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EURAS Journal of Health (EJOH) is a peer-reviewed international scientific open access periodical published in accordance with independent, unbiased, and double-blind peer-review principles. It publishes two issues per year. The publication language of the journal is English. The journal is the official publication of the Eurasian Universities Union (EURAS).

EJOH aims to contribute to the literature by publishing manuscripts of highest scientific level in all fields of health including medicine with clinical and basic fields, nursing, physiotherapy, audiology, nutrition and dietetics, dentistry, public health, epidemiology, and all relevant disciplines.

SCOPE

The journal targets all healthcare professionals in all health disciplines and publishes original experimental and clinical research articles, case reports, reviews of experts in a specific field, letters to the editors and brief reports on new methods or techniques or preliminary results of original studies. The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

From The Editor

Welcome to the EURAS Journal of Health (EJOH)!

From the beginning, we underlined the multidiciplinary frame of our journal in the health field and this current issue presents a good example of our intention. Thanks to all our authors, reviewers and editors.

We continue to invite and welcome works from our international colleagues and look forward to the future submissions.

Thanks for joining us.

With best regards,
Prof. Zeynep Çiğdem KAYACAN, M.D.

Monitoring Air Pollution Impacts of COVID-19 in India

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İlknur DÖNMEZ[4], Ali GÜNEŞ[5]

Abstract

Objective: Air quality is an important issue that is affecting human health, flora, fauna, and ecosystems. Vehicular pollution, demolition, construction, and population burst are the main reasons for degrading air quality. Hence, the main aim of the study is to monitor, analyse, as well as predict the air pollution component i.e., particulate matter before and after the lockdown of COVID-19 in various Indian cities of India.

Methods: The data collected is from Central Pollution Control Board (CPCB) of India from 2015-2020 for the pollutants such as PM2.5 and PM10. Pre-Processing techniques such as removal of null values using MICE imputer on multivariate data, merging the columns, and minmax feature scaling is applied. The cities are classified and further subdivided based on Terrain (coastal, mountainous and plains) and based on Population (highly populated and less populated). The study predicts the values for Particulate matter by using the Seasonal Autoregressive Integrated Moving Average (SARIMA) model using optimal hyperparameters for better prediction.

Results: The presented system for Air Quality Index (AQI) values includes 2020 data, and the forecasted results were highly optimistic. Further, this scenario is pure since 2020 is an outlier. A better prediction may be possible by skipping 2020. The performance of the forecasting model is calculated by the Root Mean Squared Error (RMSE) error which may help control the degraded air quality. The predicted AQI values for the year 2021 are predicted through SARIMA and produced 18.301 RMSE value for Lucknow and 46.198 for Delhi.

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Conclusion: COVID-19 restricted human activities in 2020, and the air quality level significantly improved. This paper presents a model to forecast AQI values in various Indian cities for the coming year by considering surge reduction in various pollutant levels. In Future work, a hybrid approach of models can be followed to make predictions.

Keywords: *COVID-19, Air Quality, Particulate Matter, Data Analysis, Environmental Air Pollutants*

Introduction

COVID-19 first made contact in Wuhan, China, in December 2019. SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus 2) was declared a global pandemic by the World Health Organization (WHO), and the world entered a state of lockdown. In India, the first case reported was on 30th January 2020, followed by a countrywide lockdown from 25th March 2020 (1). Total mortalities due to coronavirus has already surpassed three million. The virus has reportedly mutated, making it even more dangerous. Multiple variants of coronavirus are active throughout the globe. Every variant goes through gradual mutation depending on the regional conditions and show slightly different properties (2). Infection and mortality rates vary depending on the variant as different variants react differently to certain regional conditions. Transmission and mortality rates have proven to be influenced by several factors. These factors include air temperature, wind speed, pollution, and other geographical conditions (3). PM2.5 is the main culprit in cases of air pollution affecting the pandemic. Even in the lockdown period, the levels of PM2.5 emission are still alarming. The main reason for this is the crop burning and forest fires, which have plagued multiple countries in 2020. Particulate matter in the air act as a carrier for the virus, increasing transmission rates (4). The damage done to the immune system increases the mortality rate due to coronavirus, as the host becomes more susceptible to it. Previous studies show that the severity of air pollution correlates to the severity of COVID cases.

Although the coronavirus has forced us to enter our homes for about half a year, pollution levels in the country have not diminished (5). In fact, a recent Greenpeace report suggests that nearly 2 lakhs people were killed by air pollution in serval metro cities such as Delhi, Mumbai etc. despite severe closures (6). An estimated one million deaths each year and an estimated 9.8 lakhs preterm births, equivalent to an annual economic loss of 10.7 lakh crores, are caused by air pollution from mineral oil in India, according to the report. India is estimated to bear losses amounting to 5.4 percent of India's GDP annually, the third highest cost from global air pollution (7). The current study was conducted to determine the difference between the pollution screening (PM10 and PM2.5) before and after the closing time (March 25 to June 15, 2020) and the comparable period

from 5 years ago, i.e., 2015 to 2019 to assess the impact of air quality closures in major cities of India (8).

Data Collection and Methodology

The database is taken from the World Air Quality Index historical data platform. The filtered database contains 29,531 cases for 23 Indian cities. In addition, the data includes polluting air concentrations from various cities in India arranged by day. Recorded samples were collected from January 2015 to July 2020. The reason why these cities are being considered is because these cities are centres of air pollution. Details are analysed how air pollution varies before and after the closing time. The study will determine the results of which city was most polluted and before and after the closure.

In 2016, the Government of India, under the 'Swachh Bharat Mission', introduced the 'National Air Quality Index' (NAQI) which is a published regularly by the Central Pollution Control Board (CPCB). The AQI monitoring network consists of monitoring eight major parameters for calculating the amount of air index, while the AQI personal monitoring network focuses mainly on PM10 and PM2.5 pollution. The database contains air quality data and AQI (Air Quality Index) for cities at the daily level of various stations in many Indian cities from 2015-2020.

Data Pre-Processing

In the pre-processing step, unwanted rows and null values are deleted from the dataset. This Dataset has many columns with a large number of missing values. This missing data does not affect predictions because the average value of a particular column is used to estimate Indian AQI values between 29,531 cases.

Manage and Remove Null values

Through the Data analysis, it reveals that there are many missing values. In particular, a few cities have large numbers of missing values. In the AQI column, full details can only be obtained for Delhi. So, by calculating the percentage of missing values in each column, it helps in null values removal. (Multivariate imputation with chain-binding measurements) is used in the removal of null values in multivariate data. Minmax feature scaling is performed if needed.

Air Pollutants Pattern Visualization

Air pollution level in India is analysed using Python 3.6 data viewing tools to gain insight into patterns. Figure 1 provides a better overview of pollution levels (PM10 and PM2.5) in terms of months and years. Monthly data displayed in Figure 1 shows a significant decrease in air pollution in July and August. Such an effect is likely due to the monsoon season, which occurs during these months. A significant decrease in air pollution is observed in about June, when there is a

slight rise to very high levels during the winter. This decline, height, and altitude can be attributed to the burning of crops in northern parts of India.

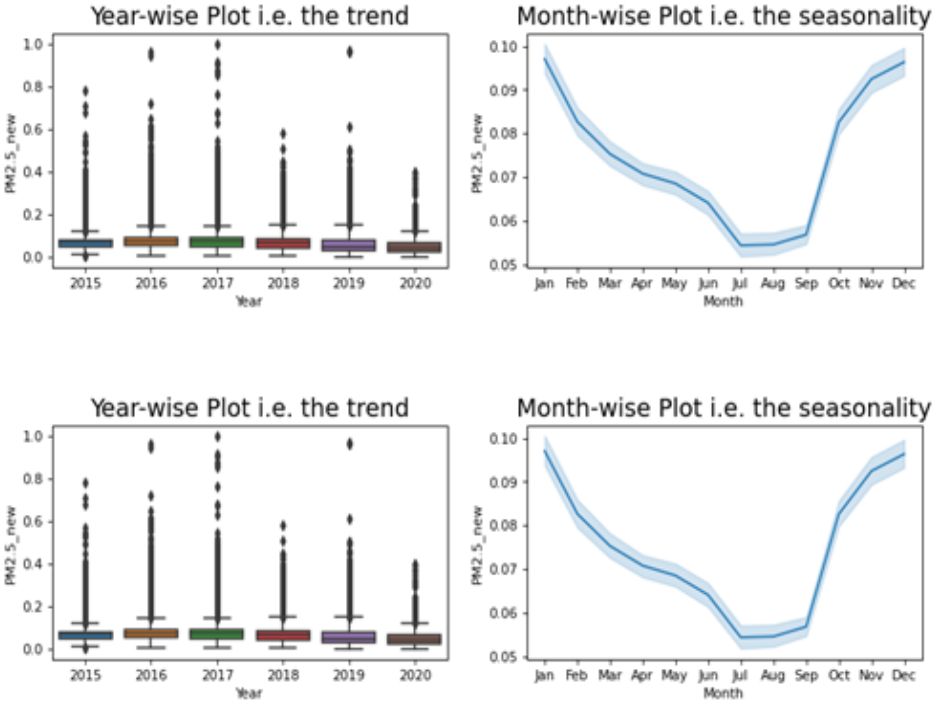

Figure 1. *Concentration level measured in terms of months in India for PM2.5 and PM10*

Analysis of the Pollutants

India remains one of the most polluted countries in the world and this has crippled the world war against coronavirus. The issue of particulate matter in air pollution is reported to act as a coronavirus carrier and increase transmission rates. Investigators have focused on PM2.5 million air pollution which is responsible for the estimated 4.2 million premature deaths each year worldwide. (9) This includes the deaths of more than a million people in China, more than half a million in India, nearly 200,000 in Europe, and more than 50,000 in the United States. Humans can also indirectly create PM10 by a combination of atmospheric chemicals. Some gases can withstand chemical reactions and form particulate matter, such as sulphur dioxide forming sulphates. While other coarse particles are subjected to such a process, these "second" particles are more common in PM2.5. As shown in Figure 2, Particulate Matter (PM2.5, PM10, etc.) has a

modest reduction all that time is still the cause of deaths related to air pollution.

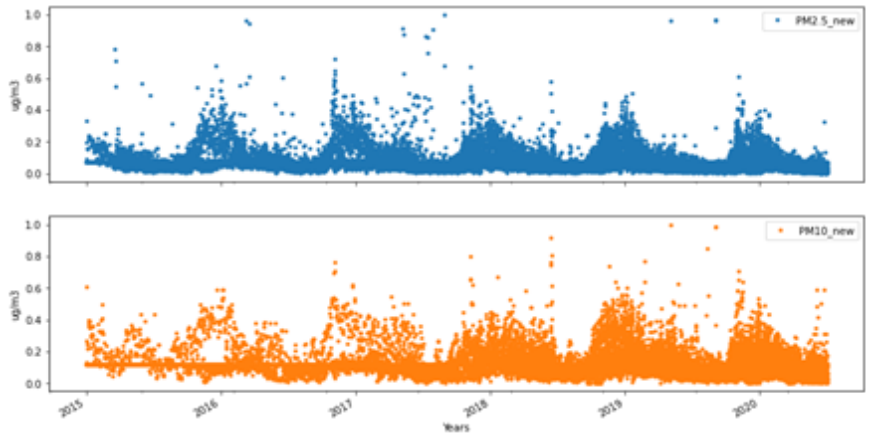

Figure 2. *Analysis of the pollutants in various years*

Proposed Classification

Various cities can be classified on the basis of terrain and on the basis of population. This classification is done so that the cities with high AQI and most polluted may be better visualized before and after the lockdown. The classification in Figure 3 is based on type of terrain is sub divided as coastal city, Mountain or hilly city and plains, with the cities as Mumbai, Shillong and Lucknow respectively. On the other hand, for the classification based on population we have highly populated (Delhi) and least populated (Visakhapatnam).

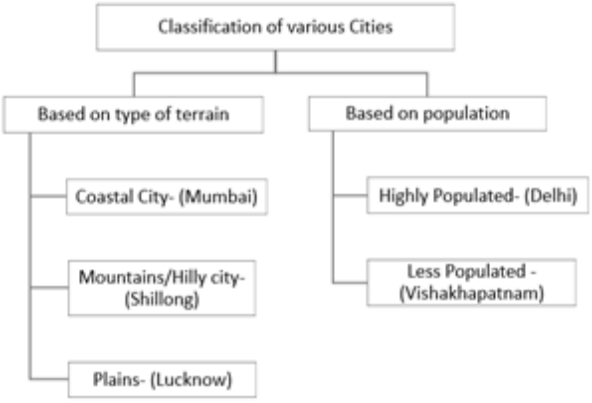

Figure 3. *Proposed classification of cities*

Effect of Lockdown on AQI

Lockdown has significantly affected AQI levels in India's leading cities. In this regard we consider the data from 2015-2020. (10) Air quality indicators (AQI) are often used by government agencies to communicate with the public how much air is currently polluted or how much it is expected to be. There are six categories of AQI level indication, namely Good, Satisfactory, Moderate, Poor, Very Poor, and Severe. The proposed AQI will consider various contaminants such as (PM10, PM2.5) for a period of 24 hours on average as determined by the National Ambient Air Quality Standards. It is interesting to note that the level of pollution in India generally decreases as summer approaches. This can also be proved by the Figure 4. Below which shows the AQI of last 5 years in India. However, the reduction of the 2020 march is very clear compared to March 2019. This could be because of lockdown. Most of the air pollution by 2020 is based on the use of domestic fuel, thermal power plants and plant heat. 2020 also shows high temperatures that have led to an unusual number of forest fires and other heat-related natural disasters, which cause air pollution. (11) Pollution levels from these sources have shown consistency and an increase in some cases. In some places, pollution levels have dropped so low that people can breathe fresh air, or see the blue sky and clear water. These improvements in air quality in some cities have allowed us to save lives. This does not mean that epidemics are good for life, but having better air quality allows us to save lives from chronic airborne diseases.

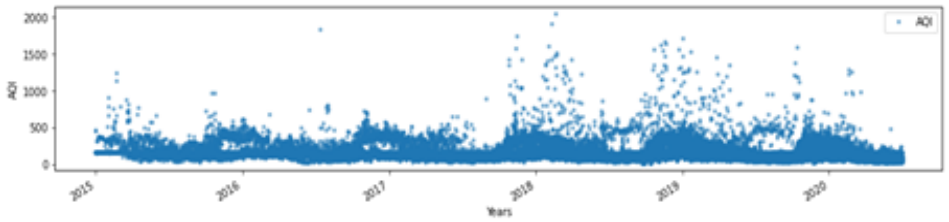

Figure 4. *AQI of India in last 5 years (2015-2020)*

Model Formation

A model to predict particulate matter values for Indian cities is proposed using Seasonal Autoregressive Integrated Moving Average (SARIMA). To forecast univariate time series data, ARIMA (Auto Regression Integrated Moving Average Models) is most preferred. The reason behind this is its inherent ability to handle trends in time series data, so it is applied in various domains. However, ARIMA cannot support time-series data with a seasonal component. An extension to ARIMA (parameters mentioned in Eq. (1)) that supports the direct modelling of the seasonal component of a series is called SARIMA (Seasonal Auto Regression

Integrated Moving Average Models). ARIMA (p, d, q) (P, D, Q) (1) where (p, d, q) are non-seasonal part of the model, (P, D, Q) is a seasonal part of the model.

Results and Discussions

The forecasting models presented in this paper are implemented using Python3.6. The optimal parameters for the customized SARIMAX model are (1, 0, 0) × (1, 0, 1, 12). Here, the numeric value 12 is used to indicate the usage of monthly data. The model does not include an external variable, so it is SARIMA. The model selection criterion is the Akaike's Information Criterion (AIC) by default. To forecast AQI values, the dataset is divided into training and testing data. The proposed SARIMA model considers AQI values from 2015 to 2018 (till June) as the training dataset, and July 2018 to June 2019 as the test dataset. The reason for excluding 2020 is that the year is an outlier because of COVID-19; therefore, including data from 2020 may deviate from the actual prediction.

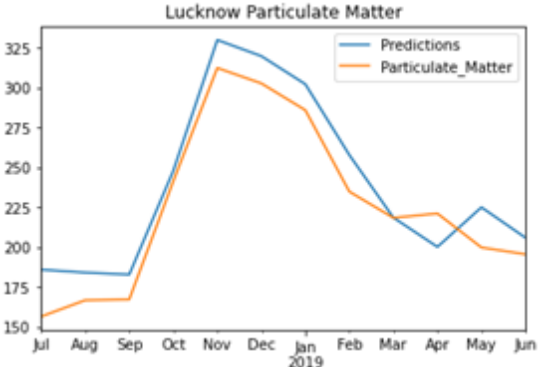

Figure 5. *Test and train prediction data of particulate matter for classification based on terrain.*

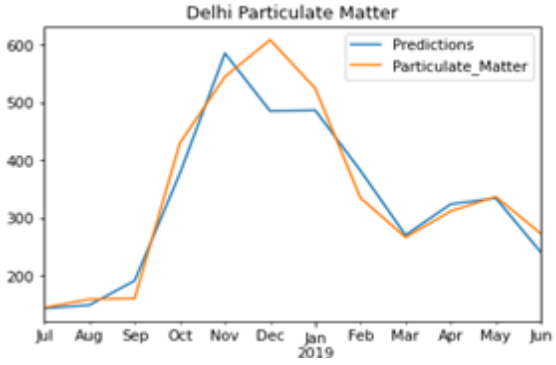

Figure 6.*Test and train prediction data of particulate matter for classification based on population.*

Figure 5 and 6 shows the performance of SARIMA in predicting the AQI values for 2020 and 2021 for classification based on terrain and population respectively. The predicted values are fairly close to our actual values obtained using SARIMA in both the figures. The error value between the existing versus forecasted results is summarized in Table 1. Figure 5 shows a comparison between the SARIMA values and the actual values in the month-wise corpus for 2019. It is quite fascinating how looking at previous values gives us so much insight into future air pollution trends. However, there is a discrepancy at the peak of the graph, where our model is unable to make predictions with high accuracy. The SARIMA model shows AQI values for 2018-2019 (Jul-Jun). Figure 6 shows the month-wise predicted results of AQI through SARIMA for 2020. The resultant data reveals a gap between the actual versus predicted AQI values.

Figure 7. *Forecasted particulate matter values through SARIMA for the year 2020–2021 of Lucknow.*

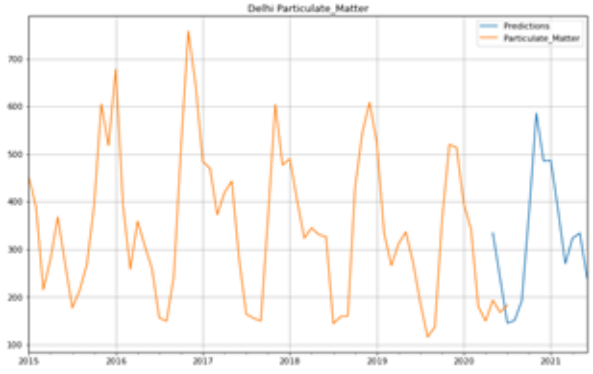

Figure 8. *Forecasted particulate matter values through SARIMA for the year 2020–2021 of Delhi.*

Table 1. Comparing the errors through SARIMA of various classifications

No.	Classification	City	Root Mean Squared Error
1	Based on Terrain	Lucknow	18.301
2	Based on Population	Delhi	46.198

The forecasting of AQI values through SARIMA is carried out and plotted in Figure 7 and 8. Predicting the levels of AQI for the upcoming year (2020–2021) is however difficult for analysts and researchers. If a predictive model considers 2020 data, there may be a chance of inaccurate prediction by the model for next year because 2020 is an outlier and also, not enough data is available for all the cities for prediction. So, to avoid the wrong predictions, the forecasting for other cities is not done. (12) However, not including the 2020 data in our dataset might lead to wrong predictions, and COVID-19 could have lasting effects that could lead to poor predictions. Consequently, the presented forecasting system for AQI values includes 2020 data, and the forecasted results are highly optimistic. Further, this scenario is pure since 2020 is an outlier. A better prediction may be possible by skipping 2020. Figure 7 shows the AQI values forecasted of Delhi using SARIMA and Figure 8 shows the AQI values of Lucknow for 2020–2021. Prediction for 2021 AQI through SARIMA produces 18.301 RMSE value for Lucknow and 46.198 for Delhi.

Conclusion

The AQI level classification models are designed using a machine learning and trained with average monthly Particulate matter (PM10 and PM2.5) values recorded in various cities in India using SARIMAX model. Many statistical tools and semi-automated tools help researchers predict air quality by considering several pollutants and seasonal parameters. However, an automated machine learning model to forecast and monitor air quality is required, especially in urban areas. COVID-19 restricted human activities in 2020, and the air quality level significantly improved. This paper presents a model to forecast AQI values in various Indian cities for the coming year by considering surge reduction in various pollutant levels. However, the main limitation to this study is because of the lack of samples in the dataset, the proposed Particulate matter model predicts the results for only 2 cities. Future work in this domain can include the hybrid approach of models to make predictions.

Acknowledgement

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Is There an Impact of Family Support on Treatment in Young Hodgkin's lymphoma Patients?

Itır ŞİRİNOĞLU DEMİRİZ[1]*, Ceren GÜMÜŞEL[2]

Abstract

Objective: Hodgkin lymphoma (HL) is a B-cell derived cancer with a bimodal incidence pattern. First peak is in early adulthood; therefore, it is one of the most common cancers in young adult group. This age group represents 30-35% of all new HL cases. The impact of physical, psychological, and social status during treatment on patient and family members are the new interests of the literature. Due to crowded family life and multiple siblings in the Turkish society, patients can receive more family support than other countries nearby. We aimed to analyze the effects of experiences of these relatives during the patient's treatment period.

Methods: For the present study twenty young adults diagnosed with HL were invited. All the patients received chemotherapy in the outpatient unit. The relatives of these patients were included as family support analysis. SF-36 test was applied to the entire study population.

Results: Twenty patients were invited for the study, 11 of them were female (55%) and 9 of them were male (45%). The median age of twenty HL patients was 31.15 (22-40). Participants defined physical alterations, exhilaration loss or gain, pain relief, sociality, and mental healing changes according to the supportive care from their family members.

Conclusion: Cancer is a completely different experience for each patient and their family. Understanding the importance of family support and the need of the patient leads us to the optimal patient-based care and harmony for treatment.

Keywords: *Hodgkin lymphoma, SF-36, family support*

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Introduction

Hodgkin lymphoma (HL) is a B-cell derived cancer which is highly curable with a bimodal incidence pattern. First peak is in early adulthood; therefore, it is one of the most common cancers in young adult group. This age group represents 30-35 % of all new HL cases (1-4).

The impact of physical, psychological, and social status during treatment on patient and family members are the new interests of the literature. For example, the lower socioeconomic status has been linked to higher risk of late complications. Ruined harmony for treatment due to unsatisfactory family support may end with increased mortality after complications. Cancer experience is personally and profoundly stressful. The main reason for this is the uncertainty of treatment related decisions, relapse possibility, as well as fear of death (5-7).

The diagnosis of lymphoma affects the patient's life in many aspects. Social relations, spiritual and religious beliefs are a wide spectrum in the context for supportive care (8). Due to crowded family life and multiple siblings in the Turkish society, patients can receive more family support than other countries nearby. We aimed to analyze the effects of experiences of these patients and their relatives during the treatment period.

Methods

Twenty young adults diagnosed with HL were invited. All the patients received the same chemotherapy protocol in the outpatient unit. The family members, siblings or wife/husband or mother/father of the patients were included as family support analysis. SF-36 test was applied to the entire study population.

Results

Five percent of the patients were living alone, 19 patients were living with their family. Fifteen percent of the patients had to quit working after they were diagnosed with lymphoma. None of the participants had co-morbidities. All the patients were aware of their diagnosis and 95% of them had researched the disease via internet network. Participant demographic variables are summarized in Table 1.

Table 1. Demographic variables of the patients

Variable		
Age Mean (Range)	31.15 (22-40)	
	n	%
Gender		
Male	9	45
Female	11	55
Education		
None	1	5
First grade	5	25
Middle grade	2	10
College	6	30
Postgraduate	6	30
Marital Status		
Married	12	60
Single	8	40
Job		
Yes	5	25
No	12	60
Social insurance		
Yes	15	75
No	5	25
Province		
City	19	95
Country	1	5
Smoking		
Yes	6	30
No	14	70
Alcohol consumption		
Yes	2	10
No	18	90

During the treatment period the most common side effects were hair loss and fatigue. Not all the patients had complained about the same side effects. The distribution is summarized in Table 2.

Table 2. Side effect distribution

Side Effects	**Yes n (%)**	**No n (%)**
Emesis	14 (70)	6 (30)
Hair loss	15 (75)	5 (25)
Numbness (hand and feet)	6 (30)	14 (70)
Anorexia, weight loss	14 (70)	6 (30)
Fatigue	16 (80)	4 (20)
Mucositis	4 (20)	16 (80)
Diarrhea	7 (35)	13 (65)

Table 3. The family member/caregiver demographic variables

Variable		
Age	36.95 (15 – 58)	
Mean (Ranger)		
	n	%
Gender		
Male	12	60
Female	8	40
Education		
None	2	10
First Grade	3	15
Middle Grade	4	20
College	7	35
Postgraduate	4	20
Marital Status		
Married	15	75
Single	5	25
Job		
Yes	7	35
No	13	65
Family Member		
Wife/husband	9	45
Parent	1	5
Sister/brother	4	20
Child	6	30

All the caregivers were aware of the patient's diagnosis. Twenty-five percent of the patient had another family member with cancer history. Only 5% of the family member needed extra help during caregiving. The answer for the question about duration of the support and care during the treatment period was summarized in Table 4.

Table 4. Family support and care during treatment.

Frequency of care/support of the patient by the family.		
	n	**%**
Continuously	8	40
Often	7	35
Only for the meals	2	10
Rare	3	15

According to these data, gender, education, marital status, working, smoking and alcohol consumption are not statistically involved parameters. The results of SF-36 test are shown in Table 5.

Table 5. SF - 36 test results.

Parameter	**Patient**				**Caregiver**			
	Decreased		**Normal**		**Decreased**		**Normal**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Physical functions	7	35	13	65	5	25	15	75
Physical role difficulty	13	65	7	35	7	35	13	65
Pain relief	11	55	9	45	9	45	11	55
General health perception	14	70	6	30	8	40	12	60
Energy-vitality	9	45	11	55	10	50	10	50
Social functionality	18	90	2	10	16	80	4	20
Emotional role difficulty	13	65	7	35	13	65	7	35
Mental health	10	50	10	50	8	40	12	60

Physical role difficulty parameter was decreased statistically significantly in patients with numbness (p=0.032). Similarly in this same group of patient's pain relief was also significantly decreased (p=0.008). Energy and vitality of the patients were significantly decreased in the numbness positive group (p=0.024) however patients with mucositis were shown to have higher vitality (p=0.043). Physical function parameters were lower in the diarrhea group (p=0.012) as well as pain relief parameter (p=0.043) and general health perception (p=0.032).

The SF-36 parameter analysis was not significant on behalf of the gender, education, and marital status of the family member but the single family members had lower physical function parameter results compared to the married ones (p=0.037), also the general health perception results were lower in the single group (p=0.035).

Discussion

The treatment tolerance rates of our young Hodgkin lymphoma patients were quite good. Frequency of side effects and resistance to side effects were also highly positive. In our analysis, it was observed that the relatives of the patients interpreted only to the side effects that would change the quality of life. No psychological or social problems were encountered, which would necessitate quitting the treatment process for any patient or relatives (1).

Although there is evidence for the positive impact of social support on the overall well-being of a cancer patient, less is known about what types of social support are most important to patients diagnosed with lymphoma. Previous research has revealed that social support may be helpful when it is optimal and in the correct timing (1-4). The level of support offered differs between the siblings, the person supporting the patient should be the right person for the survivor in their social network. Some of the patients may expect higher levels of support from their caregivers, some of them may prefer instrumental support rather than spiritual support (5).

The partner or caregiver of the patient may experience equal or greater psychological distress during the treatment. This occurs especially when the patient is male, married and with children. Although there are a lot of interpretations of social support, the most frequently used four types are emotional, informational, appraisal and instrumental support (5). In any type optimal and sufficient support is a significant factor for improved quality of life. Some changes in the patient's social network may bring some relations closer or drive them apart. Across all contexts emotional support was most frequently mentioned by participants (9).

Conclusion

In conclusion, understanding the importance of family support and the need of the patient leads us to the optimal patient-based care and harmony for treatment.

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An Evaluation of The İmpact of War on Pregnancy in Syrian Refugee Women: A Retrospective Study

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Abstract

Objective: The aim of this study was to investigate the perinatal and postpartum results of refugee Syrian pregnant women in Turkey and to evaluate the effect of the war on pregnancy.

Material and Methods: In the study, a total of 1020 women applying for pregnancy and giving birth at Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Department of Gynecology and Obstetrics Clinic between the 2014 January-2016 January dates were included, 509 of whom were Syrian refugees and 511 of whom were Turkish. By examining the files belonging to the patients retrospectively, the number of gravida, parity, birth and abortus were determined; normal, vaginal birth and caesarean section as a delivery method were recorded separately. Parameters for the birth and infants were determined individually.

Results: When the demographic information of the patients included in the study were evaluated, it was found that the age of Syrian women was significantly lower than those of Turkish women. ($p < 0.05$). In addition, the gestational week in Syrian women was significantly lower than those of Turkish women ($p < 0.05$). When the birth weight of both groups was compared, the birth weight of the Syrian women was significantly lower than those of Turkish women ($p < 0.05$). Another parameter assessed during our study is the delivery method: The cesarean delivery rate of the Syrian women was determined significantly lower than those of Turkish women ($p < 0.05$). No significant difference was observed between the two groups in the other parameters evaluated ($p > 0,05$).

Conclusion: In order to improve the antenatal care of the Syrian immigrant women; we are on the opinion that it is necessary to create ideal solutions by working with international organizations about communication and language.

Keywords: *Pregnancy, Syrian immigrants, prenatal parameter*

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Introduction

Since 2011, the number of Syrian refugees in Turkey due has been increased to 3.500.000 as of 2019 and 50% of them are women. Of Syrian refugees, 10% live in the camps in 10 provinces and 90% live in different cities of Turkey (1). In Turkey's conditions, pregnant women, living outside the camp, has difficulty in access to health services, gives birth under insufficient conditions and has difficulty in access to birth control aids and the lack of information on birth control methods (2, 3). Pregnancy is a physiological process, in some cases, it can lead to many events that may pose a life threat to both the mother and the fetus. One of the conditions that may create both morbidity or mortality risks to both the fetus and the mother is, of course, war. In the studies investigating the immigrant women who do not have adequate care during pregnancy, pregnancy diabetes, postpartum hemorrhage, perineal trauma and cesarean birth rates are reported to be quite high (4). Any medical problems that may occur in prenatal and postnatal periods during pregnancy may lead to serious complications and psychiatric disorders. On the other hand, this may affect the person's view of pregnancy and the desire to conceive again.

In the literature, evaluations about antenatal care, pregnancy and postpartum period have been made in Syrian immigrants. The main blood serum parameters of Syrian immigrants, the number of antenatal visits, vitamin and iron supplementation recommended during pregnancy were assessed. In addition, postpartum height and weight of the infant and neonatal intensive care need are also included in the evaluation. However, in the literature no studies evaluating the impact of war on pregnancy within the context of these pregnancies and comparing the perinatal parameters of the pregnant Syrians with the pregnant Turkish were found.

Access to health care should be an independent case of a person's immigrant status, it is not included as a right in the 1951 Geneva Convention, the chief legal document stating the rights of refugees and the responsibilities of host countries. Universal Declaration of Human Rights (1948), International Covenant on Economic, Social and Cultural Rights (1966), International Covenant on Civil and Political Rights (1966), International Convention on the Elimination of All Forms of Racial Discrimination (1965), Elimination of All Forms of Discrimination against Women, The combination of various legal instruments, such as the Convention (1979), the United Nations Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (1984), the Convention on the Rights of the Child (1990), makes health a fundamental human right that transcends issues of citizenship and political status.

Refugees fleeing human-made disasters become vulnerable to certain health risks due to the trauma caused by the experience of displacement, violence in conflict situations, and the harsh living conditions (lack of food, water, and hygiene) they are exposed to during and after migration. In addition to severe mental illness, the health problems associated with the mass influx of refugees include infectious, communicable, non-infectious, or chronic diseases are also included. According to the academic literature and international reports, some of the most common health problems in immigrants are listed below: Malnutrition, diarrhea, measles, malaria, respiratory infections, growth and developmental disorders in children, anemia, physical violence and related injuries, sexual abuse, sexually transmitted diseases, including HIV/AIDS, pregnancy and childbirth complications, chronic diseases and complications. Mental diseases such as depression, anxiety disorder, sleep disorder and post-traumatic stress disorder. There is a direct cause-effect relationship between malnutrition, malaria, measles, diarrheal diseases and respiratory infections, and death rates especially in the emergency phase, that is, in the first days and weeks following the migration influx. The effects of other common diseases are not associated with mortality rates, but these diseases also pose serious challenges for the displaced masses. If an effective refugee health service is not provided; Diseases such as hepatitis A, hepatitis B, sexually transmitted diseases (HIV/AIDS), measles and tuberculosis can pose serious threats to the health of refugees and local people. Refugees often face barriers to accessing local health and social services, depending on some legal, cultural, social, and economic factors in the countries they live in.

There is a growing literature on the experience of refugee population access to health services in different countries. The scarcity of properly trained interpreters, the complexity or ignorance of referral procedures, the lack of information about the services provided, and the mixing of the roles of different health professionals are other barriers to accessing health services. There are many studies focusing about Syrian refugee women in Turkey. Although Human Rights Watch (2014), AFAD (2014), and Mazlumder (2014) do not specifically address health issues, they do reveal the conditions faced by Syrian refugee women in Turkey. Grove (2015) (5) focused on the serious health risks faced by Syrian refugee women, based on information from the cited Human Rights Watch (2014) and AFAD (2014) reports. Şimşek et al. (2017) (6) conducted a comprehensive research on the health indicators of Syrian refugee women living in the Şanlıurfa region. Kahyaoğlu Süt (2017), Başel et al. (2006) (7) and Bahadır & Uçku (2015) (8) evaluated the reproductive health indicators of Syrian refugee women. In addition, Büyüktiryaki et al. (2015) (9) analyze the newborn outcomes of Syrian refugees who gave birth in a hospital in Ankara.

Erenel et al. (2017) (10) compare the pregnancy outcomes of Syrians with those of Turkish citizens and conclude that Syrian refugees lack adequate prenatal care. Tolunay et al. (2016) (11) specifically focus on pregnancy-related intraocular pressure changes in Syrian refugee women.

sIn this cross-sectional study, it was aimed to evaluate the effects of war on pregnancy. For this purpose, perinatal and postpartum results of Syrian women who came to Turkey due to the war between the 2014-2015 years and gave birth at Bakırköy Dr Sadi Konuk Training and Research Hospital were investigated, and the effect of the war on pregnancy by comparing the results obtained from Syrian women with the results from Turkish patients selected randomly who gave birth in the same date range were assessed. According to our knowledge, this research is the first study evaluating the impact of war on pregnancy in Syrian women.

Methods

In the study, a total of 1020 women applying for pregnancy and giving birth at Bakırköy Dr Sadi Konuk Training and Research Hospital, Department of Gynecology and Obstetrics Clinic between the March 2014- March 2015 dates were included, 509 of whom were Syrian refugees and 511 of whom were from Turkey. By examining the files belonging to the patients retrospectively, the number of gravida, parity, birth and abortus were determined; normal, vaginal birth and caesarean section as a delivery method were recorded separately. Parameters for the birth and infants were determined individually. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Bakırköy Dr Sadi Konuk Training and Research Hospital.

Mean, standard deviation, median, minimum–maximum, frequency and ratio values were used in descriptive statistics of the data. The distribution of variables was checked with Kolmogorov–Smirnov test. Mann-Whitney U test was used for the analysis of quantitative data. Chi-square test was used for the analysis of qualitative data. SPSS 22.0 software package was used for analysis.

Results

When the demographic information of the patients included in the study were evaluated, the age of Syrian women was significantly determined lower than those of Turkish women ($p < 0.05$). However, no significant difference was detected between the two groups in terms of gravida, parity, and abortion rates (Figure 1).

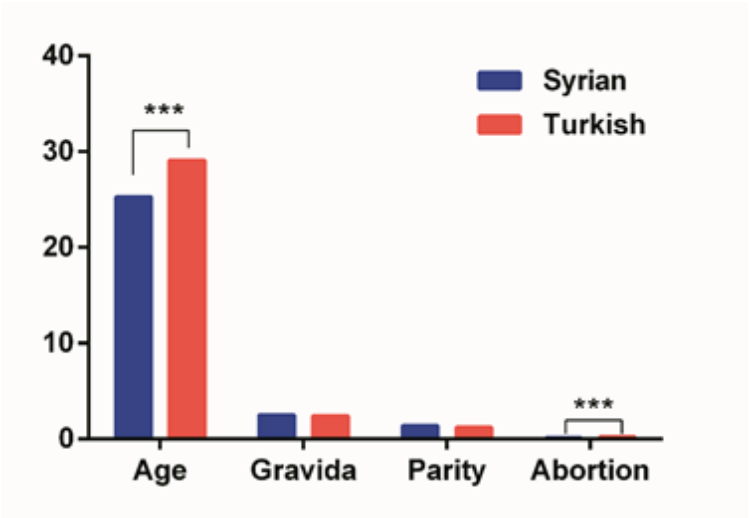

Figure 1. *Comparison of perinatal parameters between the groups (*** p<0,05)*

Another parameter assessed during our study is the type of delivery: The cesarean delivery rate of the Syrian women was significantly determined lower than those of Turkish women ($p < 0.05$; Figure 2). When the delivery method of the patients was observed, it was determined that in Syrian patients the normal birth rate was 65, 6%, cesarean rate was 33.6% and external birth (outside hospital) was 0.8% while it was determined that the normal birth rate was 51.1%, the cesarean rate was 47.9% and the external birth rate was 1.0% in Turkish patients.

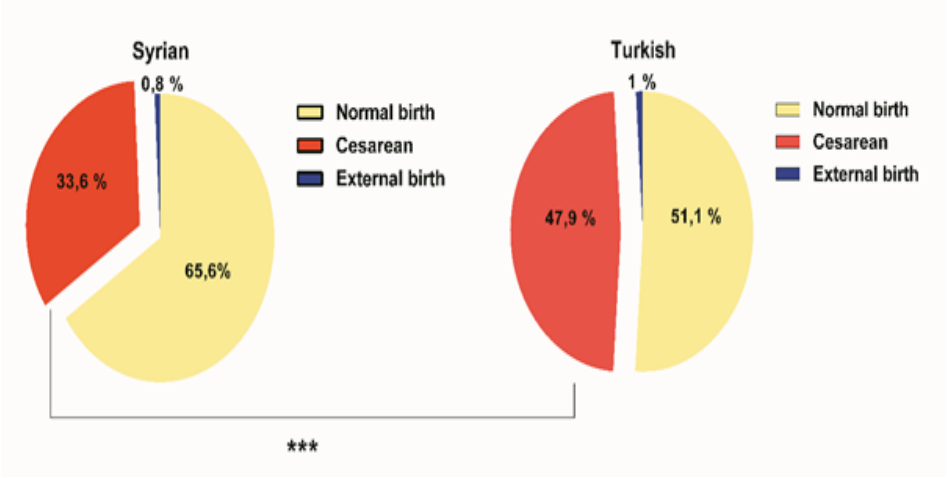

Figure 2. *Birth rates (*** p<0,05)*

The gestational week in Syrian women was significantly detected lower than those of Turkish women ($p < 0.05$; Figure 3). Besides, when the birth weight of both groups was compared, the birth weight of the Syrian women was determined significantly lower than those of Turkish women ($p < 0.05$; Figure 3).

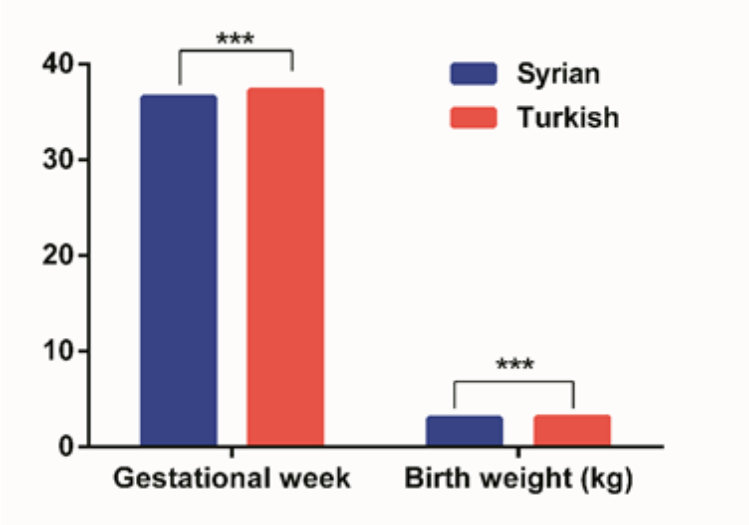

Figure 3. *Comparison of gestational week and birth weight of the groups (*** p<0,05)*

Finally, Syrian women's Apgar values (Figure 4) and perinatal mortality rates (Figure 5) in the first minute and fifth minute were compared. No significant differences were found in the comparison ($p > 0.05$) (Table 1).

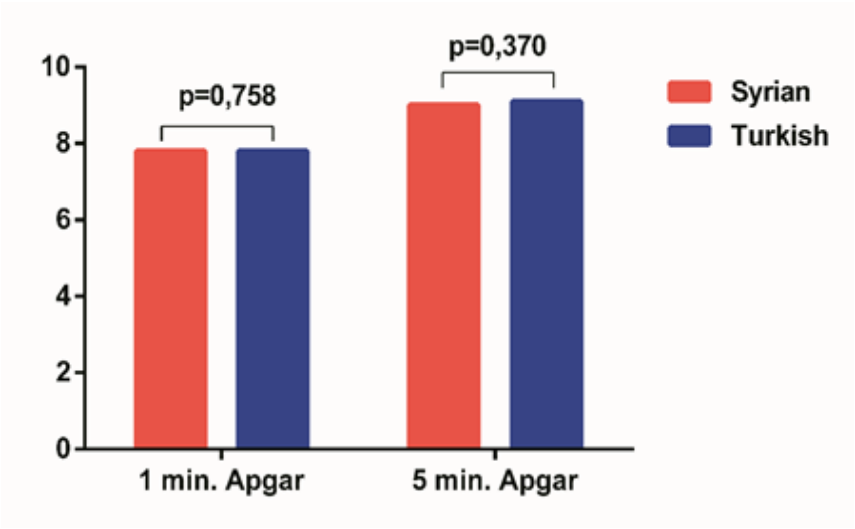

Figure 4. *Recorded Apgar score of 1 and 5 minutes*

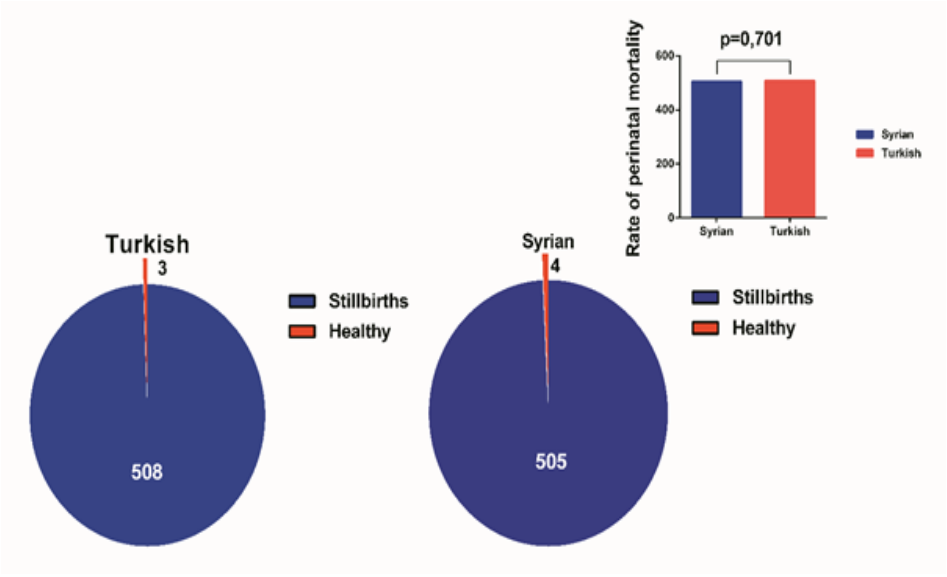

Figure 5. *Comparison of the rate of perinatal mortality*

Table 1. Comparison of the parameters between Syrian and Turkish women

	Syrian			Turkish			
	Mean± sd/n-%	Mean	(Min-Max)	Mean±sd /n-%	Mean	(Min-Max)	
Age	25,3 ± 6,2	24	15 - 46	29,1 ± 5,8	29	15 - 44	***0,000***
Gravida	2,5 ± 1,8	2	1 - 10	2,4 ± 1,4	2	1 - 1	0,166
Parity	1,4 ± 1,7	1	0 - 9	1,2 ± 1,1	1	0 - 7	0,756
Abortion	0,1 ± 0,5	0	0 - 5	0,2 ± 0,7	0	0 - 9	***0,000***
Gestation week	36,5 ± 2,7	37	22 - 43	37,3 ± 2,6	38	22 - 42	***0,000***
22 - 24 weeks	5	1,0%		2	0,4%		
25 - 29 weeks	9	1,8%		9	1,8%		
30 - 37 weeks	317	62,3 %		210	41,1 %		
38 - 43 weeks	178	35,0 %		290	56,8 %		
Brith weight (Gr)	299 ± 607	306 0	18 - 461 0 6	310 ± 664	320 0	49 - 4790 0	***0,000***
0-500 Gr	2	0,4%		1	0,2%		
501-1000 Gr	6	1,2%		5	1,0%		
1001-1500 Gr	8	1,6%		12	2,3%		
1501-2000 Gr	14	2,8%		15	2,9%		
2001-2500 Gr	40	7,9%		41	8,0%		
2501-3000 Gr	161	31,6%		98	19,2%		
3001-3500 Gr	199	39,1%		208	40,7%		
3501-4000 Gr	63	12,4%		101	19,8%		
4001 Gr	16	3,1%		30	5,9%		
1 min Apgar	7,8 ± 1,5	8	0 - 9	7,8 ± 1,5	8	0 - 9	0,758
5 min Apgar	9,0 ± 1,4	9	0 - 10	9,1 ± 1,4	9	0 - 10	0,370
Birth type							
Normal birth	334	65,6%		261	51,1%		
Cesarean	171	33,6%		245	47,9%		***0,000***
External birth	4	0,8%		5	1,0%		
Stillborn Yok	505	99,2%		508	99,4%		0,701
Var	4	0,8%		3	0,6%		

Chi-square test / Mann-Whitney U test

Discussion

According to the definition of the World Health Organization (WHO) in 1948; the health is not only the absence of disease and disability, but also a state of complete physical, mental and social well-being (12). The concept of reproductive health was first brought to the agenda at the World Conference on Population and Development held in Cairo in 1994. In addition to the definition of the WHO at the conference, the expression "reproductive health means that individuals have a satisfying and safe sex life, have the ability to reproduce, and have the freedom to decide whether to use this ability" (13). Women's reproductive health can be affected by the environment, socio-cultural and economic factors. Migration, which is a process that affects women in all these aspects, also has negative effects on women's reproductive health (14).

According to the 2014 report of the Prime Ministry Disaster and Emergency Management Presidency, a substantial number of women immigrated to Turkey due to the war that broke out in Syria. In terms of the number of births of Syrian migrant women, it is stated in the report that there were 128 daily births and 70,728 births in total in 2014. However, there is no detailed information about how, where and the results of these births (AFAD, 2014). In addition, the studies around the world have focused on Syrian immigrants in Turkey, which has been dense in number in recent years. According to the Syrian Crisis Regional reports of the United Nations Population Fund (UNFPA), 500,000 of the 1,645,000 Syrian immigrants in Turkey are Syrian women who are in reproductive age. In addition, the report states that 30,000 of these women are pregnant (15). This situation reveals that female immigrants have different and special protection needs compared to male immigrants (16). Otherwise, migrant women may encounter reproductive health problems due to both their gender and gender-based problems (17).

Possible reproductive health problems that migrant women may encounter are summarized as follows. Sexual violence is one of the leading reproductive health problems of Syrian migrant women. It is a situation that women frequently encounter during the migration process. Sexual violence based on gender inequality that immigrant women are exposed to, especially in crisis situations such as war, is one of the most important problems that threaten women's life and security (17, 18). Studies show that Syrian migrant women are subjected to sexual violence by their spouses or non-husbands. In addition, it has been determined that sexual violence against women is significantly related to reproductive health. According to a study, the rate of exposure to physical and/or sexual violence among women in war zones is over 30%. It is also estimated that around 6,000 women have been raped since the beginning of the war in Syria.

In the same study, it is reported that women suffer from more than one type of violence (19).

Most of the migrant women who have been sexually abused do not know their legal rights or do not apply to institutions that can provide support for fear of being deported. Although immigrant women have high reproductive health needs, their access to relevant services and information is limited due to legal, cultural and language barriers (14, 16). In the report of the Middle East Strategic Studies Center (ORSAM) titled Impact of Syrian Refugees on Turkey in January 2015, polygamy with Syrian women has become widespread in Turkey. In addition, it is stated that Syrian families make financial gains by marrying their daughters in exchange for money (15). In addition, to a study conducted in Turkey, 6% of marriages with Syrian migrant women took place in the form of sand marriages (Women's Center Foundation, 2017). This situation results in the abuse of Syrian women. Counseling services should be provided for women who have been sexually abused, primarily on the safety of Syrian migrant women. Especially women who have experienced sexual violence should be directed to the right centers and these women should be provided with free access to necessary services such as treatment and safe shelter. In addition, it is an important need to provide mental health support and rehabilitation services to these women (20). In addition, it is of great importance to regulate criminal sanctions against people responsible for abuse (18).

Immigrant women are more prone to sexual abuse, violence, and sexually transmitted diseases, including Human Immunodeficiency Virus (HIV). Women's reproductive health is overlooked, especially in immigrant camps. According to the results of a study conducted to evaluate the reproductive health and violence status of immigrant women, it was determined that 53.3% of women had genital tract infections. Similarly, studies conducted in Turkey show that polygamy with immigrant women has become widespread and this is an important reason for the increase in the incidence of sexually transmitted infections. In the study conducted by Gümüş et al. to determine the reproductive health problems of Syrian migrant women, it was determined that 60% of women had pathological discharge complaints (21). In addition, the immunization levels of Syrian immigrants against Hepatitis B were lower than those of the local people, and it was stated that immigrants should be considered as a risky group in terms of infectious diseases (22).

It is important to carry out regular health screenings of immigrant women in terms of sexually transmitted diseases and to add monitoring and evaluation programs to this service provision.

In addition, health education for immigrant women on safe sexual life is considered an effective step in preventing sexually transmitted diseases.

Although pregnancy and childbirth are a physiological process, they create a significant burden and stress for the female body. The existence of the infant in mother's womb, physiological changes specific to pregnancy, differences in family and social life are the sources of psychosocial reactions in this process. However, the process of pregnancy and childbirth is generally a joyful and exciting time for the parents. However, the findings of depression, anxiety, stress and distress in pregnant women are increasingly observed today (23). If the gestation period is not planned, especially in susceptible individuals it may emerge as a period of life that cause stress. Stress and anxiety during pregnancy can have negative impacts on pregnancy outcomes and on born children. Maternal stress increases corticotropin releasing hormone (CRH) release from the hypothalamus. Hypothalamus-secreted CRH stimulates pituitary adrenocorticotropin (ACTH) release and ACTH increases glucocorticoid release from the adrenal gland. Glucocorticoids have many effects in every cell of the body.

Glucocorticoids are effective on the production and release of cells involved in the immune system, many cytokines and growth factors. Therefore hypercortisolemia caused by stress can affect pregnancy by affecting many factors (cytokines, immunomodulators, etc.) effecting placenta and fetus (24). As a result, pregnancy is as far away from stress, good nutrition and control is effective on the results such as abortus and preterm delivery.

Psychological and social stress has been indicated to be an independent risk factor for preterm delivery (25). Undoubtedly, war stress and immigration are among the most crucial factors that trigger preterm delivery in women. The findings obtained in our study confirm the triggering effect of stress on preterm delivery. Accordingly, the gestational week in Syrian women was significantly determined lower than those of Turkish women ($p<0,05$; Figure 1). However, preterm delivery is a multifactorial event, and it is impossible to attribute it to a single factor. Even today, the mechanisms of action of birth are not known precisely. However, CRH has been revealed to have a birth-onset effect. Therefore, increased CRH due to stress may increase the risk of preterm delivery. Preterm delivery is the leading cause of perinatal mortality and morbidity. However, the perinatal mortality rate recorded in Syrian women who gave birth significantly earlier in our study did not indicate any significant difference compared to the rate recorded in Turkish women ($p>0,05$; Figure 5)

Hedegaard et al. (25) have indicated that maternal stress leads to the birth of low-birth-weight infants and increases the risk of preeclampsia. Our study supports the literature: the birth weight recorded in Syrian women who have undergone intense stress during gestation period was determined to be significantly lower than those of Turkish women ($p<0,005$; Figure3). Another reason for the significant low birth weight observed in the Syrian women is considered to be malnutrition and antenatal care because they may be deprived of basic human needs during the immigration and in the camps. As a matter of fact, inadequate nutrition observed in Syrian women has been reported in the literature: Demirci and his colleagues evaluated the births of Syrian immigrants and determined that the new born infants had low birth weight and low hematocrit values (26). In addition, it has been reported that children born under maternal stress are more likely to have Type II diabetes, obesity, hypertension and atopic body in the long term (23).

Animal experiments points out that maternal stress can lead to behavioral disorders in animals in the long term. In humans, there are also studies indicating that children born from mothers who are under stress may be more likely to have behavioral disorders such as irritability, concentration disorder in the long term compared to the general population (27).

In studies conducted in the literature, it has been reported that the antenatal care and the pregnancy age of Syrian immigrant women are lower and the rate of adolescent pregnancy is higher (28, 29). In the current study, when the ages of Syrian women, gravida, parity, and abortion ratios were compared with those of Turkish women, the age averages were determined to be significantly lower ($p<0,005$; Figure 1). However, the abortus rates of Syrian immigrant women were interestingly determined lower than those of Turkish women ($p<0,005$; Figure 1). To explain the reason of this decrease, advanced molecular and biochemical studies comparing Syrian women and Turkish women are needed.

When the delivery method of the patients was examined, it was determined that in Syrian patients the normal birth rate was 65, 6%, cesarean rate was 33.6% and external birth was 0.8% while it was determined that the normal birth rate was 51.1%, the cesarean rate was 47.9% and the external birth rate was 1.0% in Turkish patients. In comparison between the groups, the cesarean rate recorded in Turkish patients was determined significantly higher than the cesarean rate recorded in Syrian women ($p<0,005$; Figure 2).

Çift et al. (30), have examined Syrian women and Turkish women in a retrospective study and have observed the newborn infants' Apgar scores, birth weight and birth week. Accordingly, they did not observe a significant difference between the newborn infants' APGAR scores in the study groups. This finding of the literature is consistent with our findings. In the current study, no significant difference between the infants' APGAR scores of Syrian women and Turkish women was observed (p>0,005; Figure 4). The limitations for the present study can be listed as follows: low number of participants and lack of some information about the participants, such as perinatal information, economic conditions, place where they live and daily life conditions during pregnancy.

Conclusion

To improve the antenatal care of Syrian immigrant women; we are on the opinion that it is necessary to create ideal solutions by working with international organizations about communication and language. Also, it will contribute to the protection of both health care workers and Syrian immigrants through the inclusion of immigrants in national vaccination programs before pregnancy.

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Conflict of Interest

Author(s) declare no conflict of interest.

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Automated Detection of Alzheimer's Disease Using Wavelet Transform with Convolutional Neural Networks

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Abstract

Objective: Alzheimer's disease (AD) is a chronic disease that causes the death of nerve cells and tissue loss in the brain. It usually starts slowly and worsens over time. Individual computer aided systems are needed for early and accurate diagnosis of Alzheimer's. Magnetic resonance imaging (MRI) offers the opportunity to examine the pathological brain changes associated with AD. In recent years, neuroimaging data has been increasingly used to characterize AD with machine learning methods, offering promising tools for personalized diagnosis. Very recently, a number of studies have proposed to aid the diagnosis of AD through convolutional neural networks (CNNs).

Methods: CNN is machine learning algorithm which is used in a variety of fields, including image and pattern recognition, speech recognition, natural language processing, and video analysis. In this study Discrete wavelet transform (DWT) was used for feature extraction. DWT has attractive properties and has better image representation than other transforms like Fourier. Medical images are vulnerable to noise, they are preprocessed to remove unwanted data and improve quality. Feature extraction and classification are two essential components for the recognition system that have a significant impact on the efficiency of the system. DWT is an implementation of wavelet transform that uses a separate set of wavelet scales and translations that follow some defined rules. The aim of this study is to detect Alzheimer's disease by using convolutional neural networks and to reduce noise by preprocessing by applying DWT on the entered images.

Results: With combining DWT feature extraction and CNN algorithm for detecting Alzheimer's disease, the performance and learning rate are significantly decreased. The accuracy of the model results based on pure CNN with machine learning algorithm is higher than with than the accuracy in CNN learning without DWT future extraction. Accuracy values are 75% and 69 % successively.

Conclusion: Ultimately, this study revealed that the combination of MET–PLGA NPs with current cancer therapies holds promise for the potential of breast cancer treatment.

Keywords: Alzheimer's disease, discrete wavelet transform, DWT, convolutional neural networks, CNN.

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Introduction

Alzheimer's disease is a type of dementia that causes memory problems. Symptoms usually come on slowly and get worse over time, affecting a person's daily life, causing life-threatening problems.

Alzheimer's disease is a neurodegenerative disease that causes memory loss. According to the National Institute of Aging, Alzheimer's disease is defined as a progressive, irreversible brain disorder that gradually destroys memory and thinking skills, and even the ability to perform simple tasks. It usually starts in the mid-60s and is the most common cause of dementia. Factors such as age, gender, family history and heredity, education level, head trauma, Down syndrome, hypertension, depression, diabetes, alcohol, and cigarette use are stated as risk factors for Alzheimer's disease. The disease has a progressive structure and consists of various stages, and the quality of the care given is shaped according to the stage of the patient (1).

With aging, forgetfulness, slowing of speech, weakness, unhappiness, and increased sleepiness can be seen in people. However, these symptoms may be signs of AD, and AD is not a temporary disease. It progresses in a variable way from person to person; It makes the life of patients very difficult and seriously reduces the quality of life (2).

The most important feature of AD is that it starts without specific symptoms and progresses slowly.

Patients and their relatives cannot tell the exact time of onset of the complaints. With the thought that forgetfulness is normal in old age, it becomes difficult to detect the onset of AD. Therefore, the time to consult a physician is also delayed (3).

In the health sector, it is not possible to manage diagnosis and diagnosis only with human power. Machine learning techniques, one of the artificial intelligence technologies, are widely used in medical predictions (4). With machine learning techniques, rapid and reliable disease prediction can be made.

There are many algorithms of machine learning, and it is decided which algorithm to use according to the source of the problem and the amount of data. Different algorithms can produce specificity and sensitivity values according to the data used (5). Considering these values according to the data used, the best fit among the different algorithms is selected. In this way, the best algorithm is preferred, and the result is improved, and the time cost is reduced (5).

Wavelet transform is a type of transform used for time-frequency analysis of a signal. Especially the problems experienced during the examination of seismic data allowed the development of the "Continuous Wavelet Transform". Later, wavelet analysis was found to be applicable to a wide variety of signal types (6). In the studies conducted, wavelet transform has been used in the diagnosis of discontinuity in signals (interpretation of heart graphs can be given as an example) and in noise removal from the signal (7).

Discrete Wavelet Transform DWT can be considered as the best transform field technique among other techniques due to its multi-resolution properties and excellent time-frequency analysis and is widely used for signal processing purposes (8), (9). When an image is transformed by wavelet, 4 sub bands (low frequency component LL, horizontal detail component HL, vertical detail component LH, and diagonal detail component HH) are obtained. Because most of the image energy is concentrated in the low-frequency sub band, embedding the stamp in the low-frequency sub band causes perceptual changes in the image. However, if the stamp is embedded in the high frequency sub bands instead of the low frequency band, the durability of the stamping scheme is adversely affected. For this reason, the LL sub band, which is more resistant to many attacks than other sub bands, was preferred in this study.

The Discrete Wavelet Transform (DWT) of image signals produces a non-redundant image representation, which provides better spatial and spectral localization of image formation, compared with other multi scale representations such as Gaussian and Laplacian pyramid. Recently, Discrete Wavelet Transform has attracted more and more interest in image de-noising (10).

Similarly to this study there are several studies that applied to detect the AD disease using machine learning techniques, like the study done by Jha, Kim, Kwon (11) for diagnosis AD disease using wavelet transform, they used Dual-Tree Complex wavelet transform for image processing, the results showed that the proposed method achieved an accuracy of $90.06 \pm 0.01\%$, a sensitivity of $92.00 \pm 0.04\%$, a specificity of $87.78 \pm 0.04\%$, and a precision of $89.6 \pm 0.03\%$ and outperformed 7 state-of-the-art algorithms.

Data and Methodology

The aim of this study is to detect Alzheimer's disease using image processing and CNN machine learning. In the CNN algorithm, preprocessing will be done on the image using the wavelet's DWT library. DWT will be used to remove the noises.

Dataset

The dataset is taken from the Kaggle website. The data set, consisting of 6400 brain tomography scans, consists of normal people, people with moderate Alzheimer's disease, and people with severe Alzheimer's disease (12). In this study, we divided the brain tomography of a person into four classes as

i) normal tomography (have no Alzheimer's disease),

ii) mild disease,

iii) moderate disease,

iv) high-grade disease.

Table 1 shows descriptive statistics of images that used in testing operation of the learning of model.

Table 1. Descriptive statistics of testing images

Class Number	Class Description	Images Count	Used Images (%)
1	Normal Tomography	640	%50
2	Mild Disease	179	%14
3	Moderate Disease	12	%1
4	High-grade Disease	448	%35
Total		1279	%20

Table 2. Descriptive statistics of training images

Class Number	Class Description	Images Count	Used Images (%)
1	Normal Tomography	2560	%50
2	Mild Disease	717	%14
3	Moderate Disease	52	%1
4	High-grade Disease	1792	%35
Total		5121	%80

Figure 1 shows sample of normal brain and High-grade of AD disease brain tomography that used in our study, The brain affected by Alzheimer‘s is considerably shrunken, due to the degeneration and death of nerve cells.

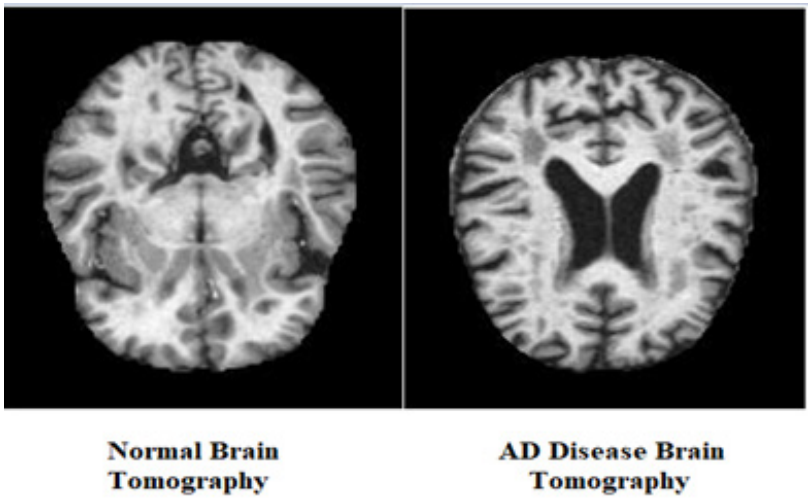

Figure 1. *Normal brain vs. Alzheimer‘s Disease*

Image Processing

Image processing is a method of converting an image into digital form and performing operations on it to obtain an enhanced image or extract some useful information from the image. It is a type where the input is an image, some kind of signal distribution, such as a video frame or a photograph, and the output can be the image, or the characteristics associated with that image. Digital x-ray is used to capture images, scan the image, or store the image in digital format like jpeg, png, so it is useful in diagnosing thepatients‘ disease. However, digital x-ray images contain images such as gaussian noise or salt and pepper noise, so they sometimes do not give a clear picture of the x-ray image. Therefore, image processing is important to remove noise in the image to improve the quality of images (13).

Convolutional Neural Networks (CNN)

Artificial Neural Networks (ANNs) are computational systems heavily inspired by the work of biological nervous systems (like the human brain). ANNs essentially consist of a large number of interconnected computational nodes (called neurons) where jobs are distributed in a distributed manner to learn collectively from the inputs in order to optimize the final output. The basic structure of an ANN can be modeled as shown in Figure 2. It is loaded in such a way as to distribute the input layer to the hidden layers, usually in the form of a multidimensional vector. The hidden layers then make decisions from the previous layer and discuss how a stochastic change within them harms or improves the final output, this is called the learning process (14).

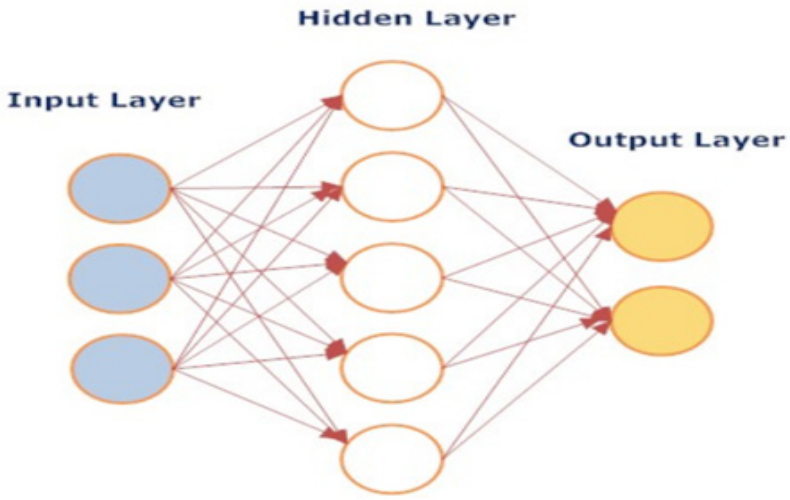

Figure 2. *ANN basic structure*

Convolutional Neural Networks (CNNs) are like traditional ANNs in that they consist of neurons that optimize themselves through learning. Each neuron will again receive an input and perform an operation that is the basis of countless ANNs. The last layer contains the loss functions associated with the classes. The only significant difference between CNNs and ANNs is that CNNs are primarily used for pattern recognition in images. This allows us to encode image-specific features into the architecture, making the network more suitable for image-oriented tasks, while further reducing the parameters required to tune the

model. One of the major limitations of traditional ANN forms is that they tend to struggle with the computational complexity required to compute image data (15). Convolutional Neural Network has produced groundbreaking results in various fields related to pattern recognition in the last decade. The most useful aspect of CNNs is to reduce the number of parameters in ANN. This success has led both researchers and developers to approach larger models to solve complex tasks which are not possible with classical ANNs. The most important assumption regarding problems solved by CNN should not have features that are spatially dependent. In other words, in a face recognition app, for example, we don‘t need to pay attention to where the faces are in the pictures. The only concern is to detect them regardless of their position in the given images. Another important aspect of CNN is to obtain abstract features when the input spreads to deeper layers (16). CNNs mainly focus on comparing input with images. It focuses on finding the architecture that will best fit the need to deal with specific data types. One of the most important differences with ANN is that the layers within the CNN consist of neurons arranged in three dimensions; The spatial dimensions of the inputs are height, width, and depth. Depth corresponds to the third dimension of an activation volume, not the total number of layers in the ANN. Neurons in any layer connect only to a small region of the layer before it.

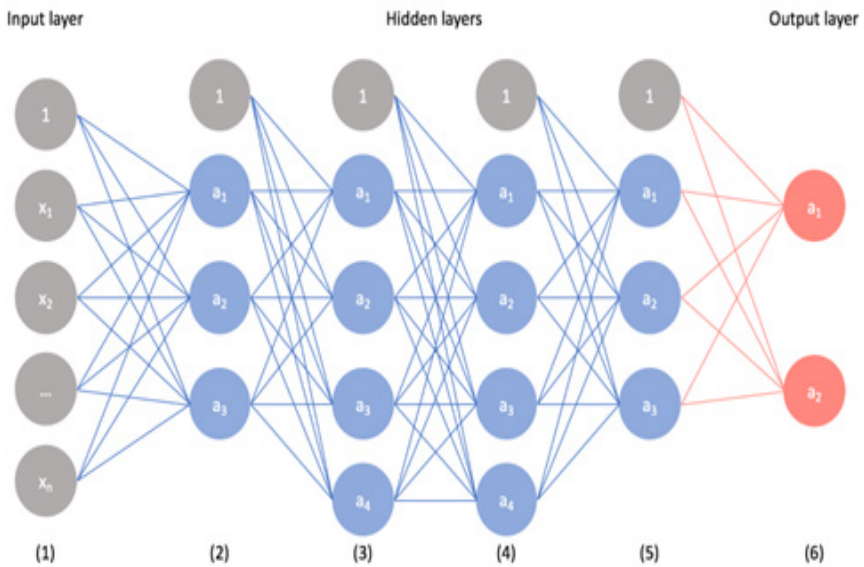

Figure 3. *CNN basic structure*

Results and Discussion

Medical images are vulnerable to noise. Therefore, noise suppression is considered a challenging task in the medical field. Medical images are preprocessed to remove unwanted data and improve quality. Feature extraction and classification are two essential components for the recognition system that have a significant impact on the efficiency of the system. In this study, DWT was used to extract relevant features. Figure 4 shows the block diagram of the proposed AH detection method. The proposed method includes the following processes: Feature extraction Feature reduction and Classification.

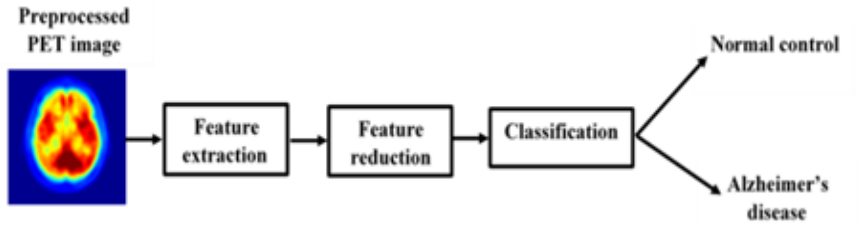

Figure 4. *Block diagram of the proposed method (15)*

Feature extraction

Feature extraction is designed to extract compact and meaningful information from the image and reduce the size by eliminating noise and unwanted data. DWT is a powerful mathematical tool that gives a multi-resolution representation of any signal or image. It decomposes the signal or image into a different frequency component and then probes each component with a resolution appropriate to its scale (17). DWT is derived from continuous wavelet transform (CWT), suitable for analysis of medical image. The strength of DWT is the use of separate sets of scales and shifts that provide sufficient information and reduce the computational load (19). In figure 5, DWT library was applied on one sample of brain MRI.

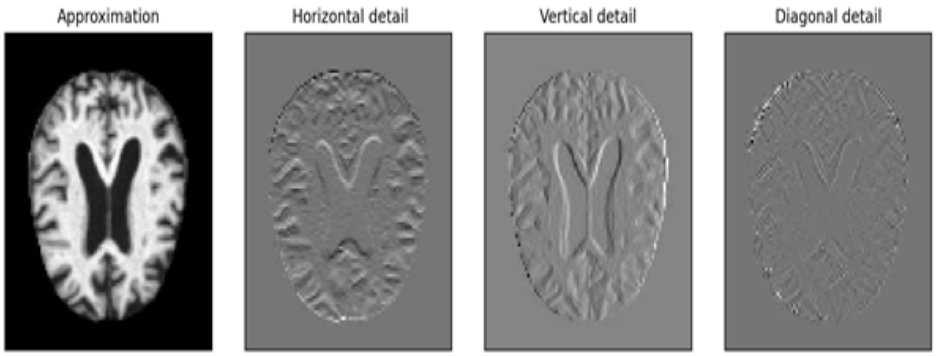

Figure 5. *Sample image preprocessing*

Conclusion and Suggestions

CNN algorithm was used to detect AD disease with machine learning, the model was processed with 6400 brain tomography, 4098 images were used for training set, 1023 images for validation and 1279 images for testing. The accuracy rate was calculated as 75%. In Figure 6, there are results showing the accuracy. The AUC (Area Under Curve) diagram was also calculated. The most popular and simple method used to measure model performance is the accuracy rate of the model. It is the ratio of the number of correctly classified samples (TP + TN) to the total number of samples (TP+TN+FP+FN). In other words, it is the ratio of the number of misclassified samples (FP+FN) to the total number of samples (TP+TN+FP+FN) (17).

$$\text{Error Rate} = \frac{FP+FN}{TP+FP+FN+TN} \qquad (17,a)$$

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN} \qquad (17,b)$$

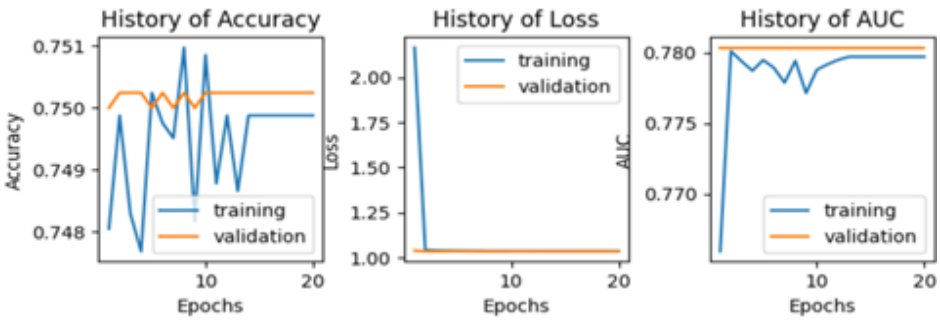

Figure 6. *Model training results*

We also used sensitivity and specificity measures to evaluate the performance of the classifiers.

Sensitivity = TP/(TP + FN) = (Number of true positive assessment)/(Number of all positive assessment).

Specificity = TN/(TN + FP) = (Number of true negative assessment)/(Number of all negative assessment).

Table 3. Comparing results between Pure CNN and CNN with DWT

Method	Accuracy	Sensitivity	Specificity
Pure CNN	0.75	0.50	0.84
CNN with DWT	0.69	0.53	0.80

It was determined that the learning time was 4 hours longer than the CNN algorithm was used with the Wavelet in Dwt library. The DWT library is used instead of MaxPooling, which is the last layer of CNN. The development has been done with Python language and the accuracy rate has reached up to 69%. Thus, we found that the normal CNN algorithm provides better performance when compared to the use of pure CNN and DWT with CNN. We can select and test different wavelet libraries to increase the accuracy.

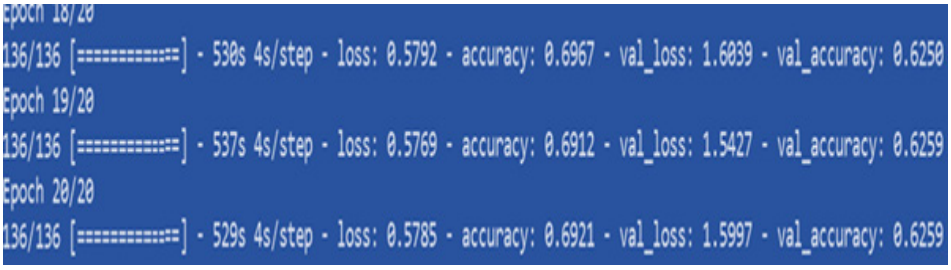

***Figure** 7. Sampling of output data based on training result.*

For future work we can use different machine learning algorithms to compare the results and get a better accuracy by using different libraries of the wavelet.

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Original Article

Forecasting the Number of Patients in the Intensive Care Unit Due To Covid-19 in Turkey by Multiple Linear Regression and Holt Time-series Methods

Sema ÜZÜLMEZ [1*], Zafer ASLAN [1]

Abstract

Objective: A novel coronavirus disease (COVID-19) pandemic originated in Wuhan, China, but has now spread around the globe. Data mining has been extensively employed throughout the pandemic's process concerning huge public health and many major consequences in the social, cultural, economic, political, legal, and military spheres. Using data mining methods, provinces, regions, and nations determined cases, mortality rates, and epidemic spread rates. Patients with severe disease suffered substantial respiratory distress and were treated in intensive care units. Hospital demand for intensive care surged due to the increasing number of intensive care units.

Methods: Due to the COVID-19 pandemic in Turkey, this study tried to anticipate the number of patients admitted to the intensive care unit between March 27, 2020, and June 5, 2020, using data from the Turkish Ministry of Health. The study compared methods using multiple linear regression and Holt Time Series analysis.

Results: The R2 value of the multiple regression method was calculated as 0.93. Since the value of 0.93 for the R2 result gives a value close to 1, the model fit is significant. According to the analysis results, the RMSE values taken from the established models are as follows. The multiple Linear Regression RMSE value is 22.221, Holt Time Series RMSE value is 39.815. Accordingly, since the Regression model produces realistic and meaningful data in the 71-day intensive care patient number in a 7-day study, the established model fit produces better forecast results than the Holt time series method.

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Conclusion: The results of the present study highlighted the use of a variety of non-pharmacological behavior management techniques among dental specialists, although few acknowledged having adequate skills to apply the techniques. The choice of the technique was mainly influenced by the children`s factors.

Keywords: *COVID-19, Intensive Care, Regression Analysis, Holt Time Series, Pandemic*

Introduction

Pandemics caused by viruses have appeared with different names many times in human history and have caused high mortality rates. After being reported to the World Health Organization (WHO) on December 31, 2019, the coronavirus disease, which caused a worldwide crisis, spread rapidly all over the world under the name of the COVID-19 epidemic. The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020, as the epidemic spread to different continents (1). With the pandemic, data analysis methods gained importance. The number of cases and death rates in the countries were reported due to these analyses. All health centers in Turkey started analyzing the daily number of cases, the number of intensive care patients, and mortality rates and sent the data to the Turkish Ministry of Health (2). The needs were determined with the data analysis, and quick action was taken. As in other countries, many scientific studies arose to cope with the pandemic in Turkey. The data used in the study are real data published by the Turkish Ministry of Health due to the COVID-19 pandemic in Turkey. In the study, 71-day intensive care inpatient data were used to make predictions, and predictions were produced for 7 days and analyzed. The analysis was made using data mining methods, and the best forecast method was chosen according to the analysis results. Python was preferred as the software language and analyzes were made with two data mining methods; libraries used in Python: Pandas, Matplotlib, Numpy, and Sklearn.

This study will help determine how present healthcare services should increase their capacity in the coming days to accommodate the expected volume of cases. Given the expected numbers, this study aims to provide communities and the government a sense of how swiftly this epidemic is growing and alert them to the initiatives that need to be taken. The number of COVID-19 epidemic cases in the G8 countries, Germany, the United Kingdom, France, specific countries, and Turkey was computed and forecasted in this study utilizing multiple curve Forecasting models, Box-Jenkins and Brown Holt linear, exponential smoothing techniques (3). Because the epidemic's beginning date differs by nation, the models are studied and applied separately for each country. The forecasts depict how the epidemic will proceed in the next days, based on the present high rate of cases.Time series forecasting involves examining earlier observations of a random variable to construct a model that best reflects the underlying relationship and its patterns.

The model then forecasts the future values of this random variable. This method is especially beneficial when there is little or no information about the underlying data-generating distribution. There is no explanatory model capable of correctly linking the prediction variable to other explanatory variables (4).

Methods

Data Review

The data used in the study are real data obtained from the web page of the Turkish Ministry of Health. The data are 71-day intensive care real inpatient data as of March 27, 2020, and analyses were carried out by producing forecasts with data mining methods. Multiple Linear Regression and Holt Time Series methods were used in the analysis, and the analysis results were compared. Python was chosen as the programming language. The intensive care patient data set used is as in Table 1.

Table 1. Sample dataset used for analysis (Turkish Ministry of Health) *

Date	Intensive care Number of patients	Intubated Number of patients	Recovering Number of patients
27.03.2020	344	241	42
28.03.2020	445	309	70
29.03.2020	568	394	105
30.03.2020	725	523	162
31.03.2020	847	622	243
01.04.2020	979	692	692
02.04.2020	1.101	783	415
03.04.2020	1.251	867	484
04.04.2020	1.311	909	786
…	…	…	…
30.05.2020	649	308	126984
31.05.2020	648	287	127973
01.06.2020	651	283	128947
02.06.2020	633	271	129921
03.06.2020	612	261	130852
04.06.2020	602	265	131778
05.06.2020	592	269	133400

** Table 1 includes the official intensive care patient data, sampled for analysis. On January 10, 2020, the Coronavirus Scientific Advisory Board was established under the Ministry of Health to combat the COVID-19 disease in Turkey (2). The Board took the necessary precautions and decisions based on these data.*

Multiple Linear Regression

Multiple Linear Regression is a sub-extension of Simple Linear Regression. It is used to predict the value of a variable based on the value of two or more variables. The variable we want to predict is called the Dependent Variable. The variables we use to forecast the value of the dependent variable are called "Independent Variables." Multiple Linear Regression also allows us to determine the model's overall fit and the relative contribution of each predictor to the total variance explained, as seen in Eq.

Multiple Linear Regression Formula (5):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

Y: The dependent Variable,

X: The independent Variable,

$\boldsymbol{\beta_0, \beta_1}$ **:** B represents the coefficients.

RMSE (Root Mean Square Error)

To measure the performance of the models used in the predictions made by regression, the root of the sum of squares of mean error is calculated as seen in Eq.

RMSE (Root Mean Square Error) Formula (5):

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{n}}$$

R SQUARE (R squared regression)

In regression analysis, after the regression Forecasting model is established, the regression coefficients, which are the coefficient of determination and called R2, are calculated. In this way, according to the result of the coefficients, the suitability of the established model is observed in Eq. (6)

R2 Formula: $$\mathbf{R^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (\hat{y}_i - \bar{y}_i)^2}}$$

$0 \leq R2 \leq 1$ takes a value between R2, when it takes a value close to 1, it can be assumed that the established model is compatible (7).

Holt time-series models

The theoretical foundations of the exponential smoothing method were first introduced in 1958 by C.C. Dropped by Holt. Holt's simple form of exponential smoothing method is applied for time series that do not contain seasonal and trend elements. The exponential smoothing method is a method that can be used in all series with a variable trend and is constantly updated by considering the latest changes and increases in the data. It is double exponential smoothing.

Holt for this Forecasting method produced one prediction and two-level equations (6).

Forecasting Equation: $\hat{y}t+h|t = lt + hbt$ (8)

Level Equation: $lt = \alpha yt + (1 - \alpha)\ (lt-1 + bt-1)$ (9)

Trend Equation: $bt = \beta\ (lt + lt-1) + (1 - \beta)\ bt-1$ (10)

Holt Model Selection Criteria:

There are criteria calculated within the model to make the best choice among Holt models. AIC and BIC, which constitute these criteria, are explained as follows.

AIC: AIC, known as the Akaike information criterion, is a technique for forecasting the probability of a model predicting future values. A good model is the one with the lowest AIC among other benchmarks. AIC aims to make the best choice among Holt-Winters models. Accordingly, a lower AIC value indicates a better fit with the model (11).

BIC: BIC, known as Bayesian information criterion, is a criterion for measuring the balance between model selection and model fit. A lower BIC value indicates a better fit see Eq. (11). The following equations are used when forecasting the AIC and BIC of a model (11, 12):

AIC = -2*In(L)+2*k

BIC = -2*In(L)+2*In(N)*k

Results

The future 7-day forecast results of the Multiple Linear Regression model created in Python and the actual number of intensive care patients received from the Turkish Ministry of Health are given in Table 3. In Python, which is used as a programming language, Pandas, Numpy, matplotlib. pyplot libraries and Sklearn were used. To make a Multiple Linear Regression forecast within the program, R2 value and β coefficient values were calculated. In addition, the RMSE value was calculated for the Multiple Linear Regression model.

Since the R2 value gives a value which is very close to 1, the model fit is significant. As seen from table 2, Multiple linear regression formula calculation and dependent and independent variable information, model outputs are shown in Table 2. Multiple Linear Regression gave the results RMSE: 22.221, R2: 0.937.

Y: The dependent Variable, **X:** The independent Variable and $\boldsymbol{\beta_0, \beta_1}$: B represents the coefficients (13).

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n$$

$Y =$ -300.270+1.985* +0.002* ...

Table 2. Calculated Multiple Regression model

Index ['IntensiveCare', 'Intubated', 'Intubated', 'Recovering']	
Forecast	R2 = 0.937
[[667.472]	
[[667.472]	B coefficients = [[1.985 0.0028]]
[623.346]	
[602.254]	RMSE = 22.221
[585.012]	
[595.551]	B0 coefficient = [[-300.270]]
[608.043]]	

Table 3. Actual and forecasted number of intensive care patients, using Multiple Linear Regression method.

Date	Intensive Care Actual	Intensive Care Forecast with Multiple Linear Regression
30.05.2020	649	667,47
31.05.2020	648	628,55
01.06.2020	651	623,35
02.06.2020	633	602,25
03.06.2020	612	585,01
04.06.2020	602	595,55
05.06.2020	592	608,04

The 7-day forecast results of the Holt Time Series model made in Python and the actual number of intensive care patients received from the Turkish Ministry of Health are given in Table 6. In addition, the Holt Time Series RMSE value was calculated. Holt time series AIC and BIC values are shown in Table 4. The RMSE for the Holt model was calculated as 39.815. The details are given in Table 5.

Table 4. Holt Model results

Dep. variable	endog	**No. observations**	63
Model	Holt	**SSE**	308207.685
Optimized	False	**AIC**	543.210
Trend	Multiplicative	**BIC**	551.782
Seasonal	None	AICC	544.710
Seasonal Periods	None	Box-Cox	False
Box-Cox-Coeff	None		

As it is seen from equation (11, 12)

AIC = -2*In(L)+2*k

BIC = -*In(L)+2*In(N)*k

where AIC is the Akaike information criterion. 2K – 2 is the AIC function (loglikelihood). Lower AIC values show a better-fit model, and a model with a delta-AIC (the difference of the two AIC values being compared) greater than -2 is deemed considerably better than the model to which it is compared (11). Furthermore, BIC stands for Bayesian information criterion where BIC is calculated as BIC = -2 * loglikelihood + d * log(N), where N is the training set random sample and d is the overall parameters. A lower BIC score indicates a better model (14).

Table 4 shows the optimized False AIC is 543.210 while Multiplicative BIC is 551.782 (11, 12).

Table 5. Coeff code optimized results

Coeff	Code	Optimized	
smoothing_level	0.8000000	Alpha	False
smoothing_slope	0.2000000	Beta	False
initial_leve	1445.0000	1.0	False
initial_slope	1.2764045	b.0	
RMSE = 39.815			

According to Table 6, it is seen that the actual number of intensive care patients with the forecasts made with the Holt time series is close to each other on some days.

Table 6. Actual and forecasted number of intensive care patients, using Holt time series method.

Date	Intensive Care Actual	Intensive Care Forecast with Holt time series
30.05.2020	649	643,91
31.05.2020	648	625,07
01.06.2020	651	606,77
02.06.2020	633	589,01
03.06.2020	612	571,78
04.06.2020	602	555,04
05.06.2020	592	538,80

According to the Holt Time Series analysis, the estimated number of intensive care patients in Turkey between the dates specified in the study and the next 7 days is given in Figure 1.

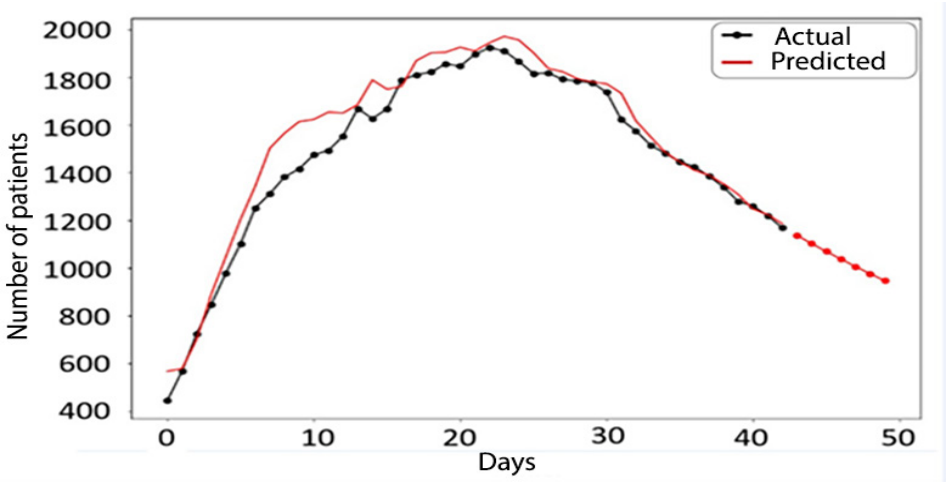

Figure 1. *Intensive care patient forecasting by Holt Time Series Model*

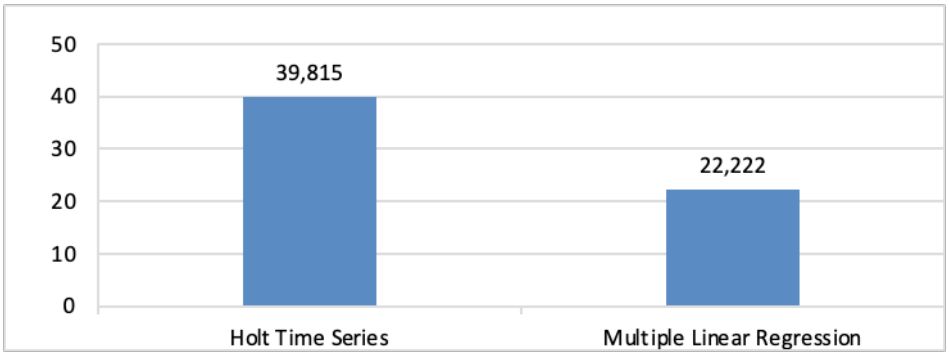

Figure 2. *Root Mean Square Error (RMSE) comparison of Holt Time Series and Multiple Linear Regression Methods*

Table 7. The actual number of intensive care patients and the forecasted results with regression analysis and Holt time series methods.

Date	Actual	Regression Forecast	Holt Forecast
30.05.2020	649	667,47	643,91
31.05.2020	648	628,55	625,07
01.06.2020	651	623,35	606,77
02.06.2020	633	602,25	589,01
03.06.2020	612	585,01	571,78
04.06.2020	602	595,55	555,04
05.06.2020	592	608,04	538,80

Table 8. COVID-19 patient outcome data*

	Number	Mean	Std	Min	25%	50%	75%	Max
Total Cases	36	9.62	1.44	768	8.47	4.76	1.01	6.63
Active	36	2.75	7.63	0.00	1.23	3.10	2.15	4.44
Discharged	36	9.46	1.41	755	8.36	4.65	1.00	6.48
Deaths	36	1.31	2.46	4.00	8.23	5.62	1.38	1.41
Active Ratio	36	3.04	4.87	0.00	3.75	1.35	3.60	2.61
Discharge Ratio	36	9.84	6.22		9.80	9.83	9.86	9.99
Death Ratio	36	1.29	5.63	0.04	9.62	1.31	1.66	2.75
Population	36	3.97	5.05	660	1.69	2.41	6.97	2.31

**The mean value and standard deviations (std) and the lowest (min) and maximum (max) quantiles are all in close correlation with one another. Mean, and standard deviation are often used metrics of central tendency and variability in data from scale variables. If data are not normally distributed, some researchers prefer reporting median and quartiles instead.*

Discussion

As a result of the analyses examined in the literature review studies, important predictions were made about the intensive care units. It was ensured that the intensive care unit needs that may arise in the future were determined in advance. Analysis by Meares and Jones (15) calculated the R2 value and a summary of results of 0.96. The R2 value of the multiple regression method in our study is 0.93. Our model fit and the success rate in the estimations are very close to each other and have values close to the predictable truth.

Ankaralı (7) stated that the time series model was less successful than the second method, as in our study. Although the prediction sizes of the two models are close, the time series analysis by Du et al. (16) was made in monthly periods due to the incubation period, to obtain 0.95 impressions in the forecasting. The authors aimed also to model the diurnal variation of infection criteria. The results showed that Germany and South Korea were at the top of the countries that control the process best and that the process in our country was similar to the countries that spread rapidly in the first 10 days. Pandey et al. (17) applied the SEIR (Susceptible-Exposed-Infected-Recovered) model and regression model in India for forecasts based on data collected from the John Hopkins University repository in January and March. The performance of the models was evaluated using the Root Mean Squared Log Error (RMSLE), obtaining 1.52 and 1.75 for the SEIR model. Weekly estimates were used in our study.

Meares and Jones (15) made forecasts for the number of intensive care beds and ventilators using different statistical models using daily data announced by official sources. In case of possible increases in the number of intensive care patients, future forecasts were made with the Gompertz and Time Series model for the number of beds and ventilators needed. SPSS and MINITAB programs were used in the calculations.

While the pandemic has been rising since February 2020 in Italy, useful estimations and forecasts have been made in the resource facility for the intensive care staff, intensive care unit, and intensive care beds needed (7).

Use of thermal camera for controlling the epidemic at airport entrances and exits, was evaluated by data mining methods, and 46% (95% confidence interval) of infected passengers could not be detected (13). Another study analyzed the probability of the virus spread to 369 cities in China from Wuhan, where the coronavirus emerged, using time series methods (14). The data and instructions that are constantly updated and instantly shared on the official website of the World Health Organization (WHO) were examined by the document analysis method. Therefore, between December 31, 2019, and March 10, 2020, the data related to the travel restrictions applied by the governments as a precautionary measure, the curfews applied in the regions where the epidemic was detected, the special measures that directly affect the tourism sector, such as the canceled international sports and arts events were evaluated within the scope of the study (18).

A study aimed to prepare the Asian intensive care unit community for the negativities in the epidemic's future. A joint study was conducted for the intensive care needs of patients with COVID-19 regarding critical patient management, and they analyzed it with the Post-hoc Analysis method (19). Despite claims by Özşahin et al. (1) that the virus is unstoppable, efforts to overcome are carried out mainly by artificial intelligence and medical advancements.

Study by Kayış (20) evaluated the 2019-nCoV process in our country, and the applicability of the growth model was examined between March 11 and April 27 in Turkey, using the 2019-nCoV data officially published by the Ministry of Health. The author proposed a Gompertz growth model to forecast the need for the number of intensive care patient beds, intensive care patients and doctors in our country (5). Another study aimed to analyze the clinical determinants of COVID-19 in patients living in Wuhan, China. Using retrospective data concerning patients with laboratory-confirmed SARS infection from the Jin Yin-tan Hospital and Tongji Hospital database, a multicenter study was conducted to forecast COVID-19 cases of death and discharge. For statistical analysis, continuous measurements were shown as mean (SD) or median (IQR) compared to Student's t-test or Mann-Whitney-Wilcoxon test (18). Using Natural Language Processing, Text Mining, and Network Analysis to analyze the community of tweets about the COVID-19 outbreak, they identified overall responses to the pandemic and how those responses differed over time worldwide until January 22, 2020.

Accurate and rapid diagnosis of suspected cases of COVID-19 plays a crucial role in quarantine measures and medical treatments. Zheng et al. (10) developed a weakly supervised deep learning-based software system for automatic COVID-19 detection in chest CTs.
Ahamed and Samad (21) explain that a graph-based model was developed using summaries of 10,683 scientific papers to find key information on three topics: genome research on transmission, drug types, and coronavirus. To obtain more topic-oriented information, they created a footer for each of the three topics.

Conclusion

In our study, it was seen that the prediction success was good in the two models used to forecast the number of intensive care patients but the forecasted numbers with the Multiple Linear Regression method were closer to the daily actual values. Therefore, the Multiple Linear Regression method should be preferred, with a lower error in line with the specified values, to help determine the deficiencies in terms of occupancy rates in intensive care units, review the intensive care bed capacities and the number of ventilators, as well as to meet the needs without delay. Based on the prediction of conditions in a probable severe pandemic such as COVID-19 in future, new data input to the Long Short-Term Memory (LSTM) techniques can also be studied, resulting in a smaller forecasting error than that in Holt Time Series.

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Primary Nasopharyngeal Neuroendocrine Carcinoma: An Extremely Rare Clinical Entity

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Abstract

Head and neck neuroendocrine carcinomas are rare, and the most common site of origin in this region is the larynx. Primary nasopharyngeal neuroendocrine carcinoma is very rare, and the number of cases reported so far is 12 patients. We present a 52-year-old female patient with a complaint of cervical mass, diagnosed with nasopharyngeal neuroendocrine carcinoma with pathological and radiological examinations. Panendoscopic upper respiratory tract examination of the patient showed a lesion suspicious of malignancy in the right Rosenmüller fossa. Biopsies performed from cervical lymphadenopathy and nasopharyngeal mass, revealed the diagnosis of poorly differentiated high-grade nasopharyngeal neuroendocrine carcinoma. The patient was referred to medical oncology department for chemotherapy and no recurrent lesion was found in the 1-year follow-up. Recognition of this rare tumor is important for disease management and patient prognosis. To draw attention to this rare clinical picture we would like to present our case in terms of diagnosis and treatment, together with a brief review of literature.

Keywords: *neuroendocrine carcinoma, nasopharynx carcinoma, head and neck cancers*

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Introduction

Neuroendocrine tumors are rare tumors that develop from neuroendocrine cells in the body. The most common sites are the lungs and the gastrointestinal tract (1). Neuroendocrine tumors are extremely rare in the head and neck region. The most common sites in the head and neck are larynx, sinonasal tract and parotid gland, respectively (2). Head and neck neuroendocrine carcinomas are usually seen in the 6th and 7th decades with prominent male predominance (3). Head and neck neuroendocrine carcinomas are classified according to WHO as such; poorly differentiated (> 10 mitosis/10 HPF), moderately differentiated (2-10 mitosis / 10 HPF with necrosis) and well differentiated (minimal nuclear atypia and <2 mitosis / 10 HPF). Poorly differentiated neuroendocrine carcinomas are further divided into two as large cell (LCNEC) and small cell neuroendocrine carcinoma (SCNEC). These malignant tumors have an aggressive course and a 5-year life expectancy of less than 20% (2).

Symptoms and signs in nasopharyngeal neuroendocrine carcinoma are similar to nasopharyngeal carcinoma; lymphadenopathy in the neck, especially in the posterior cervical triangle, nasal obstruction, epistaxis, serous otitis media due to Eustachian tube dysfunction. Among the etiological agents, smoking and human papilloma virus can be shown, which are also prevalent in squamous cell carcinoma of the oral cavity and oropharynx. While non-neuroendocrine tumors of the nasopharynx are largely associated with EBV, the role of EBV in the development of neuroendocrine carcinoma is not fully known. EBV is seen as a prognostic factor for nasopharyngeal malignancies. Treatment response and life expectancy are higher in EBV-positive nasopharyngeal carcinomas and lymphomas compared to EBV-negative malignancies (4).

In this case presentation, it was aimed to present this rare malignancy of head and neck region in the light of the literature and to provide additional information on the prognosis and follow-up, which were inadequately reported due to its rare occurrence.

Case Presentation

A 52-year-old female patient presented with the complaint of multiple swellings on the neck for 6 months. In physical examination, bilateral submandibular, level 2-3 lymphadenopathies were palpated. Endoscopic examination revealed a suspicious mass lesion in the right Rosenmüller fossa of nasopharynx. Ultrasonography (USG) examination revealed multiple lymphadenopathies in bilateral cervical lymphatic chain, with disappearance of the hilus formation, showing peripheral vascularity, with the largest being 38x16mm.

Contrast-enhanced nasopharyngeal magnetic resonance imaging (MRI) revealed thickening of the posterior wall of the nasopharynx and multiple lymphadenopathies at levels 1-2-3-4 of the neck (Figures 1A-1B). Intense FDG uptake (SUVmax: 24) in the right Rosenmüller fossa and a hypermetabolic nodular lesion with high suspicion for malignancy in the right parapharyngeal space (SUVmax: 16) was seen in positron emission tomography-computerized tomography (PET/CT) scan. In addition, conglomerated lymphadenopathies accompanied by intense FDG uptake (SUVmax: 28) were observed in bilateral cervical lymphatics. Moreover, multiple lymphadenopathies reaching 2 cm in size, with increased FDG intake in PET/CT in the right preauricular, right superficial parotid, bilateral supraclavicular lymph node stations and mediastinum, were observed.

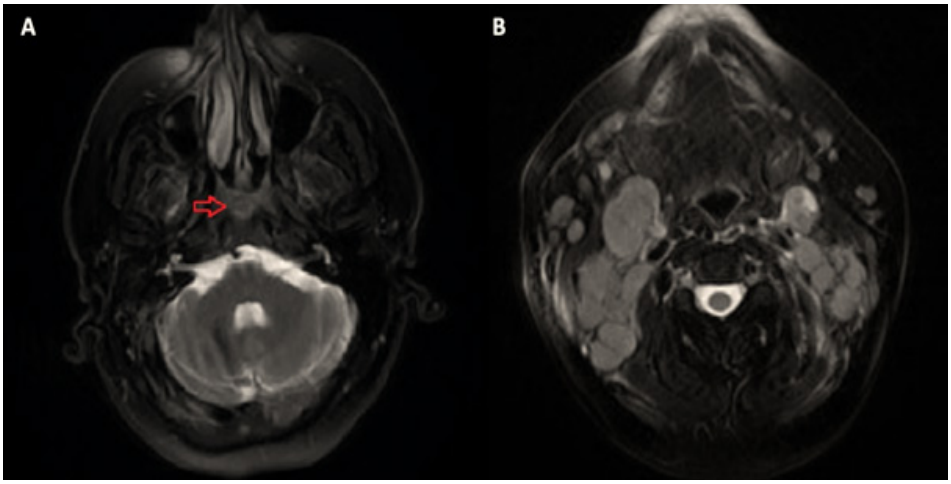

Figure 1. *(A) Axial section of the nasopharyngeal MRI shows an asymmetrically thickness in the posterior wall of the nasopharynx at the right side. (B) Axial section of the cervical MRI shows multiple conglomerated lymphadenopathies in the bilateral cervical lymphatic chain.*

Discohesive, atypical, pleomorphic cells which observed in fine needle aspiration cytology slides from cervical lymphadenopathy was interpreted as a metastasis of a malignant neoplasm. Histopathological examination of the incisional biopsy specimen from the nasopharynx revealed that the tumor cells formed a solid pattern with diffuse synaptophysin (Figure 2A) and cytokeratin-7 positivity (Figure 2B). EBER (Epstein-Barr virus-encoded small RNAs) and chromogranin was negative, while p40 showed focal nuclear positivity. In the light of these findings, according to WHO's classification, the patient was diagnosed with poorly differentiated (high-grade) carcinoma of the nasopharynx.

The patient was scanned with 68Ga-DOTATATE PET/CT, which is a specific imaging method for neuroendocrine carcinoma. Since there was no other foci in the body expressing somatostatin receptor type 2, the lesion was interpreted as primary nasopharyngeal neuroendocrine carcinoma. Chemotherapy regimen which contains cisplatin + etoposide was applied to patient by medical oncology department. After a 1-year follow-up, PET/CT scan showed no pathological FDG uptake in nasopharynx and bilateral cervical lymphatics.

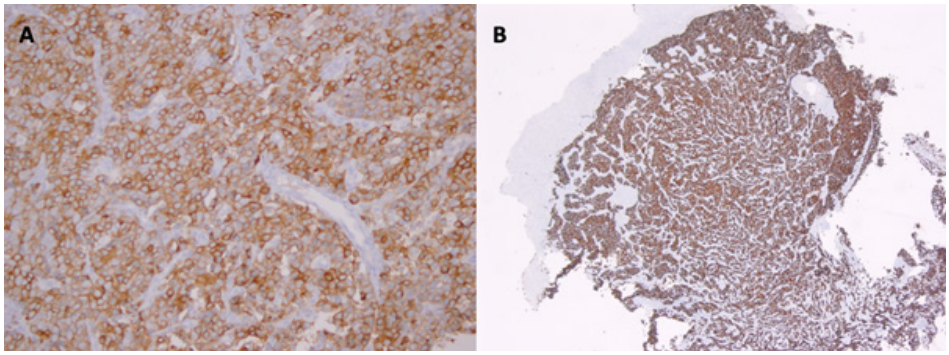

Figure 2. *Light microscopic image. (A) Cytokeratin-7 positivity in tumor cells. (B) Synaptophysin positivity in tumor cells with immunohistochemical staining.*

Discussion

Primary head and neck neuroendocrine carcinomas are extremely rare. Therefore in case of neuroendocrine carcinoma in a subsite of head and neck, primary versus metastasis differentiation should be made firstly (5, 6). Small cell carcinoma of the lung may be presented as extra-pulmonary neuroendocrine carcinoma focus due to its aggressive course. For this reason, while thorax CT had an important place in the approach to head and neck neuroendocrine carcinomas in the past, nowadays, whole body scanning should be performed with 68Ga-DOTATATE PET-CT, which is a neuroendocrine carcinoma specific imaging method.

The most common malignancy of the nasopharynx is non-keratinized undifferentiated carcinoma originating from the nasopharyngeal mucosal layer and is closely related to EBV. However nasopharyngeal neuroendocrine carcinoma is extremely rare. Among 12 cases reported to date, it was more common in males at a ratio of 10:2. Ten out of twelve cases reported to date have been reported as poorly differentiated. Three of these were reported as small cell neuroendocrine carcinoma, five as large cell neuroendocrine carcinoma and EBV was positive in three of the large cell neuroendocrine carcinoma cases (3, 7, 8, 9, 10). In the other two cases, EBV serology is unknown. For this reason, it is thought that EBV may be responsible for large cell nasopharyngeal neuroendocrine carcinoma (3).

It has been shown that the sensitivity of EBV-positive patients to chemotherapy and radiotherapy is higher than that of EBV-negative cases, so it has been estimated that EBV may be an important criterion in prognosis even if it did not play a role in etiology (3).

The treatment modality in head and neck neuroendocrine carcinomas depends on whether the tumor is resectable or unresectable or metastatic. Surgical treatment and adjuvant chemoradiotherapy is the treatment of choice for resectable tumors, while chemoradiotherapy alone is preferred for unresectable and metastatic tumors. Histopathologic characteristics of the tumor are also important factors for the treatment choice. While chemoradiotherapy is preferred primarily for small cell neuroendocrine carcinomas; surgery comes to the fore in non-small cell neuroendocrine carcinomas (11). In a 20-year case follow-up study consisting of 16 cases; 11 of the patients had poorly-differentiated, 4 had moderately-differentiated, and 1 had well-differentiated neuroendocrine carcinoma in the head and neck region; with no statistically significant difference between moderately differentiated carcinoma and poorly differentiated carcinoma in terms of 2-year survival after treatment (%37.5 vs. %35.4) (12).

The follow-up of only 7 of 12 patients diagnosed with nasopharyngeal neuroendocrine carcinoma has been reported. In 6 cases of poorly differentiated nasopharyngeal neuroendocrine carcinoma with known follow-up, 2 patients were cured and 4 patients died despite treatment. In the case with well-differentiated nasopharyngeal neuroendocrine carcinoma, the patient was followed up with the disease for 7 years (3). In a case of small cell nasopharyngeal neuroendocrine carcinoma in 2007, a 43-year-old male patient died after 38 months of follow-up despite combined chemoradiotherapy (13). However, in another case report presented in 2011, a 41-year-old male patient diagnosed with small cell nasopharynx neuroendocrine carcinoma was said to be cured after 9 months of follow-up with combined chemoradiotherapy (14). Hence, the prognosis is expected to be poor especially in small cell nasopharyngeal neuroendocrine carcinoma due to poor differentiation, but there is insufficient data about the prognosis due to the low number of reported cases. Since the cases reported so far were mostly handled according to their histopathological characteristics, there is not enough information about follow-up and prognosis.

Conclusion

Nasopharyngeal neuroendocrine carcinoma is extremely rare. Most of the cases reported to date were poorly differentiated carcinomas and a significant proportion of them had a poor prognosis. Although nasopharyngeal neuroendocrine carcinomas are not among the common nasopharyngeal malignancies; it should be considered in the differential diagnosis of patients with complaints of hearing

loss due to serous otitis media, nasal obstruction, epistaxis, neck mass especially in the posterior cervical triangle. Since it has poor prognosis, as far as we know, combined treatment with chemotherapy and concomitant radiotherapy should be initiated, as soon as possible.

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WRITING RULES

Manuscript Preparation

General Rules

Articles should be organized according to the ICMJE recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals updated in December 2019 (http://www.icmje.org/icmje-recommendations.pdf). CONSORT (www.consort-statement.org) for randomized trials, STROBE for observational studies (http://strobe-statement.org/), PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/), STARD for studies of diagnostic accuracy (http://www.equator-network.org/reporting-guidelines /stard/), ARRIVE for experimental animal studies (https://arriveguidelines.org/), and TREND for non- randomized public behavior (https://www.cdc.gov/trendstatement/) are other guidelines to help authors design their articles.

The upper limit of plagiarism determined by the editorial board for the journal is 20 percent. The filtering options in the plagiarism detection program are set to neglect references, quotes, and text sections of less than five words.

If there is an institution that supports the study, the last word of the article title should have an asterisk (*) and the information on the same page should be given as a footnote.

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A separate title page should be submitted and this page should include:

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- Name(s), affiliations, highest academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Nameandaddress,phone(includingthemobilephonenumber) number and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript without fufilling the authorship criteria.

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An English abstract should be submitted with all kind of manuscripts with the exception of Brief Reports and Letters to the Editor. The abstract of an Original Article should be

constructed with subheadings (Objective, Methods, Results, and Conclusion). All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition. Please refer to Table 1 below for word count specifications.

Keywords

All manuscripts except Brief reports and Letters to the Editor must be accompanied by a minimum of three to a maximum of six keywords at the end of the abstract. Keywords should be selected from Medical Subject Headings (MeSH) of Index Medicus (https://www.nlm.nih.gov/mesh/MBrowser.html) Keywords will be used for subject indexing.

Table 1. *Limits in Manuscript Types*

Article Type	Text Words	Abstract Words	Keywords	References	Tables	Figures/ Images
Original Article	7.500	300	5	30	10	10
Review Article	10.000	250	5	50	10	20
Case Report	1.500	200	3	20	1	10
Brief Report	2.000	200	3	20	1	10
Letter to the Editor	1.000	No abstract	No keywords	10	1	No figures/ images

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are found to be conflicting with this guideline, will be rejected and will not be issued.

Manuscript Types

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Original Article: Research article is the most important type of manuscript because it provides new information as a result of original research. The main text of original articles should be structured in detail with Introduction, Materials and Methods, Results, Discussion, and Conclusion subtitles and sections. Conclusions are supported by statistical analysis which is mainly necessary. Statistical analyses must be in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489–93).

Information on statistical analyses should be supplied in a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be included. Units should be prepared in accordance with the International System of Units (SI).
Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

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current level of knowledge of a topic and guide future studies in the field. EJOH may also invite submissions from such authors. The main text should contain Introduction, Research Consequences, and Conclusion sections.

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Page Layout: Standart A4-sized format. Margins: top 3.5; down 2.5; left 2.5; right 2 cm with 170 mm X 240 mm overall text space.

Font: Times New Roman style and 11 pt. font size are used for the whole text. All article should be justified. Single line spacing should be used throughout the main text and between the paragraphs.

Title: Bold capital letters in 14-pt must be used fort he main title. Subtitles should be written in bold and 11 pt,. After the title, author names, author ORCID numbers and e-mail addresses should be stated in 11 pt font size, with two lines of space.

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When a drug, product, hardware, or software program is mentioned within the main text,

product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: “Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)”

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