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Country Differences in Lenght of Stay in Intensive-Care Unit of Severe COVID-19 Patients During the Pandemic: A Retrospective Descriptive Research

COVID-19 Pandemisinde, Ağır Hastaların Yoğun Bakımda Kalma Sürelerinin Ülkeler Arasındaki Farklılıkları: Retrospektif Tanımlayıcı Araştırma

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ABSTRACT Objective: Health systems of countries face various challenges during epidemics and pandemics. Countries differ in hospital admission of coronavirus disease-2019 (COVID-19) patients and the treatment procedures followed. The aim of this study is to reveal the relation between the number of critical COVID-19 patients (CP) and the mortality rate [death number (DN)] as well as the country differences in patients' length of stay in intensive-care unit (ICU). **Material and Methods:** The research is a retrospective type, analyzed with a time series model. The 7 countries with the highest number of ICU beds (Türkiye, USA, UK, France, Spain, Italy and Germany) were included in the study. The 6-month period (1 August 2020-31 January 2021) has been analyzed. Koyck model has been used to measure the lagged impact of CP on DN. **Results:** The country with the highest positive correlation rate between the number of CP and DN is Spain. Almost all of the COVID-19 deaths in Türkiye are among severe COVID-19 patients who stayed in ICU. Results display that there is a strong relation between CP and DN in Türkiye, Spain and Italy. The death rate per million people, Türkiye has the lowest DN. It has also been seen that the period needed for the changes in the number of CP to have a dramatic effect on DN is the shortest in the UK and longest in Türkiye. **Conclusion:** Although CoV infects a small part of billions of people, there will be many critically ill patients in need of ICU, so countries must already take precautions against possible future waves of the pandemic and prepare their health systems in advance.

Keywords: COVID-19; intensive care unit; death

ÖZET Amaç: Ülkelerin sağlık sistemleri, salgın hastalıklar sırasında çeşitli zorluklarla karşı karşıyadır. Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] hastalarının hastaneler tarafından kabulü ve uygulanan tedavi prosedürleri ülkeler arasında farklılıklar göstermektedir. Araştırmanın amacı, COVID-19 pandemi sürecinde ağır hasta [critical patient (CP)] sayıları ile vefat sayıları [death number (DN)] arasındaki ilişkiyi ve değişik ülkelerdeki hastaların yoğun bakım ünitesine [intensive-care unit (ICU)] bağlı geçen sürelerindeki farklılıkları ortaya koymaktır. **Gereç ve Yöntemler:** Araştırma retrospektif tipte, zaman serisi analizi yapılmış bir çalışmadır. ICU yatak sayısı en yüksek olan 7 ülke (Türkiye, ABD, İngiltere, Fransa, İspanya, İtalya ve Almanya) araştırmaya dâhil edilmiştir. Altı aylık dönem (1 Ağustos 2020-31 Ocak 2021) analiz edilmiştir. Koyck modeli, CP'nin DN üzerindeki gecikmeli etkisini ölçmek için kullanılmıştır. **Bulgular:** CP sayısının, ölüm oranları üzerindeki pozitif etkisinin en yüksek olduğu ülke İspanya'dır. Türkiye'de COVID-19'a bağlı ölümlerin neredeyse tamamı ICU hastalarından kaynaklanmaktadır. Sonuçlar; Türkiye, İspanya ve İtalya'da CP ve DN arasında güçlü bir ilişki olduğunu göstermektedir. Milyon kişi başına ölüm oranlarında, Türkiye en düşük ölüm oranlarına sahiptir. CP sayılarında meydana gelen değişimin, DN'leri önemli ölçüde etkilemesi (dramatically effect) için geçmesi gereken sürenin en kısa olduğu ülke İngiltere ve en uzun olduğu ülke Türkiye olarak tespit edilmiştir. **Sonuç:** CoV milyarlarca insandan az bir kısmını enfekte etse de ICU'ya muhtaç durumda birçok kritik hasta olacağından, ülkeler sağlık sistemlerinde pandemilerin muhtemel diğer dalgalarına karşı gerekli önlemleri şimdiden almalı ve kendilerini hazırlamalıdırlar.

Anahtar Kelimeler: COVID-19; yoğun bakım ünitesi; ölüm

The syptoms of COVID-19 are described as mild, moderate and severe. Asypmtomatic cases, mild cases, cases with no pneumonia or mild pneumonia and patients under 50 with no underlying medical conditions can be treated as outpatients by being informed about the progression of the disease and

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home isolation procedures.[1] On the other hand, intensive care treatment is required for the patients with higher risk of developing more serious complications and the ones in need of support.

According to Turkish Republic Ministry of Health guidelines, the patients showing the symptoms listed below or the ones identified through anamnesis are considered as severe or intensive care COVID-19 patients. Some of the complications required for the admission to intensive-care unit (ICU) are respiratory rate ≥30, signs of dyspnea or respiratory distress, bilateral infiltrations or multilobar involvement on chest radiography, hypotension, renal-liver function test disorders, presence of an immunosuppressive disease and arrhythmia.[2]

Pandemics tend to have a higher mortality rate among the elderly although they are more common (morbidity) in young individuals.[3] Epidemics require a multidisciplinary approach to patient care. Intensive care workers and units play a significant role in the treatment of severe cases.[4] During COVID-19 pandemics, problems have been observed in the provision of healthcare service even in the countries with high ICU capacity. In the study, the correlation between the mortality rate [death number (DN)] and the number of critical patients (CP) with the highest probability of death during the pandemics has been examined with the delayed Koyck model and the differences in the length of ICU stay in various countries have been revealed.

MATERIAL AND METHODS

Mortality is connected to the health resources of countries. However, invasive ventilator and ICU are insufficient in the treatment of critically-ill and severe patients.[5] With the outbreak of COVID-19, demand for ICU has increased worldwide. The success in the treatment of severe patients will reduce mortality and the negative effects of the epidemic on the society. For this research; ethics committee approval was obtained from Süleyman Demirel University, with the decision of meeting number 112 on October 14, 2021. The research is a retrospective type, analyzed with a time series model. The study was conducted according to the guidelines laid down in the Declaration of Helsinki.

It has been observed that there are not enough studies on the admission of COVID-19 patients to ICU and whether the procedures followed in the treatments applied influence the survival of the patients or their lenght of stay in ICU. 7 most affected countries by the pandemic (Türkiye, USA, UK, French, Spain, Italy and Germany) with the highest ICU bed numbers have been included in the scope of the study.[6-12] The data used in the emprical analysis have been obtained from daily reports announced by the Ministry of Health of these countries. Koyck model was used to measure the lagged impact of CP on DN. CP was taken as the dependent variable and DN was taken as independent variable in the study. The correlation between CP and DN caused by COVID-19 in these countries included in the sample group has been analyzed by using the distributed lagged model (DLM). Republic of Türkiye Ministry of Health has started to announce the number of CP as of July 29, 2020. For this reason, the research period has been determined as a 6-month period between August 1, 2020 and January 31, 2021.

Model predictions were made using the dLagM package in R 4.0.3 program.[13] Initially, Rolling correlations and their standard deviation values were calculated in order to test the validity of the relationship between the series. Next, Koyck model, one of the DLMs, was used to specify the reflection time of the changes in CP numbers on DN. As for the limitations of the study, accepting the information shared by the Ministries of Health of the countries whose data were used as accurate and inclusion of seven countries in the study can be given.

RESULTS

Firstly, the Rolling correlation method was used to be able to measure the strenght of the correlation between CP and DN by considering the tendency in CP. Rolling correlation coefficients depend on how data and width are determined and different coefficients are calculated at intervals specified based on various criteria. The tendency between two variables was tried to be determined by calculating the Rolling correlation coefficients with 1, 2, 3 and 4 week intervals.

Rolling correlations in T level can be calculated as follows by assuming A and B are N-dimensional vectors and A represents the number of CP and B represents DN:

$$RC_T\,(t) = \text{Corr}\,[\mathbf{A}\,(t, t+T), \mathbf{B}\,(t, t+T)] \quad (1)$$

In the equation number (1), *t* shows time while Corr shows the correlation coefficient. *t* series consist of observations that continue at one-day intervals from *t=1* to N. *T* indicates the length of subsets. Besides this, the performance of time series depends on to what extent the real world dynamics are embedded in noisy, short and non-stationary observations.[14] Variability may arise if the rolling correlation coefficients between two time series are calculated at low frequencies. While working with short and low time series, there is a risk that white noises might be regarded as signals.[15] While signal includes data, noise doesn't. Therefore, a method based on the standard deviations of Gershunov et al., rolling correlations was used to distinguish signal from noise. In this method, after the calculation of standard errors for each combination of running window width and population correlation coefficients obtained by Monte Carlo simulation, running correlations were compared according to the 95th and 5th percentiles of these standard errors (Table 1).[15]

Rolling correlation standard deviation values are outside the limits, except for the width 7 in France. Accordingly, the signal between CP and DN is valid at 7, 14, 21 and 28 lengths and Rolling correlations display a valid relation. As for France, this situation is valid for wider lengths such as 21 and 28. According to the Pearson correlation coefficients between CP and DN, a strong and positive correlation is observed between two variables in all countries. The strongest positive and linear relationship is in Italy while the weakest is in the USA. Besides, correlation coefficients show a strong relationship between CP and DN in countries. The Rolling correlation coefficients between CP and DN are shown in Figure 1.

In Figure 1, the horizontal straight line shows the average of the Rolling correlation coefficients and the dashed red lines show the boundaries of the 95% confidence interval of Rolling correlation coefficients. Moreover, there are also rolling correlation coefficients for 7, 14, 21 and 28 width of days. In all countries, it is observed that as width increases rolling correlation coefficients decrease. A higher variability is seen in the 7-day relationship level. In France, it is seen that the correlation between CP and DN is weakened except for the second wave period when the cases intensify. The correlation between CP and DN increases in a positive direction especially when the case trends start to rise in the second wave period in Türkiye and Italy. Secondly, in the study, the correlation between CP and DN is examined with the Koyck model by taking the lagged effects into account.

DLM observes not only the current period value of the changes that variables display but also the previous period values of explanatory variable. Based on this, if how many periods to go back in time for the explanatory variable has been defined, equation is called finite distributed lag model.

$$y_t = \alpha + \beta_0 x_t + \beta_1 x_{t-1} + \cdots + \beta_k x_{(t-k)} + \varepsilon_t,\ t = k+1, \ldots, T$$

$$= \alpha + \sum_{i=0}^{k} (\beta_i x_{t-i} + \varepsilon_t \quad (2)$$

Where ε_t *IN* (σ_ε^2). In the equation (2), β_i coefficients are called lag weights. The Koyck approach assumes that lag weights decrease geometrically towards the past ($\beta_i = \beta_0 \varphi^k$). There might be multicollinearity problem between the independent variables due to the fact that the lags of the same independent variable are included in the model and lagging observations are correlated. Besides, the lag lenght (*k*) is unknown. Even if (*k*) is known, if this number is too large and the sample size is too small, the parametres cannot be predicted because of the degree of freedom. The Koyck transformation is an effective way to address these disadvantages. The Koyck transformation of DLM is as belows:

$$y_t = \alpha + \beta_0\,(x_t + \varphi x_{t-1} + \varphi^2 x_{t-2} + \cdots + \varphi^k x_{t-k}) + \varepsilon_t$$

$$y_t = \alpha(1-\varphi) + \varphi y_{t-1} + \beta_0 x_t + (\varepsilon_t - \varphi\varepsilon_{t-1})$$

$$y_t = \alpha(1-\varphi) + \varphi y_{t-1} + \beta_0 x_t + \omega_t$$

In equation (3), a finite DLM model is obtained afer Koyck transformation. In the model, $(0<\varphi<1)$ is the rate of decrease of distributed lag.

The closer φ coefficient is to 1, the more decrease in β_i is observed.[16] With Koyck model, measurements can be obtained to see when the changes in the independent variable will have a significant effect on the dependent variable. These measurements are mean lag or median lag numbers.

$$\text{Mean lag number} = \frac{\varphi}{1-\varphi}$$

$$\text{Median lag number} = \frac{-\log(2)}{\log(\varphi)}$$

Mean lag number refers to the time required for a one unit change in variable x to have a detectable effect on dependent variable y. Median lag number shows how many periods after a one-unit change in x variable will cause half of the total change in y variable. A period lag of the dependent variable (y_{t-1}) is connected to error term (ω_t) and since error term is connected to (ω_t), (ε_t) ve (ε_{t-1}) components, the parametres in dLagM package can be estimated with instrumental variables approach.

The results of the Koyck model which analyzes the relationship between the number of CP and deaths of countries with geometric DLM are shown in Table 2. The Wu-Hausman test, which compares consistancy of instrumental variables with ordinary least-squares estimates, offers a way to test the significance of the correlation between the error term and the dependent variable.

TABLE 1: Pearson correlations and 95th and 5th percentiles of the standard deviation of running correlations.

Country	Pearson Correlation	Width	Standart deviation of runnig correlation	95th	5th
USA	0.821	7	0.472	0.242	0.107
		14	0.261	0.148	0.057
		21	0.199	0.105	0.037
		28	0.177	0.085	0.026
Germany	0.843	7	0.448	0.241	0.097
		14	0.293	0.128	0.051
		21	0.283	0.095	0.034
		28	0.281	0.079	0.023
France	0.829	*7*	*0.131*	*0.244*	*0.107*
		14	*0.124*	*0.139*	*0.054*
		21	0.131	0.104	0.036
		28	0.136	0.081	0.025
UK	0.892	7	0.499	0.194	0.067
		14	0.329	0.092	0.034
		31	0.314	0.066	0.024
		28	0.311	0.055	0.016
Spain	0.857	7	0.307	0.233	0.088
		14	0.210	0.117	0.044
		21	0.229	0.087	0.028
		28	0.250	0.068	0.021
Italy	0.957	7	0.496	0.089	0.028
		14	0.407	0.039	0.014
		21	0.337	0.027	0.009
		28	0.331	0.023	0.007
Türkiye	0.906	7	0.496	0.167	0.058
		14	0.455	0.087	0.031
		21	0.421	0.064	0.021
		28	0.371	0.048	0.015

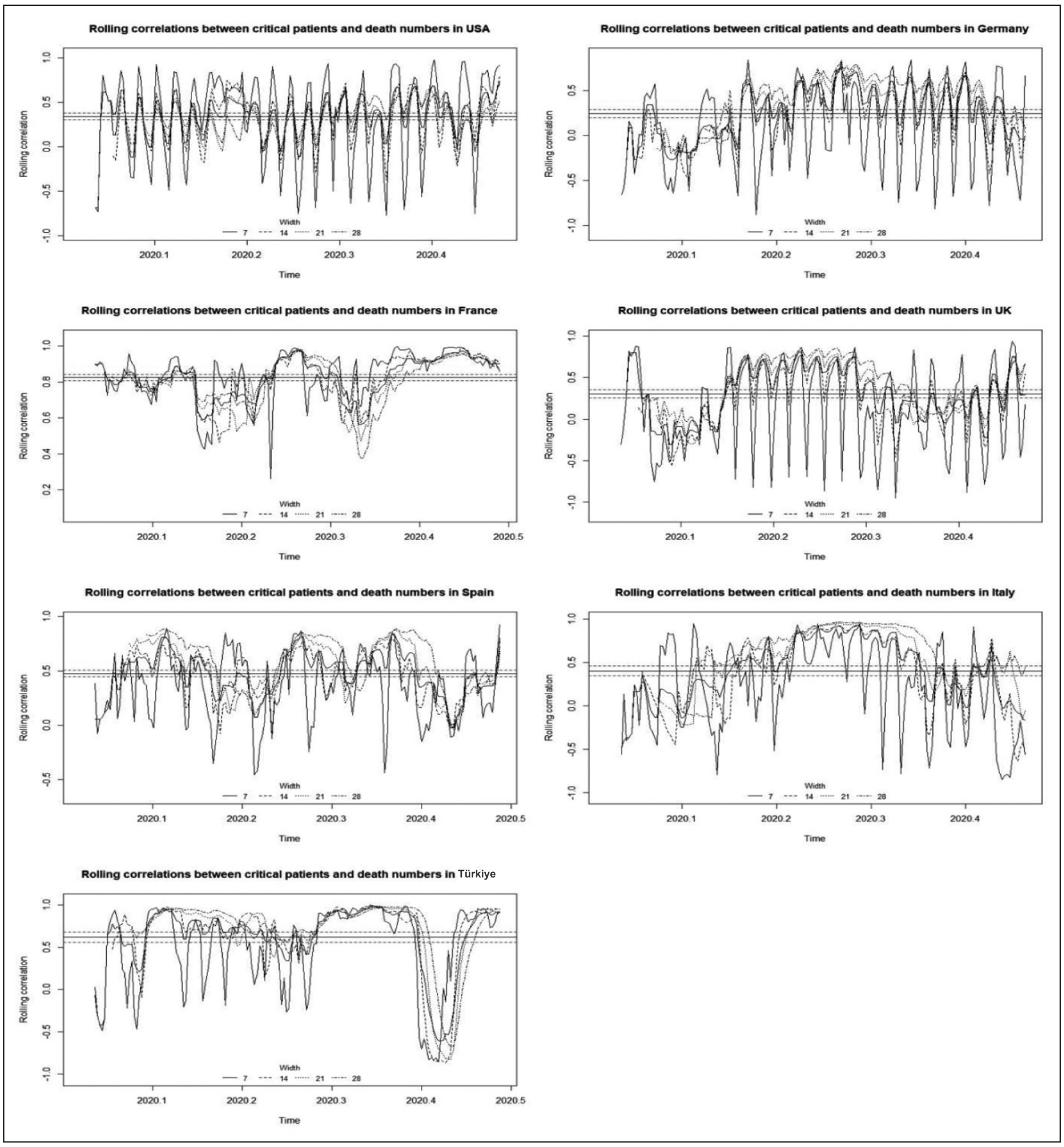

FIGURE 1: Rolling correlations between critical patients and death number in countries.

TABLE 2: The results of Koyck Model for critical patients and death number.

	USA	Germany	France	UK	Spain	Italy	Türkiye
ϕ	0.530	0.608*	0.846**	0.371*	0.753*	0.357*	0.934*
β_θ	0.085*	0.046*	0.042*	0.212*	0.691*	0.125*	0.003*
Wald Test	262*	363.2*	288.5*	377.9*	1148*	1048*	2277*
R^2	0.763	0.820	0.776	0.823	0.932	0.929	0.996
Weak Instruments	661109.45*	11506330*	242.74*	266013.7*	125.274*	10647.4*	350975.5*
Durbin-h	0.861	0.721	0.212	1.186	-0.312	0.191	0.067
Mean Lag Number	1.128	1.551	5.535	0.591	3.050	0.557	14.164
Median Lag Number	1.092	1.393	4.173	0.700	2.444	0.674	10.160

Notes: *and** shows signifinance at the level of 0.01 and 0.05 respectively. Weak instrument is an F test of first stage regression for weak instruments. Wu -Hausman test measures endogeneity caused by the relation between error term and explanatory variable. Durbin-h tests null hypothesis of no serial correlation in AR models.

If there is endogeneity, it is concluded that the instrumental variable estimator is consistent while the ordinary least-squares estimator is inconsistent. According to the Wu-Hausman test results shown in Table 2, it can be said that there is a significant endogeneity bias in the equations of all countries. Therefore, instrumental variable approach was used in the estimations of equations. The Durbin-h test, which analyzes serial correlation in autoregressive models, has a standard normal distribution. If the test values are among ±1.96 values, null hypothesis cannot be disregarded. Accordingly, there is no serial correlation problem in any models φ and β_0 parametres belonging to each country are positively and statistically significant. The country with the highest positive effect of CP number on DN is Spain. In this country, when a one-unit increase in CP numbers occurs, an increase of 0.691 units in DN is observed. The countries with the highest multiple determination coefficients are, respectively, Türkiye, Spain and Italy. The 99.6% of the changes in DNs can be explained with CP numbers. Although the results display that there is a strong correlation between CP and DN in Türkiye, Spain and Italy, they don't give information about the reasons behind higher DN than that of other countries and the drawbacks of health services. On the other hand, when compared to DNs per million, it is clear that Türkiye has the lowest DN (Figure 2).

Mean lag number and median lag number coefficients provide information on treatment procedures of the countries for CP, the effectiveness of health services on these patients and the duration of keeping patients' alive. Mean lag number displays the time required for the changes in the number CP to dramatically affect the number of deaths. The country with the shortest time is the UK and the one with the longest time is Türkiye. Median lag number shows how many periods after a one-unit change in the number of CP will make half of the total change in DN. According to median lag number values, the shortest time is seen in the UK and the longest time is seen in Türkiye.

The time required for the changes in the number of CP treated in ICU due to COVID-19 to have a significant effect on DN is 14.164 days while that is 0.557 days in Italy. In other words, 93.4% of the changes in DN in Türkiye take place in 14.164 days. After Türkiye, the countries with the longest time needed for an effect are France (5.535 days), and Spain (3.050 days). For Germany (1.551 days) and the USA (1.128 days), the time needed for the changes in the number of CP to have an effect on the mortality rate is a little more than one day while it is less than one day in Italy and the UK.

According to Median lag number values, the time needed for a shocking change in the number of CP to make changes in the DN by half is the longest in Türkiye. The country with the shortest period (0.674 days) is the UK, while Türkiye is 10.160 days. After Türkiye, the countries with the longest time are France (5.535 days) and Spain (2.44 days). For Germany (1.393 days) and USA (1.092 days), this time is over one day while that is less than one day in Italy and UK.

Figure 3 shows the distribution graph between the mean lag number and the number of deaths per million people. Türkiye is the country where the death rate per million is the lowest and the time of increase in the rate of CP' turning into mortality is the longest. France is the second country with the longest time of keeping CP alive in ICU although the death rate per millon is high. Although Germany is the second country with the lowest death rate per million, the changes in the number of serious patients in this country are reflected on the death figures in a very short period like 1.551 days. The USA, Italy and the UK are the countries with the highest DN per million people. In these countries, the time required for the shocking changes in the number CP to have a significant effect on the mortality is less than one day.

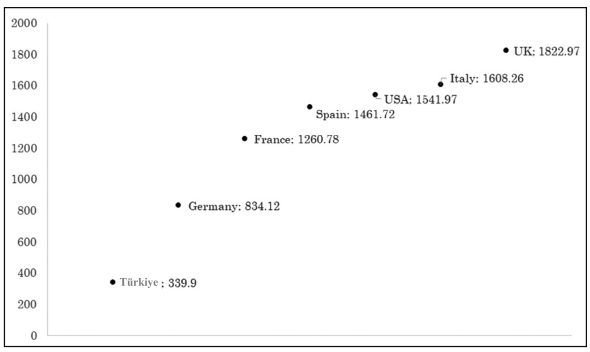

FIGURE 2: Death number per million by country as of February 2021.[17]

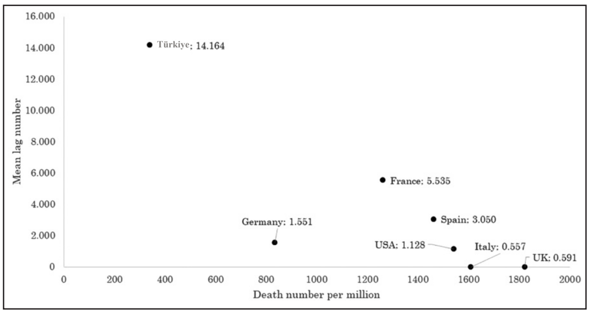

FIGURE 3: Scatter plot between mean lag number and death numbers per million.

DISCUSSION

Health systems try to meet the demands with a limited number of intensive care beds during pandemics period. Healthcare practitioners must follow clinical and experimental studies and scientific literature every day and benefit from the experiences of outbreak-related clinicians in the other parts of the world while striving to respond to the growing demand.[4] Mortality rate varies by country and conditions. Some studies conducted in different countries and their results are given below.

In the study conducted based on the data published by Chinese Centre for Disease Control and Prevention until February 2020, the case and mortality rate in ICU was reported as 49%.[18]

9-11% of all positive cases infected between 1-11 March 2020 in Italy were taken into ICU.[19] It was seen that more than 0.15% of the local people died in the first wave of the COVID-19 outbreak. It was understood that official statistics underreported the number of deaths by approximately 60%.[20] February-April 2020, 12 deaths per 1,000 patient days were found in another study, which surveyed patients in intensive care in the Lombardy region of Italy.[21]

In the study conducted by Püschel and Sperhake; it has been demonstrated that Germany took the necessary measures on time to slow the spread of the virus and they didn't face any problems in occupancy rates in ICU services.[22] However, the results obtained from our study, where the data until 2021 were processed, revealed that in Germany the changes in the number of ICU CPs were reflected on the DN in a very short time such as 1.358.

In another study conducted by Bravata et al., it was found that the COVID-19 patients treated in ICUs during the periods of the highest demand for intensive care had an approximately twice more risk of death compared to those treated in periods of low demand.[23] It is concluded that the changes in the mortality of ICU patients during the periods of high demand is related to ICU capacities of the countries and the coordination of healthcare professionals.

In the study conducted on 146 polymerase chain reaction+ adult patients (average age is 77) with severe respiratory failure in a hospital in Paris, examination was carried out for the period of March-April 2020. It was found that 11.7% of the patients were transferred to ICU, and 21.9% died at the end of the 14th day.[24] It was found that mortality was broadly consistent across the world in continental subgroup analysis in Asia, Europe and North America. While the reported fatalities were over 50% in March 2020, that rate approached to 40% at the end of May 2020. As a result of systematic review and meta-analysis of ICU results in COVID-19 patients, the mortality rate in ICU was found to be 41.6% in international studies.[25]

In another study that sought an answer to the question of whether hospitals have sufficient resources as the COVID-19 epidemic continues, it was found that there was a weak positive correlation between sampled 183 ICU beds for 100,000 people and COVID-19 mortality.[26]

In the studies of Hazard et al.; the length of stay of the patients in the intensive care, treated with or without mechanical vantilation, was evaluated. It was found that for two group, the expected lenght of stay in ICU on the 28th day was 15.05 and 19.62 days while the mechanical ventilation time was 7.97 and 9.85 days.[27] It is thought that examining different treatment procedures applied by countries in ICUs may yield more meaningful results when compared with the success percentages.

Türkiye in the Mediteranean basin, is similar to the densely populated regions such as France, Spain and Italy in terms of the total number of cases.

However, fewer DN were observed in Türkiye than these countries due to the factors such as the excessive number of the young people in the total number of patients who died and high number of ICUs.[28] The findings obtained in this study support this result.

As countries step up their efforts to prevent or delay the spread of COVID-19, the world must be ready for the possibility of failure in deterrence and mitigation initiatives. Healthcare workers must prepare themselves for overwhelming patient fluctuations, and ICU bed capacities should be reviewed.[29]

CONCLUSION

In this study, it was aimed at determining the correlation between CP and DN by using Rolling Correlation and Koyck model. It is thought that a vigilant observation is necessary to monitor its future adaptation, viral evolution, potency to infect, transmissibility and pathogenicity due to the pandemic potential of 2019-new type CoV. The rate of virus transmission and measures vary in countries. For this reason, it can be said that the results of this research will be useful in terms of mutations in other pandemic stages and preparation for a possible 2^{nd} wave.

The number of ICU beds for 100,000 people is 29.4 in the USA, 6.6 in the UK, 9.7 in Spain, 12.5 in Italy, 46.5 in Türkiye, 38.7 in Germany, 11.6 in France. Whether the high number of intensive care beds is effective in low mortality in Türkiye can be discussed in future studies.[30]

Necessary planning should be made for early diagnosis, isolation of patients, administrative processes in emergency and ICU clinics and to prevent the spread of infection. Ministries of Health and hospital administrators must keep their ICU bed capacities at an optimum level. All healthcare professionals, especially those in charge of ICU units, should be prepared for new fluctuations and the risks for aggressive progression.

Countries had better be compared in ICU, CP and DN numbers and the influence of alterations in their treatment procedures on mortality should be discussed. Preventing deaths in other countries should be aimed by taking the countries struggling with the pandemics more successfully as models. For instance, the examination of ICU processes of Türkiye and Spain by other countries and the evaluation of patient treatment steps in different countries by International Scientifc Committees can be recommended by keeping the latest reflection time of number of CP on DN in mind. Since our study is retrospective, it can be suggested to carry out new research that will include more countries with new data when the pandemic processes progress in order to verify these findings.

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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: *Hakan Demirgil, Ramazan Erdem, Oğuzhan Yüksel;* ***Design:*** *Hakan Demirgil;* ***Control/Supervision:*** *Ramazan Erdem;* ***Data Collection and/or Processing:*** *Hakan Demirgil;* ***Analysis and/or Interpretation:*** *Hakan Demirgil, Oğuzhan Yüksel;* ***Literature Review:*** *Oğuzhan Yüksel;* ***Writing the Article:*** *Oğuzhan Yüksel, Hakan Demirgil;* ***Critical Review:*** *Oğuzhan Yüksel, Hakan Demirgil, Ramazan Erdem;* ***References and Fundings:*** *Hakan Demirgil, Oğuzhan Yüksel.*

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