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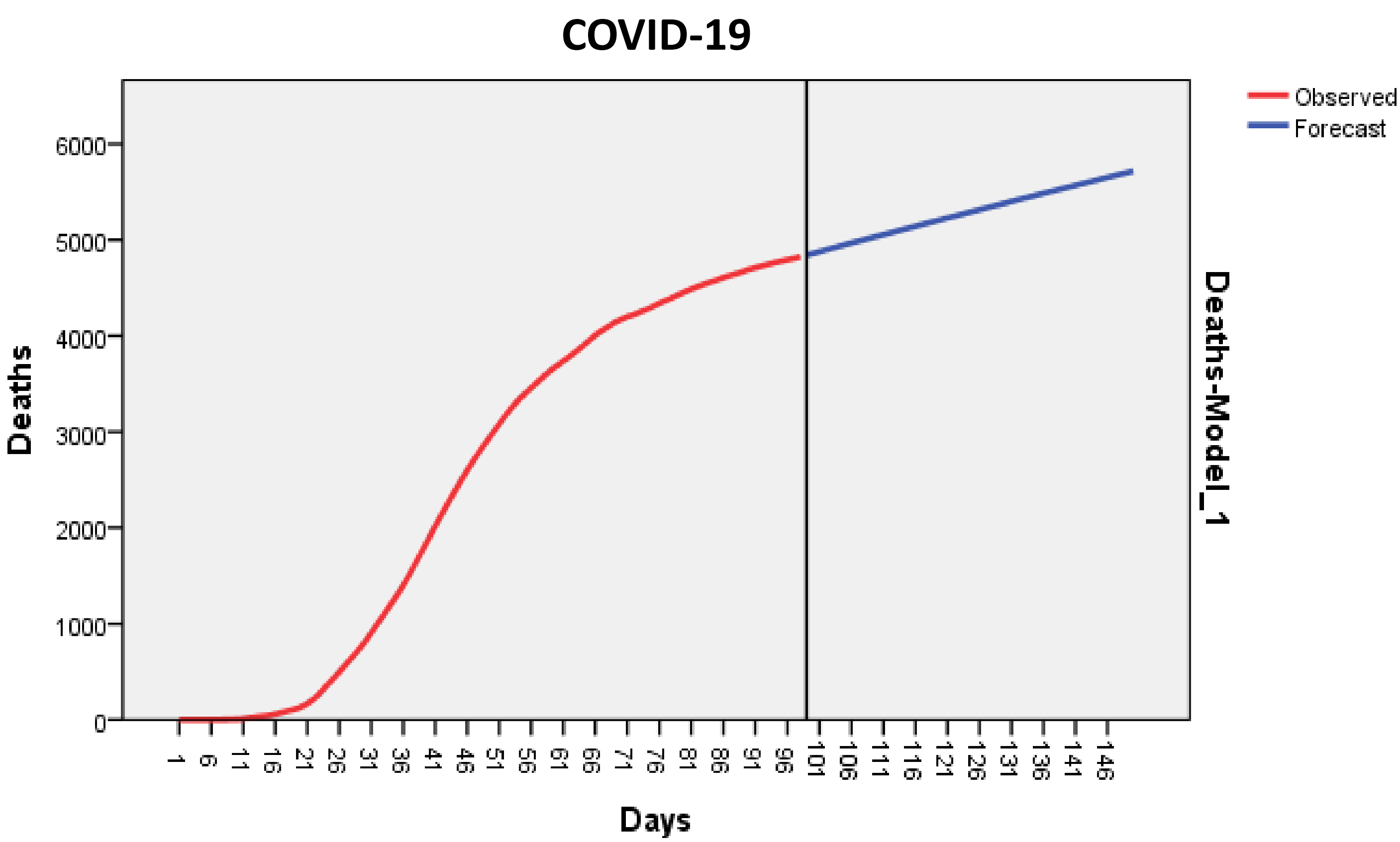

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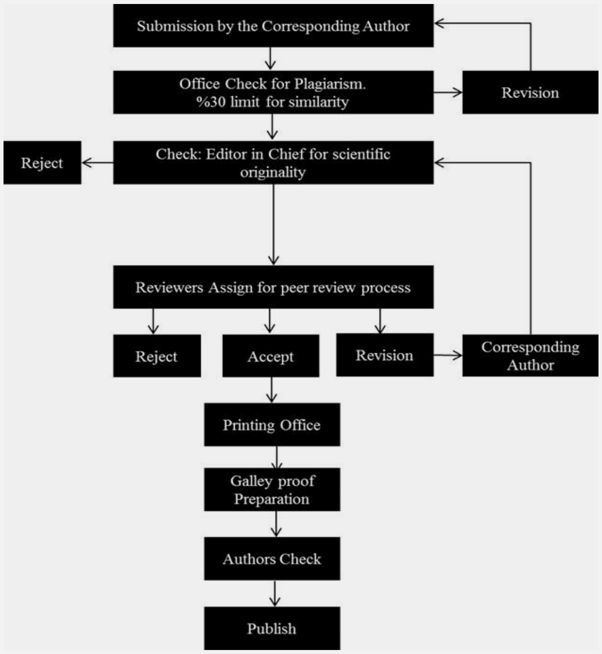

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Blood group A is a negative risk factor for peripheric blood stem cell mobilization in allogeneic donors

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Abstract

Objective: Many factors, including advanced age and female gender, have been identified as negative factors for peripheric blood hematopoietic stem cell (HSC) mobilization. Similarly, blood group antigens may have an effect on the release of HSCs from the bone marrow niche into the periphery. We aimed to study the effect of ABO and Rh blood groups on peripheral blood HSC mobilization in healthy donors.

Material and Method: The data of 314 healthy donors who underwent peripheric blood HSC mobilization in our center were analyzed retrospectively.

Results: The number of CD34+ cells collected on the first day and in total was the least in donors with blood group A. A statistically significant relation was found between ABO blood groups and the number of CD34+ cells collected on the first day and in total. No relation was found between Rh positivity and the number of CD34+ cells collected.

Conclusion: According to our research in the literature, this is the first study that investigates whether blood groups have an effect on the release of HSCs from the bone marrow niche into the periphery and we observed that blood group A is a negative risk factor for peripheric blood HSC mobilization.

Keywords: blood groups, peripheric, stem cell, mobilization, healthy donors

Introduction

Proteins, glycoproteins, and glycolipids on the surface of erythrocytes define the blood groups' antigens (1). Today, the number of serologically described blood group antigens is more than 600. The majority of blood group antigens are glycoproteins and they are generally described according to their oligosaccharide and amino acid series.

The antigens of ABO blood groups are present on the extracellular membranes of erythrocytes and these antigens are described as complex carbohydrate molecules (2). Besides ABO blood group, Rh blood group is found in the system and at least 45 independent antigens are formed (3).

Progenitor cells constitute only 0.01-0.05% of all nucleated cells in peripheral blood (4,5). Progenitor cells adhere to the micro-environment of the bone marrow with various interactions. The stroma of the bone marrow contains stromal cell-derived factor 1 (SDF-1), vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule-1(ICAM-1) and P-selectin glycoprotein ligand, all of which are ligands for stem cell adhesion molecules (6-8). Inhibition of these receptor-ligand interactions cause increases in the mobilization of progenitor cells (6,7,9).

It has been shown that selectins have a role in the homing of hematopoietic stem cells (HSCs) in the bone marrow (10, 11). On the other hand, ICAM-1 has a role in leukocyte migration, adhesion, and activation, in addition, it may have a role in the regulation of HSC functions (12-16). In previous studies, a relation was found between ABO blood groups and the expression of ICAM-1 and P- selectin (17-21). In the study conducted by Zhang et al, they revealed that blood group A is related to the lowest expression of ICAM-1 and P- selectin (22).

Studies have shown that the number of HSCs infused is closely related to transplant outcomes. Since early neutrophil and platelet engraftment are thought to have a positive effect on survival, risk factors for HSC mobilization should be identified (23-26).

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As it has been shown that blood group A is associated with lowest expression levels of ICAM-1 and P-selectin, and as selectins play a role in the bone marrow homing of HSCs and ICAM-1 has a role in cell migration; we hypothesized that blood group A may be a negative risk factor for peripheral HSC mobilization. To reveal this, we aimed to study the effect of blood groups on peripheral blood HSC mobilization in healthy donors.

Material and Methods

In this study, the data of healthy allogeneic donors at the age of 18 years and older, who underwent peripheric blood HSC mobilization at our center were analyzed retrospectively. The study was conducted according to the criteria set by the declaration of Helsinki. Each donor signed informed consent before HSC collection. Ethics approval for the study was obtained from the Ethics Committee of the University of Health Sciences, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Center.

Donors were mobilized with a total of 10 μg/kg subcutaneous granulocyte colony-stimulating factor (G-CSF) in 2 divided doses (2×5 μg/kg). On the 4th day, if the peripheric blood CD34+ cells' count is ⩾50/μL, stem cells started to be collected; if not, G-CSF dose was omitted in the donors whose white blood count (WBC) is ⩾ 75.000/mm3 and the G-CSF dose was reduced by half for the donors whose WBC is ⩾50.000/mm3, in other donors, G-CSF continued with the same dose and on the 5th day, peripheric blood-derived stem HSCs were collected with a continuous flow blood separator (Fresenius Kabi, COM.TEC, Germany). A total volume of 150 to 400 mL/kg blood was processed for each apheresis at a flow rate of 50 to 60 mL/min. When the number of CD34+ cells collected could not reach the target, G-CSF was continued and the apheresis procedure was repeated the following day. Filgrastim was used in 204 (87.9%) donors and lenograstim was used in 28 (12.1%) donors. Mobilization failure was defined as a CD34+ cell collection below 2 × 10^6 CD34 + cells / kg.

IBM SPSS Statistics (version 21) was used for statistical analysis. Descriptive statistics were used to summarize the data. The suitability of the variables to normal distribution was examined by visual (histogram and graphs) and analytical methods (Shapiro-Wilk and Kolmogorov-Smirnov test). Categorical data were expressed as a ratio, and numerical data were expressed as median and mean ± standard deviation. Kruskal Wallis tests were used for comparison of non-parametric numerical data between groups. P values <0,05 were treated as statistically significant

Results

A total of 314 healthy donors were included in the study. The median age was 35 years (range 19 to 65 years). 195 (62,1%) donors were female and 119 (37,9%) were male. The target number of CD34 + cells (5 x 10^6 / kg) was reached on day 4 in 221 (70,4.%) donors. In 213 (67,8 %) donors 1 apheresis procedure was performed to achieve the targeted CD34 + cell count (5 x 10^6 / kg), 2 apheresis procedure was performed in 96 (30,6%) donors and 3 apheresis procedure was performed in 5 (1,6%) donors. There was no donor with the number of HSC collected below 2 x 10^6 / kg. The median number of HSCs in the first and total apheresis products were 6,74 x 106 / kg and 7,60 x 10^6 / kg, respectively.

The number of CD34+ cells collected on the first day and in total was the least in donors with blood group A. A statistically significant relation was found between ABO blood groups and the number of CD34+ cells collected on the first day and in total. The median number of the apheresis procedure to achieve target was 1 in all ABO blood groups (Table 1).

277 healthy donors were Rh positive and 37 donors were Rh-negative. No statistically significant relation was found between Rh positivity and the number of CD34+ cells collected on the first day and in total (Table 2).

The number of CD34+ cells collected on the first day and in total was the least in A Rh-positive allogeneic donors (Table 3).

Table 1: Mobilization results of donors according to ABO blood groups

Blood Groups	CD34+ cells collected on the 1st day (median) (10^6/kg)	CD34+ cells collected in total (median) (10^6/kg)	CD34+ cells collected on the first day(median) (/µl)
A (n=113)	5,77 (2-16,6)	6,90 (2,8-20,9)	1073 (200-10207)
B (n=67)	7,93(2,9-26,3)	8 (3-26,3)	1637 (432-5030)
0 (n=114)	6,94 (2 -21)	8 (2,9-21)	1472 (356-4375)
AB (n=20)	7,08 (2,9-16,6)	8,67 (4,7-16,6)	1773 (827-3067)
p-value	0,003**	0,039*	0,001**

Table 2: Mobilization results of donors according to Rh groups

Blood Group	CD34+ cells collected on the first day (median) (10^6/kg)	CD34+ cells collected in total (median) (10^6/kg)	CD34+ cells collected on the first day (median) (/µl)
Rh positive (n=277)	6,83 (2 -26,3)	7,64 (3-26,3)	1317 (200-5030)
Rh negative (n=37)	6,4 (2,5-12,9)	6,9 (2,9-20,9)	1252 (510-10207)
p-value	0,508	0,382	0,547

Table 3: Mobilization results of donors according to ABO and Rh groups

Blood Group	CD34+ cells collected on the first day (median) (10^6/kg)	CD34+ cells collected in total (median) (10^6/kg)	CD34+ cells collected on the first day (median) (/µl)
A Rh (+) (n=95)	5,59 (2-16,6)	6,77 (2,8-16,6)	1065 (200-2708)
A Rh (-) (n=18)	5,71(2,5-11,2)	7(4,5-20,9)	1221 (800-10207)
B Rh (+) (n=62)	7,94 (2-26,3)	8 (2-26,3)	1728 (432-5030)
B Rh (-) (n=5)	7,15(2,9-12,9)	8,5 (3,5-12,9)	1349 (560-1631)
0 Rh (+) (n=102)	6,87 (2-21)	8 (2,2-21)	1494 (356-4375)
0 Rh (-) (n=12)	8,59 (2,8-11,6)	7,40 (2,9-11,6)	1162 (510-2346)
AB Rh (+) (n=18)	6,69 (2,9-16,6)	8,3 (4,7-16,6)	1773 (827-3067)
AB Rh (-) (n=2)	8,67(8,4-8,8)	8,67 (8,5-8,8)	2085 (1297-2874)
p-value	0,042**	0,193	0,000**

Discussion

Allogeneic stem cell transplantation (Allo-SCT) is a potentially curative treatment for a variety of benign and malignant hematological diseases. A successful Allo-SCT depends on the infusion of an adequate quantity of HSCs (27,28). Compared to HSC mobilization in healthy donors, there are more factors affecting the amount of HSCs collected in patients with hematologic malignancy, such as underlying disease, radiotherapy history, type, and number of chemotherapies. As there are more factors affecting the amount of HSCs collected in patients with hematologic malignancy, in this retrospective study, we aimed to analyze the effect of donor blood groups on peripheral blood HSC mobilization in healthy donors.

Mobilization failure rate has been reported as 2-40% in various studies (29-34). The prevalence of mobilization failure was 7.6% in the study conducted by Özkurt et al., where mobilization failure was defined as a collection of less than 2×10^6 CD34+ cell/kg (35). In our study, similarly, mobilization failure was accepted as a cell collection less than 2×10^6 CD34+ cell/kg; and there was no mobilization failure.

To prevent mobilization failure, the factors that have a negative impact on the amount of CD34+ cells collected should be demonstrated. Many factors, including advanced age and female gender, have been identified as negative factors for peripheric blood HSC mobilization (36-38). Similarly, blood group antigens may have an effect on the release of HSCs from the bone marrow niche into the periphery. In a European ancestry population, it was observed that the A1 blood group allele was associated with the lowest expression levels of ICAM-1 and P-selectin (20). In our study, the number of CD34+ cells collected on the first day and in total was the least in donors with blood group A. A statistically significant relation was found between ABO blood groups and number of CD34+ cells collected on the first day and in total.

Human leukocyte antigen (HLA) allele compatibility, young age, and male donor are important factors in allogeneic donor selection. In order to prevent erythrocyte engraftment failure, major and minor ABO blood group incompatibility between patient and donor is avoided. However, the choice of mobilization method (G-CSF, G-CSF + chemotherapy, or plerixafor) in autologous stem cell collection is made according to the patient's mobilization risk factors. Therefore, identification of all factors affecting HSC mobilization is of great importance.

Conclusion

According to our research in the literature, this is the first study that investigates whether blood groups have an effect on the release of HSCs from the bone marrow niche into the periphery and we observed that blood group A is a negative risk factor for peripheric blood HSC mobilization. Further studies are needed to reveal all the factors affecting mobilization in order to achieve an adequate number of CD34+ cells.

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Questionnaire-based evaluation of satisfaction levels in patients receiving chemotherapy through implanted venous access ports

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Abstract

Objective: This study aimed to evaluate the effect of totally implanted venous access ports on the quality of life and patient satisfaction of cancer patients.

Materials and Methods: The study was comprised of patients who underwent implantation of a central venous port catheter (CVPC) for chemotherapy treatment at our hospital's oncology department and continued with follow-up and treatment. The researchers conducted face-to-face interviews with the participants in which the latter responded to 15 questions concerning the effects of the port catheter on daily quality of life and satisfaction with the implantation procedure.

Results: A total of 260 patients participated in the study. Port-related complications were observed in 54 patients (20.7%), the most common being catheter occlusion. Participants expressed high levels of satisfaction and stated that the CVPC had a positive effect on their quality of life. Overall satisfaction and quality of life were significantly different for patients who experienced complications compared to those without, however, with the former reporting decreased satisfaction and increased stress and anxiety levels. Nevertheless, there was no significant difference between the patients who developed complications and those who did not concern their response to the statement: "Faced with a similar situation requiring a port catheter, I would make the same decision" (54.5% versus 52%, p = .188).

Conclusion: Most patients reported overall satisfaction with the CVPC system while noting a minor negative impact on daily life. Complications related to the implantation procedure have statistically been shown to be a predictor of satisfaction and quality of life.

Keywords: Cancer, central venous, port, catheter, patient satisfaction

Introduction

Cancer is one of the leading causes of mortality on a global scale, with the number of new cases increasing every year. Patients frequently experience negative psychological as well as physical outcomes resulting from the disease and its treatment (1). This has led to an increase in studies not only on cancer response rates and survival times but also on patients' quality of life. In addition to cancer itself, the methods used to treat it, such as surgery, chemotherapy, feeding tubes used for enteral nutrition, and central venous catheters, have a significant impact on the quality of life (2, 3).

Central venous catheters are attached to patients with malignant or chronic diseases to provide easier vascular access during treatment. The use of such catheters is generally preferred for patients requiring long-term treatment and/or multiple treatments at intervals (4).

While port catheters constitute a major convenience for cancer patients, nonetheless complications may develop during their placement or use. In the early period, pneumothorax, hemothorax, malposition, malfunction, arrhythmia, cardiac perforation, port pocket hematoma, embolism, arteriovenous fistula, left thoracic ductus lesion, and/or phrenic or brachial plexus lesions may occur. During the late period, skin necrosis, catheter breakage, embolism, infection, catheter occlusion and disconnection, extravasation of fluids, difficulty in detecting the port, and aspiration of blood have been encountered (5).

Studies on venous port systems generally focus on risks and complications, with patient perception considered of secondary importance. However, in recent years, there has been an increased emphasis on the patient's point of view regarding medical procedures (6), and different tools have

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been developed to evaluate patients' quality of life. Thus, physical health no longer remains the sole meaningful outcome when assessing the success of a medical procedure (7). Psychosocial factors, for example, can positively affect perceived cancer pain (8). For this reason, greater importance is now placed on the quality of life for patients with extended life expectancy, as well as on their experiences with the medical procedures they undergo.

This study aimed to evaluate the effect of a single type of totally implantable venous catheter on the daily life and patient satisfaction of cancer patients

Material and Methods

Patients

Patients who received a central venous port catheter (CVPC) at our hospital's oncology department and continued with follow-up and treatment were included in the study. The criteria for inclusion were as follows: minimum age of 18, a diagnosis of malignant disease, chemotherapy treatment with a CVPC, conscientious response to the researchers' questions, and a life expectancy of 6 months or longer. Data concerning patients' age, gender, performance status, educational status, diagnosis, treatments received, the total number of central venous port catheters applied, port insertion and removal dates, and types of complications (thrombosis, infection, and mechanical) were recorded. Port insertion and removal dates were obtained by interviewing the patients and referencing hospital records. The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Implantation procedure

Coagulation parameters of the patients including prothrombin time, INR, activated partial thromboplastin time, and platelet counts were examined before the procedure. During the procedure, all patients were non-invasively monitored. As the first choice, the right subclavian vein was preferred due to the convenience of access and satisfactory cosmetic outcomes. For patients who had a history of right mastectomy, receiving radiotherapy on the right thoracic side, or in the presence of unavailability of right subclavian vein for vascular access due to the several causes, the left subclavian or internal juguler venous route was used. All procedures were performed under local anesthesia with sterile conditions in the operating room. The subclavian vein was percutaneously punctured using the Seldinger needle through landmark technique. The needle was placed under the inferior margin of the one-third lateral of the clavicle in a horizontal plane and gingerly directed with a negative aspiration toward the anterior margin of the trachea at the level of the suprasternal notch. Following the aspiration of venous blood, a 0.035-inch guidewire was inserted through the needle, until an arrhythmia trace was seen on the monitor. If an arrhythmia trace was not seen or there was a suspicion on guidewire location, a fluoroscopic examination was performed to detect the location of the wire. A subcutaneous pocket was created above the second costa for the placement of the port reservoir through making a transverse incision with a size of approximately 2-3 cm. A tunnel was formed between the puncture site and subcutaneous pocket. A silicone catheter with a diameter of 7 or 8 F was inserted through the tunnel, and a tip of the catheter was connected to the reservoir placed into the subcutaneous pocket. A peel-away sheath combined with a vascular dilator was passed over the guidewire. Following the dilator and guidewire removal, the catheter was inserted through the sheath. After the catheter was advanced, it was confirmed by c-arm scope that the catheter tip was in the vena cava superior or cava-atrial junction. The reservoir and catheter were washed with a 20-mL isotonic sodium chloride solution and, then, the reservoir was filled with a 5-mL isotonic sodium chloride solution containing 100 U/mL of unfractionated heparin. The base of the reservoir was fixed to the fascia of the pectoralis major muscle with the absorbable sutures, and the skin was sutured using the polypropylene threads. At the end of the procedure, the port catheter localization was checked with posteroanterior chest radiography. Experienced nurses were responsible for the maintenance and use of these devices during treatment. Patients were evaluated after undergoing at least 4 weeks of treatment, and those who had received a port catheter for chemotherapy were recorded.

Questionnaire and survey design

A 15-item questionnaire was designed to evaluate patient satisfaction with the implantation procedure, the effects of the port catheter on the overall quality of life, and psychosocial issues. The organization of the questionnaire followed that used in a previous similar study (7). While one objective was to consider everyday situations in which a port can be inconvenient or unpleasant, focus was also directed at the positive aspects of having a port, especially with regard to receiving treatment. The questions in the survey were evaluated by the means of face-to-face interviews with the patients. Patients were requested to choose the most suitable of five possible responses to each statement, these being "strongly disagree", "somewhat disagree", "neither agree nor disagree", "somewhat agree", and "strongly agree".

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are presented as counts. Categorical variables were compared using the Chi-square test or Fisher exact test for small samples. Values of $p<0.05$ were considered statistically significant. The statistical analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA) for Windows

Results

A total of 260 patients agreed to participate in the study. The most common diagnosis was colon cancer, followed by stomach cancer and head and neck cancer. The mean age was 56 years and men comprised 52% of the participants. Half of the patient population consisted of primary school graduates. Of those included in the study, 60% were patients with Stage 4 disease, and the most frequently used treatment protocol was the FOLFOX regimen. Patient characteristics, including demographic data as well as disease type, severity, and treatment, are shown in Table 1.

The average number of catheter days of the patients was 431. Port-related complications were observed in 54 patients (20.7%), the most frequent complication being catheter occlusion. Port-specific information is presented in Table 2.

A total of 157 patients (59.6%) stated that they experience little or no pain during the insertion of their ports. Only six patients reported experiencing a lot of pain while receiving treatment during port use, while 229 (87.1%) patients stated that they did not feel any significant discomfort or pain during treatment.

Stress and anxiety levels following port insertion were scattered across the entire spectrum of possible responses. Of the participants, 87% reported little or no cosmetic discomfort resulting from the port. Ten patients (3.8%) stated that answering questions regarding the effect of the port on daily life was quite disturbing.

Twenty-one patients (8%) reported the perception of carrying foreign bodies in the body of the port catheter to be quite high. In response to the statement "Faced with a similar situation requiring a port catheter, I would make the same decision", 142 (54%) patients replied in the affirmative ("strongly agree" or "somewhat agree"), with the remaining responding negatively. One hundred and ninety-two patients (73%) strongly or somewhat agreed that their port catheters facilitated the treatment process and positively affected their quality of life. A total of 220 patients (83.6%) reported being able to enjoy their leisure time and were happy that their hospital stays were short, either strongly or somewhat agreeing with the relevant statement. Detailed survey results are shown in Table 3.

The effects of CVPC on general satisfaction levels and quality of life differed significantly according to whether or not patients experienced complications. In patients with complications, satisfaction decreased and stress and anxiety levels increased compared to those without complications.

The rate of positive responses to the question "Would you recommend attaching port to other patients?" was also lower for patients who developed complications. Nevertheless, there was no significant difference between patients with complications and those without in response to the statement "Faced with a similar situation requiring a port catheter, I would make the same decision" (54.5% versus 52%, p = .188) (see Table 4 for more details)

Table 1: Patient characteristics

	n (%)
Gender	
Male	137 (52.1)
Female	126 (47.9)
Age, years	
Mean ± SD	56.3 ± 11.1
Education	
College education	30 (11.4)
High school education	32 (12.2)
Lower than high school	20 (7.6)
Primary school	131 (49.8)
Illiterate	50 (19)
Malignant neoplasms	
Colorectal cancer	148 (56.3)
Gastric cancer	66 (25.1)
Hepatobiliary cancer	5 (1.9)
Breast cancer	10 (3.8)
Head and neck cancer	20 (7.6)
Others	14 (5.3)
Access site	
Right subclavian vein	241 (91.6)
Left subclavian vein	22 (8.4)
Primary Indication	
Chemotherapy	245 (92)
Parenteral nutrition	0
Reliable venous access	18 (8)
Stage	
I (adjuvant treatment)	2 (0.8)
II (adjuvant treatment)	12 (4.6)
III (adjuvant treatment)	91 (34.6)
IV (palliative treatment)	158 (60.1)
Chemotherapy	
FOLFOX	104 (39.5)
FOLFOX + Bevacizumab	34 (12.9)
FOLFOX + anti-EGFR	8 (3)
FOLFIRI + Bevacizumab	12 (4.6)
FOLFIRI + anti-EGFR	18 (6.8)
FLOT	26 (9.9)
CF	14 (5.3)
CF + anti-EGFR	4 (1.5)
TCF	18 (6.8)
Others	25 (9.5)
Previous IV Chemotherapy	
Yes	104 (39.5)
No	159 (60.5)
Number of treatment rounds	
1st round	185 (70.3)
2nd round	72 (27.4)
3rd round	6 (2.3)

Table 2: Port-specific information

	n (%)
Patients with complications	54 (20.5)
Total observation time	112.164 days
Catheter days (mean ± SD, range)	431.4±537.3 (30- 2033)
Complications	
Infection	16 (6.1)
Occlusion	22 (8.4)
Pneumothorax	2 (0.8)
Subcutaneous hemorrhage	2 (0.8)
Displacement	8 (3)
Skin ulceration	2 (0.8)
Analgesia requiring pain	2 (0.8)
Patients whose ports were removed port due to complications	40 (15.2)

Table 3: Patient evaluations of their ports

Statment	Strongly disagree n (%)	Somewhat disagree n (%)	Neither agree nor disagree n (%)	Somewhat agree n (%)	Strongly agree n (%)
I felt pain during the initial insertion of the port	38 (14.4)	119 (45.2)	68 (25.9)	18 (6.8)	20 (7.6)
I felt pain while receiving treatment using the port	139 (52.9)	90 (34.2)	28 (10.6)	6 (2.3)	0
The port restricts my arm movements	97 (36.9)	114 (43.3)	38 (14.4)	12 (4.6)	2 (0.8)
The port prevents (engel) me from performing daily tasks	98 (37.3)	119 (45.2)	36 (13.7)	10 (3.8)	0
When treatment is finished the port causes me discomfort	80 (30.4)	92 (35)	63 (24)	28 (10.6)	0
I avoid bathing as much as possible because of the port	124 (47.1)	101 (38.4)	28 (10.6)	10 (3.8)	0
Having the port in my body creates the sensation of carrying a foreign object	114 (43.3)	62 (23.6)	66 (25.1)	19 (7.2)	2 (0.8)
My stress and anxiety increased after the port was inserted	88 (33.5)	77 (29.3)	68 (25.9)	28 (10.6)	2 (0.8)
I feel uncomfortable with my appearance due to the port	179 (68.1)	50 (19)	22 (8.4)	10 (3.8)	2 (0.8)
Criticism of the port by those close to me has affected me	177 (67.3)	42 (16)	20 (7.6)	22 (8.4)	2 (0.8)
I would recommend having a port to other patients	10 (3.8)	22 (8.4)	59 (22.4)	114 (43.3)	58 (22.1)
Faced with a similar situation requiring a port catheter, I would make the same decision	28 (10.6)	41 (15.6)	52 (19.8)	106 (40.3)	36 (13.7)
I am happy that I can shorten my hospital stays and enjoy my leisure time	2 (0.8)	12 (4.6)	29 (11)	160 (60.8)	60 (22.8)
Having a port has had a positive effect on my quality of life	2 (0.8)	10 (3.8)	59 (22.4)	116 (44.1)	76 (28.9)
I have access to adequate support for the use and maintenance of my port from other health institutions	73 (27.8)	90 (34.2)	42 (16)	48 (18.3)	10 (3.8)

Table 4: Association of main objectives with complications

		Answer n (%)					
		Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree	*p*
Having a port has had a positive effect on my quality of life	NC	0 (0)	4 (1.9)	45 (21.1)	98 (46)	66 (31)	**< .001**
	C(s)	2 (4)	6 (12)	14 (28)	18 (36)	10 (20)	
Faced with a similar situation, I would make the same decision	NC	18 (8.5)	35 (16.4)	44 (20.7)	86 (40.4)	30 (14.1)	.188
	C(s)	10 (20)	6 (12)	8 (16)	20 (40)	6 (12)	
I would recommend having a port to other patients	NC	8 (3.8)	10 (4.7)	49 (23)	98 (46)	48 (22.5)	**< .001**
	C(s)	2 (4)	12 (24)	10 (20)	16 (32)	10 (20)	
When treatment is finished the port causes me discomfort	NC	70 (32.9)	80 (37.6)	49 (23)	14 (6.6)	0 (0)	**< .001**
	C(s)	10 (20)	12 (24)	14 (28)	14 (28)	0 (0)	
My stress and anxiety increased after the port was inserted	NC	78 (36.6)	65 (30.5)	50 (23.5)	18 (8.5)	2 (0.9)	**.018**
	C(s)	10 (20)	12 (24)	18 (36)	10 (20)	0 (0)	
The port restricts my arm movements	NC	85 (39.9)	96 (45.1)	24 (11.3)	8 (3.8)	0 (0)	**< .001**
	C(s)	12 (24)	18 (36)	14 (28)	4 (8)	2 (4)	
I avoid bathing as much as possible because of the port	NC	110 (51.6)	77 (36.2)	22 (10.3)	4 (1.9)	0 (0)	**.001**
	C(s)	14 (28)	24 (48)	6 (12)	6 (12)	0 (0)	
Having the port in my body creates the sensation of carrying a foreign object	NC	96 (45.1)	50 (23.5)	52 (24.4)	15 (7)	0 (0)	**.049**
	C(s)	18 (36)	12 (24)	14 (28)	4 (8)	2 (4)	

NC; No Complication(s), C(s); Complication(s)

Discussion

Central venous port catheters are employed to deliver chemotherapy treatment for many cancer patients. Chemotherapy by infusion is an important tool for the safe and effective delivery of anti-cancer drugs (9,10). The objective of the present study was to analyze the effects of CVPC on daily life and patient satisfaction in cancer patients treated following standard clinical practices. Our survey results confirmed the generally positive perception of CVPC on the part of cancer patients, similar to findings previously reported in the literature (6, 7, 11-13). A majority of the participants reported that CVPC had a positive effect on their overall quality of life and that they were better able to enjoy their leisure time thanks to shortened hospital stays enabled by the use of CVPC.

The majority of patients did not experience any significant discomfort or pain during the implantation procedure. In some studies, participants reported that the insertion of a port catheter was not a painful procedure (7, 12). In one study similar to our own, 62% of the patients stated that the attachment of their ports caused them little or no pain (14). An overwhelming majority (90%) of the patients in that study found the use of the port to be neither painful nor uncomfortable. In the present study, this rate was 87%. Most of our patients expressed that they were not disturbed during normal activities and that they were able to carry out their daily tasks. In 80% of our cases, arm mobility was affected only slightly or not all. Although most patients did not experience the sensation of having a foreign object in the body due to the CVPC, some patients did report increased stress and anxiety levels following port insertion.

Feelings about one's physical appearance vary according to the patient's perspective, and individual perception is of critical importance for satisfaction. Much as the cosmetic result of a medical procedure may have a significant effect on overall life satisfaction, an individual's feelings regarding his/her appearance are similarly important, even when battling the disease. Changes in appearance have been found to play a critical role in patient compliance during treatment (15, 16). In some studies (7, 12), the percentage of patients complaining about the cosmetic results of the port catheter was higher than in our study, which had a greater percentage of patients reporting overall satisfaction. Only two young female patients diagnosed with breast cancer in the present study expressed cosmetic dissatisfaction. The high satisfaction rates observed in our study may also be due to regional and cultural differences.

When our patients were asked whether others' opinions had influenced them in any way before the insertion of the port catheter, the majority replied that they had merely followed their doctors' advice and had not discussed their decision with anyone. Although this response may simply have resulted from a high level of trust in physicians, it may also have been due to the doctors not discussing intravenous chemotherapy with their patients. More than half of our patients were not able to receive port catheter care from health institutions other than our hospital, possibly because family practitioners lack experience using a port catheter, which requires special needles. This situation constituted an extra inconvenience for our patients, thus negatively affecting the quality of life.

The overall safety of CVPC systems has been demonstrated by their low complication rates (12,17-19). The high complication rate of our study was consistent with the results of some studies in the literature (7,13,20). The most common complications that we encountered were port occlusion and infection. Satisfaction with the port catheter was evaluated on a comparative basis between patients with and without complications; there were significant differences between the two groups regarding its effects on daily tasks and quality of life. Patients who developed complications reported lower satisfaction rates and experienced higher levels of stress and anxiety following port implantation. While 28% of the patients with complications responded negatively to the question "Would you recommend inserting a port to other patients?", only 8% of the patients without complications responded negatively, a statistically significant difference. A previous study found no significant difference between these two groups (12). In response to the question of whether, in similar circumstances, they would again choose to have a port inserted, there was no significant difference between the responses of patients with and without complications. More than half of the patients in both groups answered this question in the affirmative, either as somewhat agree or strongly agree. In a questionnaire-based study conducted by Nagel et al., no statistically significant difference was observed between these groups concerning this issue (7). Although our results indicate that low complication rates may have led to higher levels of satisfaction, the general outlook of patients concerning the use of CPVC is positive.

There are limitations to this study that should be noted. First, no analysis was performed according to the disease stage of our patients. Advanced stage disease is an important risk factor for upper limb venous thrombosis associated with CVPC use (21). In addition to disease stage, patient performance status and even sociocultural factors affect life expectancy, yet these patient groups were not analyzed separately.

Conclusion

With the increasing use of continuous infusion chemotherapy regimens and the need to improve patient quality of life, the future will likely see a significant increase in demand for CVPC. Although most of the patients surveyed reported overall satisfaction with the CVPC system and experienced only a low negative impact on daily life as a result, in some respects the feedback was less positive. For example, an increase in complications stemming from the implantation procedure was found to statistically be a predictor of satisfaction. Therefore, actions taken to reduce the frequency and severity of complications will not only improve patients' experiences using CVPC but also increase the satisfaction and well-being of patients undergoing treatment over long periods.

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Prognostic factors and curative radiotherapy results in patients with octogenarian bladder cancer

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Abstract

Objective: In this retrospective research, we aimed to evaluate the survival outcomes and survival-related prognostic factors in octogenarian (>80 years) bladder cancer patients.

Material and Methods: A total of 17 patients receiving radiotherapy or chemoradiotherapy treatment for bladder cancer in octogenarian patients were included in the study.

Results: In total 17 patients, 13 patients (76.5%) had Stage II, 2 patients (11.8.%) had Stage III and stage IVa. Median follow-up was 23 months (6-72 months).While median overall survival (OS) was 14 months, median disease-free survival (DFS) was 13 months.Overall survival and disease-free survival rates for 6 months and 1st years were 70.6%, 35% and 64.3%, 24.1%, respectively. No prognostic factors were found in the univariate Cox regression analysis for overall survival. In multivariate Cox regression analysis, we found stage (hazard ratio [HR] = 3.009. 95% confidence interval [CI] = 1.003–9.029, p = 0.049), radiotherapy doses (HR = 241,226, 95% CI = 5.421–107.679, p = 0.005) and Charlson co-morbidity index (HR = 0.161 95% CI = 0.035–0.748, p = 0.020) as independent prognostic factors for overall survival.

Conlusion: Curative radiotherapy can be used for older (>80 years) patients with invasive bladder cancer. Nonetheless, the co-morbidity disease should be a consideration before radiotherapy and chemoradiotherapy administration.

Keywords: Urinary, bladder cancer, radiotherapy, 80 and over

Introduction

Bladder cancers are generally seen in older ages and are more aggressive in elderly patients (1). It is more common in men. Usually, 25-30% is non-invasive bladder cancer, while 75% is invasive bladder cancer at the time of diagnosis. The most crucial treatment option in invasive bladder cancer is maximal transurethral resection (TUR) and radical cystectomy (RC). Due to additional diseases, advanced age, and surgical complications, RC cannot be applied (2). In these patients, another treatment option, bladder-sparing treatment (curative chemoradiotherapy), is recommended. But, curative chemoradiotherapy cannot be applied in patients with elderly bladder cancer, which is generally not suitable for surgery, due to toxicity. Curative radiotherapy alone is preferred more frequently than chemoradiotherapy. The effect of this treatment on survival is lower than chemoradiotherapy in many studies (3-4). This is a significant challenge, especially in patients who are 80 years and above (octogenarian).

In this study, we examined the prognostic factors that affect survival and our curative radiotherapy results in patients with octogenarian bladder cancer.

Material and Methods

In this retrospective study, we evaluated 17 patients over 80 years of age who were diagnosed with invasive bladder cancer in Istanbul Training and Research Hospital, Department of Radiation Oncology between 2011 and 2018. TUR was applied to each patient for diagnosis and treatment purposes. After the TUR, we evaluated patients who were not eligible for surgery due to their additional diseases or did not want radical surgery for curative chemoradiotherapy (bladder preserving therapy). Before the treatment, all patients were given for hemogram and detailed biochemistry tests. The only radiotherapy was applied to patients who were not suitable for chemoradiotherapy (for bladder preservation therapy applied, small tumors (5 cm), unifocal disease, microscopic complete transurethral resection (R0-1), the absence of urethral obstruction or hydronephrosis, absence of lymph node metastasis, in situ and need not be carcinoma report). Patients were staged to the AJCC staging system (7th edition). According to the Helsinki declaration, the study was approved by the local ethics committee of The University of Health Science, Istanbul Training and Research Hospital, Turkey, and Human Research Ethics

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Committee (approve number: 2020/ 2234). Informed consent was obtained from all patients after a thorough explanation of the study.

The Charlson comorbidity index was used to assess comorbidities (5). Curative chemoradiotherapy (CRT) or radiotherapy (RT) was decided according to the patients' Karnofsky Performance Status (KPS). This scoring is from 0 to 100, and we divided it as above 70 and below. Pathology and laboratory values were taken from hospital files and treatment and follow-up information from patient records.

Overall survival (OS) was defined as the time between the date of diagnosis and the last contact or death. Disease-free survival (DFS) was the period between the date of diagnosis and the time of local tumor recurrence and metastasis.

Radiotherapy and Chemoradiotherapy Data

All patients received TUR. All patients received external beam RT in 1.8 to 2.0 Gy daily fractions with 18 MV photon beams, five days a week. Radiation doses were applied to the bladder or tumor to 60 Gy after 40-45Gy. Radiation treatment was carried out using field-in field IMRT and 4- field box 3-Dimension conformal technique.

Chemotherapy protocol Cisplatin 35 mg / m^2, weekly to be administered by the Medical Oncology Clinic.

Treatment Toxicity and Follow-up

Treatment toxicity was evaluated with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (6). During RT, patients were assessed at least once a week with a clinical examination, and their blood counts and biochemistries were analyzed. The treatment responses were evaluated by using cystoscopy. Subsequent controls included physical examinations and cystoscopy and radiological imaging every three months. Follow-ups were conducted every three months for the first two years and every six months for years 3 through 5. During the follow-up period, a magnetic resonance imaging (MRI) examination was requested in patients with suspected local or regional recurrence.

Statistical analysis

Nominal and ordinal data were described with frequency analysis, whereas scale parameters were described with mean and standard deviations. Kaplan Meier analysis was used for OS and DFS analysis. A Cox proportional hazard model was applied for multivariate analysis to determine independent prognostic factors. All analyses were performed at 95% confidence level with a 0.05 significance level at SPSS 17.0 for windows program.

Results

Table 1 presents some baseline characteristics of patients and treatment features.

The mean age of the patients was 82.1 (range 80-89) years. 12 (70.6%) of the patients were male, and 5 (29.4%) were female. All patients had a history of smoking. While 47.1% (8) patients were still smoking, 52.9% (9) had ex-smoker.In our hospital, 76.5% (13) of the patients had invasive urothelial carcinoma and 23.5% (4) other histopathology. In terms of stage, 76.5% (13) of patients were stage II, and 11.8% (2) were stage III and IV. Karnofsky performance status was 61.1% (10) patients ⩾70, 38.9% (7) patients had a <70 KPS. Considering the co-morbidity index of Charlson according to additional diseases, the score was 2-3 in 55.6% (9) patients, 4-5 in 33.3% (6) patients, and 6-7 in 11.1% (2) patients. Almost all of the patients received 88.2% only curative radiotherapy, while only 11.2% (2) received chemoradiotherapy. Radiotherapy doses were different. Therapeutic radiotherapy doses (60 Gy) were taken by 77.8% (14) of patients. Three patients discontinued the treatment after 40 to 45 Gy. Recurrence was observed in 3 patients (56.6%), distant metastasis detected in 4 patients (42.5%). RT and CRT treatments were well tolerated. It was seen in 4 (32.5%) patients with grade 2 diarrhea stage II. Urinary frequency was most common in stage II and stage III patients. Two patients in stage II required hospitalization due to late side effects.

Table 1: Patients and treatment characterics

	Patient (n)	%
Age, Mean ± SD (years)	82.12 ± 2.64(80-89)	
Sex		
Male	12	70.6
Female	5	29.4
Smoking Status		
Smoker	8	47.1
Ex-smoker	9	52.9
Histopathology		
Invasive urothelial Ca.	13	76.5
Other	4	23.5
Stage		
II	13	76.5
III	2	11.8
Iva	2	11.8
Karnofsky Performance Status		
≥70	10	61.1
<70	7	38.9
Charlson Co-morbidity Index		
2-3	9	55.6
4-5	6	33.3
6-7	2	11.1
Radiotherapy doses		
40 Gy	1	5.6
45 Gy	2	11.1
60 Gy	14	77.8
Chemoradiotherapy	2	11.8
Radiotherapy (alone)	15	88.2
Metastasis	4	68
Recurrence	3	56.6
Follow-up, Mean±SD (month)	23 ± 20.48 (6-72)	
Exitus	14	
Alive	3	

SD: Standart deriviation

Median follow-up time was 23 months (6-72 months). Median OS was 13 months, OS rates were 70.6% for six months, while 1-year survival was 35%. Overall survival, according to the stage, is showed in Figure-1. Median DFS was 14 months, DFS rates were 64.3% for six months, and 1-year DFS was 24.1%. At the time of analysis, three patients were alive, and 14 patients died.

No factor affecting survival was found statistically significant in univariate analysis. According to the multivariate analysis, stage (p=0.049), RT doses (p=0.005), and Charlson co-morbidity index (p=0.020) were determined to be an independent prognostic factor for OS (Table-2). There was a threefold increase in mortality in patients stage III and IV as compared with the patient's stage II.

Similarly, RT doses were found independent prognostic factor for overall survival, and mortality was increased by 214 fold in received 60 Gy compared 40 Gy in patients. Charlson co-morbidity index also was found independent prognostic factor for death and overall survival. It was increased by 0.1 fold score 2-3 compared 6-7 score.

Table 2. Univariate and multivariate analyses of factors for prediction of overall-survival

	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Sex				
Male	1		1	
Female	0.685(0.204-2.299)	0.541	1.101(0.008-1.365)	0.084
Smoking Status				
Smoker	1		1	
Ex-smoker	1.440(0.447-4.643)	0.641	0.324(0.031-3.393)	0.347
Histopathology				
Invasive Urothelial	1		1	
Others	1.239(0.374-4.109)	0.726	0.921(0.185-4.584)	0.920
Stage				
II	1		1	
III	1.909(0.874-7.973)	0.105	3.009(1.003-9.029)	0.049
Iva	0.151(0.151-2.034)	0.154	2.873(0.986-8.374)	0.053
KPS				
≥70	1		1	
<70	1.803(0.573-5.677)	0.314	2.432(0.433-13.653)	0.313
Charlson Co-morbidity Index				
2-3	1		1	
4-5	0.546(0.230-1.283)	0.165	0.203(0.049-8.826)	0.057
6-7	0.674(0.231-4.726)	0.178	0.161(0.035-0.748)	0.020
Radiotherapy doses				
60 Gy	1		1	
45 Gy	1.468(0.456-5.246)	0.678	7.834(0.694-88.429)	0.096
40 Gy	1.791(0.500-6.4169	0.371	241.22(5.421-107.679)	0.005
Chemoradiotherapy				
Present	1		1	
Absent (Radiotherapy alone)	1.791(0.370-7.973)	0.491	2.039(0.241-17.226)	0.513

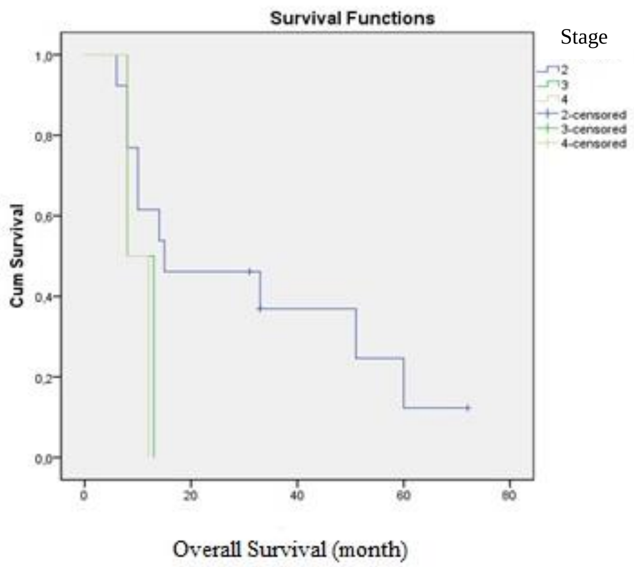

Figure 1: Overall survival according to the stages.

Discussion

Bladder cancer is more common in older adults. The average age of diagnosis is 72 years. Today, with increasing life expectancy, the curative treatments to be more critical in octogenarians.

Maximal TUR and radical cystectomy is a primary curative treatment in bladder cancer. Despite the improvements in surgical techniques, sometimes it is not possible due to additional diseases. Bladder-conserving treatment (TUR and after chemoradiotherapy) is the preferred treatment option for invasive bladder cancer patients. The European Association of Urology Guidelines consider it appropriate to add radiotherapy alone or in combination with chemotherapy after the maximum TUR in patients who are not eligible for radical cystectomy (7). While 5-year overall survival was 36-74%, 5-year disease-free survival was 50-82%. Similarly, in the study conducted by Erlangen University, the five and 10-year survival rates of patients receiving bladder-sparing treatment were 51% and 31%, respectively (8).

However, in these studies, the patient's age is younger than our research. Studies with Octogenarian are generally very few. In these studies, patients received a TUR alone as primary treatment (9). The patients were then followed up. In our study, we applied radiotherapy or chemoradiotherapy after TUR.

Fischer-valuck et al. compared treatment modalities in an octogenarian with muscle-invasive bladder cancer patients (10). They found the OS for 14 month. The 3-year and 5-year survival rates were 26.3% and 14.5%. They found that the survival of CRT and radical surgery is equal to each other, but CRT has a superior treatment modality than radiotherapy alone. In our study, the median OS was 13 months and similar to Fischer-valuck et al. study.

However, our patients do not have three and 5-years of survival. Moreover, only three patients took CRT. Almost all patients received RT alone. Charlson's co-morbidity index is to use geriatric oncology patients. Our patients

were generally found to be 2-3 points. We found that this score was an independent prognostic factor in multivariate analysis. Similar, other studies found Charlson's co-morbidity score was an independent prognostic factor in octogenarians (10-11).

Stage of bladder cancer is an essential factor that affects the course of the disease and survival rate. Studies conducted in the literature regarding the stage and progression of the disease, and different results have been reported (12-13-14). We found that stage II was an independent prognostic factor for OS in octogenarians.

In many studies on elderly bladder cancer, radiotherapy dose was applied over 60 Gy. Median 58.6 Gy (range 54-62.8) was used in the study of Lee et al., 60-70 Gy was received in the study of Korpics et al., and a median 64.8 Gy was used in the study of Hsieh et al. (15, 16, 17). Similar to the above studies, we applied a median of 60 Gy to the bladder. Curative radiotherapy dose is also an essential prognostic factor in elderly bladder cancer patients. RT was well tolerated by all patients. In our study, three patients received CRT, while 14 patients received radiotherapy alone. Patients who break the treatment were CRT used patients. Diarrhea and urinary frequency were the most common side effect. Our side effect results were similar to other studies (15, 16, 17, 18).

A limitation of our study was almost all patients stage II. The number of patients receiving RT alone or CRT is minimal in terms of which one is more effective. It was not clear whether the cause of death was due to the additional disease.

Conclusion

According to the study results, radiotherapy alone or CRT can be performed in octogenarians who have longer life expectancies.When deciding curative treatment in patients with invasive bladder cancer over 80 years of age, we should be highly selective, especially with co-morbidity diseases, and we comprehensive assessment is required

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Relationship between FDG-PET/CT and hematological parameters in squamous cell lung cancer without distant metastasis

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Abstract

Objective: This study aimed to investigate the relationship between 18Fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) parameters and hematological parameters in squamous cell lung cancer without distant metastasis and to investigate the prognostic value of these parameters.

Patients and Methods: This study included 155 patients who underwent 18F-FDG PET/CT imaging for squamous cell lung cancer. Metabolic and hematological parameters were analyzed. Metabolic parameters included maximum and mean standardized uptake values (SUVmax and SUVmean), metabolic tumor volume (MTV), total lesional glycolysis (TLG), and maximum tumor-to-blood SUV ratio (SURmax). Hematological parameters included neutrophil, lymphocyte, platelet, neutrophil/lymphocyte count ratio (NLR), and platelet/lymphocyte count ratio (PLR)

Results: Overall survival was significantly shorter in patients with TLG > 194, NLR > 3.3, and PLR > 157.2 ($p < 0.001$, $p = 0.001$, and $p = 0.001$, respectively). There was a poor correlation between TLG and NLR ($p < 0.001$, $r = 0.302$), TLG and PLR ($p < 0.001$, $r = 0.304$). TLG (> 194; hazard ratio 1.704, 95% CI 1.056–2.751, $p = 0.027$) and Tumor-Node-Metastasis (TNM)-based staging (stage II; hazard ratio 1.965, 95% CI 0.739–5.227, $p = 0.019$) were independent prognostic factors for overall survival.

Conclusion: While PET/CT metabolic parameters had both predictive and independent prognostic values in squamous cell lung cancers, PLR and NLR had only predictive values. It shows that PET/CT metabolic parameters related to the course of the disease are more valuable than hematological parameters in squamous cell lung cancer.

Keywords: 18F-FDG PET/CT, Neutrophil/Lymphocyte Ratio, Squamous Cell Lung Cancer, Prognosis

Introduction

Cancer is the leading cause of death for people under 70 years old in many countries worldwide. Lung cancer is also the most common type of cancer. Also, it is the most common cause of cancer-related death in males and second in women after breast cancer (1). Good knowledge of the prognostic factors associated with the type of cancer can guide the clinician in planning treatment and contribute to predicting recurrence and survival during follow-up. Well-known prognostic factors in lung cancer include TNM classification, age, sex, histological subtype, and some genetic factors that can be related to lung cancer (2).

18F-FDG PET/CT is an imaging modality that is frequently applied for oncologic purposes and allows for monitoring the metabolic activity of the tumor. 18F-FDG PET/CT imaging is recommended for the diagnosis of suspected lung masses (3) and is frequently used in lung cancer staging and treatment response evaluation. Studies have shown that PET metabolic parameters of primary tumors are prognostic factors in patients with non-small cell lung cancer (NSCLC) (4-6). In these studies, SUVmax, volume-based MTV and TLG have been considered as important prognostic factors.

While the search for prognostic biomarkers continues in lung cancer, some published studies have revealed some inflammatory parameters in the blood that may be related to prognosis. Neutrophil count in tumor stroma has been shown to predict undesirable outcomes and tumor-associated lymphocytes are associated with a better prognosis (7). According to another studies, the NLR value has been dedicated as a prognostic factor (8-10).

This study aimed to investigate the prognostic value of 18F-FDG PET/CT metabolic parameters and hematological parameters in patients with squamous cell lung cancer without distant metastasis. Another aim was to investigate the relationship between them

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Material and Methods

Patients

Included in this retrospective study were 155 patients who underwent 18F-FDG PET/CT imaging in our clinic between May 2016 and December 2017 who had squamous cell lung cancer without distant metastasis. Patients whose pre-treatment PET CT imaging results and hematological parameter counts were measured simultaneously were enrolled in the study. Patients who had distant metastasis or whose clinicopathological information could not be reached were excluded. The staging of the patients was performed with the 8th edition of the TNM staging system of the International Lung Cancer Study Association (IASLC). The median follow-up period of patients was 23 months (1-33). Neutrophil, lymphocyte, and platelet counts of patients were recorded. NLR was calculated by the neutrophil/lymphocyte count ratio. PLR value was calculated by the platelet/lymphocyte count.

FDG PET / CT Imaging and Analysis

After a 6-hour fasting period, patients with blood glucose < 200 mg / dL received intravenous administration of 8–11 mCi 18F-FDG. 18F-FDG PET/CT images were performed using the PHILIPS GEMINI TF 16 Slices PET/CT device. The vertex-upper femoral area was scanned one hour after injection. CT imaging (140 kV, 100mAs, 5 mm slice) was performed firstly and thereafter PET imaging was conducted. PET and CT images were uploaded to a workstation and then interpreted. In axial images, the area of interest (VOI) was drawn to include tumor tissue in the lung semi-automatically. 41% SUV was accepted as the threshold to calculate SUVmean and MTV of each lesion automatically at the workstation. TLG was calculated by multiplying SUVmean with MTV. For SURmax, a SUVmean measurement of blood was measured from the descending aorta.

Statistical Analysis

All statistical analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL). Overall survival time was calculated as the time between death or last follow-up from the initial FDG-PET/CT imaging. The area under the curve (AUC) and cut-off values were calculated using the Receiver Operator Characteristic (ROC) analysis to evaluate the overall life prediction of PET/CT metabolic parameters and hematological parameters. A Spearman correlation test was used for correlation evaluation. To evaluate the effect of age, sex, histopathological and hematological parameters, and PET parameters on survival, a multivariate Cox regression analysis was used. Survival analyses were performed using Kaplan–Meier with log-rank test. P < 0.05 was considered statistically significant.

Results

Of the 155 patients included in the study, 11 (7%) were female and 144 (93%) were male. The mean age of the patients was 67.6 ± 7.2 years. Median survival was 21 (1–33) months. Patients were followed up for 33 months. At the end of the follow-up period, 100 (64.5%) patients died and 55 (35.5%) patients were alive. During the follow-up, 110 (71%) patients had progression and 45 (29%) patients had stable disease or complete response. While 40 (26%) patients underwent the surgical operation for treatment, 115 (74%) patients had received only chemotherapy and radiotherapy. The demographic and clinicopathological characteristics of the patients are summarized in Table 1.

Table 1. Demographic and clinicopathological characteristics of the patients

	All patients (*n* = 155)
	***n* (%)**
Gender	
Female	**11 (7.1)**
Male	**144 (92.9)**
Status	
Alive	**55 (35.5)**
Dead	**100 (64.5)**
Stage TNM (8th edition)	
1a1	**1 (0.6)**
1a2	**6 (3.9)**
1a3	**10 (6.5)**
1b	**7 (4.5)**
2a	**8 (5.2)**
2b	**21 (13.5)**
3a	**50 (32.3)**
3b	**33 (21.3)**
3c	**19 (12.3)**
	Mean ± SD/ median (min–max)
Age	67.6 ±7.2
SUVmax	16 (4-48)
SUVmean	8,51±2.9
MTV	34 (1-591)
TLG	314 (3.3-5674.6)
SURmax	10.02±4.2
Neutrophil	6.9 (2.8-17.3)
Lymphocyte	2.0±0.87
Platelets	334 (73-771)
NLR	3.6 (1.7-17.3)
PLR	174.62 (53.4-830)

SUVmax: maximum standardized uptake value; SUVmean: mean standardized uptake value; TLG: total lesion glycolysis; MTV: metabolic tumor volume; SUR max: maximum standard tumor-to-blood, NLR: neutrophil/lymphocyte ratio, PLR: Platelets/lymphocyte ratio.

For predicting overall survival, the AUC for the 18F-FDG PET/CT metabolic parameters belonged to TLG (0.719, p < 0.001) (Figure 1). When the cut-off value of TLG is taken as 194, sensitivity was 73% and specificity was 62%. AUC values were 0.689 for SUVmax, 0.697 for SUVmean, 0.707 for MTV, and 0.595 for SURmax.

For predicting overall survival, the AUC for the hematological parameters belonged to NLR (0.647, p = 0.002) and PLR (0.652, p = 0.002) (Figure 2). When the cut-off value for NLR was taken as 3.3, sensitivity was 66% and specificity was 58%. When the cut-off value for PLR was taken as 157.2, sensitivity was 69% and specificity was 56%. AUC value was 0.62 for platelets (p = 0.01).

Figure 1. ROC curves for 18F-FDG PET/CT parameters

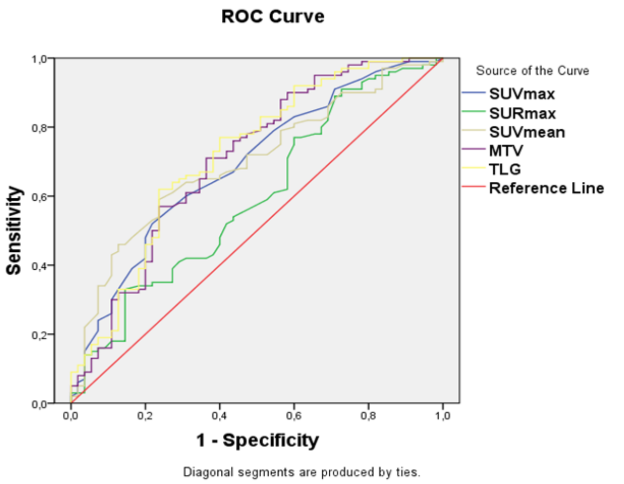
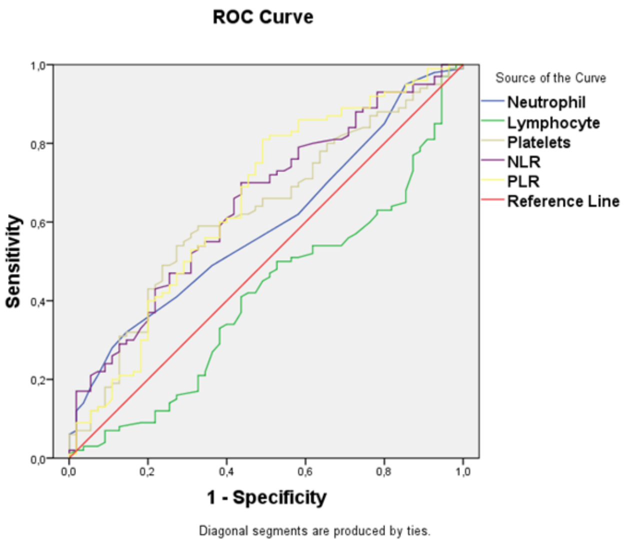
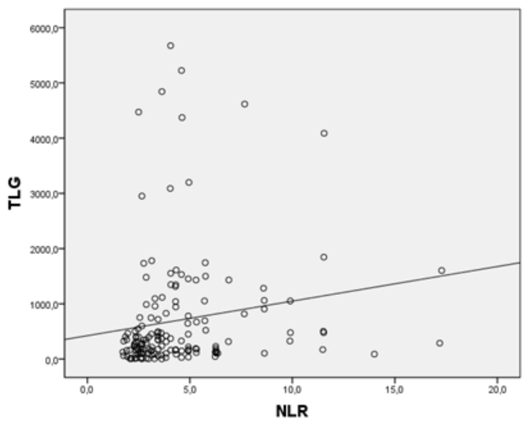


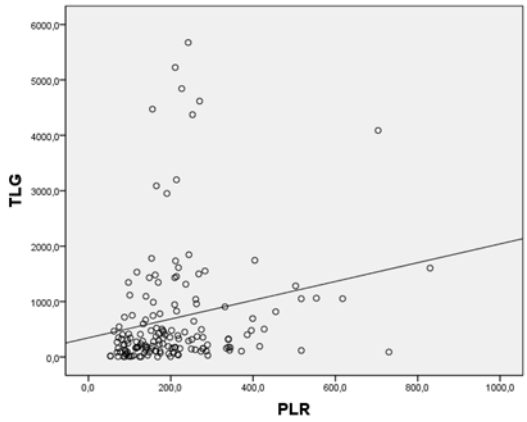
Figure 2. ROC curves for hematologic parameters



There was a poor correlation between TLG and NLR ($p < 0.001$, $r = 0.302$) and TLG and PLR ($p < 0.001$, $r = 0.304$) (Figure 3).

Figure 3. Correlations between TLG and both PRL and NRL

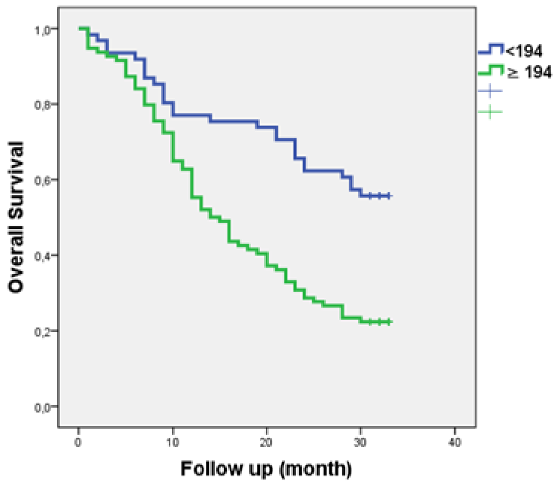




The Kaplan–Meier analysis for the overall survival, taking into account the cut-off values for TLG, is shown in Figure 4. When 194 cut-off values were used for TLG, there was a significant difference in overall survival ($p < 0.001$).

The mean survival was 25 months in patients with TLG < 194 and 17 months in patients with TLG ⩾ 194.

Figure 4. Kaplan–Meier curve depicting the overall survival according to TLG ($p < 0.001$)



The Kaplan–Meier analysis for the overall survival, taking into account the cut-off values for NLR and PLR are shown in Figure 5. There was a significant difference in overall survival when the cut-off value of 3.3 was used for NLR ($p = 0.001$) and when the cut-off value of 157.2 was used for PLR ($p = 0.001$).

Mean survival was 24 months in patients with NLR < 3.3 and 18 months in patients with NLR ⩾ 3.3. Mean survival was 24.9 months in patients with PLR < 157.2 and 17.3 months in patients with PLR ⩾ 157.2.

In the multivariate Cox regression analysis for overall survival, TNM stage (stage III; hazard ratio 3.362, 95% CI 1.360–8.310, $p = 0.009$) and TLG (> 194; hazard ratio 1.704, 95% CI 1.056–2.751, $p = 0.029$) were independent prognostic factors (Table 2). However, gender, age, NLR, and PLR were not.

Figure 5. Kaplan–Meier curve depicting the overall survival according to NLR (p = 0.001) (a) and PLR (p = 0.001) (b)

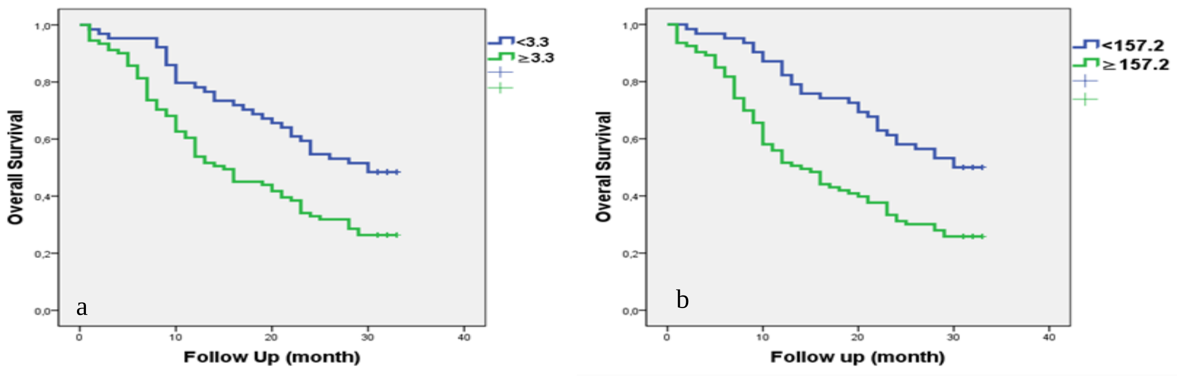


Table 2. Results of multivariate Cox regression analysis for overall survival

Variables	Wald	HR	95 % CI	P
Sex (M)	0.095	0.876	0.378-2.033	0.830
Age (>65)	0.560	1.181	0.763-1.828	0.559
TNM stage	8.538	NA	NA	0.033*
II	1.832	1.965	0.739-5.227	0.019*
III	6.895	3.362	1.360-8.310	0.106
TLG (>194)	4.763	1.704	1.056-2.751	0.027*
NLR (<3.3)	3.016	1.478	0.951-2.297	0.294
PLR (<157.2)	1.710	0.721	0.441-1.177	0.191

TNM: The TNM Classification of Malignant Tumors; **TLG:** total lesion glycolysis; **NLR:** neutrophil/lymphocyte ratio, **PLR:** Platelets/lymphocyte ratio.

Discussion

In our study, TLG was the most valuable metabolic parameter in estimating general life expectancy in squamous cell lung cancer without distant metastasis, while the most valuable hematological parameters were NLR and PLR. There was a poor correlation between TLG and the hematological parameters. In multivariate analysis, in terms of overall survival, the TNM stage and TLG were independent prognostic factors, whereas NLR and PLR were not.

18F-FDG PET/CT is widely used for staging, detecting of the recurrence, determining target volume for RT, and evaluating responses to chemotherapy and chemoradiotherapy in lung cancer patients (11). Studies have shown that SUVmax and volumetric parameters of primary tumors at 18F-FDG PET/CT are important prognostic factors in NSCLC patients (4,12,13). In a study by Dong et al., the patients with high SUVmax in their primary tumors had shorter overall survival and a higher risk of distant metastasis (12). In the meta-analysis conducted by Liu et al. found a higher risk of recurrence and death in NSCLC patients with high SUVmax, MTV, and TLG values of primary tumors (13). In the study by Im et al., the risk of death was higher in NSCLC patients with high MTV or TLG, and MTV and TLG were significant prognostic factors in both stage I/II and stage III/IV patients (4). There are a few studies in the literature investigating the prognostic value of PET/CT in patients with squamous cell lung cancer, a subtype of NSCLC. One of them was the work of Zhang and his colleagues (14).

In this study, overall survival was significantly lower in patients with SUVmax greater than 11.2. Also, SUVmax was an independent risk factor. In the study of Ito et al. (15), the SUVmax of the tumor was associated with recurrence in both adenocarcinoma and squamous cancer subtypes in patients with lung cancer. In our study, the most valuable 18F-FDG PET/CT parameter in estimating the risk of death was found to be TLG. According to these results, a significantly shorter overall survival is expected in patients with TLG > 194. In addition to this, they had a predictive value for survival in SUVmax, SUVmean, and MTV, and had similar AUC values.

Recent studies have shown that inflammatory markers have prognostic value in patients with NSCLC. One of these studies is the work of Wang et al (16). According to this study, the NLR rate is a useful clinical index for predicting overall survival and treatment response in patients with NSCLC. In a similar study by Peng et al. patients with high NLR (> 5) had a worse prognosis and worse response to treatment (7). Mizuguchi et al. (17) reported that NSCLC patients with a low NLR rate had a better prognosis. In meta-analyzes which other similar studies in the literature are analyzed; they indicated that NLR is a prognostic factor in lung cancer (18-20). A study by Minami et al (21). showed that patients with NLR < 5.28 had longer overall survival and progression-free survival in patients with squamous cell lung cancer. In that study, they showed that the lymphocyte monocyte ratio (LMR) also had predictive value.

They also reported that LMR is an independent risk factor, unlike NLR. Significantly shorter overall survival is expected in patients with > 3.1 NLR in our study. But NLR and PRL were not an independent risk factor in patients with squamous cell lung cancer. Our results were similar to Minami et al.'s research.

Neutrophils and type T and B lymphocytes play important roles in tumor inflammation, and the imbalance between neutrophils and lymphocytes is thought to be secondary to tumor hypoxia or necrosis. Therefore, the NLR may reflect the imbalance between neutrophils and lymphocytes in cancer patients and is thought to be indicative of systemic inflammation (18). 18F-FDG PET/CT provides quantitative information about the metabolic activity of the tumor. FDG is a glucose analog. Generally, malignant cells tend to use glucose instead of free fatty acids. Besides, if malignant cells are hypoxic, they use anaerobic metabolism. Anaerobic metabolism requires much more glucose than aerobic metabolism. Even if malignant cells are not hypoxic, malignant cells tend to use anaerobic metabolism. Due to these mechanisms, cancer tissue is detected because of their higher rate of glucose metabolism than surrounding tissues (22). At the site of inflammation/infection, inflammatory cells (neutrophils, activated macrophages, and lymphocytes) increase the accumulation of 18F-FDG via a common mechanism with the tumor tissue. FDG due to such behavior in the inflammatory/infectious tissue; guidelines recommend 18F-FDG for localization of infection in cases such as peripheral osteomyelitis (non-diabetic and non-diabetic foot), spinal infection, fever of unknown origin, metastatic infection and bacteremia (23). Both NLR and 18F-FDG PET/CT metabolic parameters have been identified as independent risk factors in NSCLC. There are several studies in the literature that reveal the possible relationship with each other. Jeong et al (24). examined the relationship between SUVmax and hematological prognostic parameters (total white blood cell, neutrophil, lymphocyte, and platelet count, NLR and PLR) in patients with stage I NSCLC. In this study, SUVmax and hematological parameters showed poor correlation. They also indicated that the prognostic value of SUVmax, an indicator of FDG uptake of the tumor, was superior to hematological parameters. Another study was performed by Mirili et al.25 in patients with small-cell lung cancer. A moderate correlation was found between NLR and MTV. In a Cox regression analysis, NLR, and whole-body (WB) TLG were found to be independent risk factors associated with prognosis. There was a poor correlation between NLR/PLR and TLG in our study. TLG was an independent prognostic factor, while NLR and PLR were not.

Conclusion

As a result, PET CT metabolic parameters had both predictive and prognostic value in squamous cell lung cancers. Among the hematological parameters, PLR and NLR had predictive value, but not independent prognostic value. There was a weak correlation between TLG and PLR and NLR. This result indicates that PET/CT metabolic parameters related to the course of the disease are more valuable than hematological parameters in squamous cell lung cancer.

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Author's contributions: FD, AY; Project design, Patient examination, Treatmen, Statistical Analyses **FD;** Article preparation and revisions

Conflict of interest: The authors declare that they have no conflict of interest. The study was authorized by the Tokat GOP University local ethics committee.

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Anxiety and Depression Differences Between the Nurses Working at a COVID-19 Pandemic Hospital

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Abstract

Objective: To investigate anxiety and depression differences between the nurses working at a COVID-19 pandemic hospital in Turkey.

Material and Methods: A quantitative approach using a survey was applied. There were 331 nurses recruited by convenience sampling.

Results: Females have higher anxiety scores at a significant level (p=0.017). It was also found that nurses who have family members with chronic disease have higher depression scores than nurses who do not have at a significant level (p=0.376). Similarly, nurses who have elderly family members have higher depression and anxiety scores than nurses who do not have at a significant level (p=0.008). There was a significant difference between the nurses providing and not providing COVID-19 care for depression scores (p=0.002).

Conclusion: This study explores nurses' depression and anxiety levels. Even though this phenomenon has already been studied, the outbreak of COVID-19 draws more attention to health workers and especially nurses who are part of the pandemic context. Nurses who provide COVID-19 care have higher depression and anxiety scores. Nurses who help patients to recover from COVID-19 should be in functional mental status. Thus, governments, health organizations, and hospital administrations should take adequate steps to reduce nurses' depression and anxiety to sustain a healthy world.

Keywords: Anxiety, depression, nurse, COVID-19, Pandemic

Introduction

The world's agenda has changed as COVID-19 (Coronavirus). The situation is almost the same all around the world. Governments are trying to keep the public at home. Meantime, health workers are working harder to stop the pandemic. Although extraordinary efforts have been made to investigate the pathophysiology, clinical consequences and treatment of coronavirus disease (COVID-19), the psychological effects of this pandemic on healthcare workers cannot be ignored. Experiences from the acute reports of acute respiratory syndrome (SARS) in 2003 and COVID-19 indicate that healthcare professionals experience anxiety, stress, and fear. Similarly, a recent interview showed that health workers providing COVID-19 care are facing a mental health crisis (1). A report published by the World Health Organization warns the health worker to be careful about not feeling under pressure and stress (2). Similarly, another WHO report also warns nations about the possible rise of the depression and loneliness on health workers (3).

The psychological effects associated with the current pandemic are due to many factors such as uncertainty about the duration of the crisis, lack of proven therapies or vaccines and potential deficiencies of health resources, including personal protective equipment. Health workers are stressed out because of the possibility of their family and friends being ill, their inability to be with their families, and the social distance rules to be followed. Healthcare professionals may experience psychological distress by providing direct care to COVID-19 patients, recognizing someone who has died or died due to this disease or by quarantine or isolation. A recent study which was conducted in Wuhan, China, shows that healthcare workers have suffered adverse psychological reactions (4).

Strategies to alleviate potential stress situations are vital for ensuring a healthy and sound clinical workforce for all scenarios (4-6).

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The purpose of this study is to investigate anxiety and depression differences between the nurses working at a COVID-19 pandemic hospital. Within the scope of this main purpose, this study aims to investigate anxiety and depression differences between the nurses for their following characteristics; providing COVID-19 care, gender, education levels, marital status, department working, using protective equipment, working hours, having COVID-19 case at home, having a chronic disease, having children, having elderly family member, having a family member with chronic disease, recently coming from abroad and contacting a COVID-19 patient.

Material and Methods

The study design and protocol was approved by Harran University Ethics Committee(27/04/2020-20.08.23). The first COVID-19 case in Turkey was identified in March 2020. The hospital where this research was carried out also served as a pandemic hospital. All sections of this hospital were divided into providing COVID-19 and not providing COVID-19. All departments of the emergency room, intensive care, laboratory, service, and radiology in the hospital were divided into sections by making necessary arrangements due to COVID-19.

This study included 331 healthcare staff (nurses) working in an education and research hospital with a bed capacity of 800, where patients with suspected or diagnosed due to Covid-19 pandemics were also followed up and treated. Before the questionnaire was applied to the staff working in the units, verbal information was given about the study, and written consent was obtained from the participants who did not have any mental illness and agreed to participate in the study. The staff involved in all the services of the hospital on the week of the study was included in the research. The participants of this study were surveyed from March 30 to April 13, 2020.

The dependent variables of the study are the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) scores. Age, gender, marital status, the number of children, educational status, presence of chronic disease, the number of people living together at home, presence of individuals with chronic disease/over 65 years of age, department, weekly working time, the status of being on duty in the services provided to the patients with possible or diagnosed Covid-19 infection, access to and use of protective equipment, the workers' methods and duration of following the pandemic process of the person were determined as the independent variables of this study.

BAI and BDI scales were used to measure depression and anxiety levels. The validity and reliability of these scales were tested in previous studies (7,8). The Turkish version of the inventory was developed by Ulusoy (8).

Beck Anxiety Inventory (BAI): The inventory was determined to have sufficient reliability and validity. BAI evaluates the frequency of anxiety symptoms experienced by the individual. It is a self-assessment scale consisting of twenty-one items, and each item is scored between 0-3. With the questions asked to the patient, how much the feeling of distress disturbs him in the last week is questioned. The score range of the scale is 0-63. The high score obtained from the scale indicates the severity of the anxiety experienced by the individual (8).

Beck Depression Inventory (BDI): This inventory was developed by Beck and colleagues (7) and adapted to Turkish by Hisli (9). This inventory is a self-assessment scale applied to healthy and psychiatric patient groups. Its purpose is to identify the risk of depression and measure the level of depressive symptoms and change in severity. This form, which includes a total of 21 self-rating scales, provides a four-point Likert-type measurement. Each item gets a gradually increasing score between 0-3, and the total score is obtained by adding them up. A high total score indicates a high severity of depression. The inventory was determined to have sufficient reliability and validity (10-12).

After calculating the BDI and BAI scores, the relationship between these scores and other variables was evaluated. Beck Anxiety Inventory and Beck Depression Inventory are among the most commonly used tests that have open access (7,13).

Results

The findings of this study are categorized into three sections; descriptive analysis, mean differences, and regression analysis.

The descriptive analysis shows that the average age of the participants is 28.67±5.903 years. The average age of the nurses providing COVID-19 care is 28.58±6.323, and not providing COVID-19 care is 28.75±5,508. A chi-square test of goodness-of-fit was performed to determine whether providing COVID-19 care is equally distributed among nurses. Preference for two nurse groups is equally distributed in the population, X2(2, N= 331) = .680, p> .05. The number of female nurses (56%) is higher than male nurses (44%). Distribution for female and male is not equally distributed in the population, X2(2, N= 331) = 4.136, p< .05. Almost half the participants (44%) work at the intensive care section of the hospital, however, department distribution is not equally distributed in the population, X2(2, N= 331) = 295.810, p< .05. Most of the participants (98%) accept that they can access the protective equipment for the COVID-19 cases. Only 11% of the nurses have COVID-19 cases at their home, but 89% of them do not have COVID-19 case at their home. Some of the nurses (31%) have children, and a chi-square test of goodness-of-fit shows that having children is not equally distributed in the population, X2(2, N= 331) = 47.205, p< .05. Only a few nurses (5%) have elderly family members at home. However, 16% of the nurses report that they have a family member with chronic diseases. The percentage of nurses who contacted a patient with COVID-19 is 1 and who has friends with COVID-19 is 6. The chi-square test of goodness-of-fit analysis shows that having a family member with Covid-19 is not equally distributed in the population, X2(2, N= 331) = 831.745, p< .05 (Table 1).

Table 1. Descriptive statistics about participants

		f	%	X^2 *test*	p
Sex	Female	184	56%	4,136[b]	.042
	Male	147	44%		
Marital status	Single	149	45%	151.293[a]	.000
	Married	176	53%		
	Divorced or Widowed	6	2%		
Education level	High school	49	15%	164.015[b]	.000
	University	282	85%		
Department	Service	106	32%	295.810[c]	.000
	Operating room	22	7%		
	Intensive care	144	44%		
	Laboratory	7	2%		
	Emergency	45	14%		
	Radiology	7	2%		
Providing COVID-19 care	No	173	52%	.680[b]	.410
	Yes	158	48%		
Protective equipment	No	7	2%	303.592[b]	.000
	Yes	324	98%		
Covid-19 case at home	No	294	89%	199.544[b]	.000
	Yes	37	11%		
Chronic disease	No	300	91%	492.876[a]	.000
	Yes	31	9%		
Having children	No	228	69%	47.205[b]	.000
	Yes	103	31%		
Elderly family member	No	315	95%	270.094[b]	.000
	Yes	16	5%		
Family member with chronic diseases	No	279	84%	155.677[b]	.000
	Yes	52	16%		
Recently coming from abroad	No	319	96%	284.740[b]	.000
	Yes	12	4%		
Contact a Covid-19 patient	No	329	99%	323.048[b]	.000
	Yes	2	1%		
Family member with Covid-19	No	309	94%	831.745[d]	.000
	In family	1	0%		
	Relative	1	0%		
	Friend	19	6%		

a. 0 cells (0,0%) have expected frequencies less than 5. The minimum expected cell frequency is 110,3.
b. 0 cells (0,0%) have expected frequencies less than 5. The minimum expected cell frequency is 165,5.
c. 0 cells (0,0%) have expected frequencies less than 5. The minimum expected cell frequency is 55,2.
d. 0 cells (0,0%) have expected frequencies less than 5. The minimum expected cell frequency is 82,5.

As part of this study, the Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were applied. The participants' scores for these both inventories were analyzed based on some variables. An independent t-test and ANOVA were used to test the mean differences. Based on these analyses, there was a significant difference between female and male nurses for BAI (t=5.808, p=0.017<0.05), not for BDI (t=3.439, p=0.065<0.05).

Nurses' marital status, education levels, departments, access to protective equipment, a family member with chronic disease, recently coming from abroad, or contact a COVID-19 patient is not making any significant differences neither for their BAI scores nor for their BDI scores (Table 2).

However, there are significant differences between nurses who provide COVID-19 care and do not provide COVID-19 care for their BDI scores (t=6.382, p=0.012). Similarly, a significant difference was found between nurses who have family members with chronic disease and who don't have family members with chronic disease for their BDI scores (t=6.107, p=0.002<0.05). A significant difference was also found between nurses who have elderly family members and who don't have elderly family members for their BAI (t=7.062, p=0.008<0.05) and BDI scores (t=7.068, p=0.008<0.05). The ANOVA test results show that there are significant mean differences of BDI scores between nurses with the status of having a family member with COVID-19 (F=5.701, p=0.001<0.05) (Table 2).

The logistic regression analysis was conducted to identify which independent variables have an impact on BAI and BDI scores. The results show that to be having a family member with COVID-19 significantly affect the BAI scores (b = 2.966, t (329) =3.803, p < 0.05. The R2 value indicates that 3.9% of the total variation in the dependent variable, BAI, can be explained by the independent variable, having a family member with COVID-19.

Another regression analysis shows that following COVID-19 news significantly predicted BDI scores, (b=0.464, t (329) =3.298, p<0.05. The R2 value indicates that 2.9% of the total variation in BDI scores can be explained by the independent variable, following COVID-19 news (Table 3).

Table 2. Mean differences for BAI and BDI based on some variables

		Beck Anxiety Inventory			Beck Depression Inventory		
		X± SD	t/F	p	X± SD	t/F	p
Sex	Female	11.20 ± 10.348	5.808	.017	13.45 ± 12.027	3.439	.065
	Male	8.50 ± 9.883			11.04 ± 11.330		
Marital status	Single	9.97±10.813	.687	.504	12.62±12.388	1.104	.333
	Married	9.86±9.662			11.94±11.269		
	Divorced or Widowed	14.83±11.600			19.00±9.466		
Education level	High school	8.02±8.383	2.166	.142	13.65±12.115	.675	.412
	University	10.34±10.479			12.16±11.712		
Department	Service	11.63±10.833	1.562	.170	13.41±12.785	.835	.526
	Operating room	10.91±11.233			12.05±10.362		
	Intensive care	9.33±9.963			11.89±11.041		
	Laboratory	4.71±4.231			4.86±7.819		
	Emergency	9.60±9.822			12.51±12.137		
	Radiology	4.14±4.634			14.57±15.317		
Covid-19 care	No	9.46±10.659	1.025	.312	10.45±10.389	10.04	.002
	Yes	10.59±9.711			14.49±12.812		
Protective equipment	No	14.00±13.952	1.096	.296	14.29±16.183	.188	.665
	Yes	9.91±10.134			12.34±11.683		
Covid-19 at home	No	9.72±10.086	2.014	.157	11.80±11.067	6.382	.012
	Yes	12.24±11.107			16.95±15.748		
Chronic disease	No	9.89±10.215	2.370	.095	12.12±11.400	6.107	.002
	Yes	10.33±9.771			13.67±13.379		
Having children	No	9.94±10.348	.023	.880	12.02±11.351	.686	.408
	Yes	10.13±9.973			13.17±12.658		
Elderly family member	No	9.67±9.865	7.062	.008	11.99±11.607	7.068	.008
	Yes	16.56±14.546			19.94±12.704		
Family member with chronic disease	No	9.78±9.910	.786	.376	12.07±11.697	1.230	.268
	Yes	11.15±11.775			14.04±12.111		
Recently coming from abroad	No	10.13±10.231	1.326	.250	12.29±11.806	.470	.493
	Yes	6.67±9.670			14.67±10.857		
Contact a Covid-19 patient	No	10.02±10.231	.120	.729	12.41±11.791	.501	.479
	Yes	7.50±10.607			6.50±3.536		
Family member with Covid-19	No	9.49±9.676	5.701	.001	12.12±11.659	1.387	.247
	In family	17.00			16.00		
	Relative	.00			3.00		
	Friend	18.84±14.630			17.26±13.308		

Table 3. Regression analysis for BAI and BDI

Dependent Var.	Independent Var.	B	Beta	t	t.sig	R	R^2	Adj R^2	F	Sig
BAI	Family member with Covid-19	2.966	.205	3.803	.000	.205	.042	.039	14.459	.000
BDI	Following Covid-19 news	.464	.141	3.298	.001	.179	.032	.029	10.874	.001

Discussion

Focusing on the scope of this study, several studies found that health workers are under higher risks of depression, anxiety, and stress because of their heavy workload (14). Nurses have been under more risk during the outbreak of severe diseases, and this was reported during SARS as well (15). Similarly, during the outbreak of COVID-19, health workers are at a high risk of displaying psychological issues (16,17) and have more psychological distress and symptoms of mental illness (18). Meanwhile, researchers found that the psychological impact of quarantine can be wide-ranging, substantial, and can be long-lasting (5). Researchers found that anxiety could reduce the positive effects of social capital on sleep quality (19). Thus, counting the quarantine and hard working conditions, it is vital to sustaining the mental health of nurses.

This current study aimed to investigate the anxiety and depression differences between the nurses providing and not providing COVID-19 care. The results of this study show that there is a significant difference between the nurses providing and not providing COVID-19 care for depression scores. This finding supports previous studies (20-22). The nurses providing COVID-19 care have higher depression scores than the nurses not providing COVID-19 care do. These differences are similar for anxiety scores but it was not found significant at 0.05 level.

The female nurses have higher anxiety scores than the male nurse at a significant level. This finding is parallel to a previous study conducted by other studies (4,23-26). In another study, a gender difference was found significant for depression (27) as well. Even though female nurses' depression score was also higher than male nurses' depression scores, this difference was not found significant.

Different from a previous study (23), there is no significant difference between nurses' education levels BAI scores or BDI scores. There was no significant differences in nurses' marital status, access to protective equipment, a family member with chronic disease, recently coming from abroad, or contact a COVID-19 patient for none of the scores. Similar to a previous study (23), nurses working in the operation room have higher anxiety scores than nurses working at different sections of the hospital. Nevertheless, this difference is not found significant at the 0.05 level.

Nurses who have family members with chronic disease have higher depression scores than nurses who don't have at a significant level. Similarly, nurses who have an elderly family member at home have higher depression and anxiety scores than nurses who don't have at a significant level. This study also shows that having a family member with COVID-19 significantly predicted anxiety, and following COVID-19 news significantly predicted depression. A similar result was found in a study conducted for SARS (28) and in a recent study conducted for COVID-19 (25). On the other hand, it was reported that health worker feels anxiety when they have a lack of access to up-to-date information and communication (29). A study shows that health workers chose adaptive coping in response to SARS and reported low psychiatric morbidity (30). Nevertheless, the COVID-19 outbreak may require some special interventions to keep frontline health workers, especially female nurses, in good mental conditions (21). Besides, having a family member with COVID-19 and following news about COVID-19 are other variables that could cause depression and anxiety. Pandemic, such as COVID-19, requires careful health attention; therefore, nurses dealing with hard conditions should get more psychological and social support (31). Thus, news agencies have more responsibility to inform the public in an adequate way.

Conclusion

The results of this study have confirmed that female health workers have more anxiety scores. This study especially showed that female nurses have higher BAI scores (at significant level) and BDI scores. The study also showed that nurses providing COVID-19 care had higher depression scores. Female nurses who have a dominant number to provide COVID-19 care are important elements of the health system. The results also concludes that nurses dealing with hard conditions should get more psychological and social support .This support should be extended at all levels, such as news agency, government, public, and hospital administration.**Acknowledgement, Funding:** None.

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Investigation of acute intoxication cases followed-up in the intensive care unit: A retrospective study

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Abstract

Objective: Intoxication cases are increasing in societies day by day. Intoxication cases are followed-up and treated in Intensive Care Units (ICU). In our study, the intoxication cases followed in the intensive care unit; it is aimed to evaluate demographic data, prognosis, causing agents, mortality rates retrospectively.

Material and Methods: In the intensive care unit between the dates of January 1, 2016 and March 10, 2020, the patients who were admitted with the diagnosis of acute intoxication, age, gender, the drug is taken for poisoning or the substance they are exposed to, Glasgow Coma Scale (GCS), the number of days hospitalized, mechanical ventilation support day and the number and mortality status were evaluated retrospectively.

Results: The 88 patient applied to ICU with the diagnosis of acute intoxication, 55(62%) of them are female and 33(37%) of them are male. According to all gender data, the intoxication was found to be the highest between the ages of 17 and 30 (n: 69) and the least under 17 age (n: 2). Half of the patients (n: 44 50%) were treated in less than 2 days. With a single drug, intoxication was seen as the highest with antidepressants.

Conclusion: Intoxications occur mostly with medications and among these drugs, they are mostly seen with antidepressive medications for psychiatric treatment. When treatment is started quickly after the poisoning, the duration of hospital stay is shortened and the prognosis is better. Since poisoning varieties differ by region, this information should be known and updated by the people who treat it.

Keywords: Intoxication, Intensive Care Unit, Poisoning

Introduction

Poisoning is called damage to the organism by removing substances that disrupt vital functions and threatening life through breathing, circulation, mouth, skin and similar ways (1). The poison by the famous chemist Philippus Aureolus Theophrastus Bombastus von Hohenheim said: "Every substance is poison, no non-poisonous substance; It is the dose that separates the drug with poison"(2). Nowadays, poisonings are seen with suicidal or accidental medications, inhalation of delightful substances and dangerous gases, people in the field taking pesticides or taking household cleaning products (3). Intoxication cases usually enter the emergency department, and then follow-up and treatment in intensive care units (ICU). Cases of poisoning; varies according to gender, age, lifestyle, culture and climate. Therefore, it is important to consider the regions where these people live while diagnosing and treating poisoning cases. In our study, we retrospectively analyzed the cases accepted to our intensive care unit with the diagnosis of poisoning.

Material and Methods

In the study, after the approval of the Ethics Committee (76244175-050.04.04), the files and data processing data of the patients who were admitted to the General ICU of our hospital with the diagnosis of acute intoxication between 1 January 2016 and 10 March 2020 were analyzed retrospectively. The patients were evaluated for age, gender, drug usage for poisoning or the substance they were exposed to, Glasgow Coma Scale (GCS) to the clinic, the number of days hospitalized, the number of days that received mechanical ventilation support, and the mortality status.

Results

The demographic data of the patients are given in Table 1. Between January 1, 2016 and March 10, 2020, 88 people applied to the General ICU of our hospital with an intoxication diagnosis, of which 55 were female (62%) and 33 were male (37%). The female to male ratio was found as F / M: 1.66.

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According to all gender data, intoxication was seen to be the highest between the ages of 17 and 30 (n: 69) and the least age of under 17 (n: 2) (Table 2).

The admission to the ICU was n: 62 patients with 15 GCS, n: 3 with 3 GCS, and n: 1 with 11 GCS. The majority of patients (n:62) had 15 GCS at the entrance to the ICU. In the ICU, 44 patients were treated for 2 days or less, and 1 patients were treated for 10 days or more. Most of the patients were treated in less than 2 days. (Table 3).

There were 9 patients who needed to be connected to the mechanical ventilator in the ICU, 79 patients did not need mechanical ventilator. (Table 4). In the ICU, intoxication with a single agent was seen with the highest antidepressives (n: 11), secondly, with the highest organophosphates (n: 9).

Most patients developed intoxication with multiple agents (n: 21). Intoxication of patients with non-drug agents were seen in 23 patients, and 4 with drug agents. Intoxication with only drugs was seen in 61 (69%) patients. Non-steroidal anti-inflammatory (NSAI) 7, paracetamol was seen in 4 patients, it was unknown what patients received (n: 8). (Table 5)

Table 1. Demographic Data of participant patients

Female (n %)	**55(%62)**
Male (n %)	**33(%37)**
Under 17 Age (n)	**2**
17 age-30 Age (n)	**69**
31 age-40 Age (n)	**10**
Above 40 Age (n)	**7**
Total (Male(n)+Female(n))	**83**

Table 2. Glasgow Coma Scale

Glasgow Coma Scale	Number of Cases (n,%)
3	3(3.4%)
4	2(2.2%)
5	2(2.2%)
11	1(1.1%)
12	9(10.2%)
13	7(7.9%)
14	2(2.2%)
15	62(70.4)

Table 3. Treatment at The Intensive Care Unit

Day	Number of Cases (n,%)
Under 2 Days	44(50%)
3-5 Day	32(36.3%)
6- 10 Day	6(6.8%)
Above 10 Days	1(1.1%)

Table 4. Receiving Mechanical Ventilator

Therapy	Number of Cases (n,%)
Mechanical ventilator treatment	9(10.2%)
No mechanical ventilator treatment	79(89.7%)

Table 5. Intoxication Factors

Intoxication Factors	Number of Cases (n,%)
Multiple Drugs	22(25%)
Antidepressant Drugs	12(13.6%)
Organicphosphate	9(14.7%)
Rat poison	8(9%)
Non Steroid Anti Inflammatory	7(7.9%)
Antiepileptic	5(5.6%)
Paracetamol	4(4.5%)
Marijuana	3(3.4%)
Antihypertensives	2(2.2%)
Coumadin	2(2.2%)
Colchisine	2(2.2%)
Corrosive Substance	1(1.1%)
Insuline	1(1.1%)
Antibiotics	1(1.1%)
Mushroom	1(1.1%)
Unknown Drugs	8 (9%)
Total	**88(100%)**

Discussion

Most of the cases admitted to the hospital with intoxication were due to suicide. This condition with poor prognosis should be treated quickly, effectively and consciously. The frequency and diversity of intoxication cases differ according to regions, countries and cities of the countries. When the treatment people know the toxicity characteristics of the regions, the treatment of the patients is done more quickly and effectively. The patient should be approached quickly and consciously to exclude these harmful substances entering the body without causing toxic effects, not being absorbed by the body, or preventing harmful effects with its antidote (4,5). Poisoning affects individuals' psychological states, socioeconomic status, belief and cultural differences, and easy access to drugs. The majority of poisoning cases are reported to be with medications (45-66%).

In this study, in compatible with the literature, most of the cases occurred with drugs and it was seen that the intoxication with drugs was 69% (6). We have linked the reason why the drug poisoning is close to the upper values in the literature to be able to access the drugs in our society. In 88 patients included in the study, most of the cases were found to be female, and the ratio of the female to male was found to be F / M: 1.66. In our study, the high number of female was found to be compatible with other studies in the literature. We linked the high level of female in intoxication cases to respond quickly to socio-economic status, cultural differences, psychological pressures and difficulties (7,8). In this study, the most common viability of cases was between 17 and 30 years of age (n: 69, 78%) (Table2). This age group, which we can call young and adult, was found to be highly similar with the literature. In this group, we attribute the high incidence of intoxication cases to family incompatibility, unemployment, occupational failure, or inability to take part in society (6,8,9). Most of the patients (n: 62, 70.4%) admitted to the ICU had 15 GCS. We attribute the majority of patients entering the ICU with a high GCS value, patients coming to the hospital shortly after intoxication and early intervention in the emergency departments (4,10). There were 3 patients with GCS 3, one of them received high doses of drugs and had cardiac arrest upon entering the ICU and did not respond to the CPR. In other words, 1 case (1.13%) out of 88 cases became exitus. During the treatment in the ICU, the majority of patients (n: 79, 89.7%) did not need mechanical ventilators, 9 (10.2%) patients in need of mechanical ventilators and n: 8 of them left the hospital after their treatment was completed. In our study, we attribute the reason for the low number of patients who needed a mechanical ventilator to the patients coming to the hospital early after poisoning and the early intervention and the low toxic dose taken. In our study, half of the patients (n: 44, 50%) were treated for 2 days or less, and 1 patient received treatment for 10 days or more. With an appropriate and fast treatment approach after the early coordination of patients, the duration of treatment in ICUs is reduced and treated early. It was observed that the duration of treatment in the ICU of the patients in current study was compatible with the literatüre (6,7,8). In this study, the cases of intoxication in those who did not take multiple drugs were most frequently with anti depressants and secondly with organo phosphates. Patients receiving antidepressive treatment frequently attempt suicide because of psychological problems and easy access to the drugs they use. In this study, single drug poisoning was most common with antidepressives and it was found to be compatible with the literatüre (6,7,8,10,11). In this study, the second most frequent poisoning was seen with organophosphates. We attribute this to our region being an agricultural area. The 21 (23.8%) patients were poisoned with multiple agents and n: 61 (69%) were poisoned with drugs. It was not known what 8 patients were poisoned with. Although poisoning may vary according to the regions in our country, the most common are drugs, pesticides, domestic chemicals, toxic gases, other chemicals, plants and foods, respectively. In our study, in accordance with other poisoning data in our country, poisoning was most common with drugs and then with pesticides (12).

Conclusion

As a result, poisoning cases increase day by day and become a community problem.

Intoxications occur mostly with medications, and antidepressive agents are the most common drugs. In patients who come to a health center in a short time after poisoning and start treatment quickly,the hospital stay is shortened and the prognosis is better. Since the poisoning types differ according to the regions, this information should be followed and updated by the healthcare personnel.

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In day 150 of COVID-19 disease, forecasting the number of cases and deaths in Turkey

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Abstract

Objective: This study aims to forecast the number of deaths and cases in Turkey 150 days after (6 August 2020) the first occurrence of COVID-19 in Turkey. The data used is from 10 March 2020 (the first day has seen of COVID-19 in Turkey) to 15 June 2020 and includes people of all ages from all provinces of Turkey.

Material and Method: The relationship between cases, deaths, patients in intensive care units, intubated patients, and recovered patients, which are observations of COVID-19, was examined with a correlation matrix. Afterward, the ARIMA (0,2,4) model to forecast the number of COVID-19 cases in Turkey and the ARIMA(0,3,1) model to forecast the number of COVID-19 deaths in Turkey were established.

Result: COVID-19 cases were forecasted that there may be 266.692 cases in Turkey on 6 August in the 1st model. Subsequently, a similar forecast has been made on COVID-19 deaths in Turkey on 6 August in the 2nd model. COVID-19 deaths were forecasted that there may be 5718. The p-values of these parameters of models were observed statistically significant ($p<0.05$). Later, the stationarity of ARIMA models related to these estimates was examined. According to the Augmented Dickey-Fuller (ADF) test results, ARIMA models were stationary and statistically convenient to use ($p<0.05$). Finally, the Jarque-Bera (JB) test examining the normal distribution assumption was applied and the models were found to be normally distributed.

Conclusions: Consequently, there is an increase in both predicted cases and predicted deaths by the 150th day of COVID-19. These estimates show that the number of cases and deaths will not decrease to zero level until August 6. Factors such as the biological development of the COVID-19 virus, the rate of spread of COVID-19 disease, or the presence of COVID-19 therapy may not cause any increase in these observations. On the contrary, more than expected increase may occur in observed cases.

Keywords: COVID-19, COVID-19 Turkey, SARS-CoV-2, Coronavirus Turkey, COVID-19 forecasting.

Introduction

Many lethal diseases have emerged throughout the history of mankind. Some diseases lasted for several months and some for years. Nevertheless, mankind has always been the winner of these diseases. Plague disease, which killed 75-200 million people between 1331-1353 years; Smallpox disease, which killed 500 million people between 1877-1977 years and Influenza (Spanish flu) disease, which killed 17-100 million people between 1918-1920 years are some of the hazardous diseases that have been seen recently (1,2,3). The exact number of people who died due to these diseases is unknown, as reports on deaths were not kept clear in the years when the disease happened. Although these outbreaks are shocking to humans, from past to present, technology and medical science are in constant development with these outbreaks. Developing treatment methods have caused mortality rates to decrease.

Diseases and viruses or bacteria that cause them often have different names. Recently, the virus has emerged that affects the entire world and causes many economic, social, and health problems. The virus causing the current epidemic is called severe acute respiratory syndrome coronavirus 2, abbreviated to SARS-CoV-2. The name of the disease caused by this virus has been abbreviated as COVID-19. These names have been given by the World Health Organization (WHO) and the International Committee on Taxonomy of Viruses (ICTV) (4,5). This epidemic was first detected in the city of Wuhan, China. Wuhan is the capital of the Hubei Province and has about 11 million citizens. When the date of 29 December 2019, Chinese experts identified a cluster of similar cases of pneumonia in the city. Thus, the virus that caused these detected cases was called SARS-CoV-2 (6).

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At a later time, the first cases of COVID-19 outside of China were seen on January 13rd in Thailand and on January 16th in Japan. Due to the extraordinary increase in cases, on January 23rd the city of Wuhan and other cities in the zone were placed on lockdown by the Chinese Government. But this lockdown could not prevent the spread of the virus and COVID-19 has spread to many more countries. This spread undoubtedly led to cases in many countries around the world. By March it improved into a global pandemic that was announced by the WHO.

The most important reason for this degree of spread of COVID-19 disease is the rate at which the virus spreads. This virus, which is spread by breathing, can also be found on surfaces, especially in closed environments. Therefore, the use of N95 masks and frequent washing of the hands with soap is plenty significant. According to research in China; each person infected at an average age spreads this disease to an additional two (2.2) people. It was concluded from this research that it is likely that the outbreak will continue to spread until this number falls below 1.0 (7).

Reported illnesses from people have ranged from slight symptoms to severe illness and death for approved Coronavirus disease 2019 (COVID-19) cases. These symptoms such as fever, cough, and shortness of breath might appear in 2-14 days after exposure (based on the incubation period of MERS-CoV viruses). If you realize urgent circumstances for COVID-19, you should get medical attention instantly. Urgent circumstances include these:

•Trouble breathing,

•Persistent pain or pressure in the chest,

•New confusion or inability to arouse,

•Bluish lips or face.

But other than those on this list, many circumstances can occur, therefore, a healthcare professional should be consulted for other happening symptoms (8). Testing on someone who shows off symptoms of COVID-19 may not always produce accurate results. Success in tests is not yet 100% due to the new onset of the disease. There are a few reasons why someone infected with COVID-19 might yield a false-negative result when tested (9, 10). (i) Infected people may be in the early stage of the disease with a viral load that is too nominal to be unearthed. (ii) Infected people may own no substantial respiratory symptoms, so there could be few detectable viruses in the patient's throat and nose. (iii) There may have been trouble with sample collection, namely, there is a very little sample to test. (iv) There may have been inattentive shipping and poor handling of samples and test materials. (v) There may have been technical issues connatural in the test, e.g. virus mutation.

There is no certain antiviral treatment committed for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy is the primary treatment method for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory shortness refractory to oxygen therapy, whereas hemodynamic support is necessary for managing septic shock (11). Although this is not all exact treatment for the disease, many curing methods are being developed every day; for instance, diverse treatment methods have been developed in China, the country of origin of the disease during this process. In early times Vitro studies, chloroquine was found to block COVID-19 infection at low-micromolar concentration, with a half-maximal effective concentration (EC50) of 1.13 micrometer (μM) and a half-cytotoxic concentration (CC50) greater than 100 μM (12). These studies in China revealed that it also has potential broad-spectrum antiviral activities by rising endosomal pH entailed for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (13,14). Therefore, the anti-viral and anti-inflammatory activities of chloroquine may explain for its potent efficacy in treating patients with COVID-19 pneumonia. This treatment is recommended for inclusion in the after version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia caused by COVID-19 issued by the National Health Commission of the People's Republic of China (15). Besides, psychological treatment is also important in this process. Therapies will undoubtedly have an important place in people's defeat of COVID-19. Among these are the RNA polymerase inhibitor remdesivir, chloroquine, the antiviral medication lopinavir-ritonavir, interferon-1β, and a variety of traditional Chinese medicine yields (16).

COVID-19 in World Countries

COVID-19 has been seen in all countries in the world, except for a few countries where data cannot be obtained. Although the origin and spread of the disease first started in China, Europe and South America have become the center of the disease, especially in the latest month. Whilst in the last days, a very serious case increase has been observed especially in Russia, Brazil, Peru, India, Chile, Mexico, and the New York region of the United States of America (U.S.A.). As of 15 June 2020, the distribution of cases in countries where COVID-19 cases were detected is shown in Figure 1 (17). According to Figure 1 given, especially Russia, Brazil, and the U.S.A. are the countries where the cases are seen the most.

Figure 1: Total Confirmed Cases of COVID-19 (As of June 15, 2020) (17).

World and Top 10 Countries in COVID-19

Until 15 June 2020 (198 days), 8046465 people were infected in COVID-19 disease. 437295 of the cases died due to COVID-19. According to these data; the mortality rate of the disease is 5.42%. Though only 0.104% of the world's population own COVID-19, the high mortality rate is worrying. The top 10 countries in the case list shown are given in Table 1. These countries are the U.S.A., Brazil, Russia, India, The United Kingdom (U.K.), Spain, Italy, Peru, Iran, and Germany. The country with the highest number of cases is the U.S.A. with 2174324 patients. Together with 118121 deaths, the U.S.A. is the country with the utmost number of deaths. Germany, where 172600 cases are recovered (%91,82), is the only country that has managed to treat almost all patients. Whenever the cases were compared, Italy has the utmost mortality rate with 14.48%

COVID-19 in Turkey

According to data released by the Republic of Turkey Ministry of Health, Turkey is one of the most recent countries where COVID-19 has been seen. Although Turkey is 11th in the number of COVID-19 cases as of 15 June 2020 are in order, it ranks 17th in terms of population. And 179831 cases were detected in 97 days. Of these, 4825 died, 152364 recovered, 722 were taken to intensive care units (ICU) and 291 are treated as intubated patients.

As of June 15, "Deaths"/"Cases" rate is 2.68%, "Patients in ICU"/"Cases" rate is 0.40%, "Intubated Patients"/"Cases" rate is 0.16% and "Recovered Patients"/"Cases" rate is calculated as 84.73%.

This recovered rate is well above the world average. COVID-19 has been seen in all the provinces of Turkey and the most widespread cities are İstanbul, Ankara, İzmir, Konya, and Kocaeli. All of these provinces are big cities with a population of more than 1 million. Besides that, the total number of COVID-19 tests conducted until June 15 is 2674203. This cumulative increase in the number of tests is shown in Figure 2 (19). Conforming to these numbers announced, 6.72% of the tests performed were positive.

When Figure 3 is examined, the number of cases and recovered patients display a steady increase (19). Also, the number of patients recovering from the disease increased on 21 April 2020 with a leap. As the reasons for this leap; the necessity of a certain period of time to treat the disease completely and the positive treatment methods developed can be shown. As of June 15, the growth rates in the variables related to COVID-19 are given in Figure 4 (19). Just as the number of cases was first seen, the cases' growth rates increased quite high initially. The average value of cases growth rates was 18.35%. In the later days of the disease, it was observed that the growth rates of other variables started. The average of other growth rates found are as follows: deaths 12.66%, patients in ICU 4.64%, intubated patients 3.38%, and recovered patients 10.36%.

Table 1: Top 10 Countries in COVID-19 (17, 18).

	Confirmed Cases	Deaths	Recovered People	Active Cases	Mortality Rate (per 100)	Day since the first case
WORLD	8,066,465	437,295	4,174,782	3,454,388	5.42%	198 days
The	2.174.327	118.121	875.189	1.181.017	5.43%	154 days
Brazil	873,963	43,485	453,568	376,910	4.98%	111 days
Russia	537,210	7,091	284,539	245,580	1.32%	137 days
India	342,841	9,914	180,225	152,702	2.89%	136 days
The U.K.	296,857	41,736	1,284	253,837	14.06%	137 days
Spain	291,189	27,136	150,376	113,677	9.32%	137 days
Italy	237,290	34,371	177,010	25,909	14.48%	137 days
Peru	229,736	6,688	115,579	107,469	2.91%	102 days
Iran	189,876	8,950	150,590	30,336	4.71%	118 days
Germany	187,967	8,877	172,600	6,490	4.72%	118 days

Table 2: The Rates of Top 10 Countries in COVID-19 (As of June 15, 2020) (18)

	Population	Confirmed Cases / Population (per 100)	Deaths / Population (per 100)	Recovered People / Confirmed Cases (per 100)
WORLD	7,791,581,688	0.104%	0.006%	51.75%
The U.S.A.	330,917,584	0.657%	0.036%	40.251%
Brazil	212,492,226	0.411%	0.020%	51.898%
Russia	145,931,893	0.368%	0.005%	52.966%
India	1,379,381,861	0.025%	0.001%	52.568%
The U.K.	67,870,494	0.437%	0.061%	0.433%
Spain	46,754,035	0.623%	0.058%	51.642%
Italy	60,465,391	0.392%	0.057%	74.596%
Peru	32,949,791	0.697%	0.020%	50.309%
Iran	83,941,948	0.226%	0.011%	79.310%
Germany	83,772,567	0.224%	0.011%	91.825%

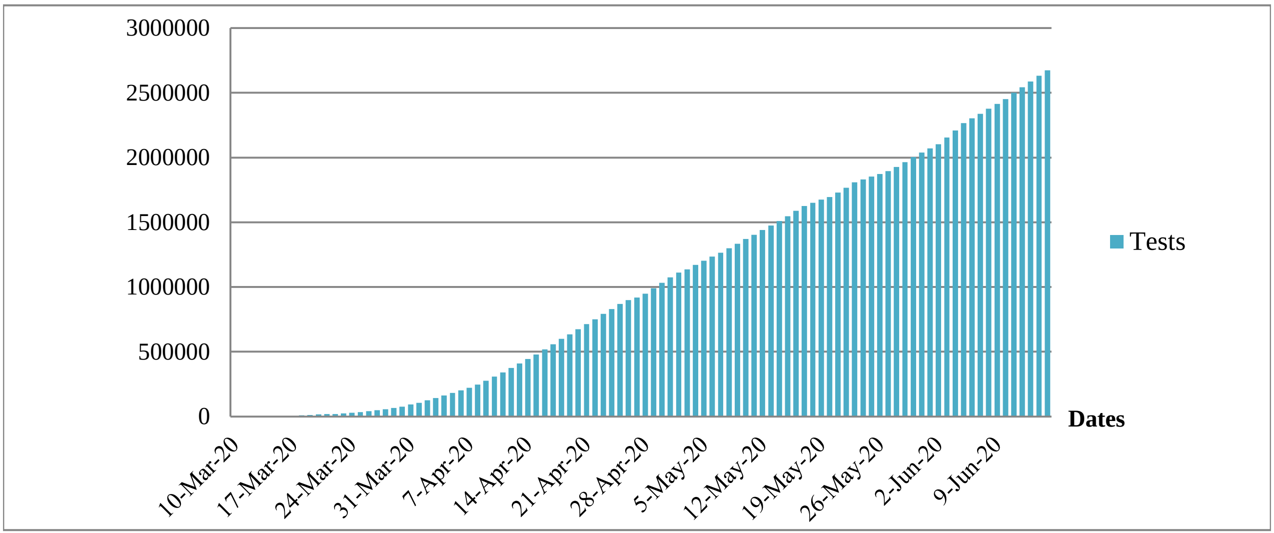

Figure 2: COVID-19 Tests in Turkey (19).

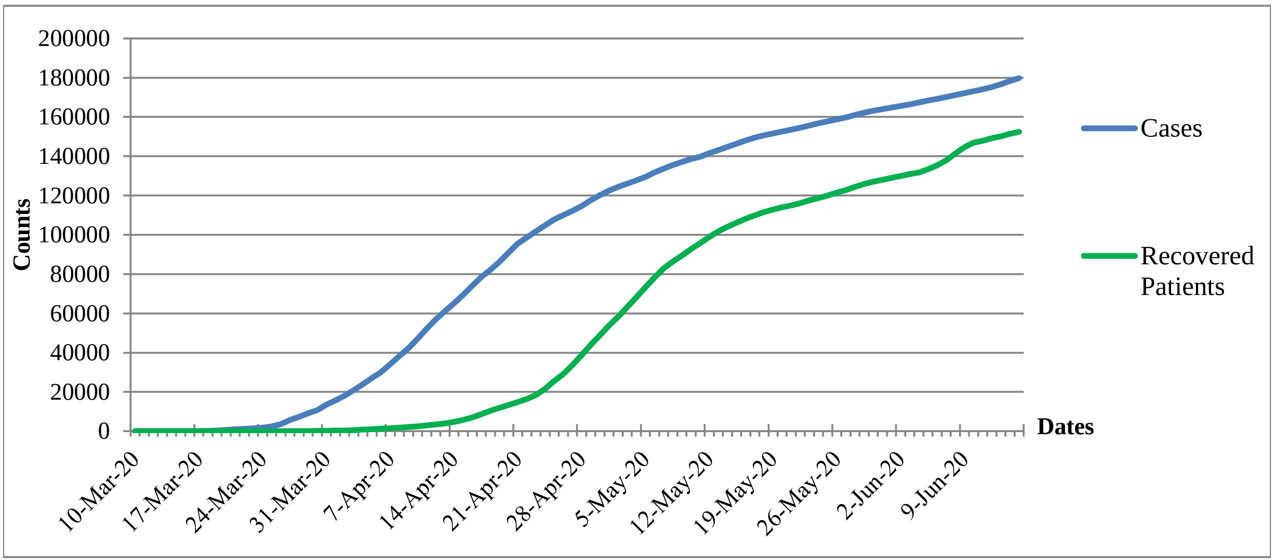

Figure 3: Cases and Recovered Patients Due to COVID-19 (19).

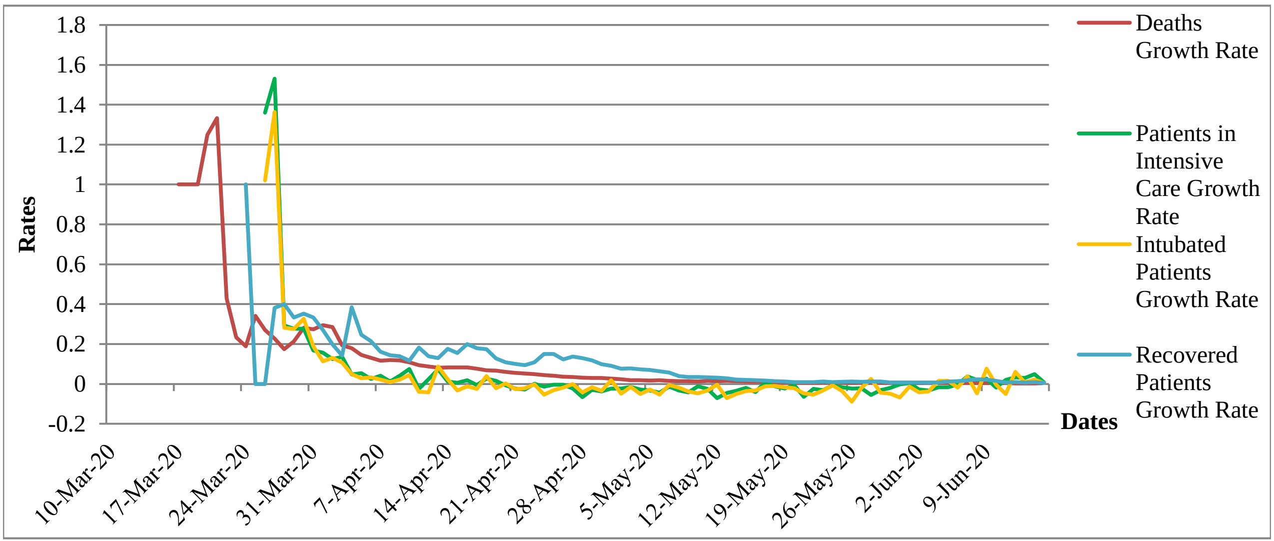

Figure 4: Growth Rates in Turkey (19)

Material and Methods

The data used is from 10 March 2020 (the first day of the disease in Turkey) to 15 June 2020. This data is disclosed on a daily basis by the Ministry of Health of the Republic of Turkey (19). This data doesn't require any ethics committee report as it is publicly published by the Ministry of Health of the Republic of Turkey.

Statistical Analysis: In the study, firstly, a correlation matrix was applied. Afterward, the most suitable models were selected with the expert modeler method to forecast cases and deaths. The most proper models for both estimates were determined as ARIMA models. The analyzes and tests realized in this section were carried out on the IBM SPSS Statistics 20 program. Finally, the stationarity of the models found was examined by using the ADF test in EViews 9 program.

A correlation matrix describes the relationship among m variables, where the cross elements are equal to the merger. The square obtained from the variance-covariance matrix is a symmetrical, mxm-sized matrix. Both of these matrices include similar information, but the correlation matrix performs it is easier to relate variables (20). In the correlation matrix, the cross values are always 1.00 (100%) since they are between the same variables. A p-value of less than 0.05 is statistically significant.

The autoregressive integrated moving average (ARIMA) models are widely utilization to model financial time series data. These models can be defined as:

$$\varphi(B)y_t = \theta(B)a_t \quad (1)$$

$$\varphi(B) = 1 - \varphi_1 B - \cdots - \varphi_p B^p ,$$

$$\theta(B) = 1 - \theta_1 B - \cdots - \theta_q B^q, B^k y_t = y_{t-1}$$

where "y_t" is the financial time series, "a_t" is a sequence of independent and identically distributed N(0, σ2) random variables. The "y_t s" can, in general, represent the difference or some other proper transformation of a non-stationary series "x_t". An appropriate portmanteau test of the hypothesis of model sufficiency is given by the Box-Pierce (BP) test or another genre called the Ljung-Box (LB) test (21, 22). These test statistics comply with a chi-square distribution asymptotically if the model assumptions are true. Simulations performed for minor sample sizes have shown (22) that the LB test performs preferably than the BP test (23). Tests for residual autocorrelation are important tools for this task. A well-known instance is the LB test for residual autocorrelation. If the residuals are correlated, then the model should be reformed. Else, the residuals are white noise and the model is adequate to represent the time series (24). While the class of ARIMA models include a wide variety of time series, it does not compass time series that display repetitive behavior or periodic patterns. This recurrent nature is the essence of seasonal time series (25).

In the previous sections of this research, the spread of COVID-19 disease in other countries has been examined and general statistical information has been given about the 10 countries where this disease is seen the most. In the results section, estimates to future on the number of cases and deaths will be performed to determine the course of COVID-19 disease in Turkey.

One of the common methods to find the integration order of variables is unit root tests. One of the most popular among these tests is the ADF test. The ADF test is a Dickey-Fuller (DF) test with additional delays added to the dependent variables to eliminate the autocorrelation problem found in the time series. (26). The ADF test (27, 28) requires regressing the 1st difference of a variable y on its lagged level, exogenous variable(s) and k lagged first differences:

$$\Delta Y_t = a + \beta T + pY_{t-1} + \sum_{i=1}^{k} \gamma_i \Delta Y_{t-i} + e_t \quad (2)$$

where "et" is an error term disturbance with mean zero and variance, "Yt" the variable in period t, "T" indicates a time-trend, "□" is the difference operator, and "k" symbolizes the number of lags of the differences in the ADF equation. The ADF test is limited by its number of lags. It reduces the power of the test to reject the null of a unit root because the raised number of lags necessitates the estimation of extra parameters and a loss of a degree of freedom (29).

The JB test examining the normal distribution assumption was applied. One of the most famed tests for normality of regression residuals is the JB test (30), which has gained great acceptance among econometricians. The test statistic JB is a function of the measures of skewness (S) and kurtosis (K) computed from the sample. Under normal distribution, the theoretical values of S and K are 0 and 3, respectively (31). The test statistic JB is defined by

$$JB = \frac{n}{6}.(S^2 + \frac{(K-3)^2}{4}) \quad (3)$$

where $S = \hat{\mu}_3/\hat{\mu}_2^{3/2}$ is an estimator of $\beta_1 = \mu_3/\mu_2^{3/2}$ and $K = \hat{\mu}_4/\hat{\mu}_2^2$an estimator of $\beta_2 = \mu_4/\mu_2^2$, and μ_2 and μ_3 are the theoretical second, 3rd and 4th central moments, respectively, with its estimates

$$\hat{\mu}_j = \frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{x})^j, \; j = 2,3,4 \quad (4)$$

The null hypothesis has to be rejected at 0.05 level if $JB \geq \chi^2_{0.05,2}$ (31)

Results

Correlation Matrix for COVID-19 in Turkey

A correlation matrix suitable for the above information is given in Table 3. COVID-19 disease in Turkey due to cases, deaths, patients in ICU, intubated patients and the number of tests performed has been investigated on this matrix. Most of the relationship values (Spearman correlation) given in Table 3 are greater than 92% and significant as statistically, which indicates an elevated correlation between variables. For instance, the relationship value between cases and deaths is 0.997. According to this correlation value, the deaths and cases up to 15 June affect each other by 99.7%.

Except for the three p-values (p>0.05) in Table 3, the p-values of all correlation values are statistically significant (p<0.05).

Forecasting Cases in Turkey with The ARIMA Model

In this analysis, the ARIMA(0,2,4) model was utilized to estimate the future values of COVID-19 deaths in Turkey. In this type (0,2,4) of the ARIMA model, the moving average (MA) is selected as 4 by taking the difference of the variables from the 2nd degree. Since the p-value is statistically significant (p>0.05), the H1a hypothesis is accepted (Table 4). The test statistic of the ARIMA(0,2,4) model shows that the defined model is appropriate for the time-series data (Ljung-Box Q Statistics = 20.423, DF= 16, p-value= 0.202) in Table 4. This implies that residuals from the model are white noise or independence.

H1a: The data are random and residuals aren't correlated.
H1b: The data aren't random and residuals are correlated.

The parameters of the ARIMA(0,2,4) model (estimate, standard error (SE), t-statistics, and p-value) are given in Table 5. According to this table, the H2a hypothesis is rejected, inasmuch as the p-values for moving averages (lag 3 and lag 4) are statistically significant (p<0.05). Thus, the ARIMA(0,2,4) model is determined to be statistically significant.

H2a: The ARIMA model is not statistically significant.
H2b: The ARIMA model is statistically significant.

COVID-19 cases in Turkey were modeled as shown in Figure 3. In this figure, the date of 10 March 2020 was taken as the first day of COVID-19, and the forecast was made until 6 August 2020, the 150th day of the disease in Turkey. As a result of this forecast, it is estimated that there may be 266692 cases in Turkey on 6 August 2020. In other words, as of June 15, the total number of cases was estimated to increase by 48.30% after 52 days

Table 3: Correlation Matrix for COVID-19 Observations in Turkey

		Cases	Deaths	Patients in ICU	Intubated Patients	Recovered Patients	Tests
Cases	Spearman Correlation	1	0.999**	-0.162	-0.275**	0.999**	1
	p-value		0.001	0.127	0.008	0.001	
Deaths	Spearman Correlation	0.999**	1	0.183*	-0.275**	0.999**	0.999**
	p-value	0.001		0.036	0.008	0.001	0.001
Patients in ICU	Spearman Correlation	-0.162	-0.162	1	0.968**	-0.162	-0.162
	p-value	0.127	0.127		0.001	0.1268	0.127
Intubated Patients	Spearman Correlation	-0.275**	-0.275**	0.968**	1	-0.275**	0.275**
	p-value	0.008	0.008	0.001		0.008	0.008
Recovered Patients	Spearman Correlation	0.999**	0.999**	-0.162	-0.275**	1	0.999**
	p-value	0.001	0.001	0.126	0.008		0.001
Tests	Spearman Correlation	1	0.999**	-0.162	-0.275**	0.999**	1
	p-value		0.001	0.127	0.008	0.001	

Note: "**" clarify that correlation is significant at the 0.05 level (1-tailed).

Table 4: Diagnostics of the ARIMA(0,2,4)

Model	Number of Predictors	Model Fit Statistics				Ljung-Box Q(18)			Number of Outliers
		R-squared	RMSE	MAE	MAPE	Statistics	DF	p-value	
Cases-Model_1	0	1.000	324.751	202.797	4.165	20.423	16	0.202	0

Table 5: The ARIMA(0,2,4) Model Parameters

Model	Estimate	SE	t	p-value
Cases-Model_1	0.217	.097	2.226	0.028
	-0.273	.098	-2.796	0.006

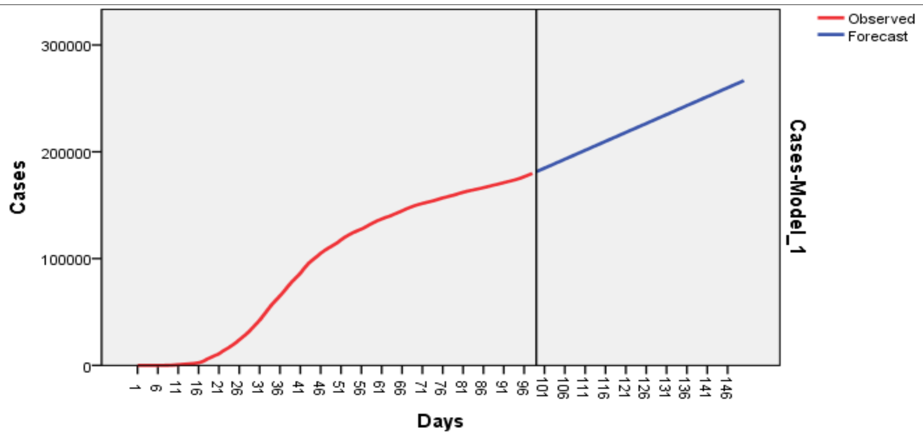

Figure 7: Forecasting Cases on the Curve

Forecasting Deaths in Turkey with The ARIMA Model

In this analysis, the ARIMA(0,3,1) model was utilized to estimate the future values of COVID-19 deaths in Turkey. In this type (0,3,1) of the ARIMA model, the MA is selected as 1 by taking the difference of the variables from the 3rd degree. Since the p-value is statistically significant (p>0.05), the H3a hypothesis is accepted (Table 6). The test statistic of the ARIMA(0,3,1) model shows that the defined model is appropriate for the time-series data (Ljung-Box Q Statistics = 17.735, DF= 19, p-value= 0.406) in Table 6.

H3a: The data are random and residuals aren't correlated.
H3b: The data aren't random and residuals are correlated.

The parameters of the ARIMA(0,3,1) model are given in Table 7. According to this table, the H4a hypothesis is rejected, since the p-value for moving average (lag 1) is statistically significant (p<0.05). Thus, the ARIMA(0,3,1) model is determined to be statistically significant.

H4a: The ARIMA model is not statistically significant.
H4b: The ARIMA model is statistically significant.

COVID-19 deaths growth rates in Turkey were modeled as shown in Figure 4. In this figure, the date of 10 March 2020 was taken as the first day of COVID-19, and the forecast was made until 6 August 2020, the 150th day of the disease in Turkey. As a result of this forecast, it is estimated that there may be 5718 deaths in Turkey on 6 August. In other words, as of June 15, the total number of deaths was estimated to increase by 18.50% after 52 days.

The ADF Test for ARIMA Models

The ARIMA(0,2,4) model used for case estimation and the ARIMA(0,3,1) model used for death estimation are time-series. For this reason, the stationarities of the observations in the models were examined. According to the results in Table 8, p-values of both models are rejected by the H5a hypothesis (p<0.05).

Thus, for "Cases-Model_1" using the ARIMA(0,2,4), the stability of the model has been provided in the 2nd degree. Likewise, for "Deaths-Model_1" using the ARIMA(0,3,1), the stability of the model was provided in the 3rd degree. The use of the ARIMA(0,2,4) and ARIMA(0,3,1) models are statistically suitable.

H5a: The ARIMA model is non-stationary and has a unit root.
H5b: The ARIMA model is stationary and hasn't a unit root.

The ACF and PACF Plots of Cases and Deaths

The ACF and PACF plots of the used time series should be given to see the non-stationary in the data graphically. ACF and PACF graphs are time series graphs used for stationarity testing. Firstly, ACF and PACF graphs are given for non-difference of cases series and the 2nd difference of cases series (Figure 9). When the 2nd difference of the cases is taken, it is seen that they are stationary.

Subsequently, ACF and PACF graphs are given for non-difference of deaths series and the 3rd difference of deaths series (Figure 10). When the 3rd difference of the cases is taken, it is seen that they are stationary. Thus, the state of stationary was also evaluated on the graphs.

The Normality of the Errors

Cases and deaths used in ARIMA models should provide the normality assumption. For this purpose, the JB test was used to find out whether the errors are suitable for normal distribution. According to the JB test results given in Table 9, p-values for both cases and deaths are greater than 0.05 (p>0.05). Thus, the H6a hypothesis cannot be rejected. Both cases and deaths are suitable for normal distribution.

H6a: Errors show a spread suitable for normal distribution.
H6b: Errors don't show a spread suitable for normal distribution.

Table 6: Diagnostics of the ARIMA(0,3,1)

Model	Number of Predictors	Model Fit Statistics				Ljung-Box Q(18)			Number of Outliers
		R-squared	RMSE	MAE	MAPE	Statistics	DF	p-value	
Deaths-Model_1	0	1.000	5.449	4.053	2.984	17.735	17	0.406	0

Table 7: The ARIMA(0,3,1) Model Parameters

Model	Estimate	SE	t	p-value
Deaths-Model_1	0.835	0.059	14.225	0.001

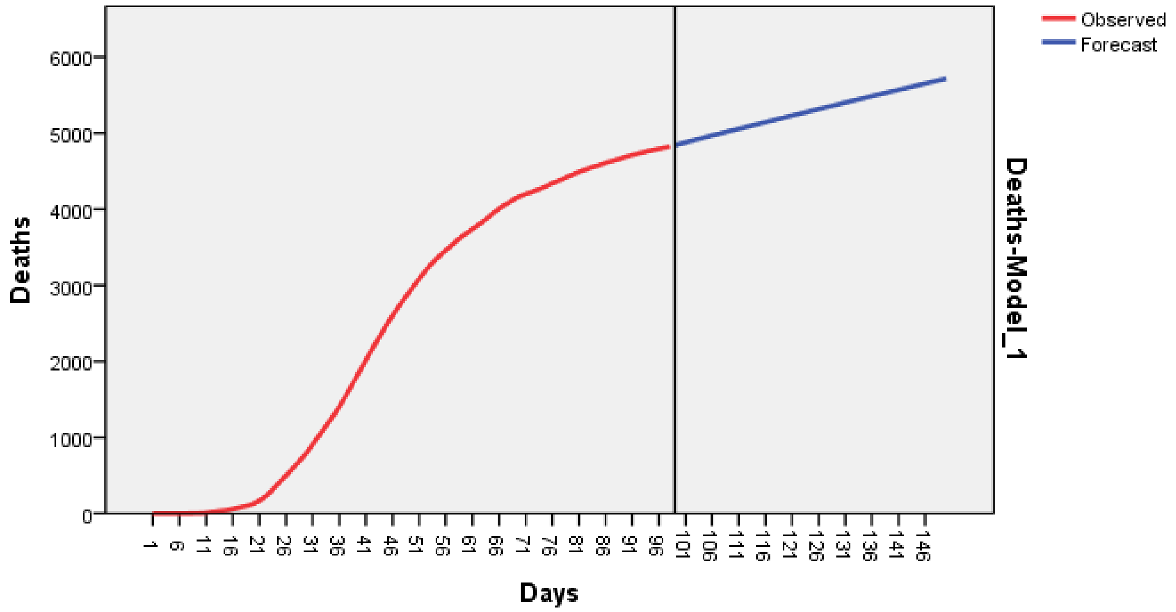

Figure 8: Forecasting Deaths on the Curve

Table 8: The ADF Test

Models	Non-Differences		Current Differences	
	t-Statistics	p-value	t-Statistics	p-value
Cases-Model_1	-0.280	0.5824	-3.822*	0.0002*
Deaths-Model_1	-0.676	0.4217	-17.844**	0.0001**

Note: *the difference of the observations from the 2nd degree was taken.
Note 2: **the difference of the observations from the 3rd degree was taken

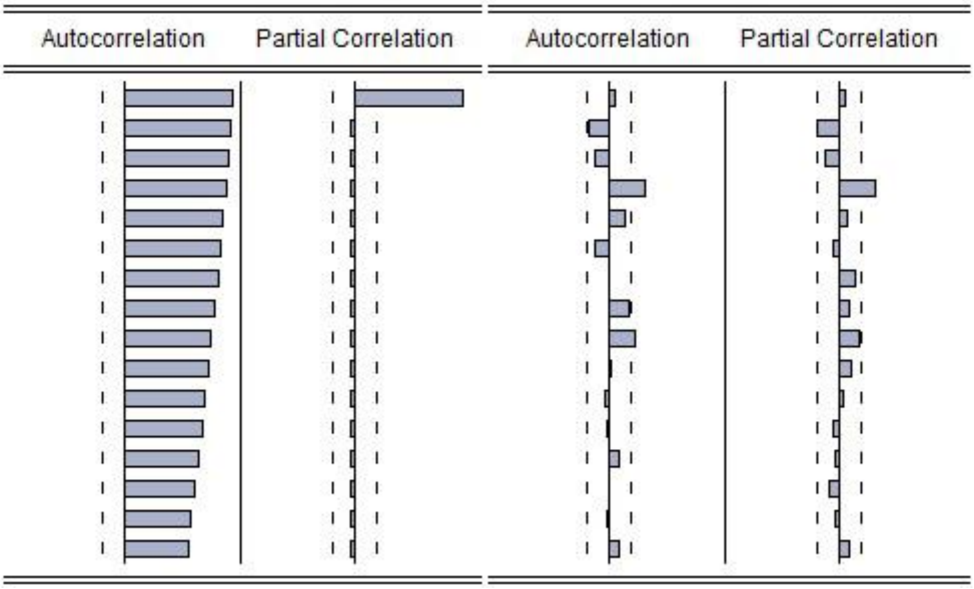

Figure 9: The ACF and PACF Plots of Cases

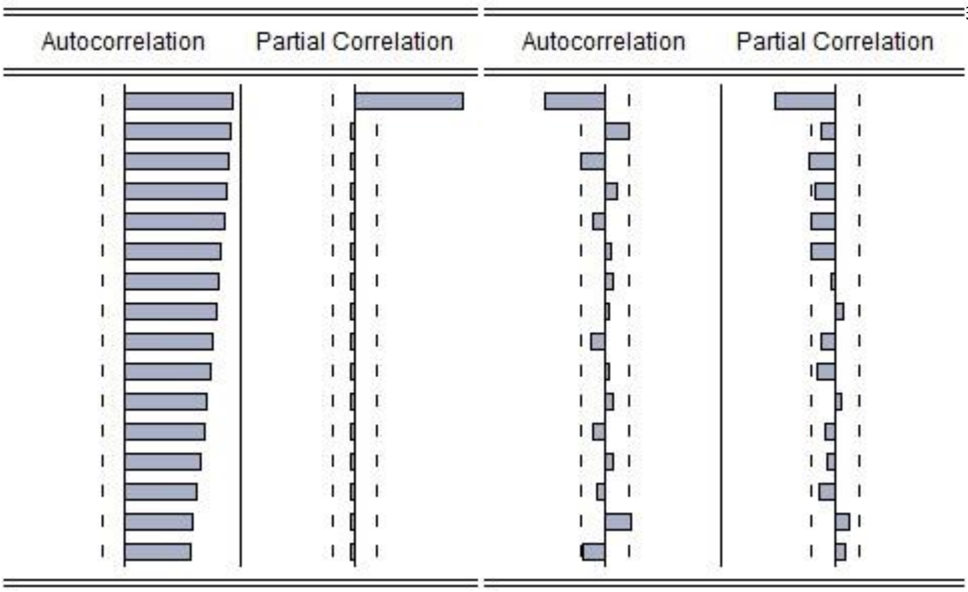

Figure 10: The ACF and PACF Plots of Deaths

Table 9: The JB Test

Statistics	Cases	Deaths
Mean	22.135	0.073
Median	4.000	0.000
Maximum	877.000	17.000
Minimum	-778.000	-16.000
Skewness	0.382	-0.089
Kurtosis	3.945	2.929
Jarque-Bera	5.918	0.147
p-value	0.051	0.928

Discussion

As of June 15, the SARS-CoV-2 virus has caused 8066465 infected people and 437295 deaths in the world. The disease caused by this virus is called COVID-19, and this disease has become a big epidemic over time. The fact that there is currently no definitive treatment and vaccine makes this disease more dangerous. Germany, which is one of the 10 countries where the disease is most common, is 1st country with the highest rate with 91.82% recovery rate, while the United Kingdom, which is another one of the 10 countries where the disease is most common, is the last country with 0.43% recovery rate. The U.S.A., Spain, and Peru, which are among the top 10 countries, are the countries with the highest number of cases when compared with their population. Likewise, Spain, Italy, and the U.K. are the countries with the highest number of deaths when compared with their population. Certainly, the fact that the elderly population in Europe is higher than other regions is one of the reasons for the high death rates.

In both the models established to predict the COVID-19 cases and COVID-19 deaths, it has been estimated that the disease may not end yet and deaths may continue. If the disease progresses in its current stable course, observations close to the predicted results may be obtained. Because these predicted values do not include possibilities such as e or the SARS-CoV-2 virus undergoing a fatal mutation. COVID-19 has a certain lethality rate, which is an average of 5.42% for the world. When this lethality rate was taken into consideration, it was observed that the estimate of death in Turkey (%2.14) was consistent and lower than the world.

The main aim of this study was to examine COVID-19 cases and deaths in Turkey and to predict their future state. At this point, Turkey, despite being one of the countries where COVID-19 cases last seen, has been one of the countries where the disease is most prevalent. On the 97th day of the disease, a total of 179831 cases and 4825 deaths estimated in Turkey. 152364 people of these cases were recovered, and the recovery rate was found as 84.73%. The death rate was found to be 2.68%, which is below the world's deaths average of 5.42%. By 15 June, 2674203 COVID-19 tests were performed. The average growth rates were found as follows: cases 18.35%, deaths 12.66%, patients in ICU 4.64%, intubated patients 3.38%, and recovered patients 10.36%.

Consequently of the analysis and models established for forecast, the following results were found: Approximately 266692 COVID-19 cases and 5718 COVID-19 deaths may occur in Turkey on the 150th day of the disease. For these alarming and increasing estimation values, Turkey must be careful and rigorously manage the process.

Thus, this hardly process, which may pass until a vaccine and an effective treatment are found, can be overcome with minimal loss.

Conclusion

Consequently of the analysis and models established for forecast, the following results were found: Approximately 266692 COVID-19 cases and 5718 COVID-19 deaths may occur in Turkey on the 150th day of the disease. For these alarming and increasing estimation values, Turkey must be careful and rigorously manage the process. Thus, this hardly process, which may pass until a vaccine and an effective treatment are found, can be overcome with minimal loss.

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Author's contributions: YAÜ, OD; Study design, Data Collection and analyses **OD;** Article preparation and revisions

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