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Estimation of the Time Dependent Reproduction Number of Novel Coronavirus (COVID 19) for Turkey in the Late Stage of the Outbreak

Türkiye İçin Salgının Geç Evresinde Yeni Tip Koronavirüsün (COVID-19) Zamana Bağlı Bulaştırma Katsayısının Tahmini

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ABSTRACT Objective: Coronavirus disease-2019 (COVID-19), which caused a big outbreak, was first detected in Wuhan, China on 31st of December, 2019, and began to spread all over the world rapidly. The first case in Turkey was detected on the 11th of March, 2020. This study aims to calculate time-dependent (TD) reproduction number (Rt) using three different serial interval values in the late phase of the COVID-19 pandemic for Turkey. **Material and Methods:** TD model was used for estimation of reproduction number. For the serial interval of the coronavirus, the serial interval values of 4±2.5 and 6±3 days were used together with the severe acute respiratory syndrome and Middle East respiratory syndrome serial interval mean of 8±3.6. Gamma distribution was used for serial interval estimates. The bootstrap method with 1,000 simulations was used for all reproduction number confidence interval estimates. **Results:** Using 8±3.6, 6±3 and 4±2.5 serial interval values, the mean reproduction number (Rt) calculated for Turkey with the TD model was 2.06 (1.92-2.21), 1.70 (1.58-1.81), and 1.39 (1.30-1.48), respectively. The confidence intervals of the reproduction number values calculated for Turkey range from 1.30 (lowest) to 2.21 (highest). **Conclusion:** According to the TD model results, from the first day when the pandemic started in Turkey to the 32nd (11th of April 2020) and 33rd (12th of April 2020) days, the Rt value decreased below 1 and the outbreak started to demonstrate a breaking point. Lower Rt in Turkey compared to the other epicenters of the world may indicate that Turkey was quicker in implementing preventive measures much earlier than the other countries.

Keywords: Coronavirus; COVID-19; reproduction number; outbreak; infectious disease; epidemiology; statistical modelling

ÖZET Amaç: Büyük bir salgına neden olan koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], ilk olarak 31 Aralık 2019'da Çin'in Wuhan şehrinde ortaya çıktı ve hızlı bir şekilde tüm dünyaya yayılmaya başladı. Türkiye'de ilk vaka 11 Mart 2020'de tespit edildi. Bu çalışma, Türkiye için COVID-19 salgınının geç evresinde 3 farklı seri aralık senaryosu kullanarak, zamana bağlı [time dependent (TD)] bulaştırma katsayısını (Rt) hesaplamayı amaçlamaktadır. **Gereç ve Yöntemler:** Bulaştırma katsayısının tahmini için TD model kullanılmıştır. Koronavirüsün seri aralığı için şiddetli akut solunum sendromu ve Orta Doğu solunum sendromu seri aralığı ortalaması (8±3,6 gün) ile birlikte 4±2,5 ve 6±3 günlük seri aralık değerleri kullanılmıştır. Seri aralık tahmini için Gamma dağılımı kullanılmıştır. Bulaştırma katsayılarının güven aralığı tahminleri için 1.000 benzetim ile Bootstrap yöntemi kullanılmıştır. **Bulgular:** TD modeli ile Türkiye için 8±3,6, 6±3 ve 4±2,5 seri aralık değerleri kullanılarak hesaplanan ortalama bulaştırma katsayıları (Rt) sırasıyla 2,06 (1,92-2,21), 1,70 (1,58-1,81) ve 1,39 (1,30-1,48) olarak bulunmuştur. Türkiye için hesaplanan bulaştırma katsayısı güven aralıklarının 1,30 (en düşük) ile 2,21 (en yüksek) arasında değiştiği belirlenmiştir. **Sonuç:** TD modeli sonuçlarına göre Türkiye'de salgının başladığı ilk günden sonra 32 (11 Nisan 2020) ve 33. (12 Nisan 2020) günlerde Rt değerinin ilk kez 1'in altına düştüğü ve salgının kırılmaya başladığı belirlenmiştir. Rt değerinin diğer ülkelere göre daha düşük olmasında diğer birçok ülkeden önce alınan önlemlerin etkili olduğu düşünülmektedir.

Anahtar kelimeler: Koronavirüs; COVID-19; bulaştırma katsayısı; salgın; bulaşıcı hastalık; epidemiyoloji; istatistiksel modelleme

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Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) belonging to β-coronavirus type of Coronaviridae family resembles the SARS-CoV virus due to high-levels of nucleotide similarities in their genomes.[1] Coronaviruses (CoV) are generally composed of a big virus family that causes human infections such as SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV). Studies conducted recently have shown that these types of coronaviruses were caused by bats.[1] The SARS-CoV-2 virus was named as the 2019 Novel Coronavirus (COVID-19) by the World Health Organization (WHO).[2] COVID-19 causes typical pneumonia conditions. Causing a big outbreak, COVID-19 was first detected in Wuhan, China on 31st of December, 2019, and began to spread all over the world rapidly.[3] The WHO declared "pandemic" on the 11th of March 2020, and the first case in Turkey was detected on the 11th of March, 2020.[4]

The pandemic began to spread rapidly in our country since March 11. Initially, on the 16th of March, decisions were made to play the sporting games without spectators until the end of April and to require special permission for the international travel of public officials. Following this, holiday was declared for one week for primary, secondary, and high schools and three weeks for universities; these durations were extended and the distance education process was started. On the 21st of March, a curfew was declared for individuals who were aged 65 and over and who had a chronic disease. On the 21st of March, workplaces such as barbers, hairdressers, cafes, restaurants, and patisseries were closed temporarily. On the 22nd of March, state institutions and organizations started to apply rotation shifts and flexible teleworking. On the 27th of March, flights in the international arrivals in Turkey were stopped, and governorship permission was required for traveling between cities. On the 3rd of April, a curfew was declared for citizens aged below 20. In addition, wearing masks was made compulsory in places like markets, and entrances and exits to the 30 metropolitan cities and Zonguldak were banned for 15 days. The first curfew was declared on the 11th of April for 48 hours in 30 big cities and Zonguldak, and similar curfews were declared at some weekends and on special days (https://tr.wikipedia.org/wiki/T%C3%BCrkiye%27de_COVID-19_pandemisi_zaman_%C3%A7izelgesi).

Reproduction number (RN) R0 demonstrates the number of cases produced from a single infected individual in a given epidemic. In other words, RN indicates the new number of infections caused by an individual who came to a society that had no virus throughout all the transmission period in the onset of the outbreak.[5] The time-dependent (TD) RN (Rt), which is calculated after the interventions applied for the outbreak are started, enables to analyze the efficiency of different interventions to take the outbreak under control.[6] RN is an important parameter for identifying the severity of the outbreak. RN gives information about the breaking point of the outbreak. Epidemiology indicates that the outbreak emerges at RN>1 and disappears at RN<1 (an infected person infects less than one person on average).[7]

Since the COVID-19 outbreak started, various studies have reported estimations about the RN values of several countries. The RN values were calculated for China by Zhou et al. and Wang et al., for Diamond Princess ship by Zhang et al., for Italy, Germany, France, and Spain by Yuan et al., for Italy and its 9 cities by D'arienzo et al., for 11 European countries (Austria, Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, Switzerland, and the United Kingdom) by Flaxman et al., and for China, India, Iran, Italy, South Korea, and the USA by Deb et al.[8-14] Although the RN values were estimated for many countries in the world, there is limited research about the RN values in Turkey. This study aims to calculate TD RN (Rt) using three different serial interval (SI) values in the late phase (the period when Rt falls below 1) of the COVID-19 pandemic for Turkey.

MATERIAL AND METHODS

TIME DEPENDENT MODEL

The TD model calculates the reproduction numbers by calculating the average over all transmission networks compatible with the observations.[15,16] The probability p_{ij} that case i with onset at time t_i was infected

by case j with onset at time t_j is calculated as $p_{ij} = \frac{N_i\ w(t_i - t_j)}{\sum_{i \neq k} N_i w\ (t_i - t_k)}$. Thus, the effective RN for case j is $R_j = \sum_i p_{ij}$ and is averaged as $R_t = \frac{1}{N_t} \sum_{\{t_j = t\}} R_j$ over all cases with the same date of onset.[15,16]

DATA SOURCE

The data set was obtained from the website (https://covid19.saglik.gov.tr) of the T.C. Ministry of Health (for the coronavirus outbreak (same data for Turkey can also be obtained from the "worldometers" website: (https://www.worldometers.info/coronavirus/country/turkey/). The deadline for obtaining data for current case numbers is 25 May 2020.

SERIAL INTERVAL

The estimation of the RN initially requires the identification of the SI distribution of the virus.[9] SI in the epidemiology of contagious diseases indicates the duration between the successive cases in a filiation (i.e., a hierarchical one-lag network of a primary case and secondary case infected by the primary case). The SI is generally estimated using the durations between the clinical symptom onsets. This process was shown in Figure 1 to better understand the concept of serial interval.[17-19] The critical parameter for these calculations is the distribution of the SIs between the serial intervals, the time between the onset of the symptoms, and the onset of the the symtoms in the secondary case infected by the primay cased. These serial intervals are summarized as means and standard deviations. Although some studies in the literature used the SI of SARS and MERS, Nishiura et al. found the SI of COVID-19 shorter than the SI of SARS Mean±SD: 4.7 (3.7, 6.0)±2.9 (1.9, 4.9) days.[3,20] It was reported that the calculations used in that study using the SARS SI could cause bias.[20] Li et al. found the mean of COVID-19 SI as 7.5±3.4 days.[21] Du et al. found the mean of the SI as 3.96±4.75 days.[22] In their meta-analysis, Park et al. reported that the SI for COVID-19 ranged from 4 to 8 days.[23] Therefore, in this study, the Rt calculations for the COVID-19 in Turkey were done using the SARS and MERS SI mean score (8±3.6) similar to the study conducted by Zhao and Deb. In addition, based on the studies in the literature, RN were also calculated within the 4±2.5 and 6±3 days SI values.[6,11,20]

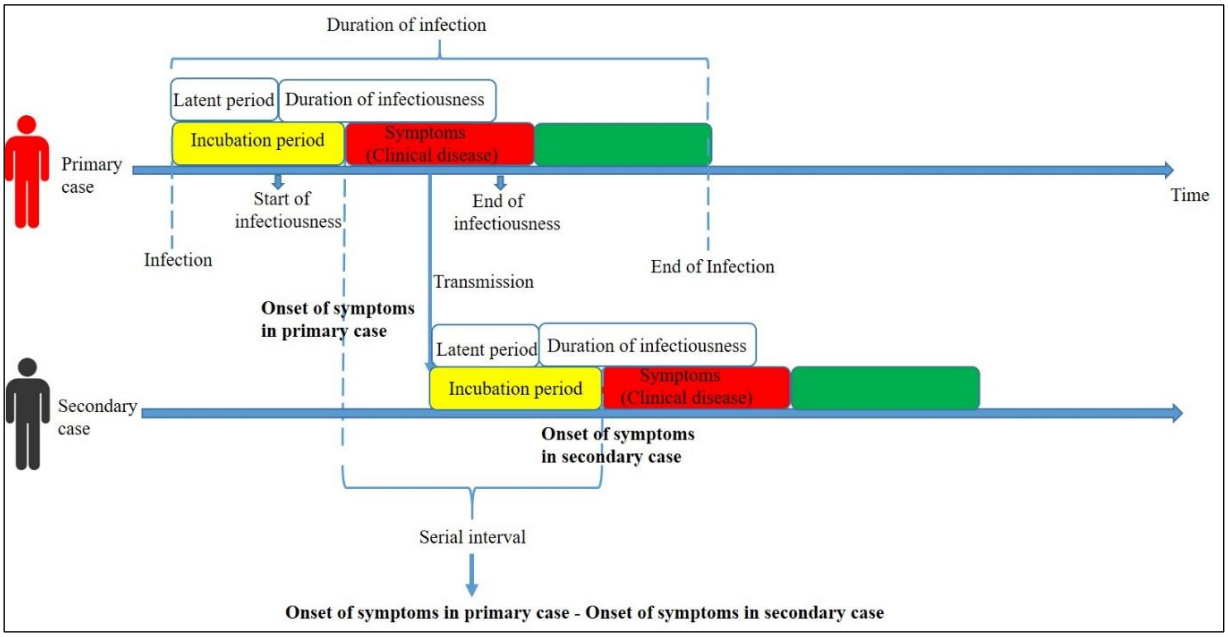


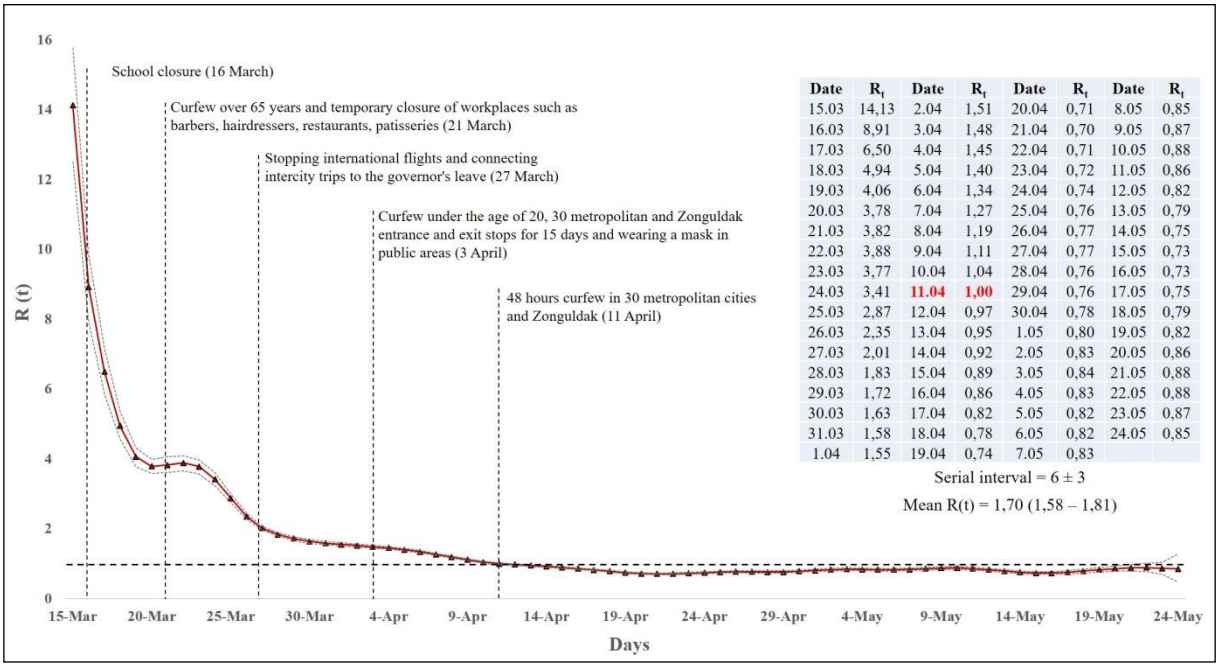
FIGURE 1: Illustration of infection timeline and serial interval of coronavirus disease-2019.

STATISTICAL ANALYSIS

To calculate the COVID-19 RN in the late phase (March 15-May 25, 2020) of the pandemic at a 95% confidence interval, we utilized the "R0" (Version 1.2-6) library in the R studio package.[15] The TD model was utilized for the Rt estimation. In line with the literature, gamma distribution was utilized for SI (with means and standard deviation) estimation (generation.time function in the R0 library). For all the Rt confidence interval estimations, 1000 bootstrap, one of the resampling techniques, was utilized.[3,10,13,22] The R studio software (Version 1.2.5042) was utilized for all the statistical analyses. The study followed the principles of the Declarations of Helsinki 2013.

RESULTS

TD RN estimates were obtained by using the number of cases between 15 March and 25 May using 3 different serial intervals. Figure 2 demonstrates the TD RN values calculated for the 6±3 SI value. The Rt value which was calculated as 14.13 (12.50-15.75) for the 6±3 SI value on the 15th of March, was found to decrease to the value of 1 (0.97-1.02) on the 11th of April and less than 1 on the 12th of April. The Rt value was calculated as 0.85 (0.47-1.27) for the 24th of May. In addition, mean Rt was found as 1.70 (1.58-1.81) for Turkey using the 6±3 serial interval.



Date	R_t	Date	R_t	Date	R_t	Date	R_t
15.03	14,13	2.04	1,51	20.04	0,71	8.05	0,85
16.03	8,91	3.04	1,48	21.04	0,70	9.05	0,87
17.03	6,50	4.04	1,45	22.04	0,71	10.05	0,88
18.03	4,94	5.04	1,40	23.04	0,72	11.05	0,86
19.03	4,06	6.04	1,34	24.04	0,74	12.05	0,82
20.03	3,78	7.04	1,27	25.04	0,76	13.05	0,79
21.03	3,82	8.04	1,19	26.04	0,77	14.05	0,75
22.03	3,88	9.04	1,11	27.04	0,77	15.05	0,73
23.03	3,77	10.04	1,04	28.04	0,76	16.05	0,73
24.03	3,41	**11.04**	**1,00**	29.04	0,76	17.05	0,75
25.03	2,87	12.04	0,97	30.04	0,78	18.05	0,79
26.03	2,35	13.04	0,95	1.05	0,80	19.05	0,82
27.03	2,01	14.04	0,92	2.05	0,83	20.05	0,86
28.03	1,83	15.04	0,89	3.05	0,84	21.05	0,88
29.03	1,72	16.04	0,86	4.05	0,83	22.05	0,88
30.03	1,63	17.04	0,82	5.05	0,82	23.05	0,87
31.03	1,58	18.04	0,78	6.05	0,82	24.05	0,85
1.04	1,55	19.04	0,74	7.05	0,83		

FIGURE 2: The time dependent reproduction number using 6±3 serial interval value for coronavirus disease-2019.

Figure 3 demonstrates the outbreak curve modeling calculated using 3 different serial intervals for the TD reproduction number.

Figure 4 demonstrates the TD RN values calculated for the 8±3.6 serial interval. The Rt value which was calculated as 22.46 (20.42-24.75) for the 8±3.6 SI value on the 15th of March, was found to decrease less than the value of 1 [0.99 (0.96-1.01)] on 11th of April. The Rt value was calculated as 0.76 (0.00-1.79) for the 24th of May. In addition, the Rt mean for Turkey was found as 2.06 (1.92-2.21) by using the 8±3.6 SI value.

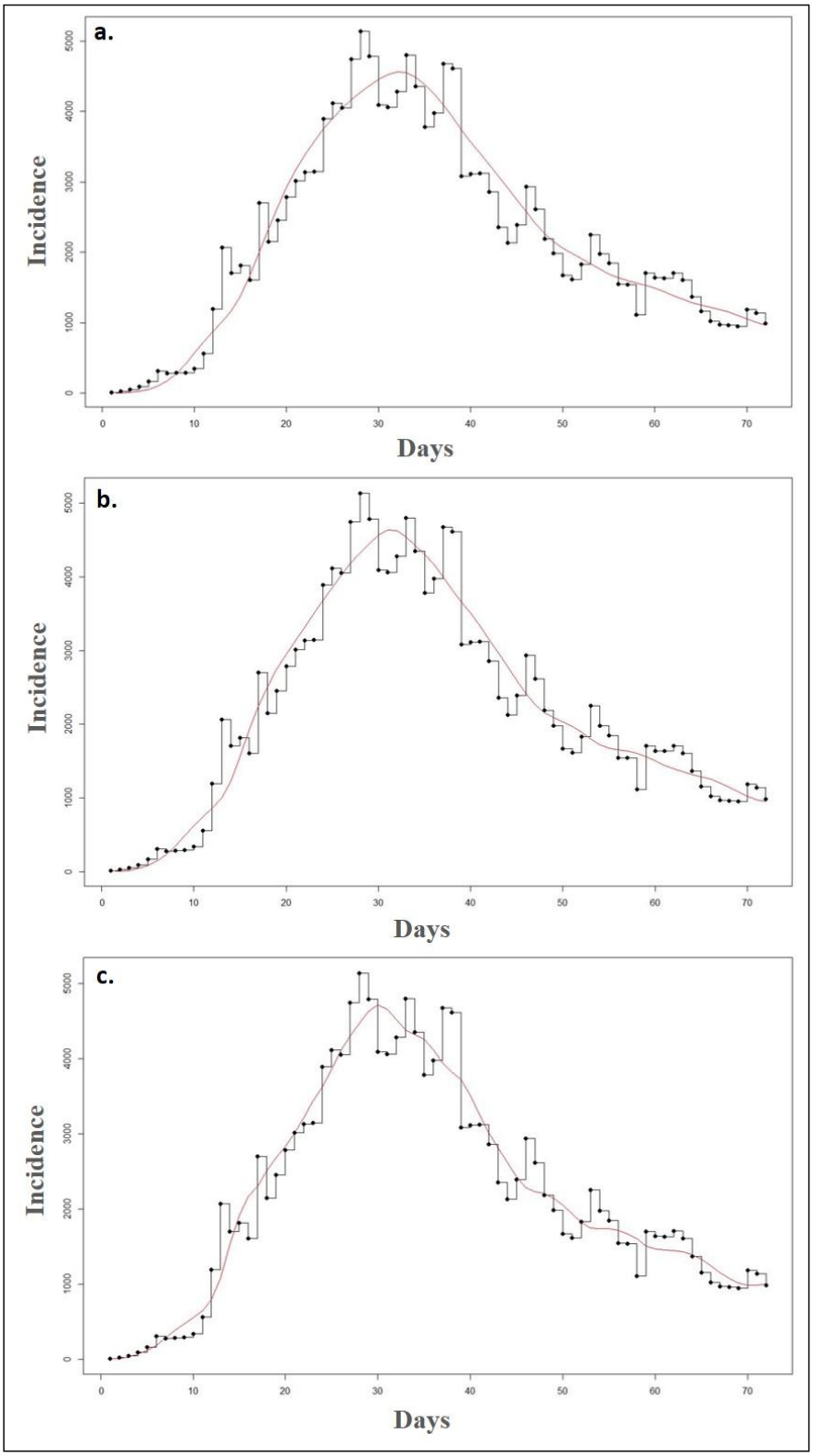
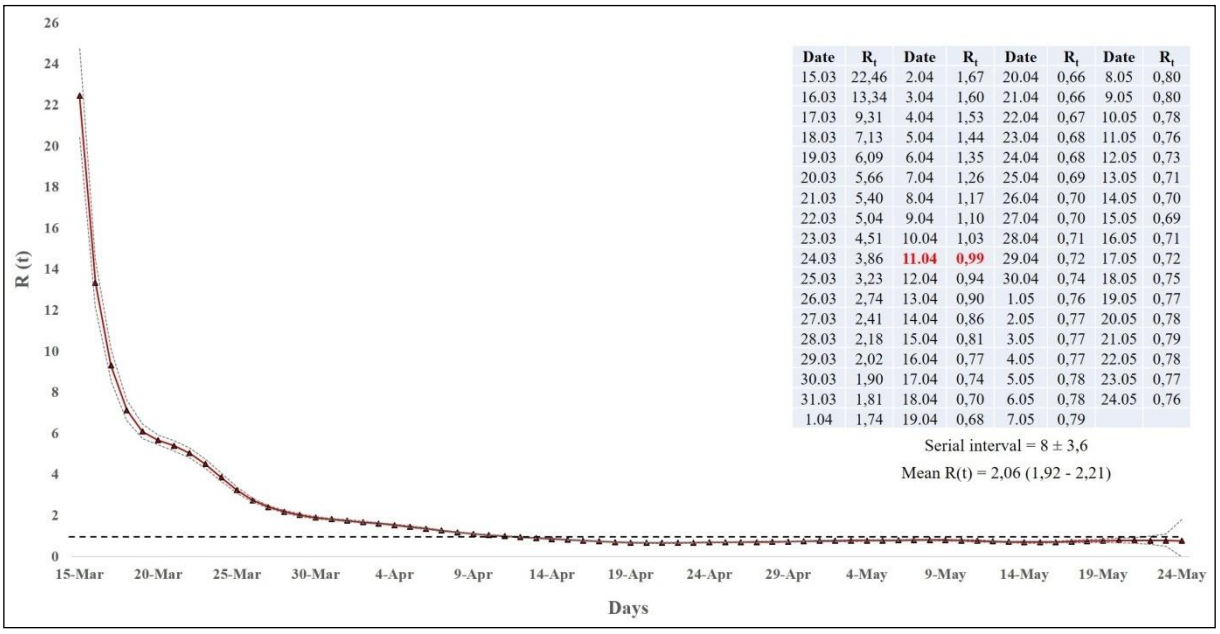


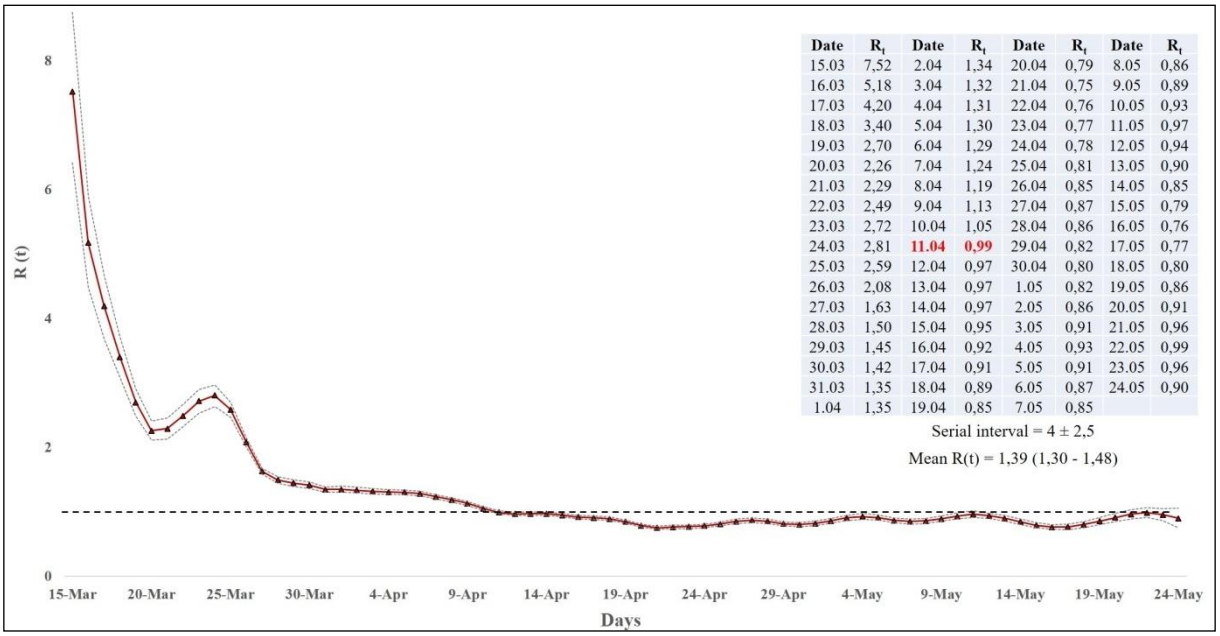
FIGURE 3: a) Outbreak curve modeling for time dependent reproduction number calculated using the 8±3.6 serial interval value. **b)** Outbreak curve modeling for time dependent reproduction number calculated using the 6±3 serial interval value. **c)** Outbreak curve modeling for time dependent reproduction number calculated using the 4±2.5 serial interval value.



Date	R_t	Date	R_t	Date	R_t	Date	R_t
15.03	22,46	2.04	1,67	20.04	0,66	8.05	0,80
16.03	13,34	3.04	1,60	21.04	0,66	9.05	0,80
17.03	9,31	4.04	1,53	22.04	0,67	10.05	0,78
18.03	7,13	5.04	1,44	23.04	0,68	11.05	0,76
19.03	6,09	6.04	1,35	24.04	0,68	12.05	0,73
20.03	5,66	7.04	1,26	25.04	0,69	13.05	0,71
21.03	5,40	8.04	1,17	26.04	0,70	14.05	0,70
22.03	5,04	9.04	1,10	27.04	0,70	15.05	0,69
23.03	4,51	10.04	1,03	28.04	0,71	16.05	0,71
24.03	3,86	**11.04**	**0,99**	29.04	0,72	17.05	0,72
25.03	3,23	12.04	0,94	30.04	0,74	18.05	0,75
26.03	2,74	13.04	0,90	1.05	0,76	19.05	0,77
27.03	2,41	14.04	0,86	2.05	0,77	20.05	0,78
28.03	2,18	15.04	0,81	3.05	0,77	21.05	0,79
29.03	2,02	16.04	0,77	4.05	0,77	22.05	0,78
30.03	1,90	17.04	0,74	5.05	0,78	23.05	0,77
31.03	1,81	18.04	0,70	6.05	0,78	24.05	0,76
1.04	1,74	19.04	0,68	7.05	0,79		

FIGURE 4: The time dependent reproduction number using 8±3.6 serial interval value for coronavirus disease-2019.

Figure 5 demonstrates the TD RN values calculated for the 4±2.5 serial interval. The Rt value which was calculated as 7.52 (6.42-8.75) for the 4±2.5 SI value on the 15th of March, was found to decrease to the value of less than 1 [0.99 (0.97-1.02)] for the first time on 11th of April. The Rt value was calculated as 0.90 (0.76-1.06) for the 24th of May. Besides, the Rt mean was found as 1.39 (1.30-1.48) for Turkey using the 4±2.5 serial interval.



Date	R_t	Date	R_t	Date	R_t	Date	R_t
15.03	7,52	2.04	1,34	20.04	0,79	8.05	0,86
16.03	5,18	3.04	1,32	21.04	0,75	9.05	0,89
17.03	4,20	4.04	1,31	22.04	0,76	10.05	0,93
18.03	3,40	5.04	1,30	23.04	0,77	11.05	0,97
19.03	2,70	6.04	1,29	24.04	0,78	12.05	0,94
20.03	2,26	7.04	1,24	25.04	0,81	13.05	0,90
21.03	2,29	8.04	1,19	26.04	0,85	14.05	0,85
22.03	2,49	9.04	1,13	27.04	0,87	15.05	0,79
23.03	2,72	10.04	1,05	28.04	0,86	16.05	0,76
24.03	2,81	**11.04**	**0,99**	29.04	0,82	17.05	0,77
25.03	2,59	12.04	0,97	30.04	0,80	18.05	0,80
26.03	2,08	13.04	0,97	1.05	0,82	19.05	0,86
27.03	1,63	14.04	0,97	2.05	0,86	20.05	0,91
28.03	1,50	15.04	0,95	3.05	0,91	21.05	0,96
29.03	1,45	16.04	0,92	4.05	0,93	22.05	0,99
30.03	1,42	17.04	0,91	5.05	0,91	23.05	0,96
31.03	1,35	18.04	0,89	6.05	0,87	24.05	0,90
1.04	1,35	19.04	0,85	7.05	0,85		

FIGURE 5: The time dependent reproduction number using 4±2.5 serial interval value for coronavirus disease-2019.

DISCUSSION

A confidence intervals of the RN values calculated using the TD Model for Turkey and 3 different serial intervals were calculated between 1.30 (lowest) and 2.21 (highest).

Yuan et al. calculated the Rt values for some European countries using the TD model with a 5.8±2.6 serial interval. These values were calculated as 3.10 (2.21-4.11) for Italy, 6.56 (2.04-12.26) for France, 4.43 (1.83-7.92) for Germany, and 3.95 (0-10.19) for Spain from February 20, 2020 to March 9, 2020.[11] In the present study, the Rt mean for a similar SI was found as 1.70 (1.58-1.81) for Turkey. When the RN values were compared with the results of the present study, it could be possible to say that the RN value of the pandemic in Turkey was lower than that of the values calculated for the European countries.

Using the TD model and the mean serial intervals of SARS and MERS (8.0±3.6), Deb et al. reported values of 2.60 for China, 1.42 for India, 2.60 for Iran, 3.00 for Italy, 2.14 for South Korea, 10.37 for the US from January 22, 2020 to March 21, 2020.[14] As for the present study, the Rt mean for the same SI was found as 2.06 (1.92-2.21). When the values we calculated were compared with the results of the present study, the RN value of the outbreak was lower than that of China, Iran, Italy, South Korea, and the US.

Using the TD model with the 4.8±2.3 serial interval, Sau et al. found the Rt mean as 0.5 for China, 2.5 for Italy, 1.5 for Iran, 0.46 for South Korea, 3.5 for Spain, 3.8 for Germany, 2.6 for France, 2.5 for the USA, 2.2 for Switzerland, 2.8 for England, 2.4 for Norway, and 2.1 for Sweden.[6] Rt mean using a similar SI was found 1.39 (1.30-1.48) for Turkey.

The present study also found the RN value of Turkey lower than that of Europe, the USA, and Iran and higher than that of China and South Korea.

SI values used were not indicated in some studies. Using the TD value, Wang et al. calculated the Rt value as 3.61 (3.52-3.70) for China.[9] Flaxman et al. found the Rt values as 0.97 (0.14-2.14) and 2.64 (1.40-4.18) for Norway and Sweden respectively.[13]

RN values calculated for the same country may demonstrate differences according to different methods used in R0 or Rt estimations, different serial intervals, and different time periods. Although RN is a valuable variable for estimating the spread potential and severity of a virus, it is affected by some important cases such as the number of cases transmitted from asymptomatic transmitters, the number of cases from outsiders, and the sensitivity of the polymerase chain reaction used for coronavirus diagnosis. A limitation of this study is that the positive cases transmitted from outside could not be reached and thus were not included in the modeling in the calculation. In addition, since the number of cases based on age and gender information was not shared in our country, comparisons could not be made on this issue.

Ridenhour et al. reported that RN could demonstrate changes depending on geographical factors due to the "environment, population structure, viral evolution, and changes in the immunity".[24] However, different RN values calculated in some European countries having similar geographical conditions such as Germany and France indicate the effects of the precautions taken by the governments.

In this study, the number of future infected patients was not estimated, only the TD RN (Rt) were calculated based on the daily number of cases described. This may be a limitation for our study. However, the RN is used to compare the transmission rate of viruses that cause more epidemics. By using the RN we obtained in this study, new epidemiological models [SIR (Susceptible, Infectious, Recovered) or SEIR] can be created to estimate future patient numbers in other studies.

CONCLUSION

In conclusion, according to the TD model results, from the first day when the pandemic started in Turkey to the 32nd (11th of April 2020) and 33rd (12th of April 2020) days, the Rt value decreased below 1 and the outbreak started to demonstrate a breaking point. Using 8±3.6, 6±3 and 4±2.5 SI values, the mean Rt calculated

for Turkey with the TD model was 2.06 (1.92-2.21), 1.70 (1.58-1.81), and 1.39 (1.30-1.48) respectively. These results show that the Rt values obtained for the outbreak in Turkey were lower than the values reported in the literature for China, the USA, and the majority of the European countries. Lower Rt in Turkey indicates than the other countries' experiences early on have been successfully evaluated by Turkey in determining the pandemic management measures to be taken in a more timely fashion many other countries such as closing schools and universities, social distancing rules, making wearing masks in closed areas compulsory, and partial curfews for citizens aged below 20 and 65 and over. This pushed the onset of the outbreak in Turkey to a much later date in Turkey than many other countries.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *S. Kenan Köse, Emre Demir;* ***Design:*** *S. Kenan Köse, Emre Demir;* ***Control/Supervision:*** *S. Kenan Köse, Emre Demir;* ***Data Collection and/or Processing:*** *S. Kenan Köse, Emre Demir, Gülçin Aydoğdu;* ***Analysis and/or Interpretation:*** *S. Kenan Köse, Emre Demir, Gülçin Aydoğdu;* ***Literature Review:*** *S. Kenan Köse, Emre Demir, Gülçin Aydoğdu;* ***Writing The Article:*** *Emre Demir, S. Kenan Köse, Gülçin Aydoğdu;* ***Critical Review:*** *S. Kenan Köse, Emre Demir.*

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