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Correlation of Magnetic Resonance Colangiopanchreatography Bile Duct Image Data With Laboratory Data

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ABSTRACT:
Purpose: Several etiologies come to the fore in gallstones' formation, especially the chemical content of bile and impaired motility of the gallbladder. This study aims to reveal the connections by evaluating the radiological images and laboratory data of patients who underwent MRCP for any reason in our center.
Material and Methods: The data of patients who underwent MRCP with a pre-diagnosis of cholestasis in a single center in 2019-2020 with the ethics committee's approval were retrospectively analyzed. Choledock diameter, presence of cholelithiasis and choledocholithiasis, and variation of the cystic duct were evaluated on MRCP images. In addition, laboratory data were examined, and the relationship between them was statistically compared.
Results: Of the 193 patients who underwent MRCP with a pre-diagnosis of bile duct pathology, 59.1% were female(n=114), 40.9% were male(n=79). Their mean age was 63.1±19.4. While the cystic duct was normal in 35.3%(n=68) of the patients, 64.7%(n=125) had anatomical variation. There was no difference between genders in terms of the presence of variation in the cystic canal. There was no significant relationship between the presence of variation and gallstones. A positive correlation was found between common bile duct diameter and presence of gallstones and WBC, neutrophil, and ALP values.
Conclusion: Although it is thought that bile duct variations may be effective in the formation of gallstones, it was observed that the variational cystic duct was not effective in gallstone formation in our case series. In MRCP, we found that the increase in the diameter of the common bile duct and the high values of WBC, neutrophils, and ALP support the presence of gallstones.
Keywords: *Choledoc diameter, Choledocholithiasis, Cholelithiasis, Cystic duct variation, MRCP*

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INTRODUCTION

Bile production is a complex process in which hepatocytes are actively involved. There is a wide range of hormones that govern the production and cycle of bile. Bile contains almost all body components (Strazzabosco & Fabris, 2008). Bile acids make up 67% of bile and is synthesized from hepatocytes. Phospholipids (lecithin) make up 22% of bile. Bile consists of 4.5% proteins, 4% cholesterols, and 2% bile pigments (bilirubin) (Reshetnyak, 2013). The produced bile is transported through the bile ducts. Most of the bile acids produced are brought to the gallbladder through the hepatic ducts. Bile acids that accumulate in the gallbladder are both concentrated and stored (Guyton & Hall, 2001). Bile, which is produced in the liver and deposited in the gallbladder due to the stimulation of the intestinal system with food, is poured into the second continent of the duodenum through the common bile duct. Bile acids aid in the digestion of fats, the absorption of fat-soluble vitamins, and the excretion of degradation products produced due to metabolic events.

Gallstone formation increases depending on age,

gender, race, and body weight. It is more common in older age, female gender, obese people, women who have given birth more than others, and blond race (Chowdhury & Lobo, 2011). It is known that many mechanisms are effective in the formation of gallstones. However, it is still not clearly elucidated (Muñoz et al., 2019).

The first method used to show gallstones and common bile duct stones is ultrasonography (USG). USG is the most commonly used method because it is both an inexpensive and non-invasive method. In cases that cannot be seen clearly with USG, the gall bladder and bile ducts can be visualized more clearly with Computed tomography (CT) and Magnetic resonance (MR) methods (Özden, et al., 2020). Magnetic resonance cholangiography (MRCP) is the second most frequently used imaging method after USG to show the bile ducts (Hanbidge, et al., 2004). MRCP is commonly used in symptomatic patients to exclude choledocholithiasis, exclude gallstone-related diseases (cholangitis and pancreatitis), and preoperative investigation of bile ducts (D'Angelo, et al., 2017). MRCP is used more than CT in bile duct pathologies because it is not exposed to radiation in the patient, does not need a contrast agent, and shows the bile ducts better. Studies have shown that MRCP is the best method for hepatobiliary system imaging (Mustafa, 2017).

Anatomical variations of both intrahepatic and extrahepatic bile ducts are common. Studies show that anatomical variations of the bile ducts are associated with stone formation, cholangitis, and pancreatitis attacks (Mortelé & Ros, 2001). Another importance of anatomical variations is that they cause iatrogenic injuries during the operation (Kapoor et al., 2002).

The most common method used to classify anatomical variations is Huang classification (Huang, et al., 1996). This classification is typed according to the relationship between the hepatic bile ducts and the cystic duct.

This study evaluated the cystic duct exit variations from the common bile duct, common bile duct diameter, presence of bile stones, and biochemical and hematological data of patients who underwent MRCP.

MATERIAL AND METHODS

Purpose and Type of the Study

This study is a research article examining retrospective data. To analyze radiological image data and laboratory data of patients who underwent MRCP with pre-diagnosis of bile duct pathology.

Sampling and Participant

In our study, archive data of patients who were admitted to Sivas Cumhuriyet University Health Services Application and Research Hospital General Internal Medicine and Gastroenterology service with abdominal pain and underwent MRCP with a pre-diagnosis of cholestasis between 01.01.2019 and 31.12.2020 were analyzed.

Data Collection Tools

In the study, MRCP images obtained using a 1.5 Tesla unit (Siemens, Acra, Germany) without contrast were used. Existing MRCPs in the study were re-evaluated in terms of gallstones' presence, the directional canal's variational status, and common bile duct diameter. Also ALT, AST, Total Bilirubin, Direct Bilirubin, ALP, GGT, Amylase, CRP, and hemogram parameters were examined as blood tests. Patients with malignancies, patients who underwent cholecystectomy, patients who underwent common bile duct surgery, and patients under 17 years of age were excluded from the study.

Statistical Analysis

Statistical comparisons were made using the statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The Kolgomogro-Smirnow test was used for normal distribution. Student T-test, Pearson Correlation analysis were used to compare parameters without normal distribution, and the Chi-Square test was used to compare categorical variables obtained by counting. The exact statistics were noted as "Mean ± standard deviation (SD)" and "Median (interquartile, IQR)". The significance level was accepted as 0.05.

Ethical Approval

This study was planned by obtaining the decision of Sivas Cumhuriyet University Non-invasive Clinical Research Ethics Committee numbered 2021-01 / 31

and the permission of the institution.

RESULTS

193 patients were included in the study. 59.1% of the cases were women (n=114), and 40.9% were men (n=79). The average age of the patients was 63.1±19.4. Choledocholithiasis in 9 patients, cholelithiasis in 60 patients, and both cholelithiasis and choledocholithiasis in 22 patients were detected in 193 MRCP patients. No stones were detected in the biliary system in 102 patients. There was no difference between genders in terms of gallstones' presence among patients who underwent MRCP (p = 0.213) (Table 1).

While the cystic duct was normal in 35.3% (n=68) of the MRCP errors, there was anatomical variation in the cystic duct in 64.8% (n=125) (Table 2). No significant difference was observed between the genders in terms of variations (p = 0.798) (Table 1). There was no significant relationship between cystic duct variations and the presence of stones in the biliary system (p = 0.138). A positive correlation was found between age and common bile duct diameter (p <0.05). It was observed that as the common bile duct diameter increased, the possibility of gallstones increased (p <0.05). It was observed that the WBC, neutrophil, and ALP values increased with gallstones' presence (Table 3). A positive correlation was found between the increase in common bile duct diameter and WBC, neutrophil, and ALP values (Table 3).

Table 1. The relationship between the variation status of the ductus cysticus and the presence of gallstones with gender was analyzed in patients who underwent MRCP

			Ductus Cysticus		Total	P	Gallstone		Total	P
			Normal	Variational			No	Yes		
Gender	Male	S	27	52	79	p=0.798[a]	46	33	79	p=0.213[b]
		%	34.2%	65.8%	100%		58.2%	41.8%	100%	
	Female	S	41	73	114		56	58	114	
		%	36.0%	64.0%	100%		49.1%	50.9%	100%	
Total		S	68	125	193		102	91	193	
		%	35.2%	64.8%	100%		52.8%	47.2%	100%	

[a] There was no significant relationship between the variational structure of the Ductus Cysticus and gender (p = 0.798).
[b] There was also no significant relationship between the presence of gallstones and gender (p = 0.213). (p <0.05 was considered significant)

Table 2. Number and incidence of variation types of the cystic channel

	Cystic Canal Variation	*n*:193	%
1	Normal	68	35.2
2	Variational	125	64.8[a]

[a] Cystic duct variation was detected in 64.8% of the patients.

DISCUSSION

Presence of stones in the biliary system is a common disease today and is one of the leading causes of abdominal pain (Hu, et al., 2017). It continues to pose a severe public health problem in developed countries. Although it has low mortality, it is a significant health problem due to its high morbidity. Due to the developments in imaging techniques such as USG and MRI, the possibility of early and accurate diagnosis has increased. With the development of ERCP and laparoscopic surgery techniques, more effective treatment has been revealed.

In the study, images and laboratory values of patients who underwent MRCP with a pre-diagnosis of biliary system pathology in our hospital were examined. It is known that MRCP, which is a non-invasive method, is a preferable method in terms of the presence of stones in the biliary system, the diameter of the common bile duct, and the evaluation of anatomic variations in the cystic canal (Wan et al., 2018). Although its clinical significance has not been clearly demonstrated yet, there are many anatomical variations of both intrahepatic and extrahepatic bile ducts. Evaluating such variations

with imaging techniques before the surgical procedure may be a warning to avoid iatrogenic bile duct injuries in surgery.

Many environmental and genetic etiological factors are involved in the formation of gallstones. The reasons such as high cholesterol saturation of bile, excessive bile concentration, lack of proteins that inhibit nucleation, and hypomotility in the gallbladder come to the fore in etiological terms (Venneman & van Erpecum, 2010).

Table 3. The relationship between choledoc diameter and gallstones with age and blood parameters was analyzed

	Choledoc Diameter (p value)	Gallstone (p value)
Age	0.000	0.021
ALT	0.801	0.246
ALP	0.047[a]	0.040[a]
Amylase	0.352	0.321
AST	0.970	0.206
CRP	0.066	0.430
D. Bilirubin	0.062	0.441
GGT	0.269	0.167
Creatine	0.851	0.418
LDH	0.558	0.216
Lymphocyte	0.716	0.449
MPV	0.958	0.090
Neutrophil	0.000[a]	0.027[a]
PLT	0.093	0.068
T. Bilirubin	0.106	0.337
WBC	0.000[a]	0.039[a]
Neutrophil/ Lymphocyte	0.065	0.095

[a] WBC, neutrophil and ALP values were found to be positively correlated with choledoc diameter and gallstones ($p < 0.05$ was considered significant).

The effect of anatomical variations of bile ducts on gallstone formation is still unclear. In the patient series examined in this study, it was observed that the cystic duct variations detected in the MRCP images were not effective in the formation of gallstones. In patients with MRCP, it was observed that the risk of stones increased as the age progressed, and consequently, the diameter of the common bile duct increased. WBC, neutrophil, and ALP values were significantly increased in patients with increased common bile duct diameter and gallstones. These elevations were found to be an expected result in biliary tract pathologies and were consistent with the literature (Mei et al., 2019).

The prediction that the presence of the variational cystic duct may increase stones' formation by negatively affecting the bile drainage was not met in our study. We think that anatomical and physiological compensation mechanisms may have come into play in this regard. Therefore, it would be more enlightening to conduct a comprehensive study including a more detailed anatomical examination, including other parts of the biliary tract.

CONCLUSION

Although it is thought that bile duct variations may be effective in the formation of gallstones, it was observed in our study that cystic duct variations were not effective in gallstone formation. We have seen that the increase in the diameter of the common bile duct and the height of WBC, neutrophils, and ALP in patients with MRCP support the presence of gallstones.

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Conflict of Interest

There is no conflict of interest.

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Research Article

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The Anticancer Effect of Cannabinoid 2 Agonist L-759,633 on C6 and SH-SY5Y Cell Lines

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ABSTRACT:
Purpose: Previous studies have shown that cannabinoid 2 agonists have anticancer effects on different cancer cell lines. However, the effect of L-759,633 on the Neuroblastoma and glioma is still uncertain. The current study was intended to investigate the potential cytotoxic effects of a cannabinoid 2 agonist L-759,633 on the C6 and SH-SY5Y cell lines.
Material and Methods: In our study, the C6 and SH-SY5Y cell lines were used. For each cell line two cell groups were prepared to examine the effect of L-759,633 on C6 glioma and SH-SY5Y cell death. It was not applied any treatment to the cells in the control groups. Various concentrations (5, 10, 20, 40 and 80 µM) of L-759,633 was applied to the cells in the L-759,633 groups. After 24 hours the cell viability was examined using XTT assay. Total oxidant status (TOS) and Total antioxidant status (TAS) in the cells were measured by commercial kits.
Results: L-759,633 at the concentrations of 5, 10, 20, 40 and 80 µM significantly decreased the cell viability in C6 cells ($p<0.001$). It also significantly increased the TOS levels ($p<0.001$) whereas didn't alter the TAS levels ($p>0.05$). On the other hand this agent did not reduce SH-SY5Y cell viability.
Conclusion: L-759,633 has antiproliferative effect on C6 cells. Additionally, one of the potential mechanisms involved in this effect is activation the oxidant generation. However this drug didn't show antiproliferative effect on SH-SY5Y cell.
Keywords: *L-759,633, Oxidative Stress, cell viability, C6 Glioma, SH-SY5Y cell*

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INTRODUCTION

Glioblastoma multiforme (GBM) is a common category of malignant main brain tumors and one of the most hostile types of cancer. The survival after identification is usually merely six months to one year (Kleihues et al., 2002; Reardon & Wen, 2006). This is mostly because of the high invasiveness and reproduction rate of GBM. In addition, GBM shows high resistance to classic chemotherapy and radiotherapy (Maher et al., 2001). Current classic therapeutic strategies for the cure of GBM are merely palliative and include focal radiotherapy and surgical resection. A vast number of chemotherapeutic drugs have already been tested, yet no notable improvement on patient survival has been brought about (Guillermo et al., 2007). Neuroblastoma (NBL) is a common extracranial solid tumor in children. It is accountable for nearly 8% of childhood cancers and is characterized by changeable clinical behaviors demonstrating molecular diversities in the tumor (Maris et al., 2007). Medication for children with high-risk neuroblastoma includes chemotherapy, surgery, autologous stem-cell transplantation, immunotherapy, and radiation therapy. Despite the multimodality therapy, children with neuroblastoma have very faint outcomes, and the survivors encounter critical side effects related to medication toxicity (London et al., 2011). Therefore, the need for novel and less-toxic medical strategies to cure the

disease is urgent.

Modulation of the endocannabinoid system has been shown in different tumors. These changes contain the levels of generated endocannabinoids and the expression of their receptors. Modulation of the CB1 and CB2 expression has been shown to be associated with cancer cell motility, proliferation, invasion, and apoptosis (Kovalchuk & Kovalchuk, 2020). The anandamide and AEG levels are 2 - 3 fold higher in colorectal cancers and adenomas than in the healthy controls (Ligresti et al., 2003). Currently, increasing evidences propose that cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC), primary ingredients of cannabis sativa, and synthetic cannabinoids have anticancer activity (Galve-Roperh et al., 2000; Guillermo et al., 2012). Many cancer kinds (lymphoma, lung cancer, thyroid cancer, glioma, pancreatic cancer, skin cancer, uterine cancer, breast cancer and prostate carcinoma) have been referred to be responsive to the antiproliferative action of cannabinoids in a vast variety of experimental models which include cancer cell lines in culture and experimental animal models (Guillermo et al., 2012). The mechanisms implicated in the anticancer effects of cannabinoids comprise proliferation prevention, growth arrest (Galanti et al., 2008), initiation of apoptosis (Carracedo et al., 2006), activation of autophagy (Vara et al., 2011), angiogenesis suppression (Portella et al., 2003), and anti-metastatic effects (McAllister et al., 2011).

Recent information supports the presence of CB_2 receptors in the nervous system, particularly in microglial cells, glioma cells and astrocytes (Fernández-Ruiz et al., 2007).

Cannabinoid 1 receptors and cannabinoid 2 receptors were discovered in human cerebral cancers (Held-Feindt et al., 2006; Ellert-Miklaszewska et al., 2007). This discovery led to investigate possible biological efficacy of cannabinoids on glioma cells in order to try to find possible therapeutic agents. Cannabinoid receptor agonists were determined to suppress glioma enlargement by modulating key signaling routes resulting in apoptosis in experimental animal models (Carracedo et al., 2006). Furthermore, cannabinoid receptor agonists downregulated Vascular Endothelial Growth Factor (VEGF) which resulted in decreasing the tumor size (Blázquez et al., 2004). Until now, according to our knowledge, no published studies have demonstrated the possible efficacy of the CB_2 receptor agonist L-759,633 against neuroblastoma and malignant glioma. Therefore, the present study was conducted to investigate the possible antitumor efficacy of this agent on C6 and SH-SY5Y cell lines.

MATERIAL and METHODS

Cell Culture

Rat glioma C6 (CRL107) and human SH-SY5Y (CRL-2266) cells was obtained from American Type Culture Collection (ATCC). (6aR,10aR) – 3-(1,1-Dimethylheptyl)-6a,7,10,10a – tetrahydro – 1-methoxy-6,6,9 – trimethyl-6H – dibenzo[b,d]pyran (L-759,633) was acquired from Sigma-Aldrich (Cayman Chemical Company, USA). The cell lines were kept in Dulbecco's modified Eagle medium (DMEM; Lonza, Walkersville, MD, USA), that was mixed with 10 % (v/v) heat-inactivated fetal bovine serum (FBS; Sigma-Aldrich St. Louis, MO, USA) and 1 % penicillin/streptomycin (Gibco Thermo Fisher Scientific). The cells were planted in a 25 cm^2 flask and incubated at 37° in a 5 % CO_2 humidified atmosphere up to they reached about an 80-90 % confluence.

Cell Viability Assay

The viability of cells were evaluated using the XTT test (Roche Diagnostic, Germany). L-759,633 was dissolved in dimethyl sulfoxide (DMSO) and diluted in DMEM before administration. Cells were cultivated in 96-well plates at the density of 1×10^4 cells for each well in 100 µl of DMEM culture media and were permitted to stick, overnight. The following 24 hours, the increasing concentrations (5, 10, 20, 40 and 80 µM) of the drug was added to the two cell lines and the plates were then incubated for 24 hours. It was not applied any treatment to the cells in the control groups. After that, 50 µl XTT labeling solution was added to wells to find out the living cells, after that the plates were incubated at 37° for 4 hours. After mixing, the absorbance of each well was obtained using a microplate reader (Thermo, Germany) at 450 nm comparing to the control. The cell viability was stated in % linked to control (100 %

of viability) (Türe et al., 2020; Taskiran et al., 2021).

The Cells Homogenate Preparation

C6 cells were treated with L-759,633 at dose of 20 µM (median dose) for 24 hours. Using sterile tubes, cells from each group (treated group and untreated group) were brought together. They were centrifuged at two thousand turns a minute for about ten minutes. Then the supernatants were eliminated. The cells deposited on the underside of the tube were suspended by mean of PBS. Repeated freeze-thaw cycles were applied to the cells to burst and allow the internal components to escape. They were centrifuged at four thousand turns a minute for about ten minutes at a temperature of 4°C. Then, the supernatants were gathered for analysis of TOS, TAS and total protein levels (Taskiran, & Ergül, 2021).

Total Antioxidant Status And Total Oxidant Status Evaluation

Concentrations of TAS and TOS in cell supernatants were measured using an automated test method, which was developed by Erel (Erel, 2004a; Erel, 2005). The total antioxidant status assay depends on controlling the reaction proportion of free radicals by determining the absorbance of colored dianisidyl radicals throughout free radical reactions starting with the generation of hydroxyl radicals. Antioxidants in the samples should prohibit coloring proportional to their concentrations. The obtained results were expressed in µmol Trolox Eq/mg protein. In the total oxidant status, ferrous ions are oxidised to ferric ions when the medium contains enough oxidizers so that the test enables TOS levels to be determined by measuring the level of ferric ions through the use of orange xylenol. To calibrate the assay, hydrogen peroxide was used. The obtained results were expressed at µmol H_2O_2 Eq/mg protein. Bradford protein assay kit (Merck Millipore, Darmstadt, Germany) was used to determination of total protein levels in samples

Statistical Analysis

The statistical significance for the tests was found out using one way ANOVA followed by a Tukey post hoc test (SPSS 14.0 for Windows) for multiple comparisons between groups. Data acquired from the cell viability tests were stated as the mean ± standard error. Significance level was determined as $p<0.05$ and $P<0.001$.

RESULTS

Effect of L-759,633 on C6 and SH-SY5Y Cell Viability

In our study, increasing doses of L-759,633 (5, 10, 20, 40 and 80 µM) were examined on cell survival in both cell lines. As shown in figure 1, the tested doses of 5, 10, 20, 40 and 80 µM L-759,633 decreased the survival of C6 cells compared to the control group ($p < 0.001$; Figure 1). The IC_{50} was found to be 14.97 µM. However, L-759,633, in all of the doses, did not alter the survival of SH-SY5Y cells compared to the control group ($p > 0.05$; Figure 2).

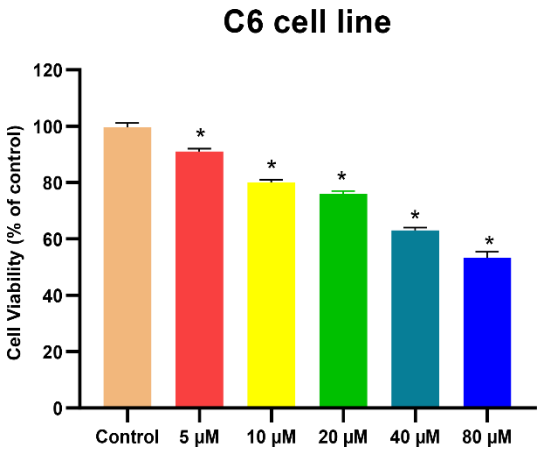

Figure 1. The effect of L-759,633 on cell viability in C6 cells. The data are given as mean ± SEM. *$p < 0.001$ as compared to the control group.

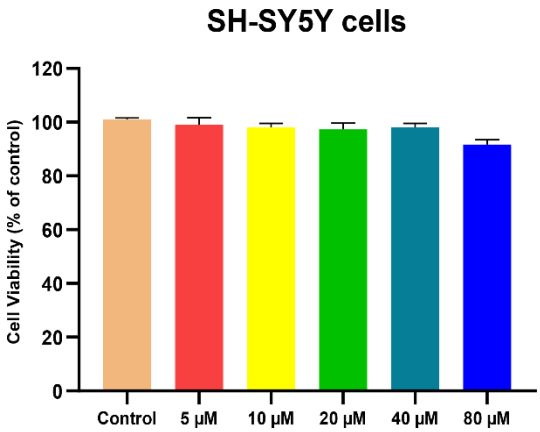

Figure 2. The effect of L-759,633 on cell viability in Human SH-SY5Y cells. The data are given as mean ± SEM. $p > 0.05$ as compared to the control group.

Effect of L-759,633 on TAS and TOS Levels in C6 Cell Line

The cells were treated with the single dose (20 µM) of L-759,633 for 24 hours. As shown in figure 3, the L-759,633 significantly increased TOS in C6 cells as compared to the control group ($p < 0.001$; Figure 3A). Besides, the L-759,633 didn't change TAS levels in C6 cells compared to the control group ($p > 0.05$; Figure 3B).

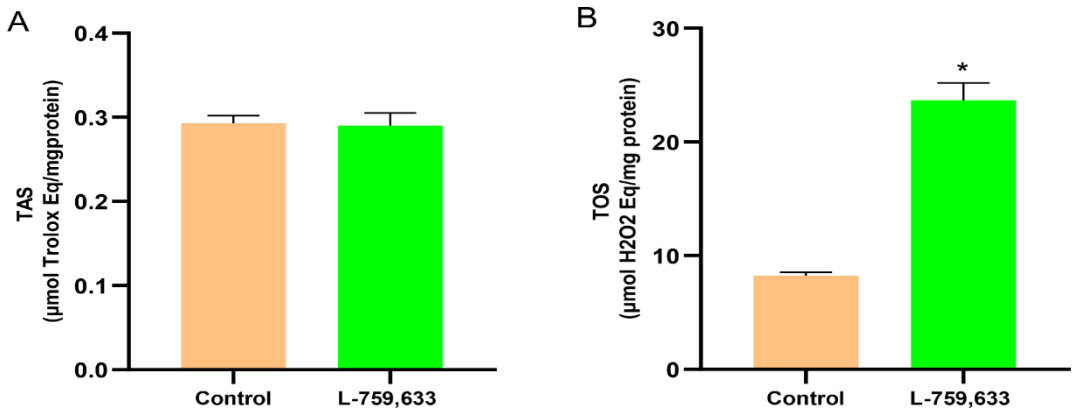

Figure 3. Effect of L-759,633 on TAS and TOS levels in C6 cells. The data are given as mean ± SEM. *$p < 0.001$ compared to the control group.

DISCUSSION

Even though there are diverse medical approaches, including chemotherapy, surgery, and radiation, the recurrence and resistance of neuroblastoma and malignant glioma frequently occur, requiring an alternative efficient medication of the diseases (Jacobsson et al., 2000; Suebsoonthron et al., 2017). It was essentially believed that except for endothelial and microglial cells, CB_2 receptors are unavailable in the central nervous system (CNS). In spite of that, the most recent studies indicated an expression of CB_2 mRNA and CB_2 immunostaining or immunoreactivity in various parts of the brain such as brainstem, basal ganglia, substantia nigra, cerebral cortex, hippocampus, and ventral tegmental area (VTA)(García et al., 2015; Den Boon et al., 2012; Lanciego et al., 2011; Onaivi et al., 2012; Van Sickle et al., 2005; Zhang et al., 2014; Schmöle et al., 2015). Since late 1990s, a large body of data has accumulated showing that different cannabinoids

produce antitumour effects in a wide range of experimental models of cancer (Velasco et al., 2016). The CB_2 receptor agonist CB13 induced a receptor expression and caused apoptosis in the cancerous cell line studied (Cianchi et al., 2008). Local application of Δ9-tetrahydrocannabinol (THC), a non selective cannabinoid agonist, in mice inoculated with a rat glioma cell line reduced the expression of the Matrix Metalloproteinase (MMP)-2, which is an enzyme correlated with a worse tumor prognosis(Blázquez et al., 2008). Selective activation of CB_2 receptors decreased both malignant cell enlargement and new blood vessels formation in human skin tumor cells (Casanova et al., 2003) as well as in the rat glioma in vivo (Sánchez et al., 2001). These data support the CB_2 receptor as a new pharmacological goal capable of suppressing glioma growth and progression (Cioni et al., 2019).

In the present study, the effects of different doses of cannabinoid 2 receptor agonist L-759,633 upon C6 and SH-SY5Y cells viability have been investigated. Selective cannabinoid 2 receptor agonist L-759,633 reduced the C6 cell viability. This reduction was dose- dependent, which aligns with what have been reported for the anticancer effects of selective CB_2 antagonists against glioma in previous studies. On the other hand, this agent did not reduce SH-SY5Y cell viability. This is in contrast to the study conducted by Wojcieszak et al. (2016) who demonstrated that CB_2 receptor agonist JWH-133 produced a concentration-dependent decline of SH-SY5Y cell viability and reproduction rate, and in contrast to the study conducted by Fisher et al. (2016) who showed that medication with cannabidiol (CBD) reduced the viability and invasiveness of NBL cells and stimulated apoptosis in vitro. In line with our study, Sezer et al. (2021) indicated that JWH-018, a non selective cannabinoid agonist, did not cause a significant reduction, in SH-SY5Y cell viability, did not modify apoptotic/necrotic rate, and did not induce genotoxicity in SH-SY5Y cells with one day exposure; Cioni et al. (2019) demonstrated that COR167 significantly decreased the proliferation of both anaplastic astrocytoma and glioblastoma in a dose-dependent manner; Sánchez et al. (2001) indicated that JWH-133 decreased the growth of tumors derived from C6 cell line, but this effect was prevented by the selective CB_2 antagonist SR144528.

The level of reactive oxygen species is one of the factors that play an significant role in the development and metastasis of tumors. In moderate levels, reactive oxygen species influence the tumor microenvironment by initiating metastasis and angiogenesis. On the other hand, the higher reactive oxygen-species-concentrations may induce a cancer cell apoptosis indicating that the reactive oxygen-species-levels critically determine tumorigenesis formations or apoptosis (Aggarwal et al., 2019; Ergul & Bakar-Ates, 2020). The total oxidant status (TOS) which is contained in diverse parameters that are used in the estimation of oxidative stress, is generally used to evaluate the overall oxidation state of samples (Erel, 2004b). In a like manner, the total antioxidant status (TAS) is used to estimate the overall antioxidant state of samples (Choi et al., 2015). In light of this knowledge, we estimated the effect of L-759,633 on TOS and TAS levels in C6 cells. Our results demonstrated that L-759,633 treatment significantly raised TOS levels in C6 cells supporting its cytotoxic effects. Yet, there was no significant alteration in TAS levels (Fig. 3). Rising TOS and not changing TAS levels, in reply to this, revealed that L-759,633 treatment clearly raises the oxidative stress in the treated C6 cells. In accordance with the relevant literature, the present findings showed that oxidative stress can be considered as a participator during cytotoxicity induced by L-759,633. However, our findings need to be confirmed by further studies which should investigate the mechanisms involved in L-759,633 anticancer activity.

CONCLUSION

The results of this study demonstrated that L-759,633, reduced the viability of C6 cells. These effects can occur, perhaps by inducing oxidative stress. Therefore, L-759,633 could have anticancer effects on the glioma cells. However this drug didn't show antiproliferative effect on SH-SY5Y cell. Further research is needed to address questions regarding possible mechanisms.

Conflict of Interests

The authors declare that they have no conflict of interest.

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Determining the Level of Knowledge Regarding Covid-19 and Protection Measures of Children Between Aged 8-12 Years

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ABSTRACT:
Purpose: This study was conducted to determine the the knowledge level of aged 8-12 years children about COVID-19 and protection measures.
Material and Methods: The sample of the descriptive study consisted of 323 children aged 8-12 years. The data were collected online with Descriptive Characteristics Form and the Information Level Form for COVID-19 and Protection Measures prepared by the researchers, and were shown with number, percentage, mean, standard deviation and chi-square analysis.
Results: The mean age of the children 9.15 ± 1.28 and 54.8% were girls. 63.2% of the children stated that they learned information about COVID-19 from television. It was found that 90.1% of children stated that COVID-19 changed their hygiene habits, 80.2% of them stated that the most effective measure to protect against COVID-19 was wearing a mask, 99.4% paid more attention to hand hygiene. It has been determined that compliance with hygiene and protection measures is higher in girls and those who have had COVID-19 infection in their family.
Conclusion: It has been determined that the majority of children have information about COVID-19 and protection measures and pay attention to wearing masks and hand hygiene. Children, who are an important group in terms of carrying and transmitting the infection, should ensure the continuity of their adaptation to protection measures by eliminating their missing information on the subject.
Keywords: *Child, COVID-19, information, protection*

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INTRODUCTION

The COVID-19 pandemic, which emerged in December 2019, is a serious health problem humanity has faced (WHO, 2020). Children are among the groups affected most by the changes brought about by the pandemic because of their developmental characteristics (Yüksek Usta and Gökcan, 2020; Akoğlu and Karaaslan, 2020; Yavaş Çelik, 2021). According to the data, 1-5% of COVID-19 cases consist of children, and deaths are less in children compared to adults (Ludvigsson, 2020). The American Pediatric Academy (APA) reported that children constitute 13.8% of the total cases, and hospitalization due to COVID-19 was not common in children (APA, 2019). However, children constitute a risky group in terms of transmission and spreading COVID-19 infection (Yavaş Çelik, 2021; Pars, 2020; Palanbek Yavaş and Arga, 2020). Even if they do not show any symptoms, children can infect people of all ages. Learning the protection methods and having the correct implementation of these methods reduces the risk of being infected by this disease and the spread rate of the disease. For this reason, it is important that children have knowledge of COVID-

19 infection and protection measures (WHO, 2020; Pars, 2020; Erdinç et al., 2020; Kardeş and Örnek, 2020). The precautions must be explained to children, such as hand hygiene, mask use, social distancing rule, staying away from ill people, and not touching surfaces in crowded environments. It was determined in previous studies that children identify COVID-19 infection as a serious disease, fear it, and apply protective measures. It was also reported that the most important knowledge sources for disease and protection measures are parents and the media (Yüksek Usta and Gökcan, 2020; Persici Toniolo et al., 2021). In a study conducted with parents, parents were found to have knowledge of COVID-19 infections and transmission risks (Abuhammad, 2020). It was seen in the literature review that there are a limited number of studies conducted to determine the level of knowledge of children on COVID-19 infection and protective measures from their parents, who constitute a significant source of knowledge for children. For this reason, this study was conducted to determine the level of knowledge of 8-12-year-old children on COVID-19 and protection routes. We believe that the results of the study will contribute to the determination of the awareness of 8-12-year-old children on COVID-19 and protection routes, and to the development of education programs.

MATERIALS AND METHODS

Design and Aims of the Study

This study, which was conducted to determine the level of knowledge of 8-12 year old children about COVİD-19 and protection measures, is a cross-sectional descriptive type.

Sampling and Participants

The population of the study consisted of children of 8-12 years of age living in Sivas city center, and the sampling consisted of 323 children who agreed to participate in the study between 04/02/2021 and 01/03/2021.

Data Collection Tools

The data were collected with the Introductory Characteristics Form, knowledge level on protective measures regarding COVID-19.

Introductory Features Form: In this form that was prepared by researchers, there are 9 questions on age, gender, class, mother's/father's educational level, having internet connection and presence of digital tools such as smartphone, tablet, and computer at home, and whether there are any family members in the family or in the environment who had COVID-19, and information sources about the disease.

Knowledge Level on COVID-19 and Protective Measures: This form that was developed by the researchers consisted of 14 questions on COVID-19 Infection, contamination routes, hand hygiene, hand washing technique, eau de cologne/disinfectant use, and mask use.

Ethical Aspect of the Study

Before the study was commenced, the Non-Interventional Clinical Research Ethics Committee of a university was received (Decision No: 2020-12/05). The consent was obtained from the parents through online forms.

Data Collection

The link that was prepared by the investigators on Google by preparing an online questionnaire was sent to the parents who had children 8-12 years of age around the researchers. The aim of the study was explained to the children on the first page and they were asked to complete the online questionnaire form.

Evaluation of the Data

The SPSS 22.0 statistical program was used for the analysis of the data. Categorical data were shown as numbers and percentages. The Chi-Square test was used when comparing the descriptive characteristics of the participants (i.e. age, gender, parents' educational levels, etc.), and the knowledge levels on COVID-19, and protective levels. The significance level was taken as 0.05.

RESULTS

The mean age of the children who participated in the study (n=323) was 9.15±1.28 (min=8, max=12), 54.8% were girls, and 30.7% were in third grade. A

total of 42.7% of the fathers and 35.3% of the mothers were university graduates, and 63.2% of children said that they had knowledge of COVID-19 from television. A total of 70% of the children had individuals with COVID-19 infection in the family (Chart 1).

A total of 98.1% of the children participating in our study stated the country from which COVID-19 first appeared was China, and 87.6% said that COVID-19 was infected through the respiratory route. All children said that masks must be attached to the nose. In our study, it was found that the responses of children regarding the protective measures regarding COVID-19, i.e. wearing masks, maintaining social distance, washing hands, and not entering crowded environments unless necessary were 33.4%, 20.3%, 20.1%, 26.2%, respectively. All of the children complied with the restriction decisions regarding COVID-19. Also, 92.9% warned their families to comply with the restriction decisions regarding COVID-19 (Table 1).

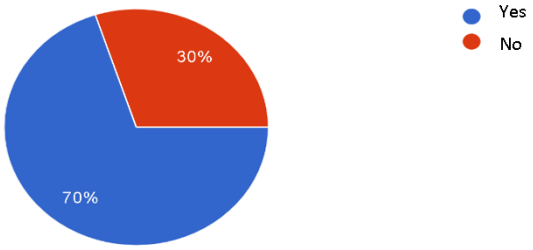

Chart 1. Having COVID-19 infection in the family

Table 1. Knowledge levels of children on COVID-19 pandemic

	n	%
Country COVID-19 first emerged		
China	317	98.1
Japan	6	1.9
COVID-19 transmission routes		
Respiratory	283	87.6
Hands	40	12.4
Correct use of masks		
Mask should include the nose	323	100
Mask should only cover the mouth	-	-
	Yes n (%)	**No n (%)**
Practices effective in protecting from COVID-19*		
Wearing a mask	258 (33.4)	65(12.5)
Social distancing	157 (20.3)	166 (31.9)
Washing hands	155 (20.1)	168 (32.3)
Not entering crowds unless necessary	203 (26.2)	120 (23.1)
Obeying COVID-19 restriction measures	323 (100)	-
Warning the family to obey the restrictions regarding COVID-19	300 (92.9)	23 (7.1)

*More than one option was marked and the percentage was calculated over the total number

A total of 90.1% of the children participating in our study said that COVID-19 changed hygiene habits, and 99.4% said that they paid more attention to washing their hands, and 99.4% of the participants washed their hands when they came home. Also, 95% of children washed their hands for at least 20 seconds with soap and water due to COVID-19; and 91.3% of children used eau de cologne or disinfectant for their hands when they were outside. A total of 96.3% of the children paid attention to changing their masks frequently because of the possibility that they may be dirty. Also, 94.1% of the children who participated in the study said that they warned other members of their families to wash their hands, and 89.8% warned them to change their masks when they became dirty (Table 2).

Table 2. Knowledge levels of children's hygiene applications to be carried out in COVID-19 pandemic

	Yes n (%)	No n (%)
COVID-19 changed hygiene habits	291(90.1)	32 (9.9)
Caring more about washing hands due to COVID-19	321(99.4)	2 (0.6)
Washing hands after coming home from outside	321(99.4)	2 (0.6)
Washing hands for at least 20 seconds with soap and water due to COVID-19	307 (95)	16(5)
Using eau de cologne or disinfectant for hands when outside	295 (91.3)	28 (8.7)
Caring for changing masks frequently as they may be dirty	311(96.3)	12 (3.7)
Warning other family members for washing hands when they come from outside	304 (94.1)	19 (5.9)
Warning other family members for changing masks when they are dirty	290 (89.8)	33 (10.2)

Table 3. Knowledge levels of children on protective measures regarding COVID-19 according to gender (n=323)

	Gender			
Protection Measures	**Female**		**Male**	
COVID-19 changed hygiene habits				
Yes	166	93.8	125	85.6
No	11	6.2	21	14.4
Test/p	*5.981/0.014*			
Washing hands for at least 20 second with soap and water due to COVID-19				
Yes	173	97.7	134	91.8
No	4	2.3	12	8.2
Test/p	*6.035/0.014*			
Using eau de cologne or disinfectant for hands when outside				
Yes	170	96.0	125	85.6
No	7	4.0	21	14.4
Test/p	*10.990/0.001*			
Warning other family members to wash their hands when they come from outside				
Yes	173	97.7	131	89.7
No	4	2.3	15	10.3
Test/p	*9.281/0.002*			
Warning other family members to change their masks when they are dirty				
Yes	168	94.9	122	83.6
No	9	5.1	24	16.4
Test/p	*11.243/0.001*			

Table 4. Protective measures applied in children's families according to having COVID-19 (n=323)

	Having COVID-19 infection in the family			
Protective Measures	**Yes**		**No**	
Social Distancing	**n**	**%**	**n**	**%**
Yes	123	54.4	36	37.1
No	103	45.6	61	62.9
Test/p	*8.138/0.004*			
Washing hands				
Yes	121	53.5	35	36.1
No	105	46.5	62	63.9
Test/p	*8.283/0.004*			
Not entering in crowds unless necessary				
Yes	153	67.7	52	53.6
No	73	32.3	45	46.4
Test/p	*5.812/0.016*			

It was found that there are significant relations between the gender of children and the change in children's hygiene habits, washing hands for at least 20 seconds, use of eau de cologne or disinfectant, and warning family members for washing their hands and changing their masks ($p < 0.05$) (Table 3).

It was found in the study that compliance to protective measures is high at a significant level in children with COVID-19 infection in the family ($p<0.05$) (Table 4).

DISCUSSION

Children constitute the risky group in terms of transmission and infection of COVID-19. In this study, the knowledge levels of 8-12-year-old children who form an important group for controlling the COVID-19 outbreak in terms of protection measures were examined. Knowledge sources are important in learning children's protection from COVID-19 routes. The United Nations International Children Emergency Fund (UNICEF) emphasized that the pandemic should be explained to children by stating that they will have difficulty in understanding this in online environments, television, or others (UNICEF, 2019). In the present study, it was found that children learned their knowledge on COVID-19 generally from television or families. Similarly, in a study that was conducted in our country, children were found to learn their knowledge on COVID-19 from the media and their parents (Yüksek Usta and Gökcan, 2020). In the study conducted with Portuguese children, it was reported that children and television news might be highly effective in understanding COVID-19 and transmission risks (Persici Toniolo et al., 2021). In the study, the majority of children knew the country in which the disease emerged correctly, 87.6% said that COVID-19 was contaminated through the respiratory route. In another study, 3-11 years of age children were generally determined to perceive the risk of COVID-19 transmission seriously (Persici Toniolo et al., 2021). In a study conducted to determine the level of knowledge of parents regarding COVID-19, the majority of parents said that COVID-19 was contaminated through the respiratory route (Abuhammad, 2020). In this respect, the knowledge of children on pandemics must be evaluated, protective measures and transmission routes should be described. Also, education should be given to children's parents regarding the transmission routes and protective measures.

The children who participated in this study said that the most effective measure in protection from COVID-19 (80.2%) was wearing masks. In a study conducted in China, approximately 97.5% of primary school students thought that wearing masks were necessary when going out (Xue et al., 2021). Also, all children identified the way that masks should be worn accurately. This result can be interpreted positively in terms of showing that children comply with the use of masks. However, it must be explained to children that the measures should be continued and they must comply with the measures. In addition to wearing masks, children should be supported to comply with other measures (UNICEF, 2020). In the study, approximately half of the children said that social distancing, washing hands, and not entering crowded environments unless necessary were effective in protection from COVID-19. Children can be given information on these measures and their importance. Another study reported that the majority of children in the preschool period knew the measures to be taken to protect from COVID-19 (Yüksek Usta and Gökcan, 2020).

A total of 90% of children who participated in the study said that COVID-19 changed their hygiene habits. It was determined that children cared about washing hands, clean their hands with cologne or disinfectant when handwashing is not possible, especially hand hygiene. In a previous study, it was determined that the majority of primary school children washed hands after coughing/sneezing to be protected from COVID-19 (Xue et al., 2021). In a study conducted with parents, it was reported that many parents thought that the best way to protect against COVID-19 for themselves was by washing hands (Abuhammad, 2020). It was determined in the study that the compliance rates of girls to hygiene habits such as washing hands and changing masks were higher. This result suggests that girls care more about hygiene and protective measures.

In this study, it was found that children who complied with protection measures warned their families in this respect. In another study, mothers

reported that their children firmly complied with the measures and warned others (Yüksek Usta and Gökcan, 2020). Also, it was found that children who had people infected with COVID-19 in their families had higher protection measure rates. In previous studies, it was reported that children were frightened that they or their family members could die from the COVID-19 infection, and for this reason, they cared about protective measures more (Persici Toniolo et al., 2021; Harper et al., 2020). The results obtained in the study support these.

CONCLUSION

It was determined that most children know the country where COVID-19 emerged, its infection routes, and think that the most effective method in protection from COVID-19 is wearing a mask, COVID-19 changed hygiene habits, and care more about washing hands. It was also determined that compliance with hygiene and protection measures was higher in girls and their families. It must be ensured that the incomplete knowledge of children, who are an important group in terms of carrying and infecting the disease, and it must be ensured that their compliance to protection measures is sustainable to take the disease under control.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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Case Report

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A Case of Psoriasis After Narrow Band UVB (NBUVB) Phototherapy for Vitiligo Treatment

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ABSTRACT:
Phototherapy methods commonly used in the treatment of vitiligo include narrow-band ultraviolet B (NB-UVB). A 23-years old male was diagnosed with vitiligo in the dermatology polyclinic and was followed up in the phototherapy unit with NBUVB treatment of 3 sessions per week; in the 42nd session psoriasis plaques were seen to have developed. We suggest that this rare but important association should be considered as a side effect of narrow-band phototherapy.

Keywords: *Psoriasis, Phototherapy, Treatment, Vitiligo*

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INTRODUCTION

Vitiligo is a widespread, acquired, auto-immune disease which is seen with hypopigmented macula and plaques that cause progressive melanocyte destruction. Phototherapy methods commonly used in the treatment of vitiligo include narrow-band ultraviolet B (NB-UVB), psoralen ultraviolet A (PUVA), excimer laser and lamps (Zubair et al, 2020). Psoriasis vulgaris is a chronic, autoimmune, inflammatory disease, seen with hyperproliferation of keratinocytes in the epidermis and affects 3.2% of the population. NB-UVB with a wavelength of 311-313 nm is a phototherapy method widely used in several dermatological diseases such as psoriasis and vitiligo. An immunomodulator effect of NB-UVB is seen in the skin through the inhibition of cytokine expression and epidermal hyperproliferation, and the capacity to present antigens to the T-cells of Langerhans cells (Yanovsky et al, 2020). In the case presented here, a patient treated with 3 sessions of NB-UVB per week for a diagnosis of vitiligo was determined with psoriasis plaques in the 42nd session.

CASE

A 23-years old male was diagnosed with vitiligo in the dermatology polyclinic and was followed up in the phototherapy unit with NB-UVB treatment of 3 sessions per week; in the 42nd session psoriasis plaques were seen to have developed. The patient had had vitiligo for 5 years and had previously tolerated treatment with no side-effects. In the physical examination of the patient in the 42nd session of treatment, squamous plaque-type lesions were determined on an erythemous base on the knees, elbows and scattered over the whole body. There were also pre-existing white, hypopigmmented macular-type vitiligo lesions widespread on the body (Figure 1). Other than phototherapy, the patient had not used any drugs

previously and had no infection. There was no systemic or dermatological disease other than vitiligo. There was no family history of psoriasis. A punch biopsy was taken to confirm the diagnosis. All the materials, and analytical and statistical methods and procedures should be explained in this section.

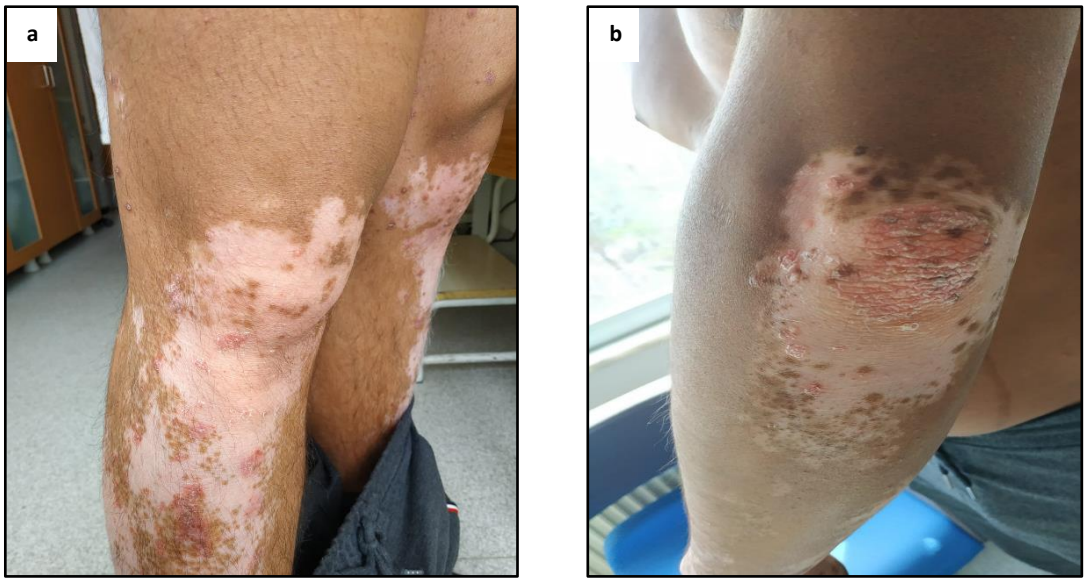

Figure 1. a) knees, **b)** elbows; erythematous, squamous plaque lesions on and around the depigmented patch

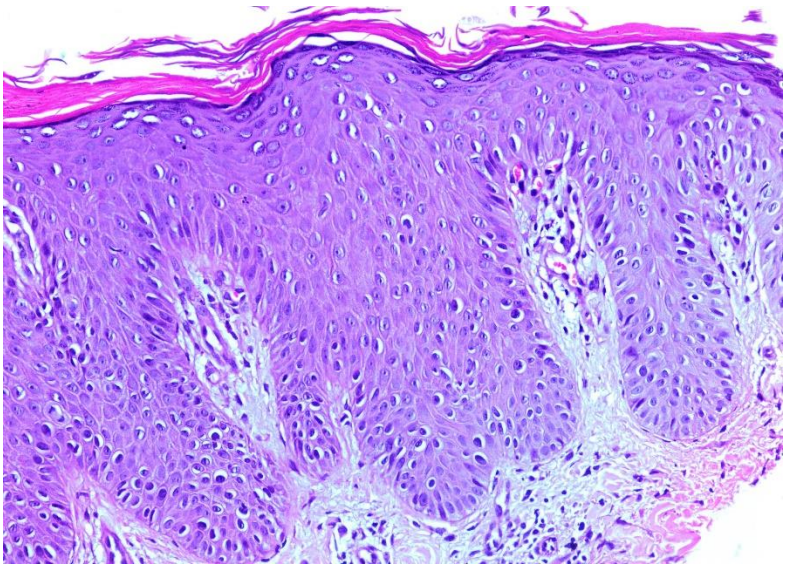

Figure 2. In the histopathological examination, hyperparakeratous and psoriasiform hyperplasia was seen

In the histopathological examination, hyperparakeratous and psoriasiform hyperplasia was seen. There was scattered hypogranulosis and exocytosis. Suprapapillar thinning was seen in the epidermis with ectasic structures in the papillary dermis. Perivascular mononuclear inflammatory cell infiltration was observed in the dermis. The histopathological findings were consistent with Psoriasis Vulgaris (Figure 2). Therefore, the phototherapy treatment of the patient was stopped. Topical steroid and moisturiser was applied as treatment for psoriasis, and after 2 weeks the lesions had decreased. Instead of phototherapy for the vitiligo, topical pimecrolimus treatment was started and the patient continued to have regular follow up. There was scattered hypogranulosis and exocytosis.

Suprapapillar thinning was seen in the epidermis with ectasic structures in the papillary dermis. Perivascular mononuclear inflammatory cell infiltration was observed in the dermis.

DISCUSSION

Psoriasis and vitiligo are commonly seen dermatological diseases, but they are rarely seen together in the same patient. Although the relationship between psoriasis and vitiligo is not fully known, cases showing this combination have been reported. In a study of 4700 psoriasis patients, Sandhu et al reported the combination of vitiligo and psoriasis in 38 patients (Sandhu et al, 2004). Giordano et al reported vitiligo with during secukinumab treatment in a psoriasis patient (Giordano et al, 2021). Goodwin et al reported the development of vitiligo patches over psoriasis lesions in a patient undergoing NB-UVB treatment for psoriasis (Goodwin et al, 2001). In another case, vitiligo lesions were reported to have developed in a patient applied with PUVA for psoriasis (Halcin et al, 1997).

During NB-UVB treatment, psoriasis lesions together with vitiligo lesions are expected to disappear or not develop. It is interesting that psoriasis lesions developed in the current patient. In previously reported cases, vitiligo has developed in psoriasis patients treated with NB-UVB, whereas the current patient was a vitiligo patient treated with NB-UVB who developed psoriasis. Cytokine levels such as tumour necrosis factor-α have been found to be high in the lesional and perilesional areas of psoriasis and vitiligo patients. It was suspected that some immunological reactions could have been activated during the NB-UVB treatment of the current patient, and this reaction could be more evident in inflammatory dermatological disease such as vitiligo. However, it may also have been related to the Koebner phenomenon because of the anatomic associations (Berger et al., 2006; Rodriguez-Martin et al., 2007).

To the best of our knowledge, this is the first case in literature of psoriasis developing in a patient with vitiligo treated with NB-UVB. We suggest that this rare but important association should be considered as a side effect of narrow-band phototherapy.

Conflict of interest: There is no conflict of interest among the authors of the article

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Research Article

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Antiviral Effects of Some Flavonoids on SARS-CoV-2

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ABSTRACT:
Purpose: Covid-19 disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a global epidemic that affects millions of lives. To date, there is no definitive cure for the disease and global vaccination efforts with newly produced vaccines will take years to complete. *In silico* studies have suggested that different flavonoids play an antiviral role against SARS-CoV-2. In this study, based on *in silico* findings, we examined the *in vitro* effects of four promising flavonoids, hesperidin, oleuropein, epigallocatechin gallate (EGCG), and myricetin.
Material and Methods: Hesperidin, oleuropein, EGCG, and myricetin have been extracted from natural plant sources and purified by using liquid chromatography (LC). Analyses of the cell toxicity and antiviral activity of these four flavonoids at different concentrations against SARS-CoV-2 were done.
Results: Our results show that CC_{50} values for EGCG, hesperidin, myricetin and oleuropein are 38 µg/ml, 25 µg/ml, >200 µg/ml and >200 µg/ml, respectively. In addition, in our hands, neither of the flavonoids we examined has antiviral effects against Sars-CoV-2 virus-infected Vero E6 cells. Our data revealed that all flavonoids we tested have Inhibitory Concentration 50 (IC_{50}) value >200 µg/ml.
Conclusion: Our results using the SARS-CoV-2 infected Vero E6 cell model were found to contradict previous *in silico* findings, and these flavonoids were found to have no antiviral effects *in vitro*. Studies investigating flavonoids' antiviral activity on SARS-CoV-2 should be directed to those other than oleuropein, hesperidin, EGCG, and myricetin.
Keywords: *Covid-19, EGCG, Hesperidin, Myricetin, Oleuropein*

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic was first reported in Wuhan in the Hubai district of the Republic of China on 31st December 2019 (Guan et al., 2020). The disease SARS-CoV-2 causes were named Covid-19. Coronaviridae Study *Group* (CSG) of the *International Committee* on *Taxonomy* of *Viruses* (ICTV) suggested classifying this isolated new type of virus as the 7th member of the coronavirus family and named SARS-CoV-2 (Coronaviridae Study Group, 2020). Members of the coronavirus family are zoonotic. They are a large family of infectious viruses that can spread from animals to humans (Zhu et al., 2020a). SARS-CoV-2 genome was reported to have 86-89% similarity with two bat SARS-like-coronavirus isolate bat-SL-CoVZC45 genomes. It also has a 79% similarity with SARS-CoV and 50% with MERS-CoV genomes. Moreover, other genomic studies revealed that the SARS-CoV-2 genome has a 96% similarity with the Bat-Cov RaTG13 isolate genome isolated from the bat species *Rhinolophus affinis* (Lu et al., 2020). It has been found that ACE2 receptors are related to SARS-CoV-2 and are the entry point of the virus (Bastolla, 2020). SARS-CoV and SARS-CoV-2 bind to the target epithelial cells expressing

angiotensin-converting enzyme 2 (ACE2) in lungs, blood vessels, kidneys, and intestines. ACE2 expression can be increased by using ibuprofen and thiazolidinediones. Increased ACE2 expression makes getting Covid-19 infection easier (Fang et al., 2020). Thus, diabetes and hypertension that are treated with such drugs may increase the risk of developing severe and lethal Covid-19 symptoms. To our knowledge, no antiviral medicine has been developed against MERS-CoV, SARS-CoV, and SARS-CoV-2, to date. So far, drugs such as Hydroxychloroquine (HCQ), Chloroquine (CQ), Favipiravir, Lopinavir/Ritonavir (LPV/r), Nitazoxanide, Tocilizumab, Ivermectin, Dexamethasone (DEX) have been used in different treatment regimens to treat Covid-19 patients (Iyer et al., 2020). According to the World Health Organization (WHO) report on 17.08.2021, there are 207784507 confirmed cases and 4370424 deaths worldwide. Turkey's first case was reported on 11.03.2020, and there are 6096816 confirmed cases and 53327 deaths to date. Currently, there is neither definite treatment nor cure for Covid-19. Moreover, current treatments are insufficient for preventing the long-term effects of Covid-19 on further complications and organ damages (Rodriguez-Morales et al., 2020). Some preliminary studies examined the effects of the potential lopinavir/ritonavir combination, commonly used for treating human immunodeficiency virus (HIV) patients, for Covid-19 treatment (Lu, 2020).

Flavonoids are shown to have antiviral effects on various viruses such as Poliovirus (Conti et al., 1990), Astrovirus (Superti et al.,1990), HIV (Clercq, 2000), Enterovirus (Genovese et al., 1995), parainfluenza virus type 3 (PIV 3), respiratory syncytial virus (RSV), and influenza virus type A (Flu A) Studies on flavonoids have shown that luteolin, apigenin, amentoflavone, quercetin (Ryu et al., 2010), puerarin, daidzein, gallocatechin gallate, and epigallocatechin gallate inhibit the original SARS-CoV 3CLpro's proteolytic activity (Nguyen et al., 2012). Green tea catechins (GTC) are the polyphenolic compounds extracted from the leaves of *Camellia sinensis* (Narotzki et al., 2012). These polyphenol-rich compounds have anti-inflammation (González et al., 2015), anti-oxidative (Chacko et al., 2010), anti-bacterial (Umashankar et al., 2018), and antiviral (Ciesek et al., 2011) properties. GTCs mainly comprise four compounds: Epigallocatechin (EGC), Epicatechin (EC), Epigallocatechin gallate (EGCG), and Epicatechin gallate (ECG). Among these, EGCG comprises 59% of the total polyphenol of GTCs and the most complex and major component that has antiviral activity against hepatitis C virus (Ciesek et al., 2011), human immunodeficiency virus (HIV) (Yamaguchi et al., 2002), Zika virus (Carneiro et al., 2016), Influenza A virus (Zhu et al., 2020b) and herpes simplex virus 1 (Isaacs et al., 2008). The antiviral mechanism of EGCG varies depending on specific virus infection and host cell response. For example, one of its antiviral mechanisms is that EGCG interacts with the virus's structural proteins and thus inhibits the recognition and binding of the cellular receptors (Li et al., 2020). Thousands of plant species synthesize phenolic compounds such as phenolic acids, phenolic alcohols, and flavonoids. However, secoiridoids containing many coumarin-like compounds synthesized only by Oleaceae family plants, including *Olea europea L*. (Silva et al., 2016). Oleuropein is the most significant of these compounds. Oleuropein belongs to the secoiridoids abundantly found in Oleaceae, Gentianaceae, Cornaleae, and some other plants. Iridoids and secoiridoids are usually glycosidic bound and produced in the secondary metabolisms of terpenes as indol and alkaloid primers (Omar, 2010). Oleuropein and derivatives have anti-inflammatory, antioxidant, antiviral, antimicrobial, and anti-proliferative properties. They also have protective effects on diabetes mellitus, cardiovascular disease, neurological diseases, cancers, and skin problems (Rigacci and Stefani, 2016).

In their *in silico* docking study of 4634 effective compounds, Leif Peterson found that flavonoids group Diosmin, epigallocatechin gallate, and hidrosmin placed 22nd, 134th, and 163rd, respectively (Peterson, 2020). In another *in silico* study, Khaerunnisa et al. suggested that drugs such as lopinavir and nelfinavir might represent a potential therapy, and luteolin-7-glucoside dimethoxy curcumin, oleuropein, apigenin-7-glucoside, curcumin, catechine, and epicatechin-gallate could be used as Covid-19 M^{pro} inhibitors (Khaerunnisa et

al., 2020). Along with quercetin and kaempferol, myricetin (3,3,4,5,5,7-hexahydroxyflavone) is a member of the flavonoid group flavonols. Various studies revealed that myricetin has antioxidant (Mendes et al., 2019) and anti-inflammatory (Wang et al., 2010) properties as well as anti-bacterial (Xu and Lee, 2001) and antiviral (Yu et al., 2012) effects. Hesperidin is one of the most important flavonoids and belongs to the flavanone class. Hesperidin (hesperetin-7-O-rutinoside) is the β-glycoside form of hesperetin and is found in citrus, especially in sweet orange (Boonpawa et al., 2017). Hesperidin has a strong antioxidant activity and important effects on the vascular system by decreasing capillary permeability and increasing its resistance. Hesperidin has also been shown to decrease cholesterol and triglyceride levels significantly and has remarkable protective effects against inflammatory diseases (Meneguzzo et al., 2020). In their recent *in silico* study, Chen et al. scanned 1500 potential substances based on 3CLpro structure. Among their results, diosmin was placed first, and hesperidin was placed second in the biflavonoid group (Chen et al., 2020). In another recent study, 80 flavonoids were scanned, and several flavonoids with various properties such as hesperidin, rutin, diosmin, apiin, diacetycurcumin, myricetin, flavone23, naringin, neohesperidin, and scutellarin could be used as an alternative therapy for SARS-Cov-2 (Adem et al., 2020). Considering the promising results of the *in silico* studies, the potential therapeutic and prophylactic effects of plant-isolated natural flavonoids should be further investigated by *in vitro* studies to reveal their efficiency. Therefore, in this study, we aimed to purify natural flavonoids EGCG, Oleuropein, Hesperidin, and Myricetin from plants and examine their antiviral effects against SARS-CoV2.

MATERIAL and METHODS

Chemicals and Standards

Acetonitrile (HPLC grade, >99.8%), formic acid (pro analysis, 98−100%), and methanol (HPLC grade, >99.8%) were obtained from ISOLAB Chemicals (Eschau, Germany). Oleuropein, hesperidin (Hesperitin 7-rutinoside), and myricitrin (Myricetin 3-O-rhamnoside) were purchased from Sigma (St. Louis, MO) and EGCG was purchased from TOCRIS Bioscience (Bristol, UK). Ultrapure water was obtained by use of Direct-Q 3 UV, Milli-Q® (Darmstadt, Germany).

Extraction of Oleuropein Compound

Extraction of oleuropein from olive leaves was performed using Cifa et al. method with some modifications (Cifá et al., 2018). Olive leaves collected from the Çanakkale region in Turkey were first washed and dried at 40°C in drying ovens. Then the dried leaves were powdered by using a laboratory mill (IKA A10 basic) and ultrasonicated using 1:10 pure water at 45°C for 60 minutes. Following this step, the liquid phase was collected using filtering and centrifuging at 5000 rpm for 10 minutes. Finally, the upper phase was analyzed using HPLC.

HPLC-DAD Analysis of Oleuropein

HPLC analysis of oleuropein was performed using Aouidi et al. method with some modifications (Aouidi et al., 2012).

Shimadzu LC-20A (Kyoto, Japan) was used for HPLC analyses. This system comprises a PDA detector (SPD-M20A) and GL Sciences Inertsil ODS-3 C18 (250 x 4.6 mm; 5 µm) HPLC column. The pre-analysis sample was filtered through a 0.45 µm filter. In addition, all the mobile phases were filtered before analysis and incubated in an ultrasonic bath for 30 minutes. The sample injection volume was set to 20 µL, and the column oven temperature was set to 25°C. The mobile phase was 5% formic acid in water (A) and acetonitrile (B) with a flow rate at 0.9 ml/min in gradient (Table 1). Chromatograms were recorded using a PDA detector set to 280 nm. All the calculations concerning the quantitative analysis were performed with oleuropein standard by matching the retention times and measurement of peak areas. Data were analyzed using LC solution software.

Extraction of EGCG Compound

Green tea leaves were obtained from the Black Sea region in Turkey. Extraction of catechins from green tea leaves was performed using Lee and Lee method (Lee and Lee, 2008). First, green tea leaves were

washed and dried at 30°C in drying ovens. Then, the dried leaves were powdered by using IKA A10 basic mill up to 100 mesh size. Powdered leaves were extracted in pure water (1:10) using an ultrasonication system. The extraction was performed at 60 °C for 30 minutes. Finally, the resulted extracts were centrifuged at 5000 rpm for 10 minutes and upper phase was recovered to be analyzed in HPLC.

Table 1. Oleuropein gradient elution used in method

Time (min.)	B%
0	5
3	15
13	25
25	35
35	45
40	50
45	100
46	5
50	5

Table 2. EGCG gradient elution used in the method

Time (min.)	B%
0	10
5	15
50	40
51	10
55	10

Table 3. Myricetin gradient elution used in the method

Time (min.)	B%
10	13
20	41,5
25	70
35	10
36	0
40	0

Table 4. Hesperidin gradient elution used in the method

Time (min.)	B%
0	15
25	35
27	70
35	70
40	15
45	15

HPLC-DAD Analysis of EGCG

Catechine content analysis of green tea leaves was performed using Dalluge et al. HPLC method with some modifications (Dalluge et al., 1998). Shimadzu LC-20A (Kyoto, Japan) was used for HPLC analyses. This system comprises a PDA detector (SPD-M20A) and GL Sciences Inertsil ODS-3 C18 (250 x 4.6 mm; 5 µm) HPLC column. The pre-analysis sample was

filtered through a 0.45 µm filter. In addition, all the mobile phases were filtered before analysis and incubated in an ultrasonic bath for 30 minutes. The sample injection volume was set to 20 µL, and the column oven temperature was set to 25°C. The mobile phase was 0.05% trifluoroacetic acid (TFA) in water (A) and 0.05% TFA in acetonitrile – methanol (40:60) (B) with a flow rate at 1.0 ml/min in gradient Table 2). Chromatograms were recorded using a PDA detector set to 210 nm. All the calculations concerning the quantitative analysis were performed with EGCG standard by matching the retention times and measurement of peak areas. Data were analyzed using LC solution software.

Extraction of Myricetin Compound

Leaves of bilberry (*Vaccinium myrtillus*) for myricetin derivatives were obtained from a local market in Malatya, Turkey. They are originated from the southeast region of Turkey. Myricetin-rich extraction from bilberry leaves was performed using Lui et al. method (Liu et al., 2014). First, the leaves were thoroughly washed and dried in drying ovens at 40°C. Dried leaves were then powdered by using a laboratory mill (IKA A10 basic) and extracted in pure water (1:10) using an ultrasonication system. The extraction was performed at 45°C for 60 minutes. After extraction, samples were centrifuged at 5000 rpm for 10 minutes and the upper phase was collected for analysis in HPLC.

HPLC-DAD Analysis of Myricetin Compound

HPLC analysis of phenolic substances in bilberry leaves was done using Sahin et al. method with some modifications (Sahin et al., 2011). HPLC analysis of hesperidin was done using Fecka and Turek method with some modifications (Fecka and Turek, 2007). Shimadzu LC-20A (Kyoto, Japan) was used for HPLC analyses. This system comprises a PDA detector (SPD-M20A) and GL Sciences Inertsil ODS-3 C18 (250 x 4.6 mm; 5 µm) HPLC column. The sample injection volume was set to 20 µL, and the column oven temperature was set to 25 °C. The mobile phase was 1% formic acid in water (A) and acetonitrile (B) with a flow rate of 1.0 ml/min in gradient (Table 3). Chromatograms were recorded using a PDA detector set to 320 nm. All the mobile phases were filtered before analysis and incubated in an ultrasonic bath for 30 minutes to degas. Data were analyzed using LC solution software.

Purification of Oleuropein, EGCG, and Myricetin by Using Prep-LC

Agilent 1260 Infinity II preparative LC system was used for the purification of oleuropein, EGCG, and myricetin. This system comprises a pump with a maximum of 50 ml/min flow rate, UV detector, fraction collector, and manual sampling unit with various injection volumes. To obtain oleuropein, EGCG, and myricetin in high purity, we first adjusted their analytical HPLC methods to the preparative LC system by the scale-up method. Obtained fractions were dried using a nitrogen evaporator. Purity analysis of the fractions was performed using analytical HPLC.

Extraction and Purification Method for Hesperidin

Peels of orange (*Citrus sinensis*) for hesperidin were obtained from the wastes of the juice plant in the Mediterranean region, Turkey. To perform dried experiments, orange peels were placed in an oven at 40°C overnight until constant weight. Hesperidin from sweet orange peels was extracted using Lahmer et al.'s method with some modifications (Lahmer et al., 2015). First, orange peels were washed and placed in drying ovens at 40°C to dry. This step is followed by powdering the peels in a laboratory mill (IKA A10 basic) and extracting them using 1:10 petroleum ether for 90 minutes. After removing the petroleum ether, the dry pellet was mixed with methanol for secondary extraction and ultrasonicated for 60 minutes at 45 °C. Following this procedure, the liquid phase was collected using filtering and centrifuging, and methanol was removed in a rotary evaporator. Lastly, the condensed phase was dissolved in 6% acetic acid to precipitate hesperidin. After centrifugation at 5000 rpm for 15 minutes, the pellet was collected and dried. Powder pellet was analyzed for hesperidin percentage using HPLC.

HPLC-DAD Analysis of Hesperidin

HPLC analysis of hesperidin was done using Fecka and Turek method with some modifications (Fecka

and Turek, 2007). Shimadzu LC-20A (Kyoto, Japan) was used for HPLC analyses. This system comprises a PDA detector (SPD-M20A) and GL Sciences Inertsil ODS-3 C18 (250 x 4.6 mm; 5 µm) HPLC column. The pre-analysis sample was dissolved in an adequate solvent and filtered through a 0.45 µm filter. In addition, all the mobile phases were filtered before analysis and incubated in an ultrasonic bath for 30 minutes. The sample injection volume was set to 20 µL, and the column oven temperature was set to 25°C. The mobile phase was 5% formic acid in water (A) and acetonitrile (B) with a flow rate at 0.9 ml/min in gradient (Table 4). Chromatograms were recorded using a PDA detector set to 280 nm. All the calculations concerning the quantitative analysis were performed with the hesperidin standard by matching the retention times and measurement of peak areas. Data were analyzed using LC solution software.

Cytotoxicity Test

In this study, we used Vero E6 cells, African green monkey (*Cercopithecus aethiops*) kidney epithelial cells (ATTC, CCL-81). Cells are cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco) with 10% Fetal Bovine Serum (FBS)(Gibco). Cell cultures were maintained at 5% CO_2 and 37° C. Cells were prepared as a $2x10^5$/ml suspension and distributed in each well of the 96-well plate at an amount of 100 µl/well. After additional culturing cells for 24 hours at 37° C and 5% CO_2 in 96-well plates, test materials that are diluted in DMEM with 1% FBS and gentamycin/fungizon at a final concentration of 200 - 0.1 µg/ml were added. For each concentration, three replicates (wells) were used. Wells that do not contain test material were used as negative controls. Cells were incubated for 72 hours at 37° C and 5% CO_2. Before analysis, wells including the negative controls were emptied, and 0.1 ml DMEM with 1% FBS and gentamycin/fungizon were freshly added to each well. After incubating for 30 minutes at 37° C and 5% CO_2, 10 µl of MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) at a concentration of 5 mg/ml was added to each well and incubated for 3 hours 37° C and 5% CO_2. After the incubation period, cells were emptied, and 100 µl /well dimethyl sulfoxide (DMSO) was added to each well to dissolve intracellular formazan crystals. After 30 minutes of incubation with DMSO, color intensity was analyzed using ELISA Microplate Reader (Tecan, Sunrise) at 570/620 nm wavelength. The percentage of cytotoxicity (%) was calculated using the formula [1-(test material - blank)/(cell control - blank)] x 100. *inhibition* percentages (%) were calculated using the formula (test material - solvent) / (cell control - solvent) X 100. Cells were prepared as a $2x10^5$/ml suspension and distributed in each well of the 96-well plate at an amount of 100 µl/well. Cell cytotoxicity 50 (CC_{50}) and inhibitor concentration 50 (IC_{50}) values were calculated using non-linear regression analysis with GraphPad software. Antiviral activity experiments of this study were done by Antimikrop R&D and Biocidal Analysis Center (Ankara, Turkey).

Antiviral Test

Cells were prepared as a $2x10^5$/ml suspension and distributed in each well of the 96-well plate at an amount of 100 µl/well. After additional culturing cells for 24 hours at 37° C and 5% CO_2 in 96-well plates, cells were infected using 100 TCID50/0.1 ml SARS-CoV-2 (clinical isolate) (GenBank: MT955161.1) in DMEM with %1 FBS for 1 hour at 37° C and 5% CO_2. After the incubation period, viral inoculation was removed, and test materials that are diluted in DMEM with 1% FBS and gentamycin/fungizon at a final concentration of 200 - 0.1 µg/ml were added. For each concentration, three replicates (wells) were used. Wells that do not contain test material were used as negative controls. In addition, eight wells with and without viruses were used as controls. Cells were incubated for 72 hours at 37° C and 5% CO_2. Before analysis, wells including the negative controls were emptied, and 0.1 ml DMEM with 1% FBS and gentamycin/fungizon were freshly added to each well. After incubating for 30 minutes at 37° C and 5% CO_2, 10 µl of MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) at a concentration of 5 mg/ml was added to each well and incubated for 3 hours 37° C and 5% CO_2. After the incubation period, cells were emptied, and 100 µl /well dimethyl sulfoxide (DMSO) was added to each well to dissolve intracellular formazan crystals. After 30 minutes of incubation with DMSO, color intensity was analyzed

using ELISA Microplate Reader (Tecan, Sunrise) at 570/620 nm wavelength. Cytopathic and inhibitory effects of each test material at each concentration were analyzed using the following formulas. % inhibition values were calculated using the formula [(Test Optical Density/Control Optical Density)×100]. Test material concentration with 50% inhibitory effect (inhibitory concentration 50, IC_{50}) values were calculated using non-linear dose-response curve: log(inhibitor) vs. normalized response Variable slope with GraphPad software.

RESULTS

Purification of Flavonoids

To examine the antiviral effects of natural flavonoids on SARS-CoV-2 infection we first purified them from respective plants using methods described in the materials-method section. Briefly, we purified Oleuropein from olive leaves originated from the Canakkale region in Turkey, EGCG from green tea leaves originated from Black Sea Region in Turkey, Hesperidin from sweet orange peels originated from Akdeniz Region in Turkey, and Myricetin from the Malatya region in Turkey. To identify their purity, the extracts were analyzed by HPLC. According to HPLC analysis, our EGCG extract has >98% purity, Hesperidin extract has >70% purity, Myricetin extract has >60% purity and Oleuropein extract has >80% purity (Figure 1 A-D).

Antiviral Properties of Flavonoids Against SARS-CoV2

We analyzed the antiviral properties of flavonoids with different concentrations (0.1-200 µg/ml) on Vero E6 cells infected with SARS-COV-2. We performed the experiments in triplicates for each concentration. We also analyzed the cell toxicity 50 (CC_{50}) values of each compound separately (Table 5). Our results show that CC50 values for EGCG, Hesperidin, Myricetin and Oleuropein are 38 µg/ml, 25 µg/ml, >200 µg/ml and >200 µg/ml, respectively (Fig. 2A-D). In addition, in our hands, neither of the flavonoids we examined has antiviral effects against Sars-CoV-2 virus-infected Vero E6 cells. Our data revealed that all flavonoids we tested have Inhibitory Concentration 50 (IC50) value >200 µg/ml (Table 5).

Table 5. IC_{50} and CC_{50} values of flavonoids on SARS-CoV-2 infected Vero E6 cells

Flavonoid Name	CC_{50} (µg/ml)	IC_{50} (µg/ml)
EGCG	38	>200
Hesperidin	25	>200
Myricetin	>200	>200
Oleuropein	>200	>200

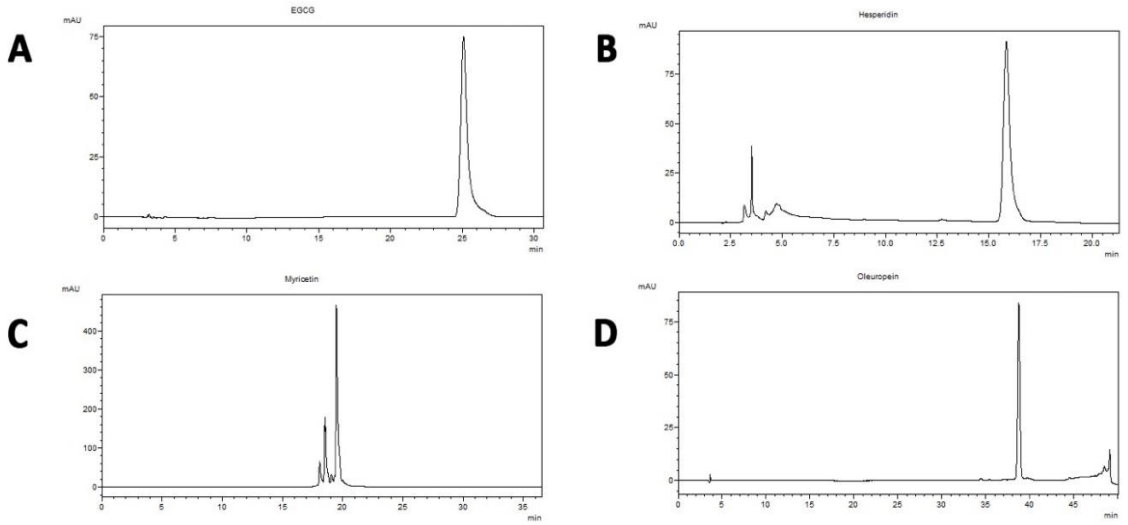

Figure 1 A-D. HPLC chromatogram of A) EGCG extract from green tea leaves acquired at 210 nm detection, B) Hesperidin extract from sweet orange peels acquired at 280 nm detection, C) Myricetin extract from bilberry leaves acquired at 320 nm detection, D) Oleuropein extracts from olive leaves acquired at 280 nm detection.

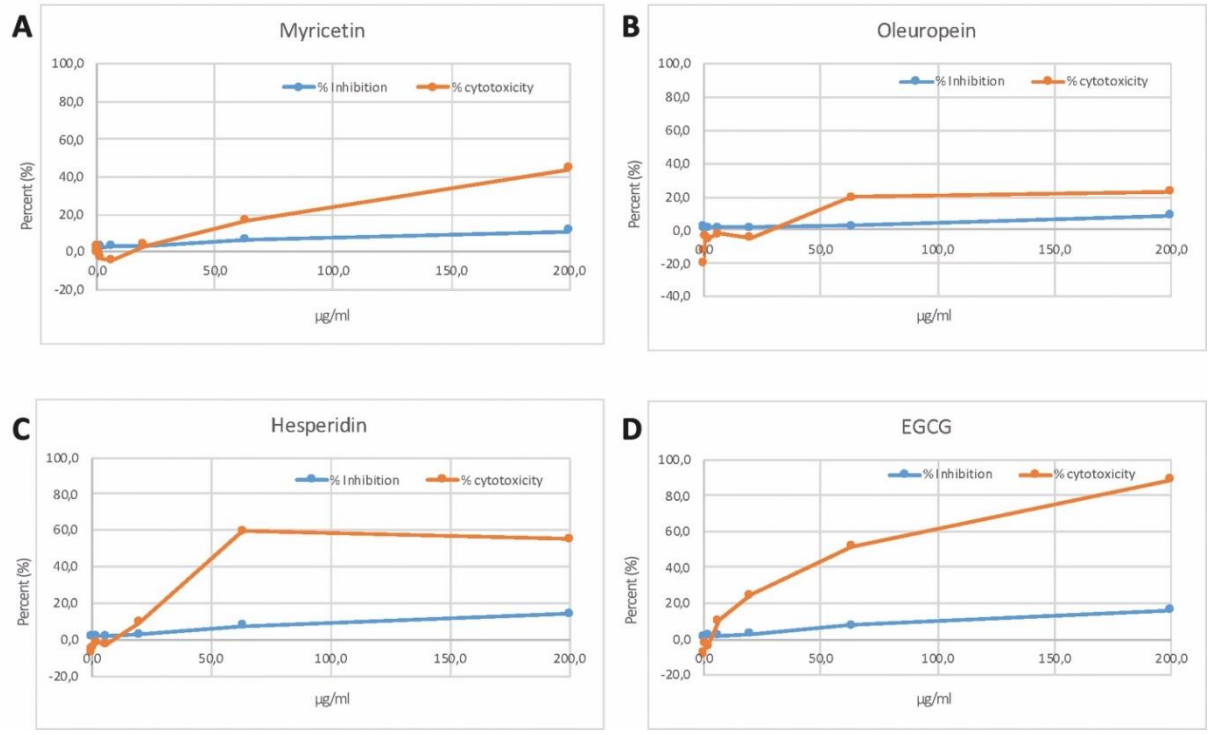

Figure 2 A-D. Antiviral (IC_{50}) and cytotoxic (CC_{50}) values of A) Myricetin, B) Oleuropein, C) Hesperidin D) EGCG on SARS-Cov-2 infected Vero E6 cell.

DISCUSSION

Following the first report in Wuhan, in December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) spread worldwide and become a pandemic. The disease SARS-CoV-2 causes was named COVID-19 and has affected millions so far. To date, there is currently no antiviral cure against SARS-CoV-2 and the vaccination of the population with recently developed vaccines will take years. Natural plant-sourced flavonoids are well known for their favorable effects on various viruses such as Poliovuris (Conti et al., 1990), Astrovirus (Superti et al.,1990), HIV (Clercq, 2000), Enterovirus (Genovese et al., 1995), respiratory syncytial virus (RSV), influenza virus type A (Flu A), and parainfluenza virus type 3 (PIV 3) (Wei et al., 2004), and thus, may offer an easily obtainable source for protection from and treatment of COVID-19.

Studies also show that most of the promising small molecules as coronavirus inhibitors are polyphenols that contain a substituted fused ring (Mani et al., 2020). Indeed, flavonoids are well-known for their diverse antiviral effects, and numerous studies have also examined their effect on SARS-CoV-2. Some of these approaches are to increase their bioavailability, and thus, improve their therapeutic efficacy (Ngwa et al., 2020) while others explore the possible use of flavonoids on recovery from COVID-19-Induced anosmia and ageusia (Koyama et al., 2021).

Several *in silico* studies suggested that flavonoids such as EGCG, hesperidin, oleuropein, and myricetin could be used as an alternative therapy for SARS-CoV-2 (Peterson, 2020; Khaerunnisa et al., 2020; Meneguzzo et al., 2020; Adem et al., 2020; Rehman MFu et al., 2021). Considering the promising results of the *in silico* studies, the potential therapeutic and prophylactic effects of plant-isolated natural flavonoids should be further investigated by *in vitro* studies to reveal their efficiency. Thus, in this study, we analyzed the antiviral effects of natural flavonoids EGCG, Oleuropein, Hesperidin, and Myricetin from plants against SARS-CoV2. Although preprint *in silico* studies showed a potential for antiviral effect, our data showed that EGCG, oleuropein, hesperidin and myricetin from plants do not have antiviral effects *in vitro* on SARS-CoV-2 infected Vero E6 cells. There might be several reasons why our *in vitro* results did not support *in silico* findings. First, the interaction of the molecules

in silico assumes an ideal environment. Some other molecules in the culture media as well as the pH and other factors might be interacting either with the docking site or with the compound itself, altering their efficiency and effect. Thus, such possible interactions and alterations may hinder the expected effect of molecules found in ideal conditions *in silico*.

CONCLUSION

Given the worldwide status and severity of SARS-CoV-2, the potential therapeutic and prophylactic effects of natural flavonoids isolated from the plant should be demonstrated by *in vitro* studies to reveal their efficacy. However, flavonoids are strong phytochemicals showing antiviral properties, and these compounds may be toxic in certain concentrations. Therefore, each molecule's safe and therapeutic levels should be tested *in vitro* and in vivo prior to clinical studies in humans. Considering the promising results of *in silico* studies, natural flavonoids EGCG, Oleuropein, Hesperidin, and Myricetin compounds were selected in this study. Our results using the SARS-CoV-2 infected Vero E6 cell model were found to contradict previous in silico findings, and these flavonoids were found to have no antiviral effects *in vitro*. Studies investigating flavonoids' antiviral activity on SARS-CoV-2 *in vitro* should be directed to those other than oleuropein, hesperidin, EGCG, and myricetin. We believe our study will stimulate further studies on the prophylaxis and treatment of coronavirus using other flavonoids and their derivatives.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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The Effect of Music Therapy on Pain, Anxiety and Vital Signs in Patients Undergoing Spinal Anaesthesia: A Randomized Controlled Trial**

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ABSTRACT:
Purpose: Music therapy has a wide range of uses in health care practice. The aim of this study was to investigate the effects of intraoperative music played during spinal anesthesia operation on the patients' intraoperative vital signs, postoperative pain, and anxiety.
Material and Methods: A randomized controlled clinical trial was conducted in the knee replacement surgery with spinal anesthesia. 90 patients were recruited and randomly assigned to either music therapy group (n:30), non-sedated group (n:30) and sedated (n:30) group respectively. The music therapy group received standard care and music intervention (self-chosen) during the operation, the non-sedated group received only standard care and the sedation was performed to the sedated group. Measures include pain, anxiety, vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate).
Results: Intraoperative respiratory rates of the music therapy group were significantly different in the three groups, but there was no difference between the groups in terms of vital signs. No complication was observed in the music therapy group during the operation, but complications were observed in the non-sedated and sedated groups. Similar postoperative pain was observed between the groups. However, the postoperative pain score was lower in the sedated group. The interventions in the music therapy group significantly altered the postoperative anxiety levels.
Conclusion: Music therapy performed during spinal anesthesia was found to be a cost-effective method that was as competent as sedation on vital signs, pain, and anxiety. Moreover, it also increased patient satisfaction.
Keywords: *Music Therapy, Postoperative Pain, Anxiety, Vital Signs, Spinal Anesthesia*

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INTRODUCTION

The surgical procedure is an important source of fear and anxiety for patients, in addition to the physical trauma. For this reason, the patients may be nervous, restless and anxious. Even though, spinal anesthesia is more advantageous compared to general anesthesia, the status of the patients' being awake and hearing all the voices and the conversations of the staff in the operation room may cause them to be afraid and uneasy about the intraoperative noise. Studies are reporting that post-operative anxiety levels are lower in patients who listen to music during spinal surgeries (Koc et al., 2009; Sener et al., 2010). Music therapy applications were first used in hospitals, mostly with anesthesia and analgesia. The researchers developed theories about the neurological effects of music therapy in the twentieth century and experimentally

investigated the physiological effects of music (Uyar & Korhan, 2011).

Music therapy affects the neuroendocrine and the autonomic nervous system, resulting in physiological and psychological changes. Music therapy, when it is listened to at low volumes and low tempos, has the ability to regulate disturbing emotions and reduce nervous transitions. As a result, it positively affects the emotional and limbic system, which is the center for excitement. Music therapy also increases endorphin release by activating the parasympathetic nervous system and stimulating the pituitary gland. Endorphin is a pain reliever and has a positive effect on perception (Bansal et al., 2010). People, who listened to music, were relaxed and felt more powerful (Chou & Lin, 2006). Music therapy has been reported in studies to be an effective method to reduce anxiety and increase relaxation levels (Scheufler et al., 2020). The benefits of music therapy include regulation of blood pressure, reduction of heart rate (Liu & Petrini, 2015), controlling respiration rate and elevation of oxygen saturation (Allen et al., 2001; Bae et al., 2014). Several studies have demonstrated that when listening to music patients shift away their attention from the noise in the environment and overheard conversation of the surgical team was also avoided or reduced (Bae et al., 2014; Kömürcü et al., 2015; Sarkar et al., 2017). The anxiety experienced during the preoperative period and the operation also causes problems in the postoperative period. The most important of these anxiety related complications are postoperative pain, weakening of the immune system, and the prolonged duration of recovery and the length of stay in the hospital. For this reason, controlling and/or eliminating anxiety is a consideration for the post-operative healing process (Chou & Lin, 2006; Vaughn et al., 2007).

Music therapy is one of the most common and oldest non-pharmacological methods used to control pain and anxiety (Karamızrak, 2014). It is an easy-to-apply, non-invasive method that has been reported to reduce surgical stress by using it without any side effects (Çelebi et al., 2020; Graversen & Sommer, 2013). Music therapy has been used in many different areas, including perioperative period anxiety and pain control, pregnant women, intensive care and colonoscopy, and has been found to have positive effects including patient satisfaction (Çelebi et al., 2020; Ko et al., 2019; Kühlmann et al., 2018; Lee et al., 2017; Nguyen et al., 2020; Surucu et al., 2018). Studies have shown that when listening to music during the surgery, the patient's anxiety decreases and accordingly, the need for analgesics and anesthetics decreases. (Bansal et al., 2010; Laframboise-otto et al., 2020). However, it has been determined that there are not enough randomized controlled trials to generate strong evidence on the subject.

MATERIAL and METHODS

Purpose and Type of the Study

The aim of this study was to investigate the effects of intraoperative music played during spinal anesthesia operation on patients' vital signs, postoperative pain, and anxiety level. This randomized controlled trial was conducted between June 2016 and June 2017 in the Orthopedics and Traumatology Clinic of Bolu Abant Izzet Baysal University hospital.

Sampling and Participant

The universe of the study consisted of patients, who underwent a planned surgery, took spinal anesthesia and knee prosthesis operation. The sample size calculation was based on the difference by the heart rate in vital signs. Heart rate (experimental group 87.59±11.04, control group 88.79±12.37) was used based on the study of Liu et al. (2015). To detect a clinically significant difference between groups with 0.85 power and at the 0.05 significance level, and standard deviation (SD)±10, 26 patients were needed in each group. To be able to detect differences in some of the secondary outcomes we planned to randomize 30 patients per group. The allocation sequence was kept by researcher until interventions start. The study was closed when 30 patients in each group were reached. Patients were divided into three groups by randomization with a computer program. A permuted block randomization scheme was used with random block sizes to prevent researcher from guessing the next patient group (Figure 1). There was no blinding as the researcher and participants knew the allocation.

The inclusion criteria for participants included: a) the patients undergoing total knee arthroplasty under spinal anesthesia b) 18 years or older; c) able to understand, read and speak Turkish, so they may complete the informed consent and questionnaires; d) have a Body Mass Index (BMI) <40; e) American Society of Anesthesiologists (ASA) class I, II or III. Patients with vision and hearing problems, not have psychiatric disease history and psychiatric drug use, not have diseases that could be evaluated as severe (such as heart, kidney, liver failure) and emergency surgeries patients were excluded from the study. The majority of patients were operated on by the same team.

Data Collection Tools

The data were collected by the researcher through the face-to-face interview technique and using an information form, an observation form for vital signs, numeric rating scale for pain and State- Trait Anxiety Inventory (STAI).

Information Form; it includes information such as the sociodemographic characteristics of the patients, the duration and type of the surgery, the type of anesthesia, and the status of having a chronic disease. Observation form was related vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure and oxygen saturation). Vital signs were recorded 15th, 30th, 60th minutes after surgery and 5th, 10th, 30th ,60th and 120 th minutes at during surgery on this form.

A Numeric Rating Scale was used by patients to rate pain intensity and pain distress. The scale begins with the absence of pain (0) and ends at the level of unbearable pain (Eti Aslan, 2002; Kömürcü et al., 2015).

State- Trait Anxiety Scale was developed by Spielberger et al. in 1970. The scale has 40 items in two constructs of state and trait. The Turkish validity and reliability studies of the scale were undertaken by Oner and Le Compte. The STAI state construct had satisfactory internal consistency (α=.90), test-retest reliability (r =.74), and concurrent validity of the STAI state construct. Cronbach's alpha coefficient was determined 0.65 for state anxiety in this study. The state anxiety scale consists of 20 items and the scale evaluate how the respondent's feeling at this moment. Each item had a 4-point Likert scale answer, from 1 (not at all) to 4 (very much so), and total score ranged from 20 (the lowest level of anxiety) to 80 (the highest level of anxiety) (Çelebi et al., 2020; Daniel T. L. Shek, 1993).

Statistical Analysis

The data analyzed using a statistical program. Continuous data were summarized as mean and standard deviation. Categorical data were summarized as frequency and percantages. If variables were normally distributed, one-way ANOVA analysis was used. Kruskal-Wallis, Wilcoxon signed rank tests were used for non-normal variables. Following the determination of the overall differences of variables, Tukey and Scheffe's test were performed for homogenous variables. Likewise, Games Howell test were performed for variables displayed non-homogenous distribution.

Ethical Approval

The ethical approval of the present study was obtained from the local ethical committee of the university hospital. The Regional Ethical Committee of Helsinki District approved the study protocol, and Registration number was (2016-89-27/07). Information was given to the patients, who were included in the study, and their written consents were obtained.

Intervention

At the beginning of the study, the purpose of the study was explained to each patient. Then, verbal and written consent of the patients was obtained. The information form was completed in the in orthopedics and traumatology service before surgery via face-to-face interviews by the researchers. STAI was applied to determine the anxiety levels of the patients before surgery. Patients were divided into three groups by randomization with a computer program. The patients in the music therapy group, before the surgery, how to use the headphones was explained and questions were answered. Patients in the music therapy group chose the music they wanted to listen from among four different music groups (relaxing, classical, mystical and Turkish folk music) and self-selected a volume

level. Music lists were selected by the researcher under the guidance of an expert. This expert works as a professor in the music department and has studies on the modes and effects of music. Music content in created groups with 60–80 beats per minute or less was offered because this rhythms has shown to yield a calming effect and a sense of well-being (Allred et al., 2010; Liu & Petrini, 2015). After spinal anesthesia was applied to the patients who were taken to the operating room music therapy was started. Music application was performed with a disposable headphones cover. Music therapy was applied until the end of surgery. The researcher was in the operating room until the end of the surgery.

Sedation (dormicum) was performed to the sedated group after spinal anesthesia based on the height and weight data and the doctor's decision. Sedation was decided during the operation. It had no effect on randomization. The patients in the non-sedated group were followed without any procedure (sedation and music). The music therapy group received standard care and music intervention (self-chosen) during the operation, the non-sedated group received only standard care and the sedation was performed to the sedated group. Standard care is nursing interventions performed before and during surgery (patient education, information). Intraoperative and postoperative vital signs (systolic and diastolic blood pressure, heart rate and respiratory rate) of patients were monitored and recorded in all three groups. The pain was assessed for all groups; firstly at the end of the operation, secondly with the transfer of the patient to the service and followed by the second evaluation at 8 hours postoperative period. STAI was applied to all three groups in postoperative periods (Figure 1).

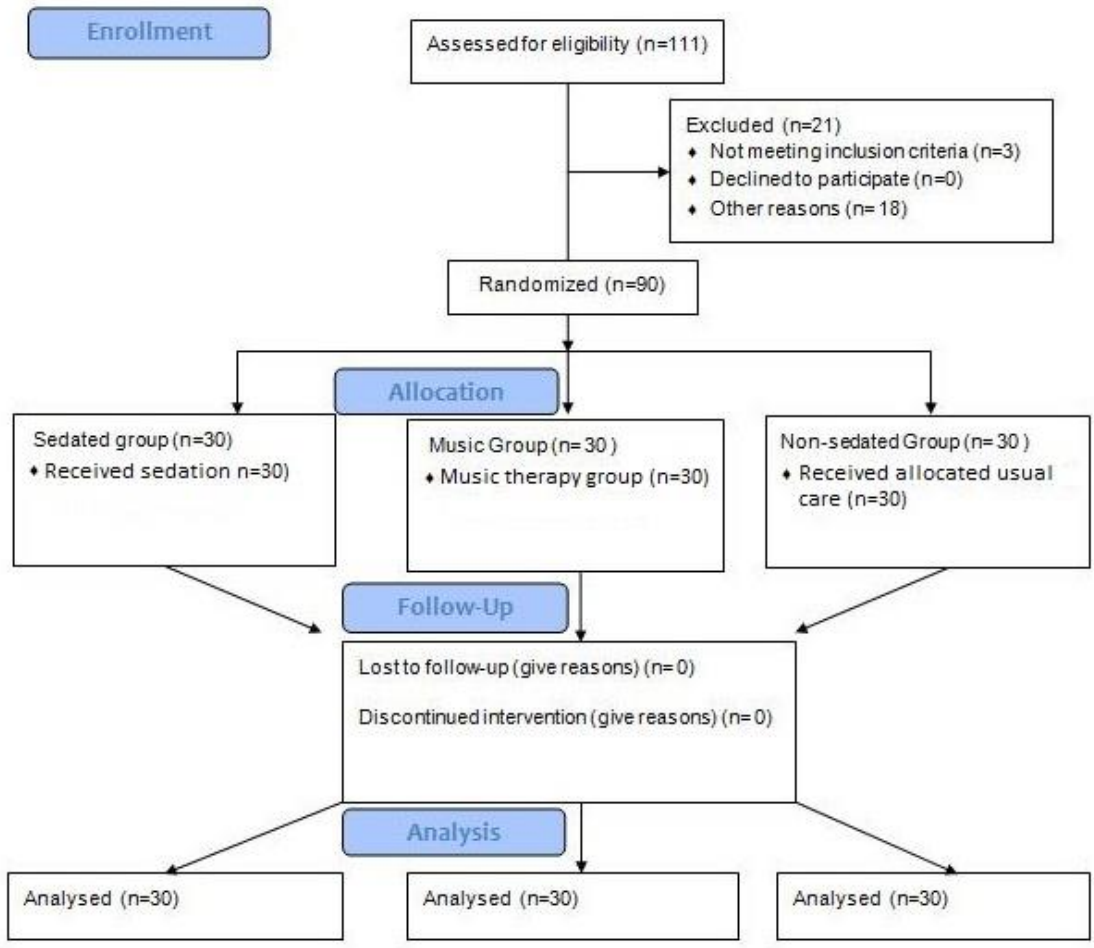

Figure 1. Flowcart of work with consort diagram

RESULTS

This study was carried out with 90 patients divided in three groups of 30 people. There was no significant difference between groups of demographic characteristics (Table 1).

In the study, it was seen that most of the patients in the music group chose mystical music (66.7%) that is followed by folk music (30.0%) and relaxing music (water and ocean sound) (3.3%). None of the patients preferred classical music.

Table 1. Demographic and introductory characteristics of the patients (n: 90)

		Music therapy group (n=30)	Sedated group (n=30)	Non-sedated group (n=30)	P value
Age (years)		68.5 (7.1)	65.8 (6.9)	66.5 (6.7)	0.313
Male/Female		7/23	3/27	3/27	0.495
BMI (kg/m^2)		30.9 (3.7)	32.8 (3.8)	32.8 (4.8)	0.120
Duration of the Operation (min)		98.6 (21.0)	98.2 (24.7)	98.7 (27.2)	0.564
Presence of Chronic Diseases (Yes/No)		19/11	22/8	23/7	0.495
Previous Operation Under Spinal Anesthesia (Yes/No)		8/22	15/15	9/21	0.124
Surgical treatment	Right TKA**	7	11	17	0.022
	Left TKA**	22	16	9	
	Bilateral TKA**	1	3	4	
ASA***	I	1	0	1	0.794
	II	22	25	22	
	III	7	5	7	

*BMI: Body Mass Index; **TKA: Total Knee Arthroplasty; ***ASA (American Society of Anaesthesiologists) Classification

Table 2. Distribution of systolic blood pressure, diastolic blood pressure, pulse rates and respiratory rates of patients in the sedated, music and control groups in intraoperative and postoperative period follow-ups (n: 90)

	Music therapy group (n=30)	Sedated group (n=30)	Non-sedated group (n=30)	p value
Intraoperative				
Pulse	75.8 (8.9)	74.4 (13.5)	76.6 (10.7)	0.730[a]
Systolic blood pressure	132.4 (1.1)	131.1 (16.5)	134.3 (12.5)	0.689[a]
Diastolic blood pressure	73.8 (7.2)	75.1 (12.5)	75.4 (6.6)	0.794[a]
Oxygen saturation	98.5 (1.0)	98.3 (1.5)	98.3 (1.4)	0.869[a]
Respiratory rate	18.5 (2.4)	20.1 (1.9)	19.0 (2.6)	0.038[b]
Postoperative				
Pulse	76.2 (10.0)	74.2 (10.6)	78.2 (10.9)	0.348[a]
Systolic blood pressure	130.6 (14.6)	126.8 (19.5	130.3 (16.9)	0.631[a]
Diastolic blood pressure	73.6 (7.2)	72.4 (9.7)	78.2 (10.9)	0.839[a]
Oxygen saturation	95.8 (1.9)	95.9 (1.8)	95.2 (1.9)	0.371[a]
Respiratory rate	20.9 (0.9)	20.6 (1.3)	20.3 (0.9)	0.101[a]

a: ANOVA test; b: Scheffe's test

Table 3. Distribution of pain scores according to groups (n: 90)

	Music therapy group (n=30)	Sedated group (n=30)	Non-sedated group (n=30)	p value
At the end of the surgery	0.1±0.7	0.2±0.9	0.5±1.3	0.321[a]
When first taken to bed at the service	0.4±1.2	0.2±0.8	0.4±1.2	0.622[a]
Pain rates (postoperative 8th hour)	5.0 ±1.3	4.9 ±1.6	5.8 ±1.6	0.051[b]

a: Kruskall Wallis; b: ANOVA test

After the intervention, a significant difference between groups regarding respiratory rates (F;2.685, p:0.04) was noted throughout the operation. Post Hoc Scheffe's test was used to determine the difference between the groups. The results showed that the music therapy group had significantly lower intraoperative mean number of respirations compared to the sedated and non-sedated groups. No significant difference existed in respect to vital signs in postoperative period (p>0.05) (Table 2).

No complications were observed during the surgery in the music therapy group. However, in the sedated group bradycardia, low blood pressure, and indications for intubation due to respiratory depression were observed in three patients. Likewise, two patients had high blood pressure and one patient had tachycardia in the non-sedated group. Postoperative pain scores of patients that were measured when the patients transferred to the service rooms were similar between the groups (p≥0.05). However, postoperative pain scores were significantly different between the groups at the postoperative 8th hour (p=0.05). Following the determination of homogenous distribution of postoperative pain data (p>0.05), Scheffe's test was performed to determine the groups with significantly different postoperative pain scores. The results showed that the sedated group had a statistically lower mean score compared to the music and non-sedated groups. The mean pain score of the music therapy group was statistically lower than the non-sedated group (Table 3).

There was no statistically significant difference between the groups in terms of preoperative and postoperative state anxiety scores (p= 0.99). However, the group with the lowest postoperative state anxiety score was the music therapy group (Table 4).

Table 4. Distribution of preoperative and postoperative state anxiety scores according to groups (n: 90)

	Music therapy group (n=30)	Sedated group (n=30)	Non-sedated group (n=30)	p value
Preoperative STAI Score	43.2 (6.4)	43.1 (5.3)	43.0 (5.0)	0.993
Postoperative STAI Score	43.2 (5.4)	45.2 (6.0)	44.4 (4.3)	0.530

The experiences of the patients participating in the study with the sounds in the operating room; 66.7% (n: 20) of the patients in the non-sedated group were uncomfortable to hear voices in the operating room ("I was scared, I wondered, I did not want to hear, I was bothered by the sounds, I became worse, it was better if I didn't hear them, I was excited, I was nervous, I panicked, the voices caused a headache, I was worried about pain in every move"), 66.7% (n: 20) of the patients in the sedation group were not affected by the sounds they heard in the operation room ("I was not affected, I liked their talks among themselves, I communicated with them, I did not feel uncomfortable, I didn't hear them), while 70.0% (n:21) of the patients in the music therapy group stated that (I slept when I listened to music, I felt peaceful, I prayed, it made me feel better, I felt like I'm in another environment because I like to listen to music) listening to music during the operation made them relax, and not hearing the sounds related to operation made them feel more peaceful.

DISCUSSION

Music therapy has positive effects on patients undergoing knee replacement surgery with spinal anesthesia on pain and stress reduction (Laframboise-otto et al., 2020). Studies have shown that music therapy is a non-pharmacological method that reduces the effects of stress on the body, regulates blood pressure, heart rate, breathing, and the emotional state of patients (Çelebi et al., 2020; Gökçek & Kaydu, 2020; Nguyen et al., 2020). In a study of Sarkar et al. (2015), vital signs of orthopedic surgery patients' under musculoskeletal spinal anesthesia were similar between music and control groups. Bae et al. (2014), reported significant

reductions in systolic and diastolic blood pressures of patients, who listened to music through the surgery. Bansal et al. (2010), reported that music had positive effects on various physiological and emotional parameters, including arterial blood pressure, heart rate, and decreased anxiety. However, in the study of Lepage et al., systolic blood pressure, pulsation, and respiratory rates were similar between the control and patient groups who listened music during intraoperative sedation under spinal anesthesia (Lepage et al., 2001). Similarly, Sarkar et al. (2015) also reported that listening music under spinal anesthesia throughout orthopedic operations did not have any significant effects on patients vital signs at any measurement time compared to the standard-care group of patients. In the current study, systolic and diastolic blood pressures, intraoperative heart rate and oxygen saturation averages were similar between groups. On the other hand, music therapy group demonstrated significantly reduced respiratory rates compared to the respiratory rate of the sedated and non-sedated groups. Knee prosthetics are postoperative pain generating surgeries due to impaired muscle integrity, bone damage, and prolonged bone healing (Zhu et al., 2017). Chen et al. (2015) stated that there was no significant difference in pain perception in the music therapy group and control group in patients, who underwent knee replacement operation. However, they stated that listening to music postoperatively resulted in less requirement for pain relievers. In a study by Sendelbach (2006), examining the effects of music on patients undergoing cardiac operation and found that the patients in the music group had lower pain and anxiety levels. Ozdemir et al. (2019) found that classical Turkish music reduced the severity of pain but increased the levels of anxiety in patients undergoing bone marrow aspiration and biopsy.

There is a high relationship between the cultural background and the individual music preference in music preference (Tang & Vezeau, 2010). Bansal et al. (2010) reported that the patients in the music group preferred to listen to religious music (48%) and folk music (22%). The study of Ovayolu et al. shows that the need for sedation in Turkish classical music listeners is reduced during colonoscopy (Ovayolu et al., 2006). Bae et al. found that when they asked the music preferences of the patients in their study, which was carried out to investigate the influence of the music on the intraoperative anxiety level, they found that they rather preferred local music (Bae et al., 2014). Consistent with the literature, in this study, it was seen that the patients in the music therapy group chose to listen to music in the form of mystical music (66.7%) and folk music (30.0%) among four music options. The music choices of patients are affected by age, culture, socio-cultural structure and religious beliefs (Bae et al., 2014; Bansal et al., 2010). It has been reported that patients listen to their choice of music over the course of the operation more effectively than standard relaxing music (Sarkar et al., 2015).In the current study, postoperative pain scores were similar between groups at the end of the surgery as well as when the patients were transferred to the bed following surgery. This might be caused by the long-lasting effects of spinal anesthesia, which can least at least four hours. Pain evaluation of patients performed at postoperative 8th hour demonstrated significant differences between groups. The sedated group had a significantly reduced compared to the music and non-sedated groups. This is most likely caused by the muscle tone control of a sedative drug used. Moreover, the mean score of pain was significantly decreased in the music therapy group compared to the non-sedated group. Leodoro et al. found that use of music in women who underwent gynecologic surgery reduced anxiety and stabilized physiologic parameters throughout the preoperative period (Labrague & McEnroe-Petitte, 2016).

According to the study of Jimenez-Jimenez et al. (2013), music therapy is considered to be advantageous without causing any adverse effects in controlling anxiety throughout the operation compared to using anxiety-relieving drugs. Bansal et al. (2010) reported that music therapy is supportive in patients undergoing regional anesthesia, such as sedative drugs for reducing anxiety and stress. Sarkar et al. (2015) found that music in orthopedic surgery patients, who were under spinal anesthesia, was effective in reducing operation-associated anxiety. Bae et al. (2014) reported significant differences in anxiety between the music and the control groups in

patients undergoing local anesthesia. In the present study, the mean postoperative anxiety scores were not significantly changed in the music therapy group; however, they were increased in the other groups. In present study, the state anxiety scores of the patients in the music therapy group did not change between pre and postoperative period, but it was increased in the other groups. The preoperative and postoperative anxiety scores of the patients did not differ between the groups, whereas the patients without sedation had lower postoperative anxiety scores.

CONCLUSION

This study is a randomize controlled trial and provides further evidence to support the practice of music therapy. Intraoperative music therapy is thought to be effective in reducing the intraoperative anxiety levels of the patients by directing their attention to other points and reducing their postoperative pain by positively affecting the vital signs of the patients. In our study, no complications were observed in the music therapy group in patients, who were followed-up throughout the operation. It was found that the majority of the patients in the non-sedated group were uncomfortable with the sounds in the operating room during the operation, and the majority of the patients in the sedated group were not affected by the sounds. Most of the patients in the music therapy group were pleased to listen to music during the surgery. As there were only postoperative findings in favor of pain as well as changes in vital signs in the patients in the sedated group, it was thought that musical therapy during surgery was as effective as sedation on pain control, anxiety, and vital signs. The patients in the music therapy group reported that listening to music during the operation relieved them. In the light of these results, music therapy is a cost-effective, reliable, non-pharmacological method for patients receiving local anesthesia. This method can be used to reduce the pain and anxiety of patients and positively affect various physiological parameters. In hospitals, it is suggested that music therapy applications can be used in patients, who do not require patient cooperation and undergo surgical operation by receiving local anesthesia. For the development of these practices, it is recommended to encourage nurses and to obtain strong evidence with a larger number of randomized controlled trials, with pre- and post-operative studies on specific groups of patients, with larger sample sizes.

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Conflict of Interest

None declared.

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Investigation of The Relationship Between Premenstrual Syndrome Symptoms and COVID-19 Psychological Distress in Nursing Students

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ABSTRACT:
Purpose: The aim of this study was examine the relationship between PMS symptoms. and COVID-19-related psychological distress of nursing students in the COVID-19 outbreak.
Material and Methods: The research is of cross-sectional type and was conducted on April 10-20, 2021. A total of 131 students were reached.
Results: 77.9% of the students had PMS symptoms. During the pandemic, 15.3% of students reported an increase in the duration of PMS complaints, and 22% reported an increase in the severity of PMS complaints. A significant difference was found between the COVID-19 psychological distress scale and the PMS scale total score, irritability, pain, appetite changes, sleep changes and bloating means.
Conclusion: It was found that students had negative changes in their menstrual characteristics and PMS complaints during the pandemic process. It may be recommended to identify and strengthen the measures that can be taken against the possible physical and psychological effects of the pandemic.
Keywords: *Premenstrual syndrome, COVID-19, Nursing students*

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INTRODUCTION

Premenstruel Syndrome (PMS) is a major public health problem that causes loss of labor force in women, decreased productivity, stress, anger, and depression (Bülez and Yalvaç 2021). In the luteal phase of the ovarian cycle the PMS phase of a disorder that occurs about a week before menstrual bleeding, ending with the onset of menstrual bleeding; changes in emotions, behavior and physical symptoms are observed (Dickerson et al., 2003; Aydın Kartal and Kaykısız, 2020). Although PMS affects the entire age group during menstruation, it is more common, especially in the 30-40 age range (Doğan et al.,2012). PMS is a major problem in adolescence with the onset of menarche. Although it is known that there are more than one hundred and fifty symptoms of PMS, its symptoms vary from person to person (Adıgüzel et al.,2007). The most common symptoms include restlessness, inability to control anger, decreased concentration, fullness and tenderness in the breasts, muscle and joint pain, tension, weight gain, anxiety, and deterioration in social relationships (Ölçer et al., 2017). Addressing PMS from adolescence will reduce the psychological and economic losses that can be seen during the childbearing age (Taşçı, 2006).

The COVID-19 pandemic, which affected the entire world, has become a global public health problem from a medical, spiritual, social and economic point of view (Gorbelanya et al., 2020). Negative effects are observed as a result of concern due to the measures taken to protect against the fear and

disease caused by the pandemic (UNICEF, 2020). Uncertainty during this period, restriction of applications to hospitals, social isolation, quarantine application, economic difficulties, restriction of access to social support networks, abstinence from daily activities, it can cause physiological changes and mood changes (Aydın-Kartal and Kaykısız, 2020). There are no studies in the literature on the direct effect of COVID-19 on menstruation. But the pandemic caused by: stress, anxiety, changes in the educational system, economic and social deficiencies can lay the foundation for the formation of PMS symptoms (UNICEF, 2020). Nurses play a key role in reducing the symptoms of PMS, an important public health problem, in providing holistic care to women experiencing PMS (Selçuk et al., 2014). Detection of PMS symptoms in nursing students will guide initiatives. Appropriate interventions will be determined, especially by uncovering the effects of the COVİD-19 pandemic from PMS. A study examining the relationship between PMS and COVID-19 psychological distress is not found in the literature. Therefore, this study was planned to examine the relationship between PMS symptoms and COVID-19 psychological distress of nursing students in the COVID-19 epidemic. In the light of the data obtained from the study, COVID-19 will benefit students in terms of taking the necessary measures for the state of psychological distress, making regulations and raising awareness of individuals on this issue.

MATERIALS AND METHODS

Type of the Study

The research is of the cross-sectional descriptive type. The research was conducted on April 10-20.

Sampling and Participant

190 female students studying in the nursing department of the Faculty of Health Sciences in eastern Turkey formed the universe of the research. In the power analysis, the sample size was calculated as 127, and the research was completed with 131 students. 68% of the universe has been reached.

Data Collection Tools

The survey form was used to collect the data. The questionnaire consisted of 3 sections: The Personal Information form with 16 questions consisting of the socio-demographic and menstrual characteristics of the students and the effects of the pandemic process on menstruation, the PMS scale and and the COVID-19 psychological distress scale.

The Personal Information Form

Personal information form was prepared by the researchers in line with the literatüre (Aydın Kartal and Kaykısız, 2020; Adıgüzel et al., 2007). Age, class, menarche age, cycle duration, period duration, smoking status, PMS symptoms they experienced, methods they used to cope with PMS were questioned. In addition, changes in the duration and severity of PMS complaints during the pandemic process, as well as the duration of menstruation, difficulty finding sanitary pads, the status of getting extra sanitary pads, and the status of COVID-19 disease were asked.

Premenstruel Syndrome Scale

Premenstruel syndrome scale was developed by Gençdoğan to determine premenstrual symptoms and to assess the severity of the symptoms in 2006. Also Gençdoğan conducted the validity and reliability study of the scale. The scale is a five-point Likert-type and consisting of 44 items. The scale questions the PMS experienced in the last three months. The scale has nine subscales: Depressive mood, anxiety, fatigue, irritability, depressive thoughts, pain, change of appetite, changes in sleep patterns and bloating. The sum of the scores obtained from these nine subscales yields the overall PMS scale score. The lowest score possible to be obtained from the scale is 44, the highest score is 220. The higher score is the higher intensity of the PMS symptoms is. While the score exceeding 50% of the highest possible score means that the person has PMS. The Cronbach's Alpha was calculated as 0.75. In this study, Cronbach's alfa was found 0.93(Gençdoğan, 2006).

COVID-19 Related Psychological Distress Scale

COVID-19 related psychological distress scale was used in the research. Ay et al. (2021) made the validity reliability of the scale developed by Feng et al. (2020) to determine the psychological distress

associated with COVID-19 in Turkey. The scale has 12 items. Scale contains two dimensions: suscipion and anxiety-fear. Items in scale are five point likert type scale. They range from 1 (strongly disagree) to 5 (strongly agree). Higher scores reflect higher psychological distress. Cronbach's alfa was found 0.88. In this study, Cronbach's alfa was found 0.91.

Data Collection

The data of the research were collected online. Consent was obtained from the students before participating in the study. The data collection time took approximately 15-20 minutes for each student.

Statistical Analysis

Data analysis was performed using SPSS 21.0 (Statistical Package for the Social Sciences, Chicago, Illinois). The data was evaluated in the SPSS 16 statistical package program. The suitability of the data for normal distribution was evaluated. Since the data fit the normal distribution, t-test and one-way variance analysis were used in independent groups. $p<0.05$ was accepted for the significance level of statistical tests.

Ethical Considerations

Permission was obtained from the scientific research and Publications Ethics Board of Bingöl University to Conduct the Research (Decision no: 92342550/044/11706). Students were informed about the importance and purpose of the study and accepted consent was obtained.

RESULTS

The mean age of the students is 21.1±1.3 and the age of the first menarche is 13.0±2.0. 33.6% of the students were reading on second grade. The students smoking rate is %4.6. %74.8 of students have regular periods. The students reported abdominal pain at 78.6%, mood changes at 76.3%, and abdominal bloating-tension disorders at 68.7% as the highest PMS complaint. The proportion of students using any method to reduce PMS ailments was found to be 45%. Distribution of students according to sociodemographic and menstrual characteristics is given in Table 1.

Changes in menstrual characteristics during the pandemic process were given in Table 2. Accordingly, 15.3% of students had an increase in the duration of PMS complaints, and 22.0% had an increase in the severity of PMS symptoms complaints. 10.7% of the students had an increase in period duration and 12.2% had a decrease. During the pandemic, the rate of difficulty finding sanitary pads was found to be 14.5%. Scores count as PMS overall means of 136.0. According to the total score cut-off score, 77.9% of them are PMS. Belief in joy was 16.7±5, depressive thought was 20.8±6.2, 8.7±3.0, urban 9.0±3.1, sleep 8.9±3.1, bloating 8.9±3.0. The student's COVID-19 Psychological Distress Scale score was found to be 42.3±9.4. The mean score, minimum and maximum values obtained from liking sub-images of PMS and COVID-19 are given in Table 3.

Considering the mean score of PMS symptoms according to the grade level, it was found to be significant ($p<0.05$). The mean PMS score of the third-year education was higher than that of the second-year education. In addition, the mean PMS score was higher in smokers and menstruating patients. No significance was found between use of any form to exit PMS and the mean score of the head. The means of the PMS scores of the students in sociodemographic and menstrual appearance are given in Table 4.

The PMS scale mean score of the students who stated that there was an increase in the duration of PMS complaints during the pandemic process was significantly higher ($p<0.05$). It was found that the severity of PMS complaints and changes in the amount of menstruation during the pandemic process did not affect the mean score of the PMS scale. Likewise, there was no relationship between the problems of finding sanitary pads and buying too many pads during the pandemic period and the mean score of the PMS scale. The distribution of the effect of the pandemic on menstrual characteristics according to the total PMS scale scores is given in Table 5. Correlation analysis between COVID-19 psychological distress scale score and PMS scale total score and sub-dimensions in students was given in Table 6. Accordingly, a significant difference was found between the COVID-19 psychological distress scale and the PMS scale total score, irritability, pain, appetite changes, sleep changes and bloating means.

Table 1. Distribution of students according to sociodemographic and menstrual characteristics (N=131)

Variables	n	%
Class		
1	16	12.2
2	44	33.6
3	37	28.2
4	34	26.0
Smoking Status		
Yes	6	4.6
No	125	95.4
Menstrual Order		
Regular	98	74.8
Irregular	33	25.2
Premenstrual Disorders*		
Abdominal Pain	103	78.6
Changes in Mood	100	76.3
Abdominal Bloating-Tension	90	68.7
Breast Tenderness	80	61.1
Back Pain	68	51.9
Mild Depression	68	51.9
Changes in Appetite	54	41.2
Headache	29	22.1
Weight Gain	22	16.8
Constipation	14	10.7
Using Methods to Deal with PMS		
Yes	59	45.0
No	72	55.0
Techniques Used to Deal with Premenstrual Disorders*		
Massage	26	19.8
Consuming Caffeine	25	19.1
Bathing	24	18.3
Hobby Activities	18	13.7
Attentive Nutrition	16	12.2
Breathing Exercise	14	10.7
Age	21.1±1.3	
First Menarche Age	13.0±2.0	
Cycle Duration	29.7±14.1	
Duration of Menstruation	6.4±1.2	

* Students responded more than once.

Table 2. Characteristics related to the effect of pandemic on menstruation process in students

Variables	n	%
PMS Complaint Period During Pandemic Process		
Increase	20	15.3
Decrease	3	2.3
Stabil	108	82.4
PMS Complaint Severity in Pandemic Process		
Increase	30	22.0
Decrease	3	2.3
Stabil	98	74.8
Duration of Menstruation in the Pandemic Process		
Increase	14	10.7
Decrease	16	12.2
Stabil	101	77.1
Having Trouble Finding Sanitary Pads During the Pandemic		
Yes	19	14.5
No	112	85.5
Purchasing Extra Sanitary Pads During the Pandemic		
Yes	71	54.2
No	60	45.8
Getting COVID-19		
Yes	33	25.2
No	98	74.8

Table 3. Distribution of premenstrual syndrome scale and COVID-19 psychological distress scale score means

PMS Sub-dimensions and Total Score	Mean±SS	Min-Max Values Received by Students	Min-Max values
Depressive Feelings	22.5±6.4	7-35	11-34
Anxiety	18.5±7.1	7-35	7-35
Fatigue	21.5±5.5	6-30	7-35
Irritability	16.7±5.3	5-25	5-25
Depressive Thoughts	20.8±6.2	7-35	7-34
Pain	8.7±3.0	3-15	3-15
Changes in Appetite	9.0±3.1	3-15	3-15
Changes in Sleep	8.9±3.1	3-15	3-15
Bloating	8.9±3.0	3-15	3-15
Total	136.0±32.3	44-220	61-210
COVID-19 Psychological Distress Scale	42.3±9.4	5-60	12-60

Table 4. Distribution of PMS scale total scores according to socio-demographic and menstrual characteristics of students

Variables	Mean±SS	Test /p
Class		
1	142.9±23.3	F=2.507/0.052 1<2
2	127.7±34.7[1]	
3	145.7±28.0[2]	
4	133.0±34.7	
Smoking Status		
Yes	169.6±25.2	t=2.667/0.009
No	134.4±31.8	
Menstrual Order		
Regular	132.4±31.5	t=2.236/0.027
Irregular	146.7±32.6	
Using Methods to Deal With PMS		
Yes	137.0±30.8	t=-0.308/0.758
No	135.2±33.7	

Table 5. Distribution of the effect of pandemic on menstrual characteristics in students according to PMS symptoms scale total scores

Factors	Mean±SS	Test /p
PMS Complaint Period During Pandemic Process		
Increase	154.95±33.3[1]	F=4.015/0.020 2<1
Decrease	133.6±31.3	
Stabil	132.7±31.2[2]	
PMS Complaint Severity in Pandemic Process		
Increase	146.5±29.9	F=2.073/0.130
Decrease	133.6±31.3	
Stabil	132.9±32.6	
Amount of Menstruation in the Pandemic Process		
Increase	150.3±36.7	t=-1.863/0.159
Decrease	140.2±35.8	
Stabil	133.4±30.8	
Having Trouble Finding Sanitary Pads During the Pandemic		
Yes	147.0±29.3	t=1.735/0.095
No	134.2±32.5	
Purchasing Extra Sanitary Pads During the Pandemic		
Yes	140.2±31.8	t=1.616/0.109
No	131.1±32.4	
Getting COVID-19		
Yes	129.6±30.7	t=-1.319/0.190
No	138.2±32.7	

Table 6. Relationship between COVID-19 psychological distress scale score and PMS scale total score and sub-dimensions

PMS Scale Total Score and Sub-Dimensions	COVID-19 Psychological Distress Scale	
	r	p
Depressive Feelings	0.078	0.379
Anxiety	0.132	0.132
Fatigue	0.167	0.056
Irritability	0.180	0.040*
Depressive Thoughts	0.150	0.060
Pain	0.191	0.029*
Changes in Appetite	0.288	0.001*
Changes in Sleep	0.228	0.009*
Bloating	0.166	0.040*
Total	0.186	0.017*

*p<0.05

DISCUSSION

In a study that examined the relationship between PMS and COVID-19 psychological distress in the pandemic period of nursing students, it was determined that the first menarche age of nursing students was 13.0±2.0, the period of menstruation was 3-7 days, and the cycle time was 29.7±14.1 days. In the study carried out by Topatan and Kahraman, the mean age of first menstruation was 13.32±1.36, the duration of menstruation was 5.74±1.54 days, and the mean menstrual cycle pattern was 28.16±2.50 days. Genç and Olmez found that 86.4% of the participants' first menstrual age range was 12-15, and 85.9% reported that the period duration was 3-7 days. Our study is in consistence with the other studies in the literature in terms of the age of the first menarche and the duration of menstruation.

The results of the present study revealed that 25.2% of the participants had menstrual irregularities. Similary, Aydın Kartal and Kaykısız reported that 30.9% of the students had menstrual irregularities (Aydın Kartal and Kaykısız, 2020). During the first 2 years after menarche, menstrual irregularity is considered normal. At the end of three years, 60-80% of adults are expected to reach the menarche form. Early detection and treatment of the condition that causes menstrual disorder is important in terms of reproductive functions (Tekirdağ, 2010).

The present study showed that the participants experienced the highest PMS complaints as 78.6% abdominal pain, 76.3% mood changes, 68.7% abdominal bloating-tension, 80% breast tenderness, 68% back pain and depression. In the study of Aydın Kartal and Kaykısız, it was reported that students mostly experience weakness, dysmenorrhea, low back pain and irritability sypmtoms (Aydın Kartal and Kaykısız, 2020). In a study conducted by Hafez et al., it was determined that nursing students experienced high levels of anxiety, irritability, increased appetite, headache, fatigue and depression. Similarly Pandian et al. found that the most common symptoms were headache and abdominal bloating (Pandian et al. 2016). These PMS symptoms can negatively affect students' social lives, family relationships, and academic success as well as reducing their life quality. Therefore, it is important to increase PMS awareness in adolescents. Students should be trained to deal with symptoms.

The rate of students using methods to reduce PMS disorders was found to be 45% in our study. Among the techniques used to cope with PMS, the highest rate was 19.8% massage, 19.1% caffeine consumption, and 18.3% bath. In a study conducted by Uzuner and Koçak (2019), it was found that the most preferred practices to cope with premenstrual complaints were to apply warm to the abdomen with 54.3% and to wear thick clothes with 51.6%. In the study of Aydın Kartal and Kaykısız, 24.5% of the participants stated that they received support from their family and friends, 19.6% paid attention to regular sleep, 15.2% did massage and 14.1% did relaxation exercises (Aydın Kartal and Kaykısız, 2020). Arslantaş et al. (2018) found that 36.7% of women preferred the use of analgesics as a coping method. According to a study conducted in Ethiopia, the rate of students using analgesics to cope with PMS was reported as 36.4% (Tolassa and Bekele, 2014). Despite the high PMS rate, none of the

participants requested medical treatment. Göker et al. (2015) found that the rate of receiving medical treatment for PMS complaints was 6.9%. As the women's health problems are considered taboo, consulting a doctor and seeking medical treatment may be delayed . For this reason, it is important to provide training and consultancy services in order to deal effectively with PMS complaints. The results of our study showed that practices for coping with PMS did not show parallelism compared to other studies. It is thought that this result is due to the change in needs during the pandemic.

In our study, 15.3% of students had an increase in the duration of PMS complaints during the pandemic process, and 22.0% had an increase in the severity of PMS complaints. 10.7% of the students had an increase in period duration and 12.2% had a decrease. In a study conducted by Aydın Kartal and Kaykısız (2020) during the pandemic period, 57.3% of students reported that their premenstrual symptoms had increased in the last three months, 13.2% reported that their symptoms had decreased and 29.5% reported no changes in symptoms. These findings show that during the pandemic period, students' removal from their social environment, difficulties caused by distance education, and the implementation of stay-at-home policy due to the pandemic negatively affected the PMS complaints and menstruation-related process.

In our study, the prevalence of PMS was 77.9%. In a study conducted by Ölçer et al. (2017), the prevalence of PMS was 55.8%, and in the study of Aba et al. (2018) 65.2%. In a study conducted with nursing students in Korea, the prevalence of PMS was 42.4%. A high prevalence of PMS in our study can be considered as a negative effect of the pandemic process. As a matter of fact, other studies were conducted before the pandemic and the prevalence of PMS was found to be lower. In addition, the fact that the participants had different socio-demographic characteristics and the difference in the measurement tools used may have affected the results. Despite this wide range, the common result stated in the literature is that the prevalence of PMS is high.

The participants in our study had a mean total score of 136.0±32.3 in the PMS score. In the study conducted by Genç and Ölmez (2021), the average PMS scale of women was 173.00±40.73. The average PMS scale score was 121.95±34.20 in Uzuner and Koçak's (2019) study, and 122.14±32.60 in Aba et al. (2018) study. Studies in the literature revealed that the mean of the PMS scale varied. It is believed that this change may be due to the fact that the participants had different socio-demographic characteristics, and that the effects of the pandemic process on PMS.

In our study, COVID-19 Psychological Distress Scale was found to be 42.3±9.4. It is noted that the psycho-social effects of pandemics on mental health are higher than predicted (Shigemura et al., 2020). It has been observed that changes in life style pave the way for the formation of negative emotions. For example, participants experienced serious anxiety due to uncertainty during the pandemic period, financial problems that may occur in the future, the possibility of contracting COVID-19 and losing loved ones (Hatun et al., 2020). COVID-19 leads to problems such as panic, anxiety, and depression in humans (Cao et al., 2020; Qiu et al., 2020). These problems were found to be more common in individuals quarantined as a result of transmission (Brooks et al., 2020). In our study, the rate of participants undergoing COVID-19 was 25.2%. Coronavirus is expressed to have serious negative socio-psychological effects even in healthy people (Tian et al., 2020). In our study, the average value of the COVID-19 Psychological Distress Scale was 42.3±9.4. The result we found showed that participants experienced psychological distress associated with COVID-19.

In our study, the rate of students smoking was 4.6%. In addition, the average PMS score was significantly higher in students who smoked. Pınar et al. reported that smoking increases the risk of PMS by 40 times (Pınar et al., 2011). Seedhom et al. noted that passive smoking is a factor associated with PMS (Seedhom et al., 2013). A study by Tschudin et al. showed that PMS was found 1.67 times more in women aged 15-54 years, in smokers compared to non-smokers (Tschudin et al., 2010). It is emphasized that smoking increases the signs of PMS, therefore it should be reduced or stopped (Johnson Berton et al., 2008). Smoking causes different health problems and thus

it is noted that it also plays a role in the development of PMS due to its negative effect on reproductive hormones (Kaya and Gölbaşı, 2016).

In our study, the proportion of students with menstrual disorders was found to be 25.2%, and the average PMS score of these students was significantly higher. Elkin (2015) found that those who did not have regular menstruation and those who suffered from menstrual pain have higher mean PMS scores. This finding is consistent with our study. Menstrual irregularity can lead to increased PMS complaints with hormonal effects. Treatment of the underlying cause of disorder is important for the continuation of PMS and reproductive functions.

In our study, 54.2% of participants said that they received extra hygenic pads during the pandemic, and 14.5% said that they had difficulty finding hygenic pads during the pandemic. No significant differences were found between excessive pad intake and difficulty in finding hygenic pads and the average PMS scale. Especially in underdeveloped countries such as African countries, the fact that it is not easy to reach the materials necessary for menstrual hygiene management may cause an increase in PMS complaints. Due to the constraint panic experienced by COVID-19 during the busy shopping period before the quarantine process, materials can be stocked by buying more than needed (Ajari, 2020). However, such an effect was not observed in our study.

According to the results of the correlation analysis between the COVID-19 psychological distress scale score and the PMS scale total score and sub-dimensions in our study, there was a significant difference between the COVID-19 psychological distress scale and the PMS scale total score, fatigue, irritability, pain, appetite changes, sleep changes and bloating mean scores. In PMS, psychological and social factors as well as physiological factors play a role in the development of genetic characteristics (Matsumoto et al., 2013; Eggert et al., 2016). A study conducted with female students in Japan also reported an association between increased stress levels and PMS (Yamamoto et al., 2009) A study conducted abroad found that the stress level of participants experiencing severe PMS was significantly higher compared to the stress levels of participants experiencing mild and moderate PMS (Khodjaeva and Khaydarova, 2013). The most basic strategy to prevent the spread of the COVID-19 epidemic is to physically remove and isolate people from each other (Centers for Disease Control and Prevention, 2020). This measure, which is protective against the epidemic, on the other hand, can become a risk factor for mental health by reducing social relations. It is suggested that social relationships may be a biological need vital to psychological well-being. Therefore, the lack of social relationships throughout isolation negatively affects the state of psychological and emotional well-being (Holt Lunstad, 2017). In their study, Duan and Zhu (2020) found that the COVID-19 epidemic increased individuals stress and anxiety levels as well as leading to mental illnesses such as insomnia, anger, and women experienced more stress. A study conducted with university students in China during the COVID-19 pandemic found high levels of stress and anxiety (Cao et al.,2020). COVID-19 increased psychological distress while psycho-behavioral and social factors were also effective in PMS development. Therefore, this study is consistrent with the literature in terms of finding significant differences between COVID-19 psychological distress and PMS symptoms: irritability, pain, appetite changes, sleep changes, and bloating averages.

The present study was not without its limitations. First, a self-completion questionnaire was used. In additipn, only a selective group of unmarried nursing students participated in the study. Therefore, this study does not aim to generalise results to the population as a whole.

CONCLUSION

COVID-19 pandemic rapidly became a global crisis and caused an emergency. This contagious virus has not only raised concerns about general public health, but has also caused many changes in the lifestyle and habits of the individuals. At the same time, it has had both physiological and psychological effects on social and individual dimensions.

In this study, the relationship between premenstrual syndrome and COVID-19 psychological distress of nursing students during the pandemic process was examined. It was found that students had negative

changes in their menstrual characteristics and PMS complaints during the pandemic process. It was determined that the students did not receive professional help in dealing with PMS complaints. The prevalence of PMS was found to be high in students. The mean PMS scale was significantly higher in students who smoke and have menstrual disorders. A significant difference was found between the mean scores of the COVID-19 psychological distress scale and the PMS scale total score, irritability, pain, appetite changes, sleep changes, and bloating of the students. In order to reduce the incidence of PMS and the severity of symptoms, students should be educated about the harms of

smoking and its relationship with PMS complaints, and attempts should be made to quit smoking. Causes of menstrual disorder should be identified and treated. Appropriate coping strategies should be taught by training on PMS. Education and initiatives are needed to reduce the psychological distress of COVID-19 during the pandemic period. Considering the dynamics that COVID-19 has changed in daily life, students should be informed about the methods of coping with the psychological effects caused by this process. Another recommendation is to conduct comprehensive studies investigating the impact of the COVID-19 pandemic on PMS.

This study reveals the importance of identifying and strengthening measures that can be taken for the possible physical and psychological effects of the pandemic, as well as strategies aimed at minimizing the risk of secondary diseases.

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Conflict of Interest

The authors declare that they have no conflict of interest

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Investigation of the Prenatal Attachment Levels of Pregnant With Depressive Symptoms**

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ABSTRACT:
Purpose: This study was conducted to determine the attachment level of pregnant women with depressive symptoms to their prenatal period baby.
Material and Methods: Research has been done in descriptive type. The universe of research was composed of pregnant women who applied to Sivas Kangal Family Health Center and Kangal State Hospital between April 10 and July 10, 2017. In the sampling, 150 pregnant women who met the criteria were included. Personal Information Form, Beck Depression Inventory and Prenatal Attachment Inventory were used to collect the data of the study. The data were collected by face to face interview method. The analysis of the data was made with the SPSS (Version: 22.0) program. In statistical analysis, the significance level was accepted as $p<0.05$.
Results: According to the data analysis results; Pregnant women are 27,02 years old on average and are married for 6,41 years, 41,4% are primary school graduates, 73,3% are housewives, 82,7% have middle-level income. The average gravida of pregnant women is 2,44 and 35,3% of them are their first pregnancy. Average gestation period is 27,76 weeks. When the BDI cut-off score was accepted as 17, the prevalence of depression in pregnant women was found to be 35,3%. The mean BDE score was determined to be 15.48 ± 10.12 (min 0-max 46). Generally, mild depression symptoms (32,6%) were found in pregnant women, while 11,3% had severe depression symptoms. The attachment levels of the pregnant women are above the average with 56.85 ± 12.64 (min 28-max 82) points. The relationship between Beck Depression Inventory and Prenatal Attachment Inventory was analyzed and a statistically negative correlation and a significant correlation was found ($p<0.05$).
Conclusion: As a result of the research, it was seen that prenatal attachment decreased as the severity of depressive symptoms of pregnant women increased. For this reason, pregnant women with depressive symptoms or diagnosed with depression in the prenatal period should be identified, if necessary, the affected pregnant woman should be planned individual training with her husband, practices should be made to improve and protect her mental health, and thus contribution should be made to increase mother-baby attachment.
Keywords: *Pregnancy, Depressive Symptom, Prenatal Attachment*

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INTRODUCTION

One of the important points in a woman's life is the pregnancy period. During pregnancy, the woman experiences some physiological changes due to the increase in hormones and the growth of the fetus, as well as psychological and social changes, and the pregnant tries to adapt to both the changes and the new roles gained during this period (Beji, 2015; Şirin & Kavlak, 2015). These physiological and physical changes that may occur in women during pregnancy are also the source of psychological changes. Psychological disorders may occur in pregnant women as a result of psychological changes (Taşkın, 2009; Beji, 2015; Şirin & Kavlak, 2015). Depression is one of the most common psychological disorders during pregnancy. The emergence of depression during pregnancy negatively affects the quality of life of the pregnant woman and therefore the health of the fetus (Kuğu & Akyüz, 2001; Savrun, 2008; Çam & Engin, 2014; Özorhan et al., 2014; Dağlar et al.,

2015). Dağlar et al. (2016) found that the rates of anxiety and depression in pregnant women were considerably higher than in the postpartum period. In many studies conducted in the world and in Turkey during the prenatal period, the rates of depression were found to be between 7.2% and 65.6%. While the rate of depression seen in pregnant women in the world is 7.2% - 40.3% (Niaz et al., 2004; Lee et al., 2007; Lancaster et al., 2010; Lee, 2016), this rate is between 27.9% and 65.6% in Turkey (Karaçam and Ancel ,2009;Tunç et al., 2012; Çelik et al., 2013; Dağlar et al., 2016; Bulut and Yiğitbaş, 2018;Yüksel et al.,2020). The data show that the rates of depression in our country are quite high compared to the countries of the world. If the depressive symptoms that occur during pregnancy are not evaluated in the early period and the necessary treatment is not applied, it can affect the mother and the fetus not only from the physiological point of view, but also from the psychological aspect (Kocabaşoğlu and Başer, 2008). The onset of pregnancy creates a bond/relationship between the mother and the fetus, and the strength of this bond is closely related to the psychological conditions experienced by the mother (Condon & Corkindale, 1997; Lindgren, 2001; Tunçel & Süt, 2019). Physiological and psychological changes experienced by the pregnant have a great effect on the bonding between mother and fetus (Eswi & Khalil, 2012; Yılmaz, 2013). The mental health of the pregnant woman and the depression she experiences are very important in terms of attachment (Öztürk et al., 2018).

Bowlby defines attachment as a strong bond between two people (Bowlby, 1969). The emotional bond formed between parents and fetus during pregnancy is defined as prenatal attachment (Condon & Corkindale, 1997; Beji & Yılmaz, 2013; Yılmaz, 2013). In a study, it was stated that the feeling of attachment between the mother and the fetus started before birth, and this attachment increased when the mother felt the movements of the fetus (Sezici et al., 2016). When the literature studies on prenatal attachment are examined, prenatal attachment has been affected by many positive or negative factors (Lindgren, 2001; Yarcheski et al., 2009; Yılmaz and Beji, 2010; Elkin, 2015; Sezici et al., 2016; Badem and Zeyneloğlu, 2021). Many studies have been conducted to date on how women and fetuses are affected physiologically during pregnancy (Diego et al., 2009; Çalık and Aktaş, 2011; Eskici et al., 2012; Mutlugüneş and Mete, 2013). When the literature is examined, depression (Karaçam & Ançel, 2009; Arslan et al., 2011; Tunç et al., 2012; Dağlar & Nur, 2014; Elkin, 2015) and prenatal attachment (Lindgren, 2001; Karaçam & Ançel, 2009; Elkin, 2015; Buko and Özkan, 2016; Metin and Pasinlioğlu, 2016) were studied separately in our country , but the extent of how it would affect attachment if depression in pregnant women is not diagnosed and treated early has not been examined. Therefore, this study was conducted to determine the prevalence of depressive symptoms and prenatal attachment level in pregnant women.

MATERIALS AND METHODS

Purpose and Type of Research

The research was carried out as a descriptive study in order to determine the level of attachment of pregnant women with depressive symptoms to their prenatal period babies.

Population and Sample of the Research

Research Ministry of Health Sivas Provincial Health Directorate Sivas Kangal State Hospital Gynecology and Obstetrics Polyclinic and T.R. It was held at the Ministry of Health Sivas Kangal Family Health Center between April 10 and July 10, 2017. The research population consisted of pregnant women with a gestational age of 14 weeks and above who applied to Kangal State Hospital and Kangal Family Health Center. The sample of the study consisted of 150 pregnant women who came for examination between 10 April and 10 July 2017. While pregnant women were taken into the sample, those who had the following criteria were selected.

- ✓ Having a gestational week of 14 weeks and above (2nd and 3rd trimester)
- ✓ Having a healthy pregnancy (not having chronic disease, gestational diabetes, eclampsia and preeclampsia, preterm birth threat, premature rupture of membranes)
- ✓ Having a healthy fetus

- ✓ Being 18 years or older
- ✓ Not having communication difficulties and mental inadequacy
- ✓ Not having received infertility treatment to get pregnant
- ✓ Not having a diagnosed depression before and during pregnancy

Data Collection Tools

Research data were collected with Personal Information Form, Beck Depression Inventory and Prenatal Attachment Inventory.

Personal Information Form

It consists of 20 questions including demographic and obstetric characteristics of the pregnant woman.

Beck Depression Inventory

It was developed by Beck (1961) to measure the behavioral manifestations of depression in adults; Turkish validity and reliability study was conducted by Hisli (1989). The scale consists of 21 questions. In the result evaluation, the scores of all questions are collected and classified according to their grades between 0 and 63 points. 0-9 points, minimal depression; 10-16 points, mild depression; 17-29 points, moderate depression; A score of 30-63 is defined as severe depression. The scale cut-off point is 17.

Prenatal Attachment Inventory

The scale developed by Muller (1993), Duyan et al. (2013) adapted it to Turkish. It was developed to explain the feelings, thoughts and situations experienced by the pregnant during pregnancy and to determine the attachment levels in the prenatal period. The scale consists of 21 items. Each item can receive points between 1-4. A minimum of 21 and a maximum of 84 points can be obtained from the scale.

Analysis of Data

The analysis of the data obtained from the research was made with the SPSS (Version: 22.0) program. Independent t test, One-Way Analysis of Variance, Mann Whitney U, Kruskal Wallis-H test were used in statistical analysis and the level of significance was accepted as $p<0.05$.

Ethical Aspect of Research

Before data collection, ethics committee approval dated 10.03.2017 and numbered 03/03 was obtained from Sivas Cumhuriyet University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. Ministry of Health Sivas Provincial Health Directorate Kangal State Hospital Gynecology and Obstetrics Polyclinic dated 20.04.2017, numbered 75.723.911-903.05.99-E.99-3825 and T.R. Written permissions were obtained from the Ministry of Health Sivas Kangal Family Health Center and dated 25.04.2017 and numbered 73192166.044.E269. The pregnant women who will participate in the study were informed about the study and their verbal and written consents were obtained.

RESULTS

42.7% of the pregnant women included in the study are between the ages of 21-25. 9.3% are illiterate and most (41.4%) are primary school graduates. 35.3% of the pregnant women have been married for 1-2 years, 73.3% are unemployed and 37.3% of their spouses are working as workers. 82.7% have a middle income and 9.3% smoke during pregnancy. 76% of the pregnant women are in the nuclear family structure and 14.7% of them live with their mother-in-law and father-in-law. Beck Depression Scale and Prenatal Attachment Scale scores were examined according to the demographic characteristics of the pregnant women. High depressive symptoms were observed in pregnant women over the age of 35, married for 5-6 years, illiterate, pregnant and pregnant spouses working as workers, and pregnant women with low income and living in a large family. Accordingly, prenatal attachment rates were also found to be low. Although low depressive symptoms were observed in pregnant smokers, prenatal attachment levels were not found significant ($p>0.05$) (Table 1).

The gestational age of 53.3% of the pregnants is 14-28 weeks. 44.0% 2-3. 35.5% of them experience their first pregnancy while they are having their first pregnancy. While 44.0% have 1-2 children, 41.3% have no living children. 39.3% of the pregnant

women who gave birth before had a normal delivery and 70.7% of them did not have a history of miscarriage. 76.7% of the pregnant women who participated in the study became pregnant voluntarily, 38.0% of them stated any gender desire.

Table1. Scale Score Comparisons According to Demographic Characteristics of Pregnants

		Beck Depression Inventory		Prenatal Attachment Inventory	
Demographic Features	***n (%)***	***x̄±SD***	***p***	***x̄±SD***	***p***
Age					
18-20	16(10.7)	19.56±9.71	0.00	56.00±8.87	0.02
21-25	64(42.7)	13.28±9.05		59.07±13.12	
26-30	30(20.0)	13.00±9.10		59.23±12.51	
31-35	29(19.3)	16.65±10.70		53.31±12.12	
35 and above	11(7.3)	26.09±10.14		48.00±12.64	
Wedding Year					
1-2	53(35.3)	11.86±8.60	0.00	63.15±11.96	0.00
3-4	25(16.7)	14.96±6.52		56.72±11.63	
5-6	23(15.3)	18.86±12.72		51.52±11.34	
7 and above	49(32.7)	18.08±10.74		52.61±11.78	
Education Level					
İlliterate	14(9.3)	29.42±7.34	0.00	43.28±12.79	0.00
Primary school graduate	62(41.3)	17.27±10.05		52.91±9.52	
High school graduate	35(23.3)	13.51±8.32		60.08±13.70	
University graduate and above	39(26.0)	9.70±6.41		65.02±9.39	
Pregnant Occupation					
Unemployed	110(73.3)	17.26±10.17	0.00	54.79±12.29	0.00
Worker	8(5.3)	19.55±11.38		57.77±15.59	
Public servant	32(21.4)	8.00±4.88		63.90±10.62	
Spouse Occupation					
Unemployed	15(10.0)	22.86±11.16	0.00	52.66±13.37	0.00
Worker	56(37.3)	18.89±10.48		51.19±12.08	
Tradesman	27(18.0)	11.62±8.09		60.85± 8.69	
Public servant	45(30.0)	9.95±6.40		64.00±11.21	
Farmer-Shepherd	7(4.7)	22.85±7.64		49.71±10.48	
Income Level					
Low	22(14.7)	27.31±10.89	0.00	46.22±10.94	0.00
Middle	124(82.7)	13.44±8.46		58.70±12.08	
High	4(2.7)	13.75±10.71		58.00±12.35	
Smoking					
Yes	14(9.3)	23.07±10.20	0.00	54.42±9.17	0.45
No	136(90.7)	14.70±9.82		57.10±12.95	
Family Type					
Nuclear family	114(76.0)	13.98±9.93	0.00	58.32±12.83	0.01
Extended family	36(24.0)	20.25±9.33		52.19±10.92	

The rate of experiencing joy and happiness when pregnant women learn of their pregnancy is 70.0%. 72.0% of the pregnant women stated that they received support from their spouses during pregnancy, whereas 6% of the pregnant women stated that they experienced violence from their spouse or family. According to the obstetric characteristics of pregnant women; Beck Depression Inventory and Prenatal Attachment Inventory scores were examined. High Beck Depression Inventory scores were found in pregnant women who had 4 or more pregnancies, had 3-4 living children, had the last normal delivery, had an unwanted pregnancy, experienced sadness when they heard about their pregnancy for the first time, had no support from a spouse, and were subjected to violence by their spouse or family. It was found that pregnant women showed low attachment. However, the factors of gestational week, miscarriage history, and sex desire were not found to be significant in terms of both the presence of depressive symptoms and attachment (Table 2).

Table 2. Scale-Score Comparisons of Pregnants According to Obstetrical Characteristics

		Beck Depression Inventory		Prenatal Attachment Inventory	
Obstetric Features	***n (%)***	***x̄±SD***	***p***	***x̄±SD***	***p***
Gravida					
First	53(35.3)	12.18±8.20	0.00	62.58±11.96	0.00
2	37(24.7)	13.62±8.82		58.86±11.13	
3	29(19.3)	16.27±8.10		49.89±10.17	
4 and above	31(20.7)	22.61±12.68		51.16±13.20	
Gestational Age					
14-28	80(53.3)	14.10±9.80	0.08	57.06±13.40	0.82
29-40	70(46.7)	17.07±10.31		56.61±11.81	
Number of children					
No children	62(41.3)	12.16±8.70	0.00	61.88±11.88	0.00
1-2 children	66(44.0)	15.31±8.56		55.63±11.34	
3-4 children	17(11.3)	26.23±12.12		44.88± 8.13	
5 or more children	5(3.4)	22.40±12.54		51.20±19.51	
Latest Delivery Type					
Cesarean Delivery	28(18.7)	15.75±12.04	0.00	55.71±11.90	0.00
Vaginal Delivery	59(39.3)	18.76±9.77		51.50±11.27	
Nulliparous	63(42.0)	12.30±8.55		62.36±12.05	
History of Abortion					
Yes	44(29.3)	15.45±9.97	0.95	56.02±13.02	0.60
No	106(70.7)	15.50±10.23		57.19±12.53	
State of Desiring Pregnancy					
Yes	115(76.7)	14.15±9.27	0.01	59.14±11.78	0.00
No	35(23.3)	19.85±11.60		49.31±12.61	
Gender Request in Pregnancy					
Male	16(10.7)	14.43±10.76	0.38	55.00±15.23	0.11
Girl	41(27.3)	14.31±0.15		60.31± 9.30	
It does not matter	93(62.0)	16.18±10.04		55.64±13.27	
When You First Hear About Pregnancy Feeling Emotion					
Joy, Happiness	105(70.0)	12.73±8.94	0.00	59.68±12.16	0.00
Sadness	6(4.0)	31.33±13.09		45.50±10.82	
Anxiety	32(21.3)	19.84±8.79		52.25± 9.70	
Fear	4(2.7)	22.25±10.68		50.00±16.49	
Other	3(2.0)	24.66±1.52		38.66±18.00	
Spouse Support					
Yes	108(72.0)	13.61±8.61	0.00	60.05±11.05	0.00
Sometime	31(20.7)	18.54±11.77		48.83±12.16	
None	11(7.3)	25.27±12.01		48.00±15.36	
Violence by Spouse or Family					
Yes	9(6.0)	28.00±9.06	0.00	45.66±14.27	0.00
No	141(94.0)	14.68±9.67		57.56±12.24	

Table 3. The Relationship Between BDI and PAI Mean Scores of Pregnants

Scales	**x̄+SD**	**Minimum**	**Maximum**	
BDI	15.48±10.12	0	46	r= -0.62 p=0.00
PAI	56.85±12.64	21	84	

Table 3 shows the mean BDI and PAI scores of pregnant women. The mean score of Beck Depression Inventory administered to pregnant women was calculated as 15.48 ± 10.12, and the mean score of Prenatal Attachment Inventory was calculated as 56.85 ± 12.64. In the correlation analysis between the scales, it was determined that there was a statistically negative and significant (r= -

0.621 p<0.05) relationship between the Beck Depression Inventory mean score and the Prenatal Attachment Inventory mean score. As the bonding rates between mother and fetus increase in the prenatal period, there is a decrease in depressive symptoms in pregnant women.

DİSCUSSİON

The findings obtained from the study carried out to determine the prevalence of depressive symptoms in pregnant women and to determine the prenatal attachment level of pregnant women who experienced symptoms were discussed in line with the literature. Most of the pregnant women included in the study are between the ages of 21-25. In our study, most of the pregnant women were primary school graduates (41.4%), unemployed (73.3%), middle-income (82.7%), and living in a nuclear family (76.0%). While most of the pregnant women (73.3%) do not work in any job, their pregnant spouses mostly work as workers (37.3%), which can be attributed to the fact that agriculture and animal husbandry are the main sources of livelihood in rural areas. 35.3% of pregnant women experience their first pregnancies, it is thought that this situation is caused by the small average age of the pregnant women. Most of the women included in the study became pregnant voluntarily and have regular pregnancy follow-ups. Despite being a rural area, the fact that regular pregnancy follow-up is in the majority has been a pleasing result in terms of healthy continuation of pregnancy. 67.7% of the pregnant women who gave birth before gave birth normally. In our study, when the BDI cutoff score was accepted as 17, the prevalence of depressive symptoms was found to be 35.3%. When pregnant women in the world and in our country were examined, the rates of depression were found to be quite high in studies conducted with many scales (Lara et al., 2009; Lancaster et al., 2010; Ali et al., 2012; Lee, 2016). In Turkey, this rate is between 27.9% - 65.6% (Karaçam and Ançel ,2009;Tunç et al., 2012; Çelik et al., 2013; Dağlar et al., 2016; Bulut and Yiğitbaş, 2018;Yüksel et al.,2020). In studies conducted with BDI, the scale score was evaluated as above 17, and it was determined that the pregnant women showed depressive symptoms between 12.0% and 45.3% (Cebeci et al., 2002; Yanıkkerem et al., 2004; Sevindik, 2005; Çelik et al., 2013; Daştan et al. ., 2015; Bulut et al., 2018). When the world and Turkish literature findings were evaluated, the level of depression and depressive symptoms in our study was found to be similar to the studies conducted with the same and different scales in the literature, and showed a value closer to the studies conducted in Turkey. When the level of depression was examined in our study, it was found that most of the pregnant women had mild depression symptoms (32.6%). When the depression levels were evaluated, it was concluded that 32% of the pregnant women experienced minimal depressive symptoms, 24% moderate and 11.3% severe depressive symptoms. In the literature, more severe depression is seen in Turkey compared to other countries in the world (Ayele et al., 2016; Sevindik, 2005; Çalık and Aktaş, 2011; Çelik et al., 2013; Zaman et al., 2018; Bulut et al., 2018). Our study shows parallelism with studies conducted in Turkey. This may be due to the excess stress of pregnant women, the lack of opportunities in rural areas and the living standards they live. In our study, the mean BDI score was found to be 15.48±10.12 (min= 0 – max= 46). In studies in the world and in Turkey, mean BDI scores vary between 10±5.77 and 17.34±1.71 points (Ayele et al., 2016; Yanıkkerem et al., 2004; Cebeci et al., 2002; Daştan et al., 2015; Zaman et al., 2018; Çalıkoğlu et al., 2018). In terms of BDI score average, the literature findings show parallelism with our study. When the BDI score averages of the pregnant women are compared according to their socio-demographic characteristics, it is seen that pregnant women over 35 years of age, 5 years or more of marriage, unemployed, and among the employees working as workers, illiterate, unemployed, and farmer-shepherd and employed spouses. It was concluded that pregnant women who work as workers, have low income, smoke, live in an extended family experience more depressive symptoms. There are studies supporting our research result in the literature (Ayele et al., 2016; Çapık et al., 2015; Field ,2017; Çalıkoğlu et al., 2018). Bilgen (2020) in his study,reported that depression in pregnant women decreased as income and education level increased, similar to our study. In our study, when the

relationship between depressive symptom levels and obstetric characteristics of pregnant women was examined, those who were multiparous (4 or more pregnancies), had a normal delivery, did not have pregnancy follow-up, had an unplanned and unwanted pregnancy, suffered from violence by their spouse or family, who were upset when they heard about the pregnancy for the first time, and had spousal support during pregnancy. Similar to our study, in a study conducted in Jamaica, lack of spousal support, exposure to violence and financial difficulties were factors that increased the level of depressive symptoms in pregnant women (Bernard et al.,2018). There was no statistical difference in depression symptoms between pregnant women with a history of miscarriage and desired gender, and pregnant women in the 2nd and 3rd trimesters (gestational age). However, more depressive symptoms are seen in third trimester pregnant women compared to second trimester pregnant women. The reason for this may be anxieties about the upcoming birth, extreme fatigue due to the limitation of movement, sleep and appetite disorders, and a decrease in the quality of life (Marakoğlu and Şahsıvar, 2008). In a study conducted in parallel with our study, when the frequency of depressive symptoms was evaluated in the pregnant group according to trimesters, there was no statistically significant difference, and the score of the third trimester pregnant women was found to be significantly higher (Zaman et al., 2018). In our study, when the mean score of the Prenatal Attachment Inventory was examined, the pregnant women showed a high attachment score by getting 56.85±12.64 (min=21 – max=84). Our study results have similar rates with most studies conducted in the world and Turkey (Eswi and Khalil, 2012; Elkin, 2015; Aksoy et al., 2016). In our study, PAI scores of pregnant women were compared according to their socio-demographic and obstetric characteristics. When the mean scores of the Prenatal Attachment Inventory were compared according to the socio-demographic characteristics of the pregnant women, it was found that the pregnant women between the ages of 26-30 were at the highest level of attachment, but when the age between the ages of 21 and 35 was evaluated, the level of prenatal attachment decreased as the age increased. It can be said that this result is due to the fact that young mothers are more interested and willing about pregnancy. In our study, attachment scores decreased as the years of marriage of pregnant women increased. This situation can be explained by the decrease in interest and desire for pregnancy. It was determined that as the education level of pregnant women increased, prenatal attachment increased. It can be said that pregnant women with a high education level are more conscious in terms of pregnancy, birth and fetus, and thus attachment increases. Attachment levels were found to be high in pregnant women whose spouses and self-employed and those with a high income level were pregnant. Some studies in the literature in recent years support this result (Damato, 2004; Yılmaz and Beji, 2010; Bakır et al., 2014; Elkin 2015; Metin and Pasinlioğlu, 2016; Dağlı, 2017; Dikmen, 2018). But Ozkan et al. (2020)'s study, on the contrary, showed that pregnant women with a high level of education had a negative impact on their PAI scores. In our study, when the relationship between other factors affecting attachment and prenatal attachment was examined, it was determined that pregnant women living in a nuclear family and receiving spousal support during pregnancy showed higher prenatal attachment. Alan (2013) and Metin and Pasinlioğlu (2016) stated in their study that there is a significant relationship between perceived social support by the mother and prenatal mother-fetus attachment. Napoli et al. (2020) emphasized in their study that if the pregnancy is planned and desired, prenatal attachment will be increased with social support and these results support our study.

When we compared some of the obstetric characteristics of the pregnant women with the mean PBE, high attachment was found in the pregnant women who had pregnancy follow-up, had no previous children or did not give birth. Yılmaz and Beji (2010), Mutlu et al. (2015) and Kırca and Savaşer (2017) also found high attachment levels of primiparous pregnant women in their studies. Differently, in the study conducted by Badem and Zeyneloğlu (2021), Özkan et al. (2020) found that the prenatal attachment levels of pregnant women who were 3 and above were high. Different results were

found in studies on the number of pregnancies factor. In our study, cesarean section among pregnant women who gave birth before showed higher attachment than those who gave normal birth. Alan and Ege (2013) in their study in pregnant women with caesarean section as opposed to our studies have indicated that low binding. The trimester of pregnancy has been one of the factors that affect the binding of our study ($p > 0.05$). Apart from this, no relationship was found between the history of miscarriage, sex desire, smoking, employment status of the spouse and prenatal attachment.

In this study, a statistically negative correlation and a significant ($r=-0.621$ $p<0.001$) relationship was found between Beck Depression Inventory and Prenatal Attachment Inventory (Table 3). As the severity of depressive symptoms of pregnant women increases, prenatal attachment decreases. No study has been found in the literature indicating the relationship between the level of depressive symptoms and prenatal attachment. However, there are some studies that can support the result of this study. In a doctoral study, databases on attachment published in the last 7 years were compiled and it was determined that pregnant women with high attachment were better psychologically and their anxiety levels were low (Alhusen et al., 2008). In a study conducted with 32 women in the USA, it was found that low anxiety level is among the factors that increase prenatal attachment (Reed, 2014). In Turkey, Mutlu et al. (2015) stated that attachment before, during and after birth is affected only by mental problems. As a result of their study, Özdemir and Çevirme (2020) stated that as the anxiety levels of pregnant women increase, their attachment scores decrease and anxiety disorder affects maternal and fetal health negatively. When these studies were examined, it was seen that anxiety was mostly addressed in terms of anxiety, and it is known that anxiety, that is, anxiety, often accompanies depressive mood clinically.

Psychological disorders and mental symptoms experienced during pregnancy contribute negatively to both the mother's quality of life and the development of the baby as a healthy individual (Devam and Cantez, 2020). İt was seen in our study that depressive symptoms experienced by pregnant women significantly affected their attachment levels. In some studies, it is clear that a healthy prenatal attachment will make positive contributions to both pregnancy and postnatal maternal-fetal attachment and will no longer pose a threat to infant health and development (Branjerdporn et al., 2017). Our work is important in order to increase prenatal attachment, to have a healthier pregnancy and to raise healthier individuals.

CONCLUSIONS AND RECOMMENDATIONS

In the study conducted to determine the prevalence of depressive symptoms in pregnant women and the level of prenatal attachment, mild depressive symptom prevalence was found at a rate of 35.3%. At the same time, a high level of prenatal attachment was found in pregnant women. It was determined that as the depression symptom levels of the pregnant women increased, their prenatal attachment decreased significantly (negatively). Depression symptoms are observed at low levels in pregnant women with high prenatal attachment level. Women should be taken by health professionals both before pregnancy and during pregnancy with their psychological aspects as well as physical follow-up. Necessary family counseling training should be given by determining whether the pregnancy is the desired pregnancy. Factors that may adversely affect mother-infant attachment in the prenatal period and may pose a risk should be determined by screening or scale studies to be added during pregnancy follow-up, and necessary preventive and therapeutic measures should be taken practices should be made to improve and protect health. Thus, it should contribute to the increase of mother-baby attachment and to start and maintain the formation of love in this process. The results of our study are of a quality that can support pregnant women to carry out follow-up studies in which psychological effects are examined in more detail as well as physical effects.

Conflict of Interest: The authors have no conflict of interest between.

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The Effect of Religious Coping Strategies Used During the Care Process on Quality of Life of Caregivers of The Elderly Patients Hospitalized in Palliative Care Unit and Internal Medicine Clinic

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ABSTRACT:
Purpose: This study was conducted with descriptive-correlational design to determine the correlation between religious coping strategies and quality of life of the caregivers of elderly patients, staying in the palliative care unit and internal medicine clinics, during the care process.
Material and Methods: The sample of the study was composed of 69 caregivers of elderly patients staying in the internal medicine clinics and palliative care unit of Sahinbey Research and Application Hospital. Caregiver Information Form, World Health Organization Quality of Life Instrument Short Form and Religious Coping Scale were applied to the participants and the data were analyzed using SPSS 22.0. Log linear model and regression analysis was used to examine the correlation between the scales.
Results: A significant correlation was determined between the caregivers' ages and the quality of life and its subscales (p=0.001). The caregivers did not use religious coping methods as their ages increased (p=0.005).
Conclusion: It was determined that age and financial situation did not affect quality of life of the caregivers. There was a positive correlation between religious coping status and quality of life of the caregivers. Consequently, it was found that religious coping methods used by the caregivers to be at peace enhanced their quality of life. It is recommended for nurses to provide training and counselling to caregivers about how care burden will be used and how quality of life will be enhanced.
Keywords: *Palliative care, Caregiver burden, Religious Coping, Quality of Life*

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INTRODUCTION

Old age is defined as individuals' decreased physical power, increased consumption, increased disability, and irreversibly impaired functions of the organism (Bahar et al., 2009). The WHO defines old age as "the decrease in the ability to adapt to environmental factors". Likewise, the WHO defines psychogeriatric aging as "old" for 65 years old and over and "very old" for 85 years old and over (Beğer and Yavuzer, 2012). Aging is a public health issue requiring a multidisciplinary service that concerns the healthcare, social, and economy systems. One of the most important social risks observed in developed communities is the need for aging-related care (Koldaş, 2017). Many countries face population aging. Today, 8.5% of the world population is over 65 years of age. In "An Aging World: 2015" report, it is estimated that this rate would increase to 17% by 2050 and the number of elderly population would reach to 1.6 billion by 2050. America's elderly population is estimated to double over the next 30 years and increase from 48 million to 88 million people by 2050 (Koldaş, 2017). According to TSI data, Turkey's elderly population was 6 million 192 thousand 962 people in 2014, it increased by 16% in the last five years and reached to 7 million 186 thousand 204 people in 2018. 44.1% of that population are male and 55.9% are female. Its rate in

the total population increased from 8% to 8.8% within five years. In accordance with all these data, it is believed that especially the second half of the current century will be "century of elderly people" in Turkey (TÜİK, 2018).

People look for a safe harbor to take refuge in whenever they are in trouble and whenever they are unable to overcome or experience an important loss in their lives. Many people find this safe harbor in religion (Beğer and Yavuzer, 2012). In their study, (Ayten and Sağır, 2015) determined that men interpreted favorably negative events and situations more and tended to ask more for God's help and support compared to women. In a challenging event, religion represents an important part of the coping structure. Religion can structure the character of an event, coping activities and consequences of this event, or may be a result of coping (Kabalak et al., 2013). According to the researchers, people's selecting any of active and passive coping methods is based on the types of religiosity which are tried to be identified (Mattis, 2002). When the results of positive and negative coping are compared, it is better understood why they got these names. This is because positive religious coping methods increase the positive development based on stress, cognitive functions and the probability of reaching spiritual results; whereas, negative religious coping methods reduce the possibility of reaching a spiritual result, the quality of life, and the ability to act independently in daily activities, and increases the possibility of having a depressive temperament. Furthermore, a study demonstrated that positive religious coping methods were used more than negative religious coping methods (Pargament et al., 2004). Religious coping is the use of cognitive and behavioral elements by using religious and spiritual sources in difficult situations (Ayten and Sağir, 2015; Ayten, 2012). In a study on the civil servants' methods of coping with stress, it was stated that the civil servants used coping methods including cognitive and behavioral methods. The study demonstrated that coping in the cognitive dimension can be beneficial if it continues in a controlled manner. In another study, it was reported that those who were satisfied with their job and did not have problems with the administration, developed a more religious attitude (Robinson and Griffiths, 2005). In another study examining prayer as a coping method in adolescents, it was stated that prayer, described as a problem-focused coping style, enables to recognize the problem, to develop alternative ways to solve the problem, to plan and to actively cope by collaborating with the Creator. According to the study, if the stressful life cannot be changed, prayer reduces emotional stress. At this point, prayer also functions in an emotion-oriented coping style by enabling to reinterpret or accept the event (Aslan, 2007). Religion brings satisfactory explanations to situations like death, birth and injustice and increases effectiveness in coping (Ayten, 2012). The studies on the spiritual beliefs and practices of high-risk pregnant women have reported that women's spirituality improves the condition of themselves and their unborn children and is a protective factor in suicide attempts. It is stated religious belief increases pregnant women's self-confidence and ability to cope with crisis (Price et al., 2007; Benute et al., 2011). A traumatic event does not necessarily take place for religious coping process; religion is only as much a part of in the coping process as it is a part of a person's life orientation system. In addition to the benefits provided by religion in coping with the challenging life events and creating a general life philosophy, it can also be asserted that it is also effective in leading a happy and satisfied life. Enjoying life and being happy are among essential criteria for defining mental health. It is generally accepted that people, who are happy and satisfied with their life, have good mental health. It is seen that many factors such as achieving happiness through meaning in life and enjoying life by participating in different activities are associated with life satisfaction (Connor et al., 2003). In a study examining the correlation between life satisfaction, holiday, and regeneration experience, it was found that individuals feel comfortable and independent from work when they have control over what they want to do and they are more satisfied with their general life (Chen and Petrick, 2013). A person's views and expectations about life constitute the characteristics of quality of life; this, of course, differs from individual to individual. When an individual is angry about the events he/she

experiences, questioning the existence of divine power and failing into despair can adversely affect the quality of life. Subjective positive evaluations of the individual who take refuge at the mercy of divine power and hoping can positively affect the quality of life (Şahin et al., 2009; Pargament et al.,2000; Pargament, 1999; Pargament et al.,1990).

Quality of life is generally defined as an individual's physical, social and psychological well-being. The World Health Organization expresses quality of life as "the perceptions of individuals about their position in the culture and values of the society they live in by considering their interests, hopes, standards, and goals" (Arpacı, et al., 2015). In a study examining the effective components on life satisfaction, it was stated the individual's physical and mental health status, lifestyle, and his/her relations with the social environment positively influenced his/her quality of life (Korkmaz et al., 2015). It is stated that health, socioeconomic level, and psychological state of the caregivers negatively affect their quality of life in case of providing long-term care. The caregivers can face situations like depression, anxiety, burnout, impaired physical health, social isolation, and economic obstacles as a result of the care burden they experience (Masat, 2018). In a study examining the effects of daily living activities of the elderly on caregiver's anxiety, it was stated that there was a very strong correlation between daily living activities of the elderly and the anxiety of the caregiver. The impaired health status of the elderly individuals was stated to increase the anxiety and depression levels in caregivers (Mahoney, et al., 2005). Providing a consultancy service prepared in line with the needs of the patient and caregiver enhances the quality of care, reduces the stress burden of the caregiver individual, and enhances the quality of life of the patient (Lampley-Dallas et al., 2001). Increasing the number of centers that can provide care to the patients and easing the access to these centers are important in terms of protecting and maintaining the mental and physical health of caregivers (Tremont, 2010; Tel et al., 2012). There are numerous factors affecting the care burden and quality of life of the caregiver. These factors are examined in three groups including caregiver's characteristics (socio-demographic characteristics, characteristics about affinity with the patient), patient's personal characteristics (disease or cancer-related characteristics) and care-related characteristics (time, intensity, type and changes in activities, etc.). All of these factors also affect the life and experiences of the caregiver (such as disruption in his/her life, economic obstacles, etc.) in addition to the care burden and quality of life (Doğan, 2015). It was reported in the studies that upon increased care burdens of the caregivers of the patients, the prevalence of infectious diseases and depression increased in caregivers, anxiety, stress, burnout, and behavioral disorders were seen in them, negative changes occurred in their health perceptions, and their quality of life were impaired (Aşiret and Kapucu, 2013; Ustaalioglu et al.,2018; Okka et al., 2018). In addition to all of these, palliative care is extremely important in order to integrate spiritual help and support services into the care provided within the scope of the healthcare services and to have healthcare professionals to support caregivers, plan proper multidimensional interventions, apply these interventions routinely, and evaluate their results (Ayten, 2012; Gökulu, 2018). The World Health Organization (WHO) emphasizes addressing the needs of family caregivers and family as one of the primary objectives of palliative care.

MATERIAL and METHODS

Purpose and Type of the Study

The purpose of this study is to determine the effect of religious coping strategies of the caregivers of elderly patients staying in palliative care unit and internal medicine clinics on their quality of life during care process.This study was conducted with descriptive-correlational design to determine the correlation between the religious coping strategies and quality of life among the caregivers of elderly patients staying in palliative care unit and internal medicine clinics during care process.

Hypotheses of the Study

H0: Religious coping strategies do not affect caregivers' quality of life.

H1: Religious coping strategies affect caregivers' quality of life.

Sampling and participant

The population of this study was composed of the caregivers of elderly patients staying in internal medicine clinics (neurology, geriatrics) and palliative care unit of Gaziantep University Sahinbey Research and Application Hospital. Because we aimed to include the entire caregiver population (n= 110) in the study, we did not calculate the sample size and did not use any sampling method. In total, 69 caregivers who provided care to an impaired elderly individual were included in this study, representing 65 % of the target population inclusion criteria were as follows: (i) caregivers who were able to speak Turkish, (ii) lived with an aged care recipient and had been bedridden for at least six months and the elderly individual was 65 years or older, (iii) caregiver who takes care of an elderly patient for at least 15 days in the hospital and It's about being ill with dementia, nutritional deficiencies or health at least 6 years old while living. Exclusion criteria were as follows: (i) being hospitalized in surgical clinics due to short hospital stay.

Data Collection Tools

The researchers collected the data of the study from the caregivers meeting the inclusion criteria using face-to-face interview method within the day-shift working hours between March and May 2021 in internal medicine clinics and palliative care unit of Sahinbey Research and Application Hospital. Data were collected by the investigator through face-to-face interviews with caregivers. The interviews lasted for approximately 40 minutes A caregiver ınformation form, World Health Organization Quality of Life Instrument Short Form and Religious Coping Scale were used. The study's independent variables included socio-demographic characteristics of the caregivers and their problems, caregiving-related characteristics, and religious coping strategies; on the other hand, the quality of the life was the dependent variable of the study.

Caregiver Information Form

The caregiver information form prepared by the researcher includes the evaluation questions about the socio-demographic characteristics of the caregivers, their caregiving-related characteristics, and their problems.

The World Health Organization Quality of Life Instrument Short Form

This questionnaire consists of four domains (Physical health, Psychological health,Social relationships, and Environment) and two items concerning Overall QoL and General health. Higher scores indicate a better subjective QoL (De Vries and Van Heck, 1995). Its Turkish adaptation was carried out Eser et al (Eser et al., 1999). Cronbach's Alpha reliability coefficients of the scale were determined as 0.76 in the physical health subscale, 0.67 in the psychological health subscale, 0.56 in the social relationships subscale, and 0.74 in the environment subscale. In the present study, Cronbach's Alpha reliability coefficients were found to be 0.67 in the social relationships subscale, 0.68 in the physical health subscale, 0.64 in the psychological health subscale, and 0.83 in the environment subscale.

Religious Coping Scale

Religious Coping Scale was developed by Pargament et al., (1988) based on the correlation between coping, religious coping and a series of psychological data of three groups having different life events. This scale has a total of 14 items and 2 subscales including 7 items (Items 1, 2, 6, 8, 9, 11, and 13) for Positive Religious Coping and 7 items (Items 3, 4, 5, 7, 10, 12, and 14) for Negative Religious Coping. Religious Coping Scale was adapted to Turkish population by Eksi in 2001 by conducting its validity and reliability. The scale is a 4-point Likert type scale. In the study by Eksi (2001), it was determined that Cronbach's alpha reliability coefficient was 0.64 for the Positive Religious Coping subscale, 0.63 for the Negative Religious Coping subscale, and 0.69 for the overall scale. In the present study, it was determined that Cronbach's alpha reliability coefficient was 0.74 for the overall scale, 0.76 for the Positive Religious Coping subscale, and 0.69 for the Negative Religious Coping subscale.

Statistical Analysis

The data were analyzed by using SPSS 22.0 statistical package program. Number, percentage, and standard deviation values were used in the data

distribution. Log linear model and regression analysis were used to compare dependent and independent variables.

Ethical Approval

All procedures performed in studies involving human participants were realized in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its later amendments or comparable ethical standards. This is an observational study. The Application Hospital Research Ethics Committee has confirmed that no ethical approval was required. İnönü Üniversity ethics committie (23.03.2021/ decision number: 2021/1837) recevied.

RESULTS

The data collected from the caregivers of the patients staying in palliative care unit and internal medicine clinic are present below. It was determined in Table 1 that the average age of the caregivers was 45.42±11.10 (25- 70 years), 66.7% were female, 66.7% were married, 71.0% had children, 40.6% were primary school graduate, 59.4% were unemployed, 52.2% had a middle level of income, 95.7% had social security, and 60.9% had no chronic disease (Table 1).

It was determined that 26.1% of the caregivers were the patients' daughters, 76.8% were living together with the patient, care process of 33.3% took 3-6 hours, 53.7% had difficulties mostly in meeting mostly physiological needs, 47.8% were trying to solve difficulties in patient care without receiving any help, 59.4% saw the care process as a religious obligation, 62.3% had no change in religious dimension during the care process, and 56.5% did not need psycho-social support during the care process (Table 2).

Table 1. Socio-Demographic Characteristics of Caregivers (n = 69)

Introductory Features	Number (n)	Percent (%)
Age (45.42±11.10; 25-70)		
Gender		
Female	46	66.7
Male	23	33.3
Marital Status		
Married	46	66.7
Single	13	18.8
Widowed/divorced	10	14.5
Number of children		
Yes	49	71.0
No	20	29.0
Educational background		
Illiterate	8	11.6
Primary school	28	40.6
High School	13	18.8
Associate degree	2	2.9
Bachelor's degree	18	26.1
Graduate degree	-	-
Working Status		
Employed	28	40.6
Unemployed	41	59.4
Income		
Low	19	27.5
Middle	36	52.2
High	13	18.8
Very high	1	1.4
Social Security		
Yes	66	95.7
No	3	4.3
Chronic disease		
Yes	27	39.1
No	42	60.9
TOTAL	69	100.0

Table 2. Process, Time and Religious Dimension of Care for the Caregivers

Characteristics	Number (n)	Percent (%)
Affinity		
Caregiver	8	11.6
Brother/sister	6	8.7
Spouse	16	23.2
Daughter	18	26.1
Son	11	15.9
Other	10	14.5
Status of Living Together		
Yes	53	76.8
No	16	23.2
Time Allocated for Care		
Doesn't take time	3	4.3
0-3 Hours	18	26.1
3-6 Hours	23	33.3
7-12 Hours	16	23.2
13 Hours and more	9	13.0
Care Difficulties		
Continuous Talking	12	17.4
Committing Violence	2	2.9
Physiological Needs	37	53.7
Suffering	7	10.1
No Care Difficulty	11	15.9
Coping with Care Problems		
Not getting help	33	47.8
Receiving support from family members	23	33.4
Caregiver support	3	4.3
Empathy	10	14.5
Religious Dimension of the Care Process		
I see it as a religious obligation.	41	59.4
I don't see it as a religious obligation.	28	40.6
Change in Religious Dimension		
Praying More	26	37.7
No Change	43	62.3
Need for Psycho-social Support		
Yes	30	43.5
No	39	56.5
TOTAL	69	100.0

Table 3. Distribution of the Mean Scores of the Scales and Their Subscales

Scales And Their Subscales	Scale Min-Max	Scale Mean±Sd
Religious Coping Total Score	**1.00-3.14**	**2.2±0.5**
Positive Religious Coping	1.00-4.00	2.8±0.7
Negative Religious Coping	1.00-2.71	1.6±0.5
Quality of Life Total Score	**43.00-97.00**	**80.36±13.76**
Quality of Independent Domain	2.00-9.00	5.3±1.9
Quality of Physical Domain	13.00-29.00	21.36±3.7
Quality of Psychological Domain	8.00-22.00	15.57±3.5
Quality of Social Domain	3.00-15.00	8.1±2.8
Quality of Environment Domain	12.00-36.00	28.86±6.1

It was determined in Table 3 that the religious coping total mean scores were 2.2±0.5, positive religious coping total mean scores were 2.8±0.7, and negative religious coping total mean scores were 1.6±0.5. WHO quality of life mean scores were 80.36±13.76, independent domain mean scores were 5.3±1.9, physical domain mean scores were 21.36±3.7, psychological domain mean scores were 15.57±3.5, social domain mean scores were 8.1±2.8, and environmental domain mean scores were 28.86±6.1

(Table 3).

Regression analysis indicated that the descriptive characteristics of caregivers, age, perceived income, and Positive Religious Coping Styles affected the quality of life and descriptive characteristics and Religious Coping Styles of the caregivers accounted for their quality of life with a variance of 56% (Figure 1).

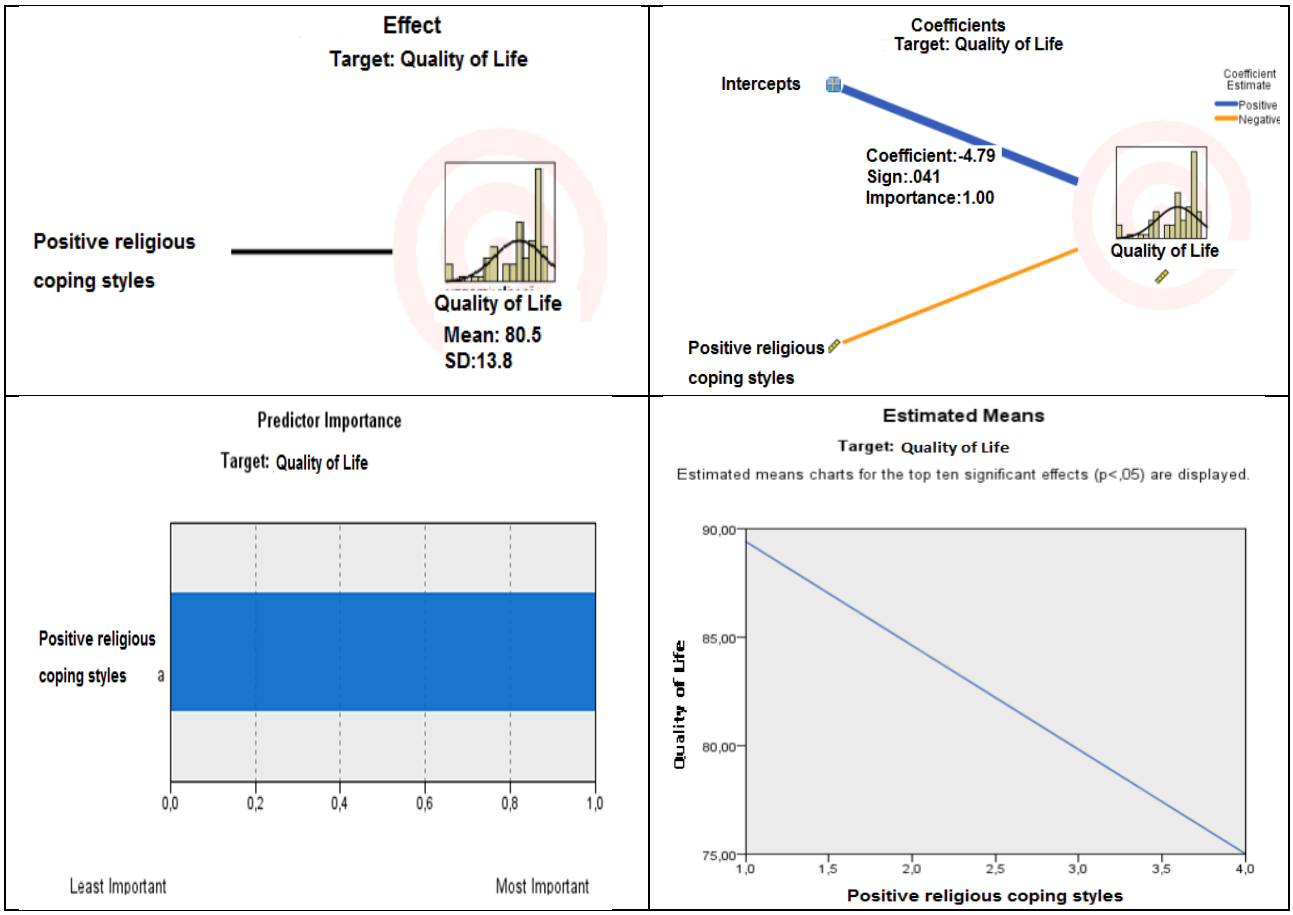

Figure 1. The Effect of Religious Coping Styles of the Caregivers on Their Quality of Life. According to the log linear model, the Positive religious coping of the caregivers was found to be the most important factor affecting the quality of life.

DISCUSSION

In this study assessing the religious coping methods used by the caregiver family members of patients suffering from chronic disease during caregiving process and their quality of life, the characteristics of the caregivers can be said to be similar to the literature (Han et al., 2017; Küçükguclu, 2009; Yeşil et al., 2016).

In the studies, it is stated that family relations of caregivers deteriorate, their family responsibilities are negatively affected, and they experience social, physical, economic and psychological problems due to their caregiving roles. All of these problems are defined as care burden (Gökulu, 2018.). In the present study, it was determined that a majority of the caregivers were the daughter and spouse of the patient, they were residing with the patient, they were unemployed and their economic status was not high. In fact, when the studies are examined, results similar to the literature are seen (Gökulu, 2018; Kalav et al., 2018; Han et al., 2017). This is associated with the necessity of showing respect for the elderly and patients in the family due to tradition and customs in Turkish society and the fact that the children feel gratitude for their parents in terms of care, the caregivers are mostly the children and spouses of the patients, the caregiving roles expected from women are adopted, and women are primary caregiver.

The socioeconomic status of family members was one of the reasons affecting the quality of life (Table 4). Individuals who had economic difficulties experienced more stress and more problems. This negatively affected their life satisfaction. There are studies in the literature reporting that the caregivers with lower socioeconomic level have higher burden and worse health (Aşiret and Kapucu, 2013; Chen and Petrick, 2013; Chen et al., 2015). Caregiver not only meets the care needs of the patient but also helps in issues like buying the medicine, shopping and providing financial support. This brings financial burden along with the care burden. The other studies showed that caregivers having economic problems had lower quality of life and high income level enhanced the quality of life (Hacialioglu et al., 2010). Economic status indicators are one of the important variables predicted by quality of life within the scope of personal social area. This result may be associated with the fact that caregivers with a good income level can identify and monitor the disease-related problems, they apply complicated treatment process without interrupting the treatment of the patients, and they can get better care, thus having a better standard of life.

As the age of the caregivers increases, their quality of life is negatively affected. In their study conducted to determine the quality of life characteristics of individuals aged 65 years and over and the influencing factors through SF-36 quality of life questionnaire, Durduran et al., in their study stated that the quality of life impaired with increasing age. It was also determined in the present study that the quality of life was negatively affected with increasing age (Durduran et al., 2018). In the study by Kalınkara et al., it was stated that caregivers experienced social isolation with age and especially their mental health was affected more by entering a new care process without experiencing exactly the self-sufficiency situation brought by age and their burnout level increased (Kalınkara and Kalaycı, 2017). In young adulthood period, the frequency of applying positive religious coping strategies such as “turning towards God, interpreting favorably, religious begging, religious convergence” increases. This result indicates that individuals question religion more with increasing age. According to Ryff who is known for her works on life satisfaction and well-being of the individual, the relationship between the age and life satisfaction is mostly affected by the evaluations about health and financial situations (Ryff, 1989). Ryff expresses that some of the individuals could better adapt to chronic diseases, weaknesses and dependency experienced along with old age while some others are negatively affected. Likewise, Balcı and Ayten could not find any significant correlation between age and life satisfaction in their study conducted on religious coping (Arvas, 2017; Ayten, 2012). However, age was found to be positively correlated with both life satisfaction and religion in some other researches (Özdemir and Taşçı, 2013). Responding to the difficulties by praising as a religious coping method and seeing these problems as a mean of test can be considered as factors that will affect the quality of life of the individual. In this context, individuals who have problems and are stuck in difficult situation tend to use more frequently religious coping activities both positively and negatively.

The most important factor affecting the quality of life is positive religious coping styles. Positive religious coping involves an individual's attitudes and behaviors to believe that Allah’s actions have a cause and negative life events have a meaning (Cirhinlioğlu, 2014). In positive religious coping, the individual tends to cooperate with Allah, believes that his/her suffering has a spiritual meaning and actively participates in problem solving. Accordingly, the use of positive religious coping mechanisms by individuals strengthens their coping of physical and mental problems. The fact that people evaluate any negative event patiently and as a test of Allah, see what happens to them as a part of spiritual maturation and are able to say "There is a charity in what is occurring" increases their life satisfaction and optimism levels. It is reported that believing in a superior being is always a guide to interpret the individual’s existence and the ultimate object of life and to endure difficulties (Çelimli and Tozlu, 2016). With the increased meaning and purpose of life, it provides additional energy to the person in struggling with difficulties and makes an important contribution to overcome the problems (Çelimli and Tozlu, 2016). Accordingly, the quality of life of

individuals increases as their tendency to interpret favorably any problem, deal with these problems patiently, turn to Allah in the difficult situation, and ask for help from Allah by judging him/herself increases. In this study, high spiritual level of the caregivers may be due to the fact that human beings have always needed to believe in a divine power and seek refuge from a superior being abinito (De, 2014). People's use of positive coping activities in the process of making sense of what happened to them and turning towards Allah enhances their quality of life. These results are compatible with the results of many studies on the correlation between religious coping and quality of life.

Mostly the social and environmental domain quality of life scores of the family members were found to be low. In the study conducted by Fertelli et al. on individuals who provide care to stroke patients at home, they found that the quality of life environment domain scores of caregivers were low (Fertelli and Tuncay, 2019). It was determined in the study conducted by Wong et al. (Wong et al., 2012) on caregivers that the quality of life of caregivers was low in psychological domain and high in physical domain. In their study Tel et al. found that the physical and environmental quality of life of individuals providing care to individuals with lung disease at home was low. The quality of life environmental domain contains items related to the individual's daily activities, recreation, access to information and health perception (Tel et al., 2012). In the present study, it was determined that Positive Religious Coping Styles and age and perceived income from descriptive characteristics of the caregivers affected the quality of life and descriptive characteristics of the caregivers and their Positive Religious Coping Styles explained their quality of life with 56% of variance. This result supports our acceptance ''Religious coping strategies affect caregivers' quality of life''. Even though it is stated in the literature that they use religious coping more with increasing age, it was estimated in the present study that religion was used more in adulthood and it predicted the quality of life together with the socioeconomic status. In the study conducted by Masat with oncologic patients, a positive and weak correlation was stated between the quality of life and religious coping methods (Masat, 2018). In their study conducted to investigate the correlation between the religious coping and life satisfaction in adults, Uysal et al., stated that there was a positive and significant correlation (Uysal et al., 2015). The reason for the differences between the literature and the present study may be the socioeconomic causes and cultural differences.

CONCLUSION

In the study, it was found that the caregivers with low socioeconomic status had low quality of life and young adults prefer religious methods more. It was concluded that the quality of life of the caregivers of elderly patients hospitalized in the internal medicine clinic and palliative care unit increased when they were using positive religious coping styles. In line with these results, to reduce care burden and to increase life satisfaction must be provided multidisciplinary approach (physician, nurse, psychologist, spiritual care professionals etc.) both caregivers and elderly patients. Day care homes should be opened to reduce the burden of care and the patient provide to support services to patients' relatives as well as to their relatives. Problems and solutions proposed in elderly care should be added to the education curriculum.

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Conflict of Interest

This article did not receive any financial fund. There is no conflict of interest regarding any person and / or institution.

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Research Article

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Determıning The Effect of Health Literacy On Healthy Life Style And Rational Drug Use By Path Analysis

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ABSTRACT:
Purpose: The main purpose of this study is; to determine the effect of health literacy on healthy lifestyle and rational drug use by path analysis.
Material and Methods: The universe of the research consists of patients and their relatives who receive health services from pharmacies operating in the city center of Bolu. The total number of questionnaires evaluated and used in data analysis is 400. SPSS 26 and AMOS 24 package programs were used in the analysis of the data. For reliability, item analysis based on item-total correlation was performed. Factors were determined by explanatory factor analysis (EFA), and the effect of health literacy on healthy lifestyle and rational drug use was determined with path analysis. With item analysis based on item-total correlation, it was seen that the data met the reliability requirement. The construct validity revealed by the explanatory factor analysis was also confirmed by path analysis.
Results: Ensuring validity and reliability; shows the existence of a structural relationship in the effect of health literacy on healthy lifestyle and rational drug use. It was determined that health literacy has a positive effect on rational drug use (β=1.055; $p<0,05$) and healthy lifestyle (β=0.496; $p<0,05$).
Conclusion: For the model, the effect of a healthy lifestyle on rational drug use, the effect of rational drug use on a healthy lifestyle, and also whether the indirect effect of health literacy on rational drug use through healthy lifestyle was examined, and it was determined that there was no effect.
Keywords: *Health literacy, Healthy lifestyle, Rational drug use, Path Analiysis*

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INTRODUCTION

Health literacy is defined by the US National Academies Medical Institute as “the degree to which individuals have the capacity to obtain, process and understand basic health information and services necessary to make appropriate health decisions” (Ratzan and Parker, 2000). There are two ways to conceptualize health literacy. The first of these is a risk factor and the other is something valuable. Health literacy as a risk factor fits best in clinical settings and focuses on improved communication between doctors and patients. Valuable things, on the other hand, refer to a set of skills needed in everyday life to make decisions that affect a person's health (Nutbeam, 2008).

Health literacy; It includes the skills individuals need to understand and guide health information, such as knowing how to use health services, improving health behaviors, increasing compliance with treatment, using drugs correctly, understanding the information provided, and making decisions about self-care and disease management (Hersh et al., 2015). Low health literacy is an important public health problem that affects the general health of individuals and increases disease-related problems. At the same time, low health literacy can make it

difficult for patients to work effectively in the healthcare system. At the same time, low health literacy; poor health status (Wang et al., 2013), lack of knowledge about medical conditions and related care (Song et al., 2012), lack of interaction with healthcare providers (Easton et al., 2013), difficulty understanding medical information, increased mortality, poor health status has consistently been associated with poor health outcomes, including increased hospitalizations (Berkman et al., 2011; Song et al., 2012), higher healthcare costs, and poorer use of preventive healthcare services (DeWalt et al., 2004).

Health-related quality of life refers to how individuals subjectively evaluate their own well-being and ability to perform physical, psychological, and social functions. There are many studies examining the relationship between health-related quality of life and health literacy in patients with chronic diseases (Wang et al., 2008). Insufficient health literacy causes many problems such as increased number of hospitalizations, increased use of emergency care services, less preference for preventive healthcare services, inadequate or regular use of medicines, inability to manage chronic diseases, inability to understand health-related messages, and waste of limited resources for health expenditures (Geboers et al., 2015).

Rational drug use by the World Health Organization (WHO); defined as “the process where patients receive medications appropriate to their clinical needs in doses that meet their individual needs, for a sufficient period of time and at the lowest cost for themselves and their communities” (WHO, 1985). Rational drug use plays a vital role in the success of treatment processes. Considering that drug use is also related to individuals' decision-making mechanisms, rational drug use and health literacy are known to cause a variety of problems worldwide (Desalegn, 2013). Levels should be considered together (Abacıgil et al., 2019).

Rational drug use is closely related to education and health literacy levels in addition to socio-cultural, economic and regulatory mechanisms. Health literacy can be defined as "the knowledge, motivation and competence of an individual in accessing, understanding, evaluating and applying information to prevent disease and improve health in daily life" (HLS-EU Consortium, 2012). Low levels of health literacy have been shown to have a negative impact on patients' compliance with medical treatment and the management of diseases, leading to a lack of knowledge about diseases, and thus being associated with higher rates of hospitalization, morbidity and premature death (Kickbusch et al., 2013). Improving the health literacy level of the population can reduce self-medication, increase treatment adherence, and thus increase awareness of rational drug use (Haaijer-Ruskamp, 1997; Tosun vd., 2018; Abacıgil, 2019).

In this study, it is aimed to determine the effect of health literacy on healthy lifestyle and rational drug use with path analysis. The fact that such a study has not been encountered in the health sector and health services field before adds originality to the study and reveals its importance, while increasing the health literacy level of the society in terms of preparing the ground for the formation of a healthier and more conscious society, it makes them behave healthier lifestyle behaviors and use drugs more rationally. It is foreseen that it will contribute to their performance. In addition, this study is aimed to be a pioneer in future studies to be carried out by expanding its scope.

MATERIAL and METHODS

Purpose and Type of the Study

Considering the purpose of the research and the problematic of the research, it was thought that the most appropriate method for achieving the aim and solving the problematic was the quantitative research method and the quantitative research method was preferred in the research. SPSS 26 and AMOS 24 statistical analysis programs were used for the analysis of the data set within the scope of the research.

Conceptual Model of the Research

Similar model studies were examined with the literature review during the model development phase and the conceptual/theoretical model of the research was created. Determining the effect of health literacy on healthy lifestyle and rational drug use with path analysis constitutes the subject of the

study. The relationships between the conceptual model of the research are shown in Figure 1.

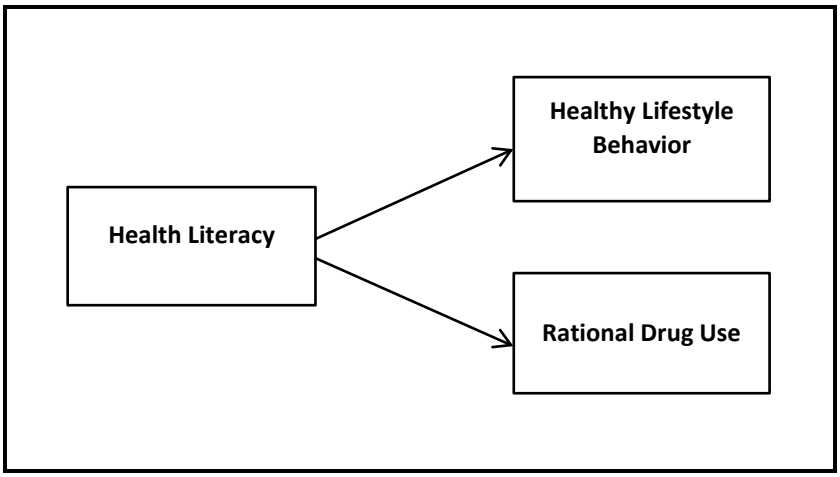


Figure 1: Conceptual Model of the Research

Research Hypothesis Development

In the literature, it has been shown that low health literacy has a negative effect on patients' compliance with medical treatment and management of diseases, leads to a lack of knowledge about diseases and is therefore associated with higher hospitalization rates, morbidity rates, and premature death (Kickbusch et al., 2013). At the same time, low health literacy; poor health status (Wang et al., 2013), lack of knowledge about medical conditions and related care (Song et al., 2012), lack of interaction with healthcare providers (Easton et al., 2013), difficulty understanding medical information, increased mortality, poor health status has consistently been associated with poor health outcomes, including increased hospitalizations (Berkman et al., 2011; Song et al., 2012), higher healthcare costs, and poorer use of preventive healthcare (DeWalt et al., 2004). The basic hypothesis developed in this direction is as follows:

"H_1: "Health literacy has a statistically significant and positive effect on healthy lifestyle and rational drug use."

Sampling and participant

The universe of the research consists of patients and their relatives who receive health services from pharmacies operating in the city center of Bolu. The sample group consists of 400 participants. The data were obtained by using face-to-face survey technique between December 1, 2019 and February 10, 2020 with the easy sampling method.

Data Collection Tools

Face to face survey technique was used as data collection method. The study was carried out as a cross-sectional study of patients and their relatives who receive health services from pharmacies operating in Bolu city center. The questionnaire form developed; It was discussed in detail with academicians and experts in the field of health management and the final version was formed. A pilot study (pre-test) was carried out on 20 people in order to ensure the structural validity of the updated questionnaire after the necessary arrangements were made in line with the criticisms made about the expressions in the questionnaire. The questionnaire form consists of four parts in total. In the first part, there are statements to determine health literacy consisting of 25 statements. In the second part, there are expressions to measure healthy lifestyle behavior consisting of 22 statements. In the third section, there are statements about rational drug use consisting of 19 propositions, while the last section includes statements about the basic characteristics of managers.

Scales Used in the Study

In order to determine the health literacy levels of the participants; The European Health Literacy Survey (HLS-EU) utilized the health literacy questionnaire

form developed by the HLS-EU Consortium within the scope of the European Health Literacy Project 2009-2012 (HLS-EU CONSORTIUM, 2012). To determine the health literacy of the participants in the research; The European Health Literacy Survey (HLS-EU), a 28-question questionnaire developed by the HLS-EU Consortium within the scope of the European Health Literacy Project 2009-2012, as it is suitable for measuring the level of health literacy at the global level due to its structural and contextual characteristics. Form was prepared by taking an example. While preparing the healthy lifestyle behavior scale; The studies of Bahar et al. (2008) and Duran et al. Finally, the scale of attitude towards rational drug use was used from scale forms developed by Çelebi (2018) and Demirtaş et al. (2018).

Statistical Analysis

SPSS 26 and AMOS 24 statistical analysis programs were used together for the analysis of the data set within the scope of the research. The data were analyzed in terms of variance, mean, frequency and percentage values, which express descriptive analysis. For reliability, item analysis based on item-total correlation was performed. Then, explanatory factor analysis and path analysis were performed.

Data Set Analysis Criteria

Criteria for Explanatory Factor Analysis

Common factor variance was taken into account to generally examine the factor load values of the items before rotation. As the factorization technique, principal component analysis, which is the most widely used and easiest to interpret in social sciences, was used. In order to exclude variables that do not measure the same structure, the lower limit for the load values in the factor in which the variables are included was accepted as 0.40. Items that were collected under more than one factor and the difference between factor loads was less than 0.10 were defined as an overlapping factor and removed from the scale. Factors with an original value above 1 are considered as important factors. As the explained variance ratio, 55% was accepted as the limit value. Rotation was performed to ensure the independence of the factors, clarity and significance in interpretation. Vertical rotation technique is used as a rotation technique.

Criteria for Path Analysis

It was checked whether the standardized loadings of the observed variables on each structure are significant and the superior convergent validity is higher than 0.5. Then, compound reliability (CR) test was performed to check validity. If the mean variance extracted for each construct was greater than the variance shared with other constructs, the case that discriminative validity was provided was checked.

Ethical Approval

The universe of the research consists of patients and their relatives who receive health services from pharmacies operating in the city center of Bolu. The sample group consists of 400 participants. The data were obtained by using face-to-face survey technique between December 1, 2019 and February 10, 2020 with the easy sampling method.

RESULTS

Reliability of Research Data

In the research, reliability measurement was made by calculating the Cronbach Alpha coefficient for each structure. The health literacy factors, which constitute the variables of the study, were subjected to reliability analysis with 25 questions, healthy lifestyle behavior factors with 22 questions, and rational drug use factors with 19 questions. Reliability coefficients for the variables are given in Table 1. Therefore, considering all dimensions, it is seen that the reliability of the study is quite high.

Demographic Findings

While 65% of the individuals participating in the research were male, 35% were female managers; 48% are middle age group (between 36-55) managers, 89% are at least high school and university graduates, 53% are middle-level managers, 48% are upper-level managers.

Findings Regarding the Explanatory Factor Analysis

Explanatory factor analysis was performed on the data constituting the participants' health literacy levels, healthy lifestyles and rational drug use. The

analyzes performed in this direction are given below.

Table 1. Reliability analysis results

Variable names	Cronbach's Alpha Coefficient
Health Literacy (HL)	0,920
Healthy Lifestyle Behaviour (HLB)	0,885
Rational Drug Use (RDU)	0,896

Table 2. Health literacy-explanatory factor analysis results

Factors	Variables	Factor Loads	Variance Explained	Self Value
Critical Health Literacy (CHR)	CHR10	,694	34,416	8,604
	CHR16	,664		
	CHR17	,637		
	CHR9	,600		
	CHR12	,538		
	CHR14	,520		
	CHR11	,484		
Functional Health Literacy (FHL)	FHL3	,728	6,716	1,679
	FHL1	,667		
	FHL2	,660		
	FHL5	,603		
	FHL4	,566		
	FHL7	,554		
	FHL6	,484		
Experiential Health Literacy (EHL)	EHL24	,726	5,168	1,292
	EHL23	,682		
	EHL25	,658		
	EHL18	,475		
	EHL22	,454		
Cognitive Health Literacy (CHL)	CHL28	,743	4,912	1,228
	CHL27	,659		
	CHL26	,528		
Interactive Health Literacy (IHL)	IHL20	,709	4,123	1,031
	IHL21	,690		
	IHL19	,545		
Evaluation Criteria	Kaiser-Meyer-Olkin Measure of Sampling Adequacy: 0,919 Approx. Chi-Square: 3774,751 Barlett's Test of Sphericity: 0,000 Extraction Method: Principal Components Rotation Method: Varimax Sum of Explained Variance: 55,335			

The result of Bartlett test is significant since p (sig) = 0.000 <0.05 for the data subjected to factor analysis to determine the sub-variables of health literacy factors. That is, there are high correlations between variables and it means that the data came from multiple normal distribution. The result is perfect, as the KMO coefficient is 0.919. For this reason, sample size is sufficient for research.

The result of the Bartlett test is significant since p (sig) = 0.000 <0.05 for the data subjected to factor analysis in order to determine the sub-variables of healthy lifestyle behavior factors. That is, there are high correlations between variables and it means that the data came from multiple normal distribution. The result is perfect as the KMO coefficient is 0.866. For this reason, sample size is sufficient for research.

The result of the Bartlett test is significant since p (sig) = 0.000 <0.05 for data subjected to factor analysis to determine the sub-variables of behavioral factors for rational drug use. That is, there are high correlations between variables and it means that the

data came from multiple normal distribution. The result is perfect as the KMO coefficient is 0.897. For this reason, sample size is sufficient for research.

Table 3. Healthy lifestyle behaviour-explanatory factor analysis results

Factors	Variables	Factor Loads	Variance Explained	Self Value
Balanced Diet (BD)	BD38	,789	29,667	6,527
	BD36	,687		
	BD35	,642		
	BD32	,625		
	BD39	,574		
	BD44	,441		
Physical Activity (PA)	PA10	,809	8,247	1,814
	PA16	,745		
	PA11	,632		
	PA9	,569		
Compatibility (C)	C52	,746	7,126	1,568
	C49	,691		
	C51	,680		
	C50	,596		
Interpersonal Relationships (IR)	IR13	,691	5,445	1,198
	IR21	,682		
	IR27	,667		
	IR15	,666		
Spiritual Development (SD)	SD23	,748	5,001	1,100
	SD24	,683		
	SD43	,537		
	SD18	,467		
Evaluation Criteria	Kaiser-Meyer-Olkin Measure of Sampling Adequacy: 0,866 Approx. Chi-Square: 2816,171 Barlett's Test of Sphericity: 0,000 Extraction Method: Principal Components Rotation Method: Varimax Sum of Explained Variance: 55,486			

Table 4. Rational Drug Use-Explanatory Factor Analysis Results

Factors	Variables	Factor Loads	Variance Explained	Self Value
Correct usage (CU)	CU2	,778	35,478	6,741
	CU1	,748		
	CU4	,703		
	CU5	,682		
	CU3	,571		
Conscious Use (CU)	CU23	,759	7,137	1,356
	CU25	,720		
	CU21	,647		
	CU26	,586		
	CU22	,573		
Effective Use (EU)	EU10	,768	6,607	1,255
	EU12	,587		
	EU13	,581		
	EU11	,541		
	EU9	,438		
	EU14	,437		
Safe Use (SU)	SU17	,768	6,077	1,155
	SU16	,749		
	SU18	,722		
Evaluation Criteria	Kaiser-Meyer-Olkin Measure of Sampling Adequacy: 0, 897 Approx. Chi-Square: 2735,135 Barlett's Test of Sphericity: 0,000 Extraction Method: Principal Components			

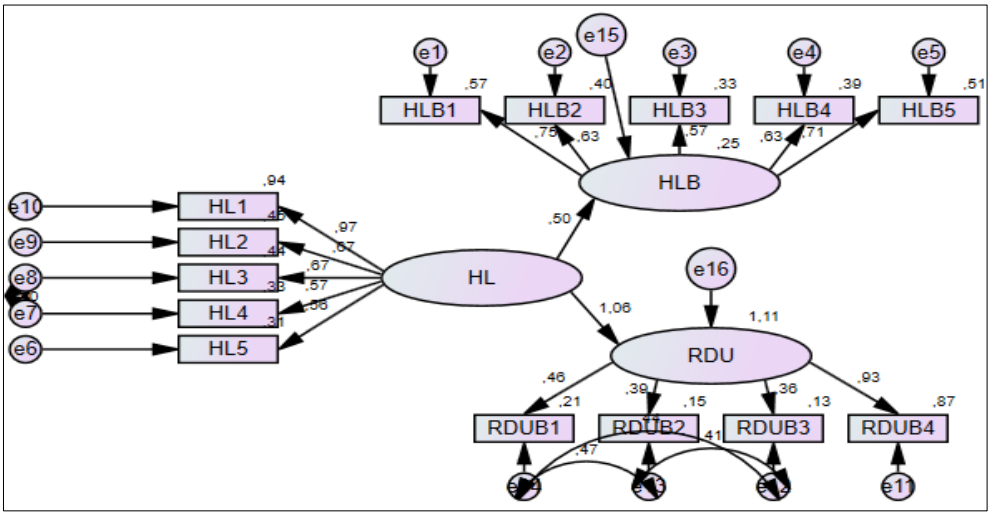
Rotation Method: Varimax
Sum of Explained Variance: 55,298

Findings Regarding Path Analysis

Path analysis is a method used to reveal the structural relationship between quantitative variables and to determine how much of the total effects of independent variables on dependent variables occur directly and how much indirectly. Path analysis with latent variables is an analysis that produces more reliable results than path analysis with observed variables. The diagram of model fit is obtained as follows.

The values of RMR, GFI, NFI, IFI, TLI, CFI given above show that the model fit is achieved. There is no limit to the values to look at. Reported values may vary according to the values that the researcher wants to draw attention to. The fit values for the created model are given below. In addition, the explained variances and reliability of the factors calculated to determine the validity and reliability of the path analysis are given in Table 5.

When the standardized values of the total effects are examined, it is seen that the total predictive power of HL to RDU is 1,055 units, and the total predictive power of HL to HLB is 0.496 units.



HL: Health Literacy; HLB: Healthy Lifestyle Behaviour; RDU: Rational Drug Use

[(X2/df: 4,263; GFI: 0.89; NFI: 0.90; CFI: 0.92; RMR: 0.044; TLI: 0.90; IFI: 92; AGFI: 0.84)]

Figure 1. Health literacy-healthy lifestyle behavior-rational drug use path diagram and goodness of compliance results

Table 5. Research model SEM results

Effects	Structural Relations	Standardized Regression Coefficients (β)	Critical Rate (C.R.)	p
Standardized Total Impact	RDU<--- HL	1,055	13,122	***
	HLB<--- HL	,496		
Standardized Direct Effect	RDU<--- HL	1,055	7,468	***
	HLB<--- HL	,496		

In Table 6 below, the values obtained after the analysis of well-accepted fit index values in the literature are shown. As a result, it was determined that health literacy significantly and positively affected rational drug use (= 1.055; p <0.05) and healthy lifestyle (= 0.496; p <0.05). For the model, the effect of a healthy lifestyle on rational drug use, the effect of rational drug use on a healthy lifestyle, and whether there is an indirect effect of health literacy on the use of smart drugs through a healthy lifestyle were also examined, and it was determined that there was no effect.

As seen in Table 6, the results obtained show that the fit indices of the proposed research model are at an acceptable level of fit. Findings obtained by explanatory factor analysis and path analysis show that the construct validity of the model is ensured.

Table 6. Structural Model Goodness of Fit Indices

General Model Compliance	Good Compliance	Acceptable Compliance	Achieved Compliance Values
x^2/sd	≤3	≤5	4.263
NFI	≥0.95	≥0.90	0.903
CFI	≥0.97	≥0.95	0.923
IFI	≥0.95	0.94-0.90	0.924
AGFI	>0.95	≥0.85	0.843
GFI	≥0.90	0.89-0.85	0.894
RMR	<0.05	<0.08	0.043

CONCLUSION

In recent years, changes have been observed in the behavior of individuals in the field of health, as in many other fields (Tamer Gencer vd., 2019). Studies in the literature have shown that people with limited health literacy have higher disease rates, worse health status, worse health outcomes, and higher health care costs than individuals with adequate literacy (Weiss et al., 2003; McCray, 2005). Over the past 20 years, researchers have identified health literacy issues, its role in understanding medical and personal care information, and its relevance to health outcomes (Speros, 2004).

This study, which was conducted in order to determine the effect of health literacy on healthy lifestyle and rational drug use, through path analysis, the universe of the research consists of patients and their relatives who receive health services from pharmacies operating in the city center of Bolu. The results obtained from the research are given below: By making path analysis; it has been observed that the effect of health literacy on healthy lifestyle and rational drug use has an acceptable index of fit. In the reliability analysis performed for all variables, it was determined that the reliability levels of the scales were high.

When the standardized values of total effects are examined, it is seen that the total predictive power of health literacy on rational drug use is 1,055 units, and the total predictive power of health literacy on healthy lifestyle is 0.496 units. In Table 6 below, the values obtained after the analysis of well-accepted fit index values in the literature are shown. As a result, it was determined that health literacy significantly and positively affected rational drug use (= 1.055; p <0.05) and healthy lifestyle behaviour (= 0.496; p <0.05). In addition, the effect of a healthy lifestyle on rational drug use, the effect of rational drug use on a healthy lifestyle, and whether there is an indirect effect of health literacy on the use of smart drugs through a healthy lifestyle were examined, and it was determined that there was no effect.

Considering that health literacy has a positive effect on rational drug use and healthy lifestyle in this study, it is recommended to increase the health literacy level of the society in general. Both health professionals and health workers and hospital management have a great role in the development of health literacy. It is suggested that health literacy should be addressed by all its stakeholders and increased through public service announcements and training provided by health professionals. In this direction, it is necessary for healthcare professionals to listen to the patient in order to communicate better with the patient, to inform the patient in all processes, and to cooperate with the patient in the preparation of written and visual messages. In addition, it is recommended that this study be conducted in different samples and with different variables.

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Research Article

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The Level of Expressed Emotion (LEE) Scale (Short Version): The Turkish Validity and Reliability Study in Patients Admitting to Dermatology Clinic

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ABSTRACT:
Purpose: The purpose of the present study was to determine the Turkish validity and reliability of the LEE Scale (short version) in patients admitted to the Dermatology Clinic, and to ensure its use in patient evaluations for dermatology and other branches.
Material and Methods: The LEE Scale (short version) had 38 items, and was developed originally in English. The scale was translated into Turkish by following the proper translation steps. The Turkish scale that was created was applied to the patients. A total of 510 people, 279 of whom were women (54.7%), and 231 men (45.3%), applying to Sivas Cumhuriyet University Hospital Dermatology Clinic were included in the study. The internal structure consistency and test-retest reliability were measured for reliability analyses. The Cronbach's Alpha Coefficient was estimated for internal consistency. The scale was applied to 50 patients twice, at baseline and two weeks later for test-retest reliability, which was also statistically evaluated with the Pearson Correlation Test. The Exploratory Factor Analysis was performed to evaluate the construct validity of the scale. The significance level was taken as $p<0.05$.
Results: The ages of the patients included in the study ranged between 18 and 72, and the mean age was 28.2±9.6. The Cronbach-Alpha Coefficient was found to be 0.915 in the internal structure consistency measurement. The correlation coefficient was calculated as r=0.868 in test-retest reliability. The total LEE scale (short version) score was a mean ± SD of 59.6 ± 14.2.
Conclusion: It was concluded in the present study that the LEE Scale (short version) is a measurement tool that can be used in a reliable and valid manner for the evaluation of emotional expressions of individuals who have dermatological diseases.
Keywords: *Expressed Emotion, Turkish version, Validation, Reliability, Dermatology*

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INTRODUCTION

Expressed Emotion (EE) is the measurement of the attitudes and behaviors of family members towards the diseased family member, and is evaluated as the measurement of the emotional quality of family life and the emotional atmosphere of the home environment. High Expressed Emotion scores involve severe criticism, hostility, or emotional over-interest in the patient (Hale et al., 2007).

The skin is an organ that reflects unrevealed conscious or unconscious emotions and mediates nonverbal communication. It is known in our present day that mental and social problems have impacts on the onset and exacerbation of many skin diseases, and mental problems occur secondarily to chronic skin diseases. The mental factor affects the course of diseases and even their treatments (Koo et al., 2000; Dalgard et al., 2018).

The relations between expressed emotions and some psychiatric and physiological diseases such as psoriasis, schizophrenia, epilepsy, depression, diabetes, obsessive-compulsive disorder, eating disorders and asthma were examined; and the relations between high emotional expression and diseases were shown in many studies. It was reported in previous studies that cultural structure,

socioeconomic level, and gender of parents are associated with EE (Ortiz, 2001; Tüzer et al., 2003).

Previous studies conducted on schizophrenia show that families with low EE levels can cope with problems better, and families with high EE levels have difficulty in coping with problems, illnesses, and patients (Butzlaff and Hooley, 1998).

The Level of Expressed Emotion (LEE) Scale is a self-assessment tool that was developed by Cole and Kazarian (1988) to understand the emotional state between a patient and a person important to the patient, and to rate some aspects of this relationship. Items are in the form of "true, often true, often false, and false". It is filled in by patients considering their relations with an important family member (key relative) in the last 3 months. It has a total of 60 items (Cole & Kazarian, 1988). The validity-reliability study and the Turkish adaptation of the scale and were conducted by Berksun (Öksüz, 2017). Gerlsma et al. (1997) developed the 38-item short version of the LEE Scale, which consists of 4 subscales; interventionism, lack of emotional support, irritability, and criticism, and its language is English (Gerlsma and Hale, 1997).

In our study, the purpose was to determine the Turkish reliability and validity of the LEE Scale (short version) in patients admitting to the Dermatology Clinic, and to ensure that it is used in patient evaluations in dermatology and other branches.

MATERIAL AND METHODS

Ethics

The Ethics Committee approval was obtained from the Ethics Committee of Sivas Cumhuriyet University (2013-05/38). The purpose and contents of the study were explained to patients, and informed consent forms were obtained from volunteers.

Subjects

The present study was conducted with patients admitted by Sivas Cumhuriyet University Hospital Dermatology Clinic; and 510 patients (279 female, 231 male) were included.

Patients who were illiterate, who had a history of psychological illness, or any condition that could affect their ability to understand the conditions of the study, and patients who were under 18 years of age were excluded from the study.

Level of Expression of Emotion (LEE) Scale (Short Version)

The 38-item short version of the LEE Scale was developed by Gerlsma and Hale in 1997. The scale consists of 38 questions, and 4 sub-dimensions, which are the interventionism dimension (7 items), the lack of emotional support dimension (19 items), the irritability dimension (7 items), and the criticism dimension (5 items). The response options are structured as "true, often true, often false, and false". The source language of the scale is English. The scale examines the attitudes of patient relatives to the patient. The English language versions of the LEE scale (short version) are presented in Appendix 1.

Translation Process

- The author who developed the scale was contacted through e-mail, and the necessary permission was obtained for the scale to be adapted into the Turkish language and to conduct the validity and reliability study of it.
- Firstly, the scale was translated into Turkish by 3 experts, two from Dermatology and one from Linguistics fields. The resulting 3 texts were combined into a common text by 2 different dermatology physicians. This text was then translated into English by a bilingual person.
- Then, the English language of the text was reviewed by the committee that consisted of linguists, clinicians, and academicians, and the language validity of the scale was approved. With this scale, whose language validity was provided, a pilot scheme was applied to 20 people, the scale was evaluated in terms of intelligibility, and the final version was created.

Statistical Analysis

The data were analyzed by the SPSS version 22.0 statistical package.

Internal consistency, test-retest reliability, item–total score correlations were used for reliability analysis. Internal consistency was tested using the Cronbach α value, whereas total–score and item–score relationships were explored by using the

Pearson correlation analysis. The scale was administered to 50 patients twice, at the beginning and two weeks later for test-retest reliability, which was statistically evaluated with the Pearson Correlation Test.

Validity analysis was carried out using the construct and convergent validity. Construct validity was tested by using the principal components factor analysis; convergent validity by Pearson correlations. The significance level of the *p* value was taken as $p<0.05$.

RESULTS

The study group consisted of 510 people, 279 women (54.7%), and 231 men (45.3%). The ages of the patients included in the study ranged between 18 and 72, and the mean age of the patients was 28.2±9.6.

When the educational status of the patients was evaluated, it was found that 398 (78.2%) were university graduates, 59 (11.5%) were high school graduates, and 53 (10.3%) were primary school graduates.

Firstly, the Kaiser-Meyer-Olkin (KMO) Coefficient was calculated to determine the adequacy of the sampling size and whether the data were suitable for Exploratory Factor Analysis, and the Bartlett's Sphericity Test was used. The KMO Coefficient was calculated as 0.928 in the application, and as a result of the Bartlett Test, it was found that the sampling size and the data were suitable for the Exploratory Factor Analysis with χ^2=6755,66, $p<0.001$ values.

In evaluating the reliability of LEE scale, an internal consistency analysis was conducted and the Cronbach's Alpha Coefficient score was 0.915.

When the corrected item-total correlation values were considered, items 4, 10, 19, 22, 27, 28, 30, and 33 were removed from the scale since their factor load value was lower than 0.45.

The first factor explained 22.478% of the total variance, the second factor 13.062%, the third factor 9.169%, and the fourth factor 7.593% of it (Table I). The cumulative amount of variance that was explained by the eigenvalues was 52.301% of the total variance, which is quite good (very close to 60%, which is considered the best lower limit) (Karagöz, 2016). For this reason, the model provided construct validity.

For reliability analysis, the test-retest was applied in 50 patients, who were selected by the Simple Random Sampling Method. The questionnaire was applied again after 2 weeks to the same group. The level (degree) of the Pearson Correlation Coefficient between the first and second applications was found to be 0.868 (86.8%). There was a very strong (very high) positive correlation between the first and second applications.

Data from the 510 patients were analyzed with factor analysis with a rotational method of varimax, and four factors were extracted: lack of emotional support (questions 1, 2, 3, 7, 8, 9, 13, 17, 21, 24, 25, 32, 36, 38); criticism (questions 5, 14, 15, 18, 29, 34, 35, 37); intrusiveness (questions 11, 16, 20, 26, 31) and irritability (questions 6, 12,23).

The total LEE scale score was a mean ± SD of 59.6 ± 14.2 points. The values for individual domains were (mean ± SD) 1.60 ± 0.55 for the lack of emotional support domain, 2.06± 0.67 for the criticism domain, 2.68±0.66 for the intrusiveness domain and 2.19± 0.80 for the irritability domain. The correlation coefficients between the total LEE scale and its subscales varied between 0.261 and 0.860. A high level correlation was detected between the total LEE scale and its subscales ($p<0.05$) (Table 2).

DISCUSSION

Expressed emotion is evaluated as a measure of the emotional quality of family life and as the emotional atmosphere of the home environment. Expression of emotion is also defined as the determinant of the family's attitude and point of view towards the patient, and it is considered as an important factor that can negatively or positively affect the course of the disease (Hoste and le Grange, 2008; Devaramane et al., 2011; Jie et al., 2018).

The skin is an organ creating a border between the internal and external environments of a person, and plays important roles in the reflection of our emotions and behaviors. It is seen that psychiatric disorders accompany approximately 40% of dermatological diseases. This rate is quite high when compared to the general population (Ermertcan et al., 2004).

Table 1. Factor analysis results of the LEE scale

Subscales	Items	Factor Value	Variance (%)	Cumulative Variance (%)
Factor 1	Item 3	0,804	**22,478**	**22,478**
	Item 13	0,780		
	Item 7	0,754		
	Item 8	0,717		
	Item 24	0,707		
	Item 32	0,698		
	Item 21	0,697		
	Item 1	0,694		
	Item 38	0,687		
	Item 9	0,678		
	Item 17	0,614		
	Item 2	0,522		
	Item 36	0,520		
	Item 25	0,480		
Factor 2	Item 34	0,720	**13,062**	**35,540**
	Item 35	0, 689		
	Item 14	0,672		
	Item 29	0,599		
	Item 15	0,564		
	Item 37	0,507		
	Item 5	0,504		
	Item 18	0,466		
Factor 3	Item 20	0,758	**9,169**	**44,708**
	Item 16	0,715		
	Item 11	0,653		
	Item 31	0,540		
	Item 26	0,501		
Factor 4	Item 23	0,720	**7,593**	**52,301**
	Item12	0,699		
	Item 6	0,533		

Table 2. Pearson correlation analysis between LEE scale domains

LEE	Lack of emotional support	Criticism	Intrusiveness	Irritability
	r	r	r	r
Lack of emotional support				
Criticism	0.596***			
Intrusiveness	0.386***	0.441***		
Irritability	0.470***	0.476***	0.261***	
Total LEE	0.842***	0.860***	0.507***	0.658***

***p<0.05

It is already known that those who are exposed to inadequate care, neglect, or abuse in their childhood carry the risk of self-harm, and the traumatic experiences, which occur in this period, cause that many psychosomatic and psycho-dermatological diseases appear (Gupta et al., 2005).

The emotional state can be the cause or trigger of the disease in many dermatological diseases. The persistence of the dermatological disease that affects the quality of life and cosmetic problems regarding the body image might also affect the emotional state causing comorbid psychiatric problems (Konstantinou, 2019).

It has been reported that emotion expressed is high in psoriasis patients. The LEE scale should be used in the evaluation of the family environment of the patients, and psychosocial support should be provided in cases with high emotional expression and patient-family interaction in psoriasis patients (Hayta et al., 2018; Chen et al., 2014).

The LEE Scale (short version), whose original form was developed by Gerlsma et al. (1997) consisting of 38 items and 4 sub-dimensions, was adapted into Turkish culture. Internal consistency and test-retest methods were used to measure the reliability of the scale. In internal structure consistency, the Cronbach's Alpha Coefficient was found to be 0.915 for the entire scale, and the correlation coefficient was r=0.868 (p<0.001) in the test-retest method. The results show that the Turkish reliability of the scale is provided. When the corrected item-total correlation values are considered, items 4, 10, 19, 22, 27, 28, 30, and 33 of the scale were removed from the scale since their factor load value was lower than 0.45 (Saraç et al., 2019).

The Exploratory Factor Analysis was used for the validity study of the scale. According to the factor matrix table, questions 1, 2, 3, 7, 8, 9, 13, 17, 21, 24, 25, 32, 36, and 38 were grouped under the first factor; questions 5, 14, 15, 18, 29, 34, 35, and 37 under the second factor; questions 11, 16, 20, 26, and 31 were grouped under the third factor; and questions 6, 12, and 23 under the fourth factor structure. By considering the meanings of the items in the factors and by making use of the transformative factor loads, in line with the original scale, the questions in the first factor were grouped under the "lack of emotional support" dimension, the questions in the second factor under the "criticism" dimension, the questions in the third factor under the "intrusiveness" dimension, and the questions in the fourth factor under the "irritability" dimension.

A high correlation was detected between the total LEE scale (short version) score and the LEE subscale scores, and it was shown that the entire scale has a significant relation with the subscales. This result supports the validity of the scale.

CONCLUSION

When all the psychometric characteristics of the LEE Scale (short version), which was adapted into Turkish culture are considered, it was concluded that the scale is a measurement tool that can be used in a reliable and valid manner for the evaluation of expressed emotion levels of patients with dermatological diseases.

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Conflict of Interest

There is no conflict of interest among the authors of the article.

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Appendix 1. The English-Language The Level of Expressed Emotion (LEE) Scale (Short Version)

Items	Untrue	Somewhat untrue	Somewhat true	True
1. Try to reassure me when I'm not feeling well	(4)	(3)	(2)	(1)
2. Are sympathetic towards me when I'm ill or upset	(4)	(3)	(2)	(1)
3. Are considerate when I'm ill	(4)	(3)	(2)	(1)
4. Can see my point of view	(4)	(3)	(2)	(1)
5. Often accuses me of making things up when I'm not feeling well	(4)	(3)	(2)	(1)
6. Are understanding if I make a mistake	(4)	(3)	(2)	(1)
7. Make me feel relaxed when they are around	(4)	(3)	(2)	(1)
8. Understand my limitations	(4)	(3)	(2)	(1)
9. Try to make me feel better when I'm ill	(4)	(3)	(2)	(1)
10. Hear me out	(4)	(3)	(2)	(1)
11. Are tolerant with me, even when I'm not meeting their expectations	(4)	(3)	(2)	(1)
12. Make me feel valuable as a person	(4)	(3)	(2)	(1)
13. Accuse me of exaggerating when I say I'm unwell	(4)	(3)	(2)	(1)
14. Calm me down when I'm upset	(4)	(3)	(2)	(1)
15. Will not help me when I'm upset	(4)	(3)	(2)	(1)
16. Are willing to gain more information to understand my condition, when I'm not feeling well	(4)	(3)	(2)	(1)
17. Will take it easy with me, even if things aren't going right	(4)	(3)	(2)	(1)
18. Don't know how to handle my feelings when I'm unwell	(4)	(3)	(2)	(1)
19. Expect the same level of effort from me, even if I don't feel well	(4)	(3)	(2)	(1)
20. Fly off the handle when I don't do something well	(4)	(3)	(2)	(1)
21. Get irritated when things don't go right	(4)	(3)	(2)	(1)
22. Make matters worse when things aren't going well	(4)	(3)	(2)	(1)
23. Get upset when I don't check in with them	(4)	(3)	(2)	(1)
24. Can cope well with stress	(4)	(3)	(2)	(1)
25. Can't think straight when things go wrong	(4)	(3)	(2)	(1)
26. Are able to be in control in stressful situations	(4)	(3)	(2)	(1)
27. Are always nosing into my business	(4)	(3)	(2)	(1)
28. Have to know everything about me	(4)	(3)	(2)	(1)
29. Are always interfering	(4)	(3)	(2)	(1)
30. Butt into my private matters	(4)	(3)	(2)	(1)
31. Often check up on me to see what I'm doing	(4)	(3)	(2)	(1)
32. Insist on knowing where I'm going	(4)	(3)	(2)	(1)
33. Don't pry into my life	(4)	(3)	(2)	(1)
34. Are critical of me	(4)	(3)	(2)	(1)
35. Get annoyed when I want something from them	(4)	(3)	(2)	(1)
36. Show me that they love me	(4)	(3)	(2)	(1)
37. Try to change me	(4)	(3)	(2)	(1)
38. Usually agree with me	(4)	(3)	(2)	(1)