the treatment should target the control of lymphocytes and the inflammatory markers.<sup>[16]</sup>

Although the unclear specific presentation of COVID-19 infected cases and similar to all other human coronaviruses (229E, OC43, HKU, and NL63), the majority of cases reported a history of multiple previous days illness or flu-like symptoms resembling seasonal influenza, mild to moderate myalgia, dizziness, fatigue, nonproductive cough, and fever. Some uncommon cases reported gastrointestinal symptoms.<sup>[4]</sup>

Regarding the pediatrics, their involvement is less than the adults and those infected with COVID-19 were reported to be mild with favorable outcomes.<sup>[20]</sup> Many studies proved that the old aged cases with comorbidities such as diabetes and previous pulmonary illness are riskier as they are commonly presented with severe dyspnea and shock and their conditions mostly deteriorate to respiratory failure.<sup>[21]</sup>

Clinical physical examination of the mild cases is usually unremarkable, but the severely affected cases are presented with pulmonary hemodynamic instability, high fever with increased respiratory rate, and heart rate associated with low oxygen saturation, which are commonly encountered. In pediatrics, hemorrhagic skin patches and oliguria may be additively seen. During chest auscultation, wheezes and crepitation may be audible.<sup>[4]</sup> The course of the infection cannot be determined, some cases end up mild pneumonia while the others deteriorate into acute respiratory distress syndrome (ARDS) that necessitates advanced life support.<sup>[20]</sup> Added to the ARDS, many other complications are observed such as septic shock, cardiac and renal injuries, and multi-system organ failure.<sup>[22]</sup>

Many diagnostic procedures might help in diagnosis and monitoring of the cases like O<sub>2</sub> saturation assessment by pulse oximetry and chest plain imaging and computed tomography (CT) scans that aid in lung visualization. Although normal CT does not rule out, the diagnosis but still considered as an excellent sensitive tool.<sup>[23]</sup> Polymerase chain reaction (PCR) is another mean that confirms the positive COVID-19 cases, analysis of serum samples revealed positive SARS-CoV-2 (2019-nCoV). RNA by PCR is considered confirmatory. CDC recommends the collection of samples from the upper and lower respiratory tract under certain precautions.<sup>[24]</sup> Other nonspecific lab finding reported among those infected with COVID-19 such as leucopenia, anemia, prolonged prothrombin time, and elevated serum lactate.<sup>[25]</sup>

Up till now, there is no effective antiviral therapy or vaccine against COVID-19 and the only option is focused on symptomatic treatment and respiratory support.<sup>[12]</sup> It is proved that a combination between the two antiretroviral drugs

lopinavir and ritonavir significantly improved the clinical condition of SARS-CoV- patients which may be useful for SARS-COV-2 patients as well.<sup>[26]</sup> Promisingly, an *in vitro* study, proved the effectiveness of remdesivir and chloroquine combination for inhibiting the novel SARS-CoV-2.<sup>[12]</sup> There is a desperate need for new medicines to treat COVID-19, a vaccine to prevent infection entirely would be even better.

Many studies were conducted and implemented many different types of predictive models to assess the current situation and predict the future rates of fatalities and deaths in different countries. Among these countries, few works of literature mentioned the situation in Iran and Pakistan;<sup>[27,28]</sup> however, there is no literature about the current situation of COVID-19 disease caused by the novel SARS-CoV-2 in Kingdom of Saudi Arabia (KSA). The present study is considered the first study that aims to estimate the spread of COVID-19 pandemic among KSA in comparison to Iran and Pakistan. Added to that, the study utilized the susceptible, infectious, recovered, and deaths (SIRD) model and smoothing spline regression model to predict the number of cases in each country during the coming weeks.

## Methods

### Study area

The current study involved all countries (20 countries) within the Eastern Mediterranean Region (Iran, Pakistan, Saudi Arabia, United Arab Emirates, Qatar, Egypt, Morocco, Iraq, Kuwait, Bahrain, Tunisia, Lebanon, Oman, Afghanistan, Jordan, Djibouti, Libya, Syria, Sudan, and Somalia). Later on, Syria, Libya, Sudan, Djibouti, and Somalia were excluded from the analysis as the appearance of the disease among those countries did not complete 4 weeks yet. The study went in detail among the three countries Iran, KSA, and Pakistan. We chose Iran and Pakistan to be compared with Saudi Arabia as both proceeded KSA in recording COVID-19 positive cases, Iran was among the first countries reported the disease appearance. Added to that, Iran and Pakistan had a relatively high number of populations among the region. Lastly and although few, there were previous studies in both Iran and Pakistan regarding COVID-19 spread.

### Data collection

Data were extracted from the WHO situational reports<sup>[6]</sup> that include all the studied variables other than the recovery data, so we got the recovery data from Worldometer<sup>[29]</sup> which was announced by the American Library Association as one of the best data sources, and it is approved and trusted by many governments. The study included 76 situational reports, starting from the situational report number 9 dated January 29, 2020, to the situational report number 85 dated April 14, 2020. The number of populations in each country was considered during data analysis.

The following daily parameters for each country were included; the number of the cumulative confirmed cases, newly confirmed cases, cumulative recovered cases, newly recovered cases, total cumulative deaths, and new deaths. Considered time is measured in days. The numbers were recorded in a spread-sheet and checked twice by different observers to avoid errors.

### Statistical analysis

The data were analyzed by R software statistical programming language, version 3.6.1 (July 5, 2019) (R Foundation for Statistical Computing). For all included countries, descriptive statistics describing the prevalence of the disease in the first 4 weeks after recording the first positive case were conducted, the proportion of infected cases was described as medians and interquartile range and compared with Kruskal-Wallis rank-sum test and Dunn (1964) Kruskal-Wallis multiple comparison test after the normality (tested with Shapiro-Wilk normality test which showed that the data are not normally distributed.  $P < 0.05$  are considered significant with 95% confidence level). The skewness of the data obtained from the different countries is logical as the disease is increasingly spreading. After that, and among the three countries, Iran, KSA, and Pakistan, the proportions of recovered and died cases were also included in the study.

As COVID19 is one of the spreading diseases in which the disease progression can be well assessed by applying the predictive models, among the three countries, Iran, Saudi Arabia, and Pakistan, we implemented the SIRD model to predict the progression of the disease in the next coming weeks. SIRD model simply represents the disease progression within a discrete area.<sup>[30]</sup> In the SIRD model and due to the short duration of the study and due unavailability of numbers of susceptible individuals, we assumed the whole population as being susceptible, this encouraged us to search for another regression predicting model that can accurately predict the numbers of infected cases in the next coming weeks. Smoothing spline regression model was conducted, and the cumulative infected cases versus time were plotted. Furthermore, the performance of the model is tested and the cumulative number of cases in the next weeks is predicted.

## Results

### Descriptive statistics and tests of significance

Table 1 showed the prevalence of the disease among the studied period. Table 2 showed the median values of cumulative infected cases in each country in the 4 weeks following the appearance of the first positive case. There were significant differences ( $P < 2.2e-16$ ) between the 15 countries regarding the proportions of cumulative infected cases to the overall population. Multiple comparison tests showed that there was a significant difference ( $P$ -value [adjusted]  $< 0.05$ ) between many countries and each other.

**Table 1:** Prevalence of coronavirus disease-19 outbreak among each studied country

Country	Prevalence (in 100,000 population)	Period
Jordan	3	3 March–1 April
Tunisia	4	3 March–1 April
Qatar	32	1 March–1 April
Kuwait	7	24 February–1 April
Oman	5	25 February–1 April
Egypt	1	15 February–1 April
UAE	7	29 January–1 April
Iraq	2	25 February–1 April
Afghanistan	6 (in million)	25 February–1 April
Bahrain	39	25 February–1 April
Morocco	2	3 March–1 April
Lebanon	8	22 February–1 April
Kingdom of Saudi Arabia	6	3 March–4 April
Iran	66	20 February–4 April
Pakistan	2	27 February–4 April

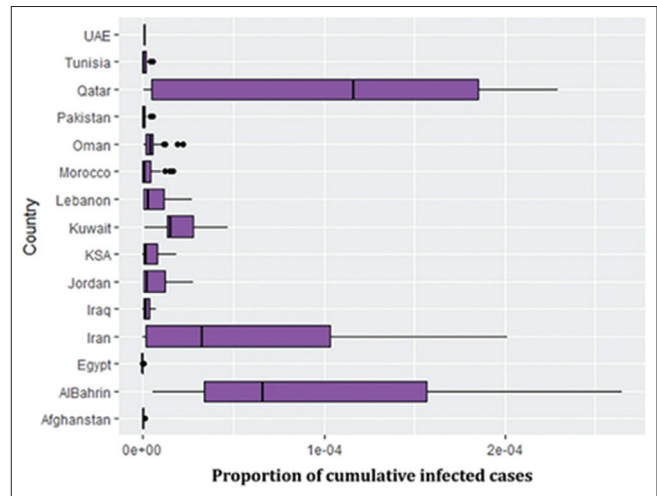
**Table 2:** Proportion of cumulative infected cases relative to total population of each studied country for the first 4 weeks of coronavirus disease-19 outbreak

Country	Median	IQR
Qatar	0.000117	0.000181
Al Bahrain	0.000066	0.000122
Iran	0.0000327	0.000102
Kuwait	0.0000155	0.0000145
Oman	0.00000384	0.00000407
Lebanon	0.00000316	0.0000111
Jordan	0.00000217	0.0000121
Iraq	0.00000163	0.00000268
Kingdom of Saudi Arabia	0.00000147	0.00000745
Morocco	0.000000935	0.00000419
UAE	0.000000863	0.000000431
Tunisia	0.000000351	0.00000151
Afghanistan	0.000000115	0.000000469
Pakistan	0.0000000906	0.00000109
Egypt	0	0.0000000261

IQR: Interquartile range

Figure 1 showed the proportion of cumulative infected cases among the studied countries in the first 4 weeks of infection. Among the whole studied countries, Qatar, Al Bahrain, and Iran showed the highest proportions consecutively.

Box plot showing that among the whole studied countries in the first 4 weeks of infection, Qatar, Al Bahrain, and Iran have the highest proportion of cumulative infected cases, respectively.



**Figure 1:** Proportion of cumulative infected cases in the first 4 weeks of infection in all studied countries. Box plot showing that among the whole studied countries in the first 4 weeks of infection, Qatar, Al Bahrain, and Iran have the highest proportion of cumulative infected cases, respectively.

The comparison was conducted in the first 4 weeks from the first infected case discovered, Qatar was significantly higher in infection rate than Afghanistan, Egypt, Iraq, Jordan, KSA, UAE, Morocco, and Pakistan. Added to that, Al Bahrain was significantly higher in infection rate than UAE, Pakistan, Oman, Lebanon, Afghanistan, Egypt, Jordan, Tunisia, Iraq, KSA, and Morocco. Finally, Iran was significantly higher in infection rate than Afghanistan, Egypt, Morocco, Pakistan, UAE, and Tunisia in the first 4 weeks from the first infected case discovered.

On the other side, Pakistan was significantly lower in infection rates than Iran, Al Bahrain, KSA, Qatar, Kuwait, Oman, and Lebanon. Egypt was significantly lower in infection rates than Al Bahrain, Qatar, KSA, Morocco, Oman, UAE, Jordan, Iran, Iraq, Kuwait, and Lebanon in the first 4 weeks from the first infected case discovered.

Regarding the scope of the current study, and among the three mentioned countries, the population number in Iran is 37,203,000 compared to 32,276,000 in Saudi Arabia. Pakistan shows the highest number of populations (193,203,000). The prevalence per 100,000 population among the three countries showed that Iran exhibited the highest prevalence (net prevalence) of infected cases 66 (38) followed by KSA 6 (4) and finally Pakistan 2 (1).

Those differences were further assessed for their significance by comparing the median values of cumulative infected, recovered, and death cases among the different countries in the first 4 weeks following the first positive case diagnosis. There was a statistically significant difference ( $P = 3.932e-07$ ) between KSA, Iran, and Pakistan by Kruskal-Wallis rank-sum

test and by comparisons between each two groups by Dunn (1964) Kruskal-Wallis multiple comparison test, it was obvious that there was a significant difference ( $P$ -value [adjusted]  $<0.05$ ) between Iran and KSA, Iran, and Pakistan and finally between KSA and Pakistan. Iran had significantly higher cumulative infected cases compared to KSA and Pakistan with median (3.274911e-05, 1.469910e-06, and 9.057830e-08), respectively, in the first 4 weeks in each country, as shown in Tables 3 and 4.

Regarding the proportion of recovered cases, there was a statistically significant difference ( $P = 6.029e-09$ ) between KSA, Iran, and Pakistan by Kruskal-Wallis rank-sum test and by comparisons between each two groups by Dunn (1964) Kruskal-Wallis multiple comparison test showing that there was a significant difference ( $P$ -value [adjusted]  $<0.05$ ) between Iran and KSA, Iran, and Pakistan and finally between KSA and Pakistan. Among the three countries, Iran had a significantly higher number of cumulative recovered cases compared to KSA and Pakistan with median (8.040908e-06, 1.858966e-07, and 5.175903e-09), respectively, in the first 4 weeks in each country Tables 5 and 6.

Regarding the cumulative deaths in the concerned countries, Tables 7 and 8, there was a statistically significant difference ( $p$ -value = 3.966e-13) between KSA, Iran, and Pakistan by Kruskal-Wallis rank-sum test and by comparisons between every two groups by Dunn (1964) Kruskal-Wallis multiple comparison tests, it was shown that there was a significant difference ( $p$ -value

**Table 3:** Proportion of cumulative infected cases relative to total population among the three studied countries for the first 4 weeks

Country	Median	IQR
Kingdom of Saudi Arabia	1.470	7.452
Iran	3.274	1.015
Pakistan	9.058	1.091

IQR: Interquartile range

**Table 4:** Dunn (1964) Kruskal-Wallis multiple comparisons in infection rate among the three studies countries for the first 4 weeks

Comparison	Z	P. unadjusted	P. adjusted
Iran-Kingdom of Saudi Arabia	2.88	0.004	0.008
Iran-Pakistan	5.43	5.708	1.712
Kingdom of Saudi Arabia-Pakistan	2.545	0.010	0.010

$P$ -values adjusted with the Holm Method

**Table 5:** Proportion of cumulative recovered cases relative to the total population among the three studied countries for the first 4 weeks

Country	Median	IQR
Kingdom of Saudi Arabia	1.859	8.443
Iran	8.041	3.726
Pakistan	5.176	6.211

IQR: Interquartile range

(adjusted)  $< 0.05$ ) between Iran and KSA and between Iran and Pakistan. Iran has a significantly higher cumulative death compared to KSA and Pakistan with median (1.052605e-06, 0, 0), respectively, in the first 4 weeks in each country. Figure 2a-c and Figure 3 illustrated that during the first 4 weeks after reporting the first case of COVID-19 in the three studied countries (Iran, Saudi Arabia, and Pakistan), Iran showed the highest number of cumulative infected, recovered, and death cases.

A curve showing that Iran has the highest number of cumulative infected, recovered, and death cases on a confidence level 95% compared to KSA and Pakistan during the first 4 weeks of infection.

### Predictive models

The current study considered the Susceptible-Infectious-Recovered-Dead (SIRD) model, a compartmentalized type model, which is a simple representation of disease progression with discrete states. When approaching modeling mathematically, we utilized a set of equations to describe bulk population dynamics.

- S: Fraction of susceptible individuals (all populations are considered susceptible)
- I: Fraction of infectious individuals
- R: Fraction of recovered individuals

**Table 6:** Dunn (1964) Kruskal-Wallis multiple comparisons in recovery rate among the three studied countries for the first 4 weeks

Comparison	Z	P. unadjusted	P. adjusted
Iran-Kingdom of Saudi Arabia	2.77	0.006	0.006
Iran-Pakistan	6.14	8.130	2.439
Kingdom of Saudi Arabia-Pakistan	3.38	0.001	0.002

$P$ -values adjusted with the Holm method

**Table 7:** Proportion of cumulative death cases relative to the total population among the three studies countries for the first 4 weeks

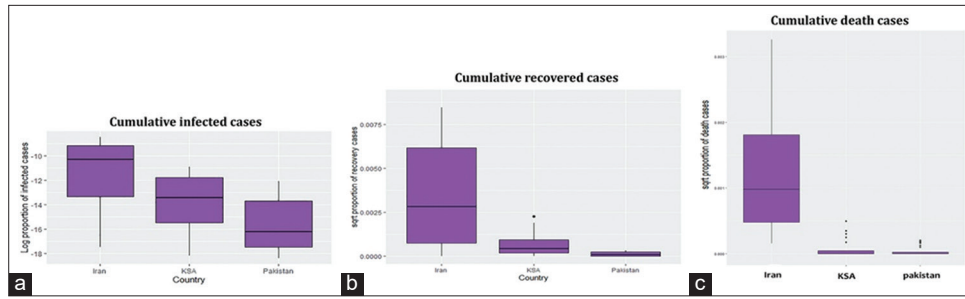
Country	Median	IQR
Kingdom of Saudi Arabia	0	7.746
Iran	1.053	3.569
Pakistan	0	2.588

IQR: Interquartile range

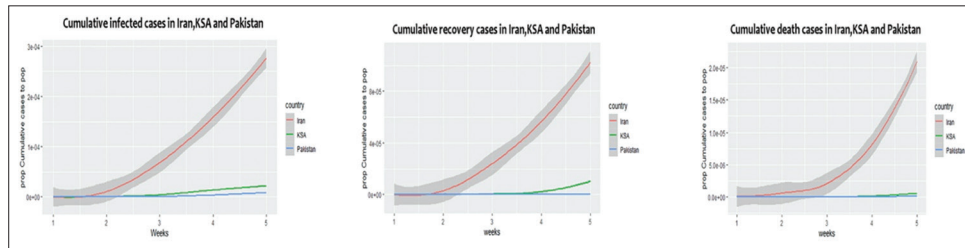
**Table 8:** Dunn (1964) Kruskal-Wallis multiple comparisons in death rate among the three studied countries for the first 4 weeks

Comparison	Z	P. unadjusted	P. adjusted
Iran-Kingdom of Saudi Arabia	6.34	2.302	4.603
Iran-Pakistan	6.73	1.672	5.016
Kingdom of Saudi Arabia-Pakistan	0.39	0.690	0.690

$P$ -values adjusted with the Holm method



**Figure 2:** Comparison between median values of cumulative infected, recovered, and death cases in Iran, Kingdom of Saudi Arabia (KSA), and Pakistan during the first 4 weeks of infection. a: Box plot showing the comparison of median values of cumulative infected cases in the three countries, Iran has a significantly higher cumulative infected cases compared to KSA and Pakistan. b: Box plot illustrating the median values of recovered cases, Iran had a significantly higher recovery median compared to KSA and Pakistan. c: Box plot showing the comparison of median values of death cases in the three countries, Iran has a significantly higher death rate compared to KSA and Pakistan



**Figure 3:** Comparison between Iran, Kingdom of Saudi Arabia (KSA), and Pakistan in the number of cumulative infected, recovered, and death cases in the first 4 weeks of infection

D: Fraction of died individual  
 $\beta$ : Transmission rate per infectious individual  
 $\gamma$ : Recovery rate  
 $\mu$ : The Death rate

$$\Delta S = S_{t+1} - S_t = -\beta I_t S_t$$

$$\Delta R = \gamma I_t$$

$$\Delta I = \beta I_t S_t - \gamma I_t - \mu I_t$$

$$\Delta D = \mu I_t$$

Conducting the SIRD compartmentalized model in Iran revealed that  $\beta = 2e-05$ ,  $\gamma = 0.008$ , and  $\mu = 0.00141$ , which reflects a very low chance of transmission rate per infectious individuals.

$R^0$  is the basic reproductive number and it equals  $\beta/\gamma$ . It represents the average of susceptible populations that can get the infection when coming in contact with a single infectious active case. If  $R^0 > 1$ , this means that the virus can spread through the population while if  $R^0 < 1$ , as in the current situations,  $R^0 = 0.0015$ , it reflects that the disease spread through direct contact with infected cases will decrease by time. The curves exhibited the plateau pattern, due to the involvement of the whole population as being susceptible. SIRD model in KSA yielded similar results as  $\beta = 2e-0.6$ ,  $\gamma = 0.006$ , and  $\mu = 0.00038$ , as shown at Figure 4. The model showed that the fraction of infectious, recovered, and dead cases reached a plateau in the period

(March 3, 2020–April 4, 2020) and  $R^0 = 0.00029 (< 1$  person infected). In Pakistan, the SIRD model reveals similar results,  $\beta = 4e-07$ ,  $\gamma = 0.00126$ , and  $\mu = 0.00041$ .  $R^0 = 0.0002$  indicates a very small transmission rate. The predictive power of the suggested model was illustrated in Figure 5, as it describes the proportion of cumulative infected (observed and simulated) concerning the time during the studied period.

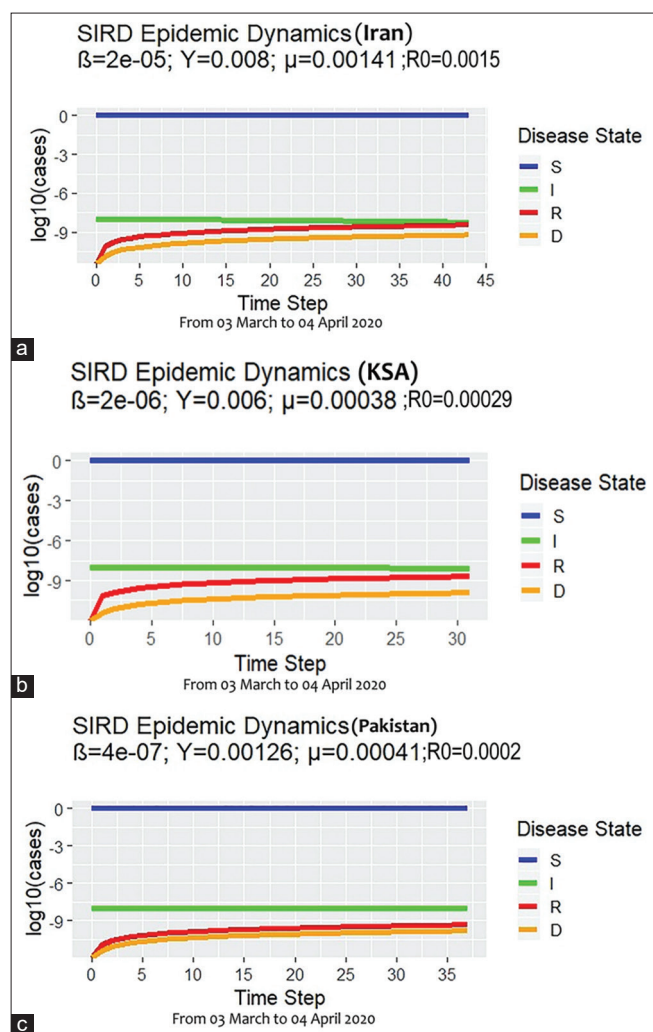
Smoothing spline regression model was conducted to predict the number of cumulative infected cases among the three mentioned countries. Figure 6 showed that the cumulative infected cases exponentially increased among the three studied countries; moreover, the performance of the predictive model when tested, the results were excellent. As the data we relied on was limited, and to predict the proportion of cumulative infected cases to all population and test the performance of the model, we split the data into knots, then we calibrated the model with the 1<sup>st</sup> days of data (from the start of positive cases till April 14) to predict the test data (the rest of data points from April 15, 2020, till May 1, 2020). Then, we compared the simulated test data from the model and the original data point to test the model’s ability in replicating the rest of the data points. The following equation was established:

$$y = \beta_0 + \beta_1 b_1(x) + \beta_2 b_2(x) + \dots + \beta_K + 3b_K + 3(x) + \epsilon$$

Where  $y$  in KSA was the square root of infected cases while in Iran and Pakistan, it was the log of infected cases.

In Iran [Figure 7a], and as our data were during the period from February 20 to April 14, the data were split into knots (0.1, 0.25, and 0.35) at a time in days, and we calibrated the model with the days of data to predict the test data. Then, the

model is used to predict the proportion of cumulative infected cases to all populations from April 15 to May 1, according to that, we expected that the cases in Iran would increase to 100485 on May 1.



**Figure 4:** SIRD epidemic dynamics model among Iran, Kingdom of Saudi Arabia (KSA), and Pakistan. SIRD model of Iran (a), KSA (b), Pakistan (c) exhibiting plateau in the three variables R, I, and D. ( $R_0 < 1$ ) for the three studies countries, means that the disease transmission will stop due to reduced number of newly infected cases. S=fraction of susceptible individuals, I=fraction of infectious individuals, R=fraction of recovered individuals, D=fraction of dead individuals

In KSA [Figure 7b], during the period from March 3 to April 14, the data were split into knots (0.5, 0.15, and 0.2) at a time in days and calibrated the model with the 1<sup>st</sup> days of data to predict the test data. Then, the model predicted the proportion of cumulative infected cases to all populations from April 15 to May 1. We expected the cases to reach to 16848 by May 1, 2020

In Pakistan [Figure 7c], during the period from February 27 to April 14, we split data into Knots (0.15, 0.25, and 0.3) at a time in days, so we calibrated the model with the 1<sup>st</sup> days of data and predicted the test data. Then, the model is used to predict the proportion of cumulative infected cases to all population from April 15 to May 1, we expected that the cases will reach 11825 by May 1, 2020.

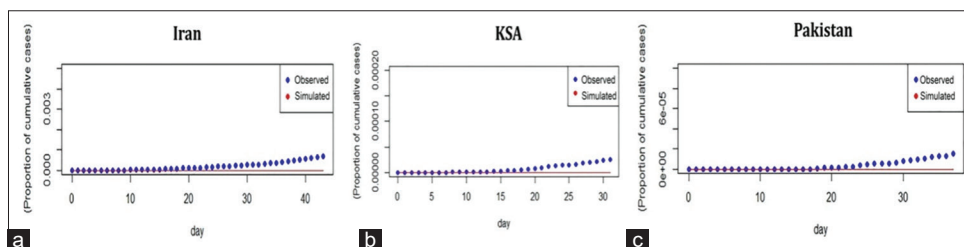
Regarding testing the performance of the suggested model, in KSA, 99.94% of cases were predicted correctly during the training period and about 99.73% during the testing period. The numbers in Iran and Pakistan were comparable, in Iran,  $R^2 = 0.9996$  and  $0.9928$  compared to  $0.9992$  and  $0.967$  in Pakistan for the training and testing periods consecutively. The root mean square error values in the three countries during the testing and training periods were  $< 1$ , as illustrated in Figure 6. Figures 8 and 9 consecutively showed the observed cumulative recovered and cumulative deaths as best fitted to the spline regression prediction curve among the three mentioned countries.

Fitting of cumulative recovered cases with the smoothing spline regression prediction model, the dots represent the observable cases while the blue line represents the simulated cases.

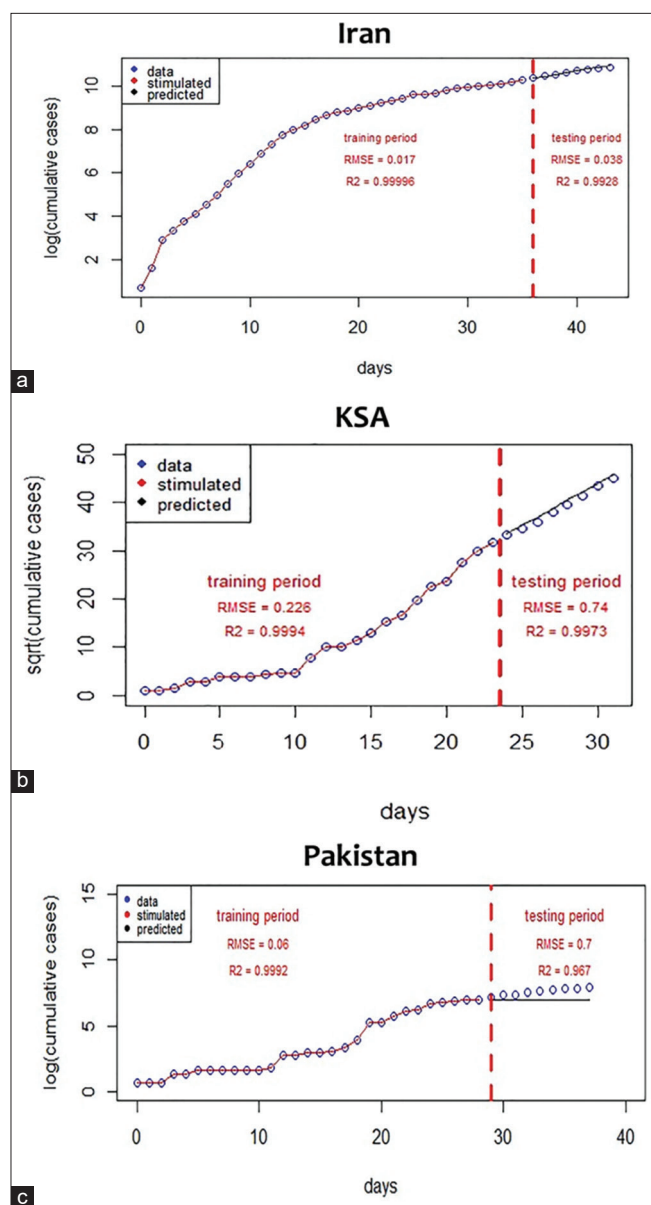
Fitting of cumulative death cases with the smoothing spline regression prediction model, the dots represent the observable cases while the blue line represents the simulated cases.

## Discussion

Among the Eastern Mediterranean Region, Qatar followed by Al Bahrain showed the highest prevalence of COVID-19. That



**Figure 5:** Simulated and observed cumulative infected cases among Iran, Kingdom of Saudi Arabia (KSA), and Pakistan. A curve showing the predictive power of SIRD model by describing the proportion of cumulative infected cases (simulated and observed) in relation to the time during the studied period, in (a) Iran, (b) KSA, and (c) Pakistan



**Figure 6:** Smoothing spline regression prediction model for cumulative infected cases in Iran, Kingdom of Saudi Arabia (KSA), and Pakistan. (a) Smoothing spline regression model for cumulative infected cases in Iran; (b) smoothing spline regression model for cumulative infected cases in KSA; (c) smoothing spline regression model for infected cumulative cases in Pakistan, spline regression model of the three studies countries showing an accurate predictive power

was obviously due to their small number of populations, as the population number in Qatar is 2,750,000 and in Al Bahrain is 1,425,000 which is considered the least population number following Djibouti among the region.

Among the three studied countries (Iran, KSA, and Pakistan), Iran significantly showed the highest number of infected cases followed by KSA and lastly Pakistan. Moreover, in a similar way, the highest recovery and deaths were also evident in Iran when compared with KSA and Pakistan. On the other

hand, the infection rate in Pakistan was less than KSA, the low infection rate observed in Pakistan was in agreement with Mukhtar and Mukhtar<sup>[31]</sup> who mentioned that due to the early strict preventive measures and screening implemented by the government, the infection rate in Pakistan was noticed to be less than other countries in the same region. Another explanation might be the lack of screening measures implemented in Pakistan if compared to KSA. However, this situation is not expected to continue as Zhan *et al.*<sup>[32]</sup> expected in their studies conducted in Iran and Pakistan that the number of infected cases would grow exponentially by time.

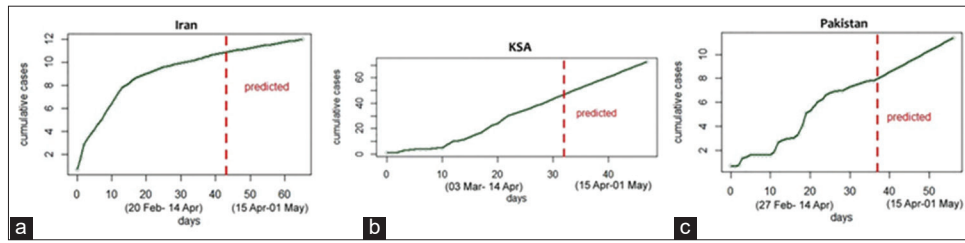
Despite the infection rate in KSA was significantly higher than Pakistan in the first 4 weeks of disease spread, there was no significant difference between them in the death rate. This might be explained by the significantly high recovery rate in KSA compared to Pakistan. The high recovery rate in KSA in comparison to Pakistan could be attributed to the more advanced health-care system in KSA in contrary to Pakistan. According to the WHO, the total expenditure on health per capita in KSA is 2466 USD compared to 129 USD in Pakistan; furthermore, the total expenditure on health as % of growth domestic product is 4.7 in KSA compared to 2.6 in Pakistan. Those results were agreed with Raza *et al.*<sup>[28]</sup> who mentioned that during the upcoming weeks, 90 million of the population are likely to become infected and the death rate is expected to increase, and if occurred, the health-care system would not be able to deal with this enormous pandemic.

Prediction of the disease peak and expected number of cases among different countries are points of interest for many researchers who built their expectations on the pattern of disease spread in similar countries. China and Italy were on top of the countries who suffered from the COVID-19 pandemic, they both reported exponential growth of infected cases and fatalities with unfortunate still wise expectations. Hence, we tried to implement a predictive model to assess the situation in the Eastern Mediterranean region, notably the situation in KSA.<sup>[33]</sup>

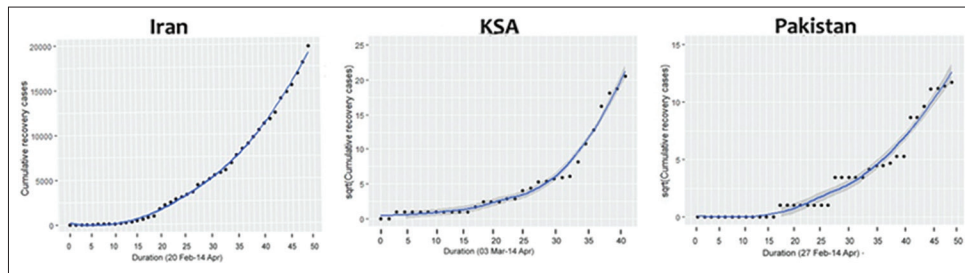
Many models were applied in different studies of different countries in the area. For instance, the augmented SEIR model was conducted in Iran by Zhan *et al.*<sup>[32]</sup> Generalized additive model and restricted maximum likelihood by Zareie *et al.*<sup>[34]</sup> and Gompertz model by Ahmadi *et al.*<sup>[27]</sup> In Pakistan, Raza *et al.*<sup>[28]</sup> and Syed and Sibgatullah (2020)<sup>[35]</sup> applied the SIR model in their studies. The studies in KSA are still lacking and up to our knowledge, this is the first study that aims to predict the coming situation in KSA.

SIRD model is one of the most predominant models used to assess the progression of communicable diseases among different societies. In this model, the whole population is classified into four categories, everyone is considered susceptible, while the other categories involved the infected, recovered, or died cases. Application of this model in Iran, Saudi Arabia, and Pakistan highlighted that the COVID19

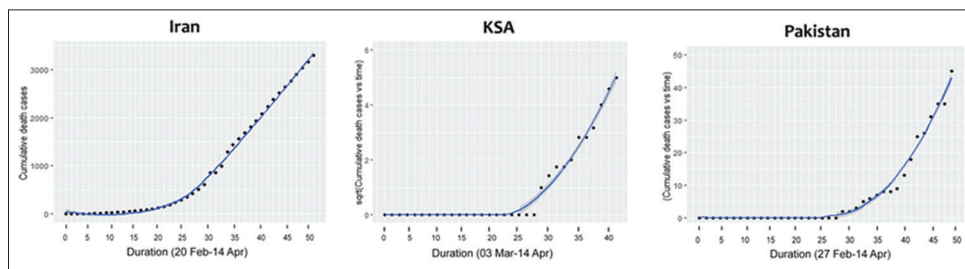




**Figure 7:** Smoothing spline regression model for observable versus predictable cumulative infected cases in Iran, Kingdom of Saudi Arabia (KSA), and Pakistan. (a) Smoothing spline regression model for cumulative infected cases in Iran, observed cases (February 20, 2020–April 14, 2020), predicted cases (April 15–May 1). (b) Smoothing spline regression model for cumulative infected cases in KSA, observed cases (March 3, 2020–April 14, 2020), predicted cases (April 15–May 1). (c) Smoothing spline regression model for cumulative infected cases in Pakistan, observed cases (February 27, 2020–April 14, 2020), predicted cases (April 15–May 1)



**Figure 8:** Smoothing spline regression prediction model for cumulative recovered cases in Iran, Kingdom of Saudi Arabia (KSA), and Pakistan



**Figure 9:** Smoothing spline regression prediction model for cumulative death cases in Iran, Kingdom of Saudi Arabia, and Pakistan

transmission rate was so slow among the three countries as  $<1$  person was expected to be infected when comes in contact with the positive case. Added to that and due to the limited data about the susceptible populations in WHO reports, the fraction of infectious, recovered, and died individuals exhibit the plateau-like curves. Fortunately, enough, the basic reproduction numbers in the three mentioned countries during the 1<sup>st</sup> weeks of the disease were evidently below that reported in Wuhan, China (3.58),<sup>[36]</sup> and Italy (2.76–3.25).<sup>[33]</sup>

According to the WHO situational reports, the spread of disease in Iran started earlier on 20<sup>th</sup> of February, the basic reproduction number mentioned in the current study that covers the period from February 20 to April 14 was 0.0015, which is less than the number mentioned by many studies conducted in Iran. Sahafizadeh and Sartoli<sup>[37]</sup> reported decreasing  $R^0$  values from 4.86 during the 1<sup>st</sup> week of the outbreak to 2.1 by March 18 and Zhao *et al.*<sup>[38]</sup> reported  $R^0$  between 2.24 and 3.58. This discrepancy in the basic reproductive number between the results obtained in the current study and other studies could be explained by the difference in the period during which

the studies were conducted. Different sources of data were another reasonable explanation, as Sahafizadeh and Sartoli<sup>[37]</sup> results were built on Iranian government reports not on WHO situational reports. However, the development of health-care services and the later preventive measures implemented by the government might be another reason. These results are in agreement with Zahiri *et al.*<sup>[39]</sup> and Li *et al.*<sup>[40]</sup> who expected more decrease in the basic reproduction number by the time.

None of the previous studies tried to use the smoothing spline regression prediction model that was utilized in the current study and proved to predict an exponential growth in cumulative infected cases among Iran, KSA, and Pakistan. However, the expected growth mentioned in the current study is not explained only by cases got the infection directly ( $R^0$ ), but also by others coming from countries where the disease is pandemic, moreover, we suppose the stability of the screening methods implemented by the governments. Those results were in agreement, other studies utilized different models as Syed and Sibgatullah<sup>[35]</sup> and with Ahmadi *et al.*,<sup>[27]</sup> who expected exponential growth of cases with time in Pakistan.

Among the Eastern Mediterranean Region, the delayed appearance of cases in KSA (March 3) in comparison to Iran and Pakistan which reported the positive cases earlier was attributed to that the early strict quarantine preventive measures implemented by KSA. Al-Tawfik and Memish<sup>[41]</sup> mentioned the preventive measures implemented by KSA government to overcome the spread of COVID-19 pandemic. On 5<sup>th</sup> of February and before the appearance of any confirmed cases, Saudi Arabia suspended the travel to China, a short time after and on 26<sup>th</sup> of February, the country suspended the entry for Umrah or tourist visa, according to Ebrahim and Memish,<sup>[42]</sup> Umrah suspension was a mandatory decision that reduced the infection rate in the country. The first case reported by the Saudi Ministry of Health was coming from Iran. Shortly after, many congregation events were canceled. By March, and as the infection rate increased, more strict preventive measures were implemented as all air flights were suspended, universities and schools were suspended, and that was followed by the partial lockdown. However, this partial lockdown was converted into complete in the Capital City Riyadh, and among the Holy Districts, Mecca and Medina.

## Conclusion and Recommendation

In the eastern Mediterranean Region, especially in KSA, Iran, and Pakistan, the cumulative infected cases were expected to grow exponentially, so the quarantine preventive measures should be maintained or even enhanced. It is expected that by May 1, 2020, the number of cumulative infected cases would rise to 16848 in KSA and 11,825 in Pakistan, while In Iran, it is expected that the number mostly will be 10,0485.

## Authors' Declaration Statements

### Limitation of the study

We recommend conducting the study on longer time intervals and comparing the predictive power of different models with the SIRD and smoothing spline regression model.

The model is based on the routine circumstantial screening measurements implemented by the different countries. Introducing of new screening methods or applying screening on a larger scale would be associated with a total number of cumulative cases that exceed those predicted in the current study.

## Ethics Approval and Consent to Participate

### Availability of data and material

The data used in this study are available and will be provided by the corresponding author on a reasonable request.

## Competing Interests

All authors declare that they have no conflicts of interest

## Funding Statement

The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Authors' Contribution

All authors contributed equally in the article.

## Acknowledgments

We would like to extend our gratitude to the WHO and Worldometer for sharing their data on their official websites and making them accessible. Furthermore, we are immensely grateful to the reviewers for their so-called insights.

ORCID ID link of the submitting author: ORCID ID: 0000-0002-0866-0981

Asmaa Sharif- ORCID ID:0000-0002-6104-562X

Sara Mattout - ORCID ID:0000-0002-3746-2757

## References

1. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J Adv Res* 2020;24:91-8.
2. WHO. Novel Coronavirus-China. Available from: <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en>. [Last accessed on 2020 Jan 12].
3. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, *et al.* Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* 2020;9:221-36.
4. 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;395:497-506.
5. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents* 2020;55:105924.
6. WHO. Coronavirus Disease 2019 (COVID-19) Situation Report 9-85. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>. [Last accessed on 2020 Apr 11].
7. Li JY, You Z, Wang Q, Zhou ZJ, Qiu Y, Luo R, *et al.* The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future. *Microbes Infect* 2020;22:80-5.
8. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020;2020:102433.
9. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727-33.
10. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, *et al.* Identification of a novel coronavirus causing severe pneumonia in human: A descriptive study. *Chin Med J (Engl)* 2020;133:1015-24.
11. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al.* Genomic characterisation

- and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 2020;395:565-74.
12. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, *et al.* The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak-an update on the status. *Mil Med Res* 2020;7:11.
  13. Rahman S, Bahar T. COVID-19: The new threat. *Int J Infect* 2020;7:e102184.
  14. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, *et al.* Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: Implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cell Mol Immunol* 2020;6:613-20.
  15. Yoo JH. The fight against the 2019-nCoV outbreak: An arduous march has just begun. *J Korean Med Sci* 2020;35:e56.
  16. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection--a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect* 2020;9:727-32.
  17. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett* 2002;532:107-10.
  18. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* 2020;5:562-9.
  19. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, *et al.* Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). *MedRxiv* 2020.
  20. Heymann DL, Shindo N. COVID-19: What is next for public health? *Lancet* 2020;395:542-5.
  21. Raoult D, Zumla A, Locatelli F, Ippolito G, Kroemer G. Coronavirus infections: Epidemiological, clinical and immunological features and hypotheses. *Cell Stress* 2020;4:66-75.
  22. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet* 2020;395:507-13.
  23. Kanne JP. Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: Key points for the radiologist. *Radiology* 2020;295:16-7.
  24. Coronavirus Disease 2019 (COVID-19). Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19). Available from: <https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>. [Last accessed on 2020 Mar 21].
  25. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020;46:846-8.
  26. Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med Int Health* 2020;25:278-80.
  27. Ahmadi A, Fadaei Y, Shirani M, Rahmani F. Modeling and forecasting trend of COVID-19 epidemic in Iran until May 13, 2020. *Med J Islamic Republic Iran* 2020;34:183-95.
  28. Raza S, Rasheed MA, Rashid MK. Transmission Potential and Severity of COVID-19 in Pakistan. Preprints 2020, 2020040004 (Doi: 10.20944/preprints202004.0004.v1).
  29. Worldometer. COVID-19 Coronavirus Pandemic. Available from: <https://www.worldometers.info/coronavirus>. [Last accessed on 2020 Apr 11].
  30. Biswas K, Sen P. Space-time dependence of corona virus (COVID-19) outbreak. *arXiv preprint arXiv:2003.03149*. 2020 Mar 06.
  31. Mukhtar F, Mukhtar N. Coronavirus (COVID-19): Let's prevent not panic. *J Ayub Med Coll Abbottabad* 2020;32:141-4.
  32. Zhan C, Chi KT, Lai Z, Hao T, Su J. Prediction of COVID-19 spreading profiles in South Korea, Italy and Iran by data-driven coding. *MedRxiv* 2020.
  33. Remuzzi A, Remuzzi G. COVID-19 and Italy: What next? *Lancet* 2020;395:1225-8.
  34. Zareie B, Roshani A, Mansournia MA, Rasouli MA, Moradi G. A model for COVID-19 prediction in Iran based on China parameters. *MedRxiv* 2020.
  35. Syed F, Sibgatullah S. Estimation of the final size of the COVID-19 epidemic in Pakistan. *MedRxiv* 2020.
  36. Chen TM, Rui J, Wang QP, Zhao ZY, Cui JA, Yin L. A mathematical model for simulating the phase-based transmissibility of a novel coronavirus. *Infect Dis Poverty* 2020;9:24.
  37. Sahafizadeh E, Sartoli S. Estimating the reproduction number of COVID-19 in Iran using epidemic modeling. *MedRxiv* 2020.
  38. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, *et al.* The basic reproduction number of novel coronavirus (2019-nCoV) estimation based on exponential growth in the early outbreak in China from 2019 to 2020: A reply to Dhungana. *Int J Infect Dis* 2020;94:148-50.
  39. Zahiri A, RafieeNasab S, Roohi E. Prediction of peak and termination of novel coronavirus covid-19 epidemic in Iran. *MedRxiv* 2020.
  40. Li L, Yang Z, Dang Z, Meng C, Huang J, Meng H, *et al.* Propagation analysis and prediction of the COVID-19. *Infect Dis Mod* 2020;5:282-92.
  41. Al-Tawfiq JA, Memish ZA. COVID-19 in the Eastern Mediterranean region and Saudi Arabia: Prevention and therapeutic strategies. *Int J Antimicrob Agents* 2020;2020:105968.
  42. Ebrahim SH, Memish ZA. COVID-19: Preparing for superspreader potential among Umrah pilgrims to Saudi Arabia. *Lancet* 2020;395:e48.