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CONTENTS

Original Article

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An evaluation of the antimicrobial activity of some commonly used wood species: the antimicrobial effect of wood

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ABSTRACT

Aims: Antibiotic resistance mechanisms in pathogenic bacteria constitute an important obstacle in the fight against infection. Controlling the spread of resistant pathogens by utilizing antimicrobial activity on their surfaces may help us in this fight. There are many plant and wood species that have been previously tested for their antibacterial and antiviral properties. In this study, walnut (*Juglans regia*), white mulberry (*Morus alba*), white oak (*Quercus alba*), yellow pine (*Pinus sylvestris*), and beech (*Fagus sylvetica*), which are among the wood species used in the production of products that are in constant contact with humans in daily life, such as furniture, doors, and beads, were examined in terms of an antistaphylococcal effect.

Methods: Five groups of tree species and glass samples selected as a positive control were cut into 1 cm^3, contaminated with *Staphylococcus aureus* solution with a concentration of 1×10^6 CFU/ml, and monitored for five days. Each day, five randomly selected samples from each group were sonicated with phosphate buffered saline. Samples taken from the sonicated solution were cultured on tryptic soy agar (Becton Dickenson, Franklin Lakes, NJ, USA), and the number of bacteria per sample was calculated. One sample selected from the uncontaminated samples was incubated with 0.5 McFarland standard bacterial solution on Mueller-Hinton agar (Oxoid, Basingstoke, Hampshire, England), and the diameter of inhibition was evaluated. The study was repeated twice. The significance level was set at 0.05.

Results: The agar diffusion method showed inhibition zone only in *Q. alba* and *M. alba*. In samples contaminated with bacteria, the highest antistaphylococcal effect was found in *Q. alba*. This was followed by *M. alba*, *P. sylvestris*, *F. sylvetica*. There was no significant difference between *J. regia* and the positive control.

Conclusion: In this study in which we wanted to emphasize the importance of the antimicrobial activity of surfaces for pathogens known to live on the surface environment, all trees except *J. regia* showed antistaphylococcal effect. It is thought that the procyanidins-phenethyl, benzyl, and benzyl-in the bark of the trees are effective. In previous studies, *Q. alba* in particular is recommended for anti-infective use due to its high inhibition effect. Antibacterial activity was also found in *F. sylvetica*, which is known to have antiviral activity. Antibacterial activity was not demonstrated for *J. regia*. In order to prevent the spread of infection in collective living areas, it is recommended that trees be selected that contain antimicrobial raw materials such as *M. alba*, *Q. alba*, *P. sylvestris*, and *F. sylvetica* and to evaluate the use of extracts from these trees as natural and edible products to combat bacteria.

Keywords: Wood, antibacterial activity, antistaphylococcal efficacy

INTRODUCTION

Antibiotic resistance mechanisms of pathogenic bacteria, which are a serious risk to human health, pose a threat to treatment. Due to the genetic diversity present in bacteria, as antibiotic use increases, antibiotic resistance also increases.[1] Therefore, antibiotic use should not be accepted as the only method in the fight against infection.

Even though most of the drugs used today are synthetic, natural products, which are the primary source of traditional medicine, still constitute the main material of 25% of modern drugs.[2,3] Plants and trees can play an effective role in the fight against bacteria with the secondary metabolites they produce.[1] The aim of this study was to evaluate the antimicrobial efficacy of wood products commonly used by people in homes and hospitals, according to their species.

Environmental contamination plays a role in the spread of bacteria, especially in locations with poor hand hygiene practices.[4] Therefore, increasing hand hygiene practice and disinfection of items in contact with individuals are important steps in preventing the development of infection.[5]

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The antimicrobial activity of the materials preferred in common use areas may help in the fight against infection.

It is known that English oak bark stops bacterial activity, and onion and garlic have antimicrobial agents including ajoene and allicin.[6-8] Most of the compounds found in tree bark are thought to be involved in protection against pathogenic microorganisms in natural habitats.[9] In this study, walnut (*Juglans regia*), white mulberry (*Morus alba*), white oak (*Quercus alba*), yellow pine (*Pinus sylvestris*), and beech (*Fagus sylvetica*) were selected for examination. Since these plants are used in daily life as furniture, doors, upholstery, and rosaries, it was aimed to answer the question "Could they be potential agents in the fight against infection?"

It is known that the incidence of *Staphylococcus aureus*, which originates from skin flora and can cause infection in every tissue in the body, has increased rapidly in Western European countries in recent years.[10] Therefore, antibacterial activity against methicillin-susceptible *S. aureus* (MSSA) strains was evaluated in this study.

METHODS

Ethics committee approval was not obtained because it was an in vitro study with atcc strain. All procedures were carried out in accordance with the ethical rules and the principles.

The trees were divided into five different groups, each group containing 32 surfaces: Group 1, *Fagus sylvetica*; Group 2, *Morus alba*; Group 3, *Pinus sylvestris*; Group 4, *Juglans regia*; and Group 5, *Quercus alba*. Glass was used as control group (sixth group). Samples of 1 cm^3 were prepared, and a clean surface was obtained by wiping the samples with a sterile moistened sponge. Six different samples randomly selected from the wiped samples were inoculated into tryptic soy agar (Becton Dickenson, Franklin Lakes, NJ, USA) and checked for growth. No growth was detected. MSSA strain (ATCC 25923, used as a standard laboratory testing control strain, susceptible to a variety of antibiotics, including methicillin) was cultured, and a suspension was prepared at a 0.5 McFarland turbidity standard in sterile saline to obtain 10^8 CFU/ml bacteria.[11] For the initial evaluation, 10 microliters of bacterial stock was inoculated on Mueller-Hinton agar (Oxoid, Basingstoke, Hampshire, England) with sterile cotton swabs. One sample from each group was placed on the inoculated agar plate with sterile tweezers. The plate was incubated at 35±2°C for 24 hours. The diameters of the inhibition zones were measured with a ruler and photographed. Ceftriaxone (30 mcg, Bioanalyse, Gdansk, Poland) was used as control.

For the second evaluation, the final concentration was set to 1×10^6 CFU/ml by photometric measurement of the turbidity resulting from serial dilution of the inoculum prepared to a 0.5 McFarland standard. A total of 180 samples (30 samples per study group) were contaminated with 10 microliters of stock solution. Samples were stored in dark, dust-protected cabinets at 22±2°C and 55±5% relative humidity. Every day for five days, five randomly selected samples from each group were placed in 1 ml of phosphate buffered saline (PBS) solution (prepared with NaCl, KCL, Na_2HPO_4 and KH_2HPO_4), sonicated, and vortexed. One hundred microliters of the vortexed solution was cultured on tryptic soy agar (Becton Dickenson, Franklin Lakes, NJ, USA) at 35±2°C for 24 hours for colony counting. The number of bacteria per sample was calculated by multiplying the number of CFUs counted by the dilution factors. Glass samples served as positive controls. The study was repeated two times.

Statistical Analysis

The statistical package for the Social Sciences version 24.0 (IBM SPSS Inc, Chicago) was used for statistical analysis. "Minimum," "maximum." and "mean" were used for descriptive statistics. The differences between groups were analyzed by the Mann Whitney U test, and within-group differences were analyzed by the Wilcoxon signed rank test. The results were evaluated at a 95% confidence interval, and the significance level (p) was set as 0.05. Ethics committee approval was not obtained because it was an in vitro study with atcc strain.

RESULTS

Initially, in the samples tested by the agar diffusion method, an inhibition zone of 12 to 8 mm was detected around *Q. alba* and *M. alba* only ($p<0.0001$). It is shown in **Figure 1** and **Figure 2**.

Figure 1. Inhibition zone of *Q. alba*

Figure 2. Inhibition zone of *M. alba*

The growth results of 180 surfaces contaminated with bacteria according to groups and days and p values compared to the control group are given in Table 1. The highest growth was detected in the control group on all days. There was no difference between the amount of growth detected in the *J. regia* samples and the control group on any day (p>0.05). *Q. alba* was the only tree in which no growth was detected from the first day. Antimicrobial properties were detected in *Q. alba*, *M. alba*, *P. sylvestris*, and *F. sylvetica*, respectively. The antimicrobial activity of *F. sylvetica* was significantly lower than the others (p<0.001).

DISCUSSION

It is known that pathogens can survive and spread in surface environments.[9] In this study, we evaluated the potential antimicrobial properties of *P. sylvestris*, *F. sylvetica*, *J. regia*, *Q. alba*, and *M. alba*, which are particularly used in the wood industry. The antibacterial properties of various wood and bark extracts have been previously described.[1,8,12-14]

To evaluate antimicrobial activity, MSSA bacteria, which can cause widespread systemic infection particularly from skin colonization, were selected. In addition to *J. regia*, MSSA was also susceptible to *P. sylvestris* and *F. sylvetica*, especially *M. alba* and *Q. alba*. Other studies involving wood and bark have also shown that Gram-positive bacteria are susceptible, and their growth is inhibited.[15] The reason for this may be that procyanidins in wood and bark form complexes with DNA, or phenol compounds inhibit protein kinases including DNA gyrase.[16,17]

It has been previously shown that *Q. alba* exhibits antibacterial activity against Staphylococcus epidermidis.[18] In another study, the use of *Q. alba* in wound healing of staphylococcal infections in case of resource scarcity was recommended.[1] In our study, the results of previous studies for *Q. alba* were supported.

Table 1. Reproduction amounts detected in groups by days

	Fagus sylvetica (CFU/ml)	*Morus alba* (CFU/ml)	*Pinus sylvestris* (CFU/ml)	*Juglans regia* (CFU/ml)	*Quercus alba* (CFU/ml)	Control (CFU/ml)
First Day						
Min	1000	0	400	2300	0	2500
Max	2000	30	800	4000	0	4000
Mean	1460	10	580	2770	0	3040
p	<0.001	<0.001	<0.001	0.143	<0.001	
Second Day						
Min	200	0	200	600	0	600
Max	900	0	500	1100	0	1000
Mean	460	0	330	830	0	730
p	<0.001	<0.001	<0.001	0.123	<0.001	
Third Day						
Min	100	0	30	300	0	300
Max	250	0	80	700	0	700
Mean	155	0	51	440	0	410
p	<0.001	<0.001	<0.001	0.436	<0.001	
Fourth Day						
Min	60	0	10	300	0	200
Max	120	0	30	500	0	600
Mean	89	0	19	340	0	320
p	<0.001	<0.001	<0.001	0.393	<0.001	
Fifth Day						
Min	60	0	10	100	0	100
Max	100	0	20	200	0	300
Mean	80	0	13	130	0	170
p	<0.001	<0.001	<0.001	0.353	<0.001	

Previous studies with the *Pinaceae* family have also shown that it has gram-positive activity compared to tetracycline.[19] In our study, the antistaphylococcal activity of *P. sylvestris* was confirmed.

It is known that the phenethyl, benzyl, and benzoyl groups contained in *M. alba* show antimicrobial activity by crossing bacterial membranes.[20] In our study, *M. alba* supported this result by showing high antimicrobial activity.

The antiviral activity of 40-Me-glucuronoxylan sulfate contained in *F. sylvetica* against HSV-1 and HSV-2 has been shown previously.[21] In our study, antibacterial activity was found to be lower than other wood species but significantly different from the control group.

It has been shown that extracts made from the leaves and stem of *J. regia* have antibacterial activity for Gram positive bacteria, especially staphylococcal antimicrobial activity and antifungal activity.[22] However, the fact that there was no difference between *J. regia* and the positive control group in our study suggests that it has no superficial activity and gains activity as a result of chemical processes.

Study Limitations

However, the limitation of this study is that we do not have information about the age and chemical content of the wood. The effect of oiling and varnishing used to prevent bedbugs on some types of furniture used in daily life could not be evaluated. Since the effect on other Gram-positive pathogens could not be evaluated, the study only measured antistaphylococcal activity. This study should be considered only as a preliminary analysis of antimicrobial activity, since microdilution, which is accepted as a reference method, was not used. The actual susceptibilities can be determined after microdilution using the sap of the trees.

CONCLUSION

Our findings showed that *M. alba* and *Q. alba* have a strong antimicrobial effect on the growth of *S. aureus*, an important pathogen, while *F. sylvetica* and *P. sylvestris* have a relatively weaker antimicrobial effect. In order to prevent the spread of infection in public living areas, it is recommended that furniture and furnishings be used whose raw materials have antimicrobial properties. The use of wood bark, which is separated as waste and by-product in industrial processes, for antimicrobial activity also increases the use of natural and renewable products.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not obtained because it was an in vitro study with atcc strain.

Informed Consent: Informed consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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The association between fibrocystic breast and thyroid autoimmunity

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ABSTRACT

Aims: The relationship between thyroid disorders and breast diseases including breast cancer and benign breast disease, has been a topic of interest and controversy. Our study aimed to investigate the potential association between autoimmune thyroid disease (ATD) and fibrocystic breast disease (FBD)

Methods: This retrospective study investigated the relationship between ATD an FBD. A total of 242 female patients aged 18 years or older were recruited for the study. Data were collected from medical records and patient interviews. The related parameters were recorded for each participant.

Results: This study included two hundred forty-two age-matched (29.78±4.55) and body mass index (BMI)-matched (24±2.38) women. A Mann-Whitney test did not find a statistically significant association between the case and control in terms of free thyroxine (FT4) (p value >0.05). There was a statistically significant difference between groups in terms of thyroid-stimulating hormone (TSH) (p value <0.001), antithyroid peroxidase (anti-TPO) (p value <0.001), and anti-thyroglobulin (anti-TG) (p value<0.001). A chi-square test did not find a statistically significant association between thyroid autoantibody and fibrocystic breast test results (p value > 0.05).

Conclusion: While our study did not find a significant association between these two conditions, other studies have reported varying results. Hormonal alterations, autoimmune factors, and genetic predispositions are among the potential mechanisms that could explain the associations observed in some studies.

Keywords: Autoimmune thyroid disease, thyroid disorders, fibrocystic breast, thyroid autoimmunity, risk factors

INTRODUCTION

Fibrocystic breast disease (FBD) affects up to 50% of women at some point during their lives.[1] It is characterized by the presence of lumps, cysts, and fibrous tissue in the breast.[2] Although there is no association between FBD and a higher breast cancer risk, it can cause discomfort, pain, and anxiety in affected women.[3] The cause of FBD is not yet known, but hormonal factors, genetic predisposition, and environmental exposures are believed to play a role in its development.[4]

Autoimmune thyroid diseases (ATDs), such as Hashimoto's thyroiditis and Graves' disease, are among the most prevalent autoimmune disorders, affecting up to 10% of the population.[5] The thyroid gland plays a critical role in regulating metabolism and other physiological processes, and its dysfunction can lead to a wide range of symptoms and complications. Recent studies have suggested a possible link between FBD and thyroid hormones.[6]

One of the possible mechanisms linking FBD and thyroid autoimmunity is estrogen's role in these conditions. Estrogen is a hormone involved in breast development and function, as well as in thyroid hormone synthesis and metabolism.[7] Estrogen dominance, a condition characterized by an imbalance between estrogen and progesterone levels, has been implicated in the development of FBD.[8] Moreover, estrogen has been shown to modulate the immune system, and its excess may contribute to the development of autoimmune diseases, including ATDs.[9] Therefore, it is possible that the effects of estrogen on breast tissue and the thyroid gland may be interrelated and that disturbances in estrogen balance may contribute to the co-occurrence of FBD and thyroid autoimmunity.

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Another possible association between FBD and thyroid autoimmunity is inflammation. Inflammation is a complex biological response to harmful stimuli, and it plays a role in FBD and ATDs pathogenesis.[10] Chronic inflammation of the breast tissue can lead to fibrosis and the formation of cysts, while inflammation of the thyroid gland can result in autoimmune damage and dysfunction.[11] It has been suggested that inflammation may be a common pathway linking various breast and thyroid disorders and that reducing inflammation may benefit both conditions.[12] Therefore, investigating the role of inflammation in FBD and thyroid autoimmunity might be useful for identifying novel strategies for prevention and treatment.

In this study, we investigated whether FBD and ATD tend to occur together. By examining a range of clinical and demographic parameters, we aimed to shed light on the pathophysiology of these conditions and their interplay. By contributing to a more detailed understanding of the complex association between breast health and thyroid function, our study may help to improve the quality of life and health outcomes of women with these conditions.

METHODS

The study was carried out with the permission of BezmiAlem Vakıf University Hospital Ethics Committee (Date: 03.04.2023 Decision No: 2023/49). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study was conducted between February 2019 and February 2023 at Bezmialem University Hospital Gynecology and Obstetrics Department. A total of 242 female patients aged 18 years or older were included in the study. The inclusion criteria were: (1) the presence of FBD as confirmed by breast sonography; and (2) availability of thyroid function test results, free thyroxine (FT4), including thyroid-stimulating hormone (TSH), anti-thyroglobulin (anti-TG), and antithyroid peroxidase (anti-TPO) antibodies. Patients with a history of thyroid, breast cancer, or other severe medical conditions were excluded from the study.

The researchers collected data from the medical records of the subjects. The following parameters were recorded for each participant: age, body mass index (BMI), TSH, FT4, anti-TPO antibodies, and anti-TG antibodies. Breast sonography was performed to confirm the presence of FBD, and the severity of FBD was graded via the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) criteria.

Statistical Analysis

The researchers described the study subjects' demographic and clinical characteristics with a series of descriptive statistics. The means ± standard deviations (SD) were presented for all continuous variables, and categorical variables were reported as frequencies and percentages. The association between laboratory values and ATD was analyzed using the Mann-Whitney U test. A Chi-square test was used to examine the association between thyroid autoantibody and fibrocystic breast. All statistical analyses were performed using SPSS 28.0, and a value of less than 0.05 was considered statistically significant.

RESULTS

This study included two hundred forty-two age-matched (29.78±4.55) and BMI-matched (24±2.38) women. The majority of study participants weren't smoker. Table 1 shown descriptive statistics of study parameters.

Table 1. Descriptive statistics of study parameters in women (n=242).

Study parameters	median (range) mean ± SD
Maternal characteristics	
Age	29(20-39)29.78±4.55
BMI	24(18.9-29.6)24±2.38
Laboratory values	
TSH	2(1-2.5)1.8±0.34
FT4	1.2(0.9-1.8)1.18±0.14
ANTI-TPO	10(1.1-144)29.85±28.84
ANTI-TG	2.1(1-126.1)18.99±23.17

SD, standard deviation; BMI, body mass index; TSH, thyroid-stimulating hormone; FT4, Free thyroxine; ANTI-TPO, Antithyroid peroxidase; ANTI-TG anti-thyroglobulin

Table 2 compared case and control groups on the study parameters.

Table 2. Comparison of case and control groups

Study parameters	Thyroid autoantibody positive Case(n=112) M±SD	Thyroid autoantibody negative Control(n=130) M±SD	p value
Laboratory values			
TSH	1.79±0.29	1.69±0.37	<0.001
FT4	1.29±0.12	1.28±0.18	0.198
Anti-TPO	49.79±16.85	4.99±1.89	<0.001
Anti-TG	38.15±18.42	1.4±0.39	<0.001

M, Mean; N, number of subjects; TSH, thyroid-stimulating hormone; FT4, Free thyroxine; Anti-TPO, Antithyroid peroxidase; Anti-TG anti-thyroglobulin.

As stated in Table 2, a Mann-Whitney test showed no significant difference between the case and control regarding FT4 (p value>0.05). The groups showed significantly different TSH values (p value<0.001). The case group was statistically higher than the control (M=1.79; SD=0.29 vs. M=1.69; SD=37). The level of Anti-TPO differed between the groups significantly

(p value<0.001). Also, the groups showed significantly different Anti-TG values (p value<0.001).

Table 3 shown the relationship between thyroid autoantibody and fibrocystic breast.

Table 3. The relationship between thyroid autoantibody and fibrocystic breast

	Positive fibrocystic breast n(%)	Negative fibrocystic breast n(%)	p value
Thyroid autoantibody			0.962
positive	77 (53.8)	53 (53.5)	
negative	66 (46.2)	46 (46.5)	

*A Chi-square test.

As stated in Table 3, a chi-square test showed no significant relationship between thyroid autoantibody and fibrocystic breast (p value > 0.05).

DISCUSSION

Some studies found association between thyroid and breast diseases, but the reasons are not yet well understood.[13] There are controversial results about the relationship between thyroid diseases and breast cancer. Some studies have reported a correlation between breast cancer and thyroid diseases, while others have concluded that there is no such relationship between the two.[14] Some studies suggest that females who suffer from hypothyroidism are more prone to develop breast cancer, but the relationship between the two conditions remains unclear.[15] Our study adds to the existing literature by investigating the association between fibrocystic breast and thyroid autoimmunity, but further research is required better to understand the association between thyroid and breast pathologies.

While several studies have reported an increased thyroid disorders prevalence in patients with breast cancer,[14,16] our study did not find a significant association between fibrocystic breast changes and thyroid autoimmunity. However, other research has suggested that thyroid dysfunction might be related to benign breast disease.[16] A study shows that 14.9% of female patients with benign breast disease were diagnosed with hypothyroidism. In addition to breast disease, the thyroid profile can be helpful in diagnosing these female patients.[14] Another study found a significant increase in breast cancer risk for patients who were positive for thyroid autoimmunity, but it was not the case for other types of thyroid diseases, such as thyroid cancer.[17]

Several mechanisms may underlie the association between thyroid and breast disorders, which are still not fully understood, but there are several factors that have been suggested as contributing to it, including genetic predisposition, environmental factors, hormonal signaling, and immune system dysfunction.[13,15] Hormonal factors may be associated with breast and thyroid diseases, as both organs are hormone-responsive and share similar hormonal pathways. For example, estrogen and progesterone receptors are present in both breast and thyroid tissues, and thyroid hormones modulate the estrogen receptors' expression in breast cancer cells.[18] Additionally, some studies have suggested that hypothyroidism might be related to breast cancer in postmenopausal women.[15] Autoimmunity and functional immune system alterations have also been proposed as predisposing factors for the association between thyroid and breast disorders.[13]

Several studies have worked on the association between thyroid and breast disorders, with varying results. One retrospective observational study found that people with Anti-TPO were significantly more likely to have breast cancer.[19] Another study reported the presence of thyroid diseases, both autoimmune and not autoimmune, in patients with breast cancer.[20] A prospective observational study found that thyroid dysfunction was associated with benign breast disease.[21] A literature review concluded that survivors of breast cancer may be at a higher risk of thyroid pathologies, including thyroid malignancy.[22] A meta-analysis found that the levels of Anti-TG, Anti-TPO, and FT3 were found to be higher in breast cancer patients.[23] These studies suggest a potential relationship between breast and thyroid diseases, although the specific mechanisms and factors involved are not yet fully understood.

A study on Korean women showed that breastfeeding had been found to be associated with a lower risk of cervical, thyroid, and breast cancer.24 Furthermore, different thyroid diseases have been found in a number of breast cancer cases, and hypothyroidism has been suggested to be associated with breast cancer in women of postmenopausal age. These results suggest a potential association between thyroid function and breast cancer risk, although further research is needed to understand better the mechanisms underlying this association. The relationship between breast feeding and cancer risk may vary across populations and be influenced by several factors such as age, parity, and hormonal status. Therefore, it is necessary to determine whether these findings can be generalized to other populations and to identify other modifiable factors that may reduce cancer risks.

Despite the potential relationship between thyroid and breast disorders, in line with our findings, some studies did not find a significant association between fibrocystic breast disease and thyroid autoimmunity. For example,

a study on patients with benign breast disease found that only 14.9% had hypothyroidism, and there was no established relation between thyroid hormone status and benign breast disorders.[25] A study has shown that the levels of anti-TPO antibodies are elevated in subjects with breast cancer, but there is no difference in the rate of autoimmune thyroiditis between healthy individuals and breast cancer patients.[26,27] These results suggest that the association between breast disease and thyroid disorders may be complex and multifactorial, and more research is needed to understand the underlying mechanisms better. Other factors like environmental exposures, genetic predisposition, and lifestyle may also modulate the risk of breast disease and thyroid disorders. Therefore, it is important to continue investigating the potential links between breast disease and thyroid disorders to identify modifiable factors that can reduce cancer risks and improve overall health outcomes in women.

Our study from patient data did not show a significant association between FBD and thyroid autoimmunity. Although some studies have suggested a relationship between thyroid autoimmunity and breast cancer, the correlation between FBD and thyroid autoimmunity remains inconclusive. Our study has some limitations, including the use of patient data, which may not represent the general population. Also, the design of the study was cross-sectional, which limits our ability to establish causality or determine the temporal relationship between the two conditions. Furthermore, the study did not account for potential confounding factors, such as age, hormonal status, and environmental exposures, which may influence the relationship between FBD and thyroid autoimmunity.

Our study adds to the existing literature on the topic and highlights the need for further research to understand the potential link between these conditions better. Future studies should use more rigorous study designs, larger sample sizes, and more comprehensive assessments of thyroid function and breast health to elucidate better the relationship between FBD and thyroid autoimmunity.

CONCLUSION

The relationship between FBD and ATD remains a topic of ongoing debate and investigation. While our cross-sectional study did not find a significant association between these two conditions, other studies have reported varying results, with some suggesting a link between thyroid and breast disorders.14-18 Hormonal alterations, autoimmune factors, and genetic predispositions are among the potential mechanisms that could explain the associations observed in some studies. Given the complexity of the relationship between breast and thyroid diseases, further research is needed to understand better the underlying mechanisms and potential links between these conditions. This knowledge could help inform clinical management and treatment strategies for patients with breast and thyroid disorders. In the meantime, it may be beneficial for physicians to consider screening for thyroid disease in patients with breast disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of BezmiAlem University Hospital Ethics Committee (Date: 03.04.2023 Decision No: 2023/49).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Treatment outcomes of patients with prostate cancer who underwent postoperative radiotherapy

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ABSTRACT

Aims: Prostate cancer is one of the most common cancers in men. Surgery, radiotherapy or active surveillance are the treatment options.Treatment is decided according to risk group of the patient.Postoperative radiotherapy is delivered in selected patients to increase the local control rates.The aim of this study is to report the treatment results of patients who received postoperative radiotherapy for localized prostate cancer.

Methods: This retrosepctive study included 78 prostate cancer patients who received postoperative radiotherapy between 2011 and 2023.All patients except who had pathologically positive lymph nodes were included into the study. Overall survival, progression free survival, and associated pathological parameters were evaluated by using IBM SPSS programme version 20.

Results: The mean follow-up time was 66.7 (IQR 25-75:41,6-89,6) months. Five and 10-year overall survival rates were 93%, and 67.3% respectively; (median (95% CI); NR (not reach): while 5 and 10-year progression-free survival rates were 90.3%, and 50.4, respectively; (median (95% CI); 135.3±(105.9-165.7). Postoperative prostate specific antigen (PSA) and pre-RT PSA values, and the effects of these parameters on progression-free survival was analyzed, median progression-free survival was higher in patients with postoperative PSA values ≤ 0.185 (135.6±24.4 vs 113.3±6.4, p:0.001). Five and 10 year overall survival and progression-free survival rates of patients with a high gleason score who underwent postoperative radiotherapy was observed lower than the others (86.9% and 46.3%, p=0.006;86.9% and 33.8%, p=0.009 respectively).

Conclusion: Postoperative radiotherapy is generated best results in progression free survival and overall survival in patients with low pre-rt psa and high gleason score prostate cancer cases

Keywords: Prostate cancer, radiotherapy, postoperative radiotherapy

INTRODUCTION

Prostate cancer is the second most common cancer in men after lung cancer.[1] The treatment approach in prostate cancer is performed as monotherapy or in combination therapy according to risk groups, and surgery, radiotherapy (RT), and active surveillance are among the treatment options in patients with localized prostate cancer.[2] Approximately 35% of patients with localized prostate cancer suffer from biochemical recurrence (BCR) after surgical treatment.[3] Therefore, additional treatments to improve biochemical and local regional control are needed.It is known that especially the group with surgical margin positivity benefits from adjuvant RT, but it has been observed that not every case with margin positivity recurs. Viers et al.[4] found decreased progression-free survival and cancer-specific survival rates in patients with tumors with a Gleason grade of ≥4 at the surgical margin.Another study evaluating the effect of Gleason grade and tumor length at the surgical margin on BCR has shown that the presence of a tumor longer than 3 mm at the surgical margin is more important than the Gleason scores in terms of BCR.[5] The clinical course of BCR is highly variable and does not always cause cancer-specific death

In a systematic review; it was observed that 30% of the patients who developed biochemical recurrence showed clinical recurrence and only 16.4% of them died from the disease, and low and high risk groups for biochemical recurrence were determined after publication of this systematic review. The group with PSA (prostate specific antigen) doubling time >1 year and ISUP (International Society of Urological Pathology) grade

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<4 was consideredat low risk, and the group with PSA doubling time <1 year and ISUP grade 4-5 as high risk for biochemical recurrence.[6] In addition, 3 randomized studies have shown that the addition of adjuvant RT to the treatment in stage T3a or T3b cases with post-surgical margin positivity, contributes favorably to biochemical recurrence-free survival.[7-9] Although there are randomized controlled studies showing the contribution of adjuvant RT, not every patient evaluated have the same disease state and application of salvage radiotherapy is allowed for these patients. However, it is not clear which patients should receive salvage treatments. In recent years, 3 important randomized controlled studies have been published on the application of postoperative adjuvant or salvage RT. When these studies and the prospectively planned ARTISTIC study were evaluated together; BCR-free survival was reportedly better in the early salvage RT group than in the adjuvant RT group, but without any statistically significant difference and approximately 50% of the patients who were scheduled for salvage RT continued to be followed up without treatment.[10-13] Studies have shown that follow-up with frequent PSA monitoring and early salvage RT in well-selected patients can provide survival results comparable with adjuvant RT by protecting patients from possible RT-related toxicity.[14,15]

Several studies evaluating predictive factors for postoperative RT have reported that salvage RT showed better biochemical recurrence-free survival at lower PSA values.[8,16] In another study, other factors predicting biochemical recurrence-free survival included pathological tumor stage, Gleason score and surgical margin positivity.[17]

The aim of this study is to evaluate patients who underwent surgery for prostate cancer and received postoperative radiotherapy in our clinic in terms of treatment outcomes and factors affecting these outcomes.

METHODS

The study was carried out with the permission of the University of Health and Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies Ethics Committee (Date: 22.09.2022, Decision No: 2022-09/169). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The clinical data of patients who underwent postoperative adjuvant or salvage RT in our clinic between January 2011 and January 2023 were evaluated retrospectively. All patients who received postoperative radiotherapy for prostate cancer excluding the patients with pathological pelvic lymph node involvement in operative pathology specimen were included in the study. The planning CT scan was performed with 3-mm slices in the supine position with empty rectum and full bladder.Prostate fossa and entire seminal vesicles bed were included in the CTV. The planning treatment volume (PTV) was generated by adding 6-8 mm isotropic expansion to the CTV, excepting 4-6 mm posteriorly. According to the International Commission of Radiation Units and Measurements recommendations, the dose was prescribed at the isocentre with a + 7%and - 5% heterogenity.18For treatment planning, the dose-volume constraints for the bladder were V65 Gy<50%;for the small bowel V45≤195 cc; for the rectum: V50 Gy≤50%, V60 Gy≤35%, and V70 Gy≤ 20%. Dose constraints for the organs at risk (OAR) were selected based upon Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data.[19] Cone beam-CT (CBCT) scan were taken prior to each delivery. Shifts were performed by aligning finally to soft tissue on CBCT. All patients have been treated with IMRT technique with daily imaging guidance. RT was delivered in 2 Gy daily fractions with 6 MV photon beams five days a week with total dose of ranging 64-72 Gy.PSA values at the time of diagnosis, first PSA values in the postoperative period, PSA values before RT after recurrence, Gleason scores indicated in pathology reports, presence of (if any) perineural (PNI), lymphovascular (LVI), and/or seminal vesicle (SV) invasion, extracapsular extension (ECE), surgical margin (SM), whether or not the patient received androgen deprivation therapy, salvage or adjuvant RT, RT volume and dose information were recorded. The treatment outcomes were assessed in terms of progression-free (PFS), and overall survival (OS) rates. Patients with a PSA value of 0.2 ng/ml and above during follow-up were considered to have relapse and PFS was evaluated as the time from the time of initial diagnosis to the time when the PSA was above 0.2 ng/ml. The effects of variables on PFS and OS were also evaluated. The final status of the patients were checked from the national death notification system.

Statistical Analysis

IBM SPSS version 20 was used in all statistical analyzes. Chi-square test was used to evaluate the frequencies of categorical variables and to compare them with each other. Independent samples t- test was used for normally distributed parameters.Mann-Whitney U test was used to compare the means between groups for non-normally distributed continuous numerical data. ROC (receiver Operating Characteristic) analysis was performed to determine the intercept value for statistically significantly different parameters between

groups and the intercept value was determined according to Youdens J index. Survival rates between groups was estimated and compared using Kaplan-Meier method. The statistical significance level was accepted as p<0.05.

RESULTS

The study population consisted of 78 patients with operated prostate cancer who received postoperative RT in our radiation oncology department between January 2011 and January 2023. Patients received adjuvant RT (n:39) or salvage RT (n:39). The mean follow-up time was 66.7 (IQR 25-75:41,6-89,6) months. The mean age was 64.9±6.7 (range 44-80 years) years. The mean PSA value at diagnosis of the patients was 14.7±9.2 ng/ml, and the median was 11 ng/ml (range 3 -42 ng/ml).The mean RT dose of the patients was 67.3±2.2 Gray (Gy), and the median was 66 Gy (range 64-72 Gy). Patients' characteristics are summarized in Table 1.

Table 1: Patients' characteristics

	n (%)
Gleason score at RP	
≥ 8	21 (26.9)
≤ 7	57 (73.1)
Surgical margin	
Positive	55 (70.5)
Negative	23 (29.5)
Extracapsular extension	
Yes	33 (42.3)
No	45 (57.7)
Seminal vesicle invasion	
Yes	14 (17.9)
No	64 (82.1)
Lymphovascular invasion	
Yes	4 (5.1)
No	74 (94.9)
Perineural invasion	
Yes	36 (46.5)
No	42 (53.8)
Androgen deprivation therapy	
Yes	28 (35.9)
No	50 (64.1)

Abbrevations: RP: Radical prostatectomy

Five and 10-year overall survival rates were 93%, and 67.3% respectively; (median (95% CI); NR (not reach): while 5 and 10-year progression-free survival rates were 90.3%, and 50.4, respectively; (median (95% CI); 135.3±(105.9-165.7) (Figures 1a, and b). When the patients were evaluated according to Gleason scores and disease progression; disease progression was observed in indicated number of patients in the low risk (n:2; 9.1%), intermediate risk (n:4; 11.4%), and high risk (n: 8; 38.1%) groups. Disease progression was observed more frequently in patients with higher Gleason scores when compared with low-risk (6.15-fold:1.13-33.7), and intermediate-risk (4.77-fold:1.22-18.65) groups.

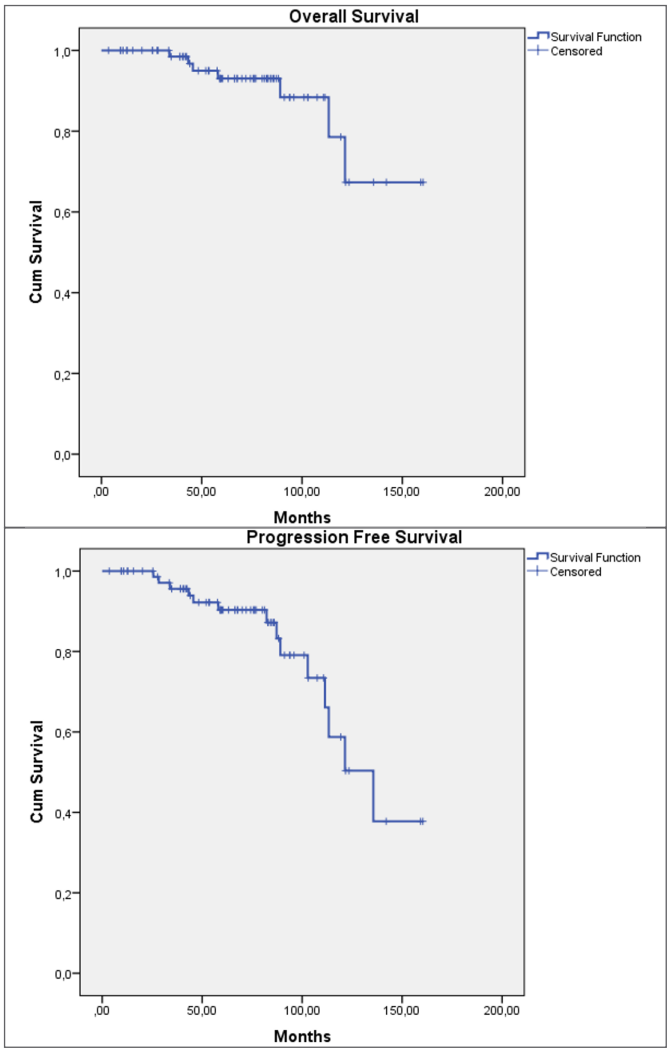

Figure 1. Overall survival **(1a)**, Progression-free survival **(1b).**

When the effects of Gleason score, PNI, LVI, SV invasion, ECE, SM, parameters on overall survival and progression-free survival were examined one by one, We observed that Gleason Score had an effect on overall and progression-free survival (Table 2).

Table 2. Relationship between gleason score and overall survival and progression-free survival

	5 years (%)	10 years (%)	Median±SD (%95 CI)	p value
Overall survival			NR	0.006
Gleason score ≤ 7	95.2	95.2	113.3± 15.4	
Gleason score ≥ 8	86.9	46.3	(83.1-143.5)	
Progression-free survival			NR	
Gleason score ≤ 7	91.5	70.6	113.3±15.7	0.009
Gleason score ≥ 8	86.9	33.8	(82.5-144.2)	

Abbrevations: SD: standard deviation; NR: not reached

When PSA values of the cases measured at the time of diagnosis, after the surgery, and before radiotherapy (pre-RT) were evaluated in terms of disease progression, We observed that the median pre-RT PSA values of the patients whose disease progressed were higher than those without disease progression. (0.28 vs 0.53, p:0.036).

The effects of the patients' PSA values at the time of diagnosis, and their postoperative PSA and pre-RT PSA values on the overall survival could not be demonstrated. In the ROC analysis performed on progressive disease using the parameters of PSA values obtained at the time of diagnosis, during postoperative period, and before RT, the area under the curve of the pre-RT PSA parameter was observed to be large enough (0.680). The intercept value was determined as 0.460 according to Youdens J index (p:0.036) (Table 3).

Table 3. ROC analysis values for progressive disease

	AUC (% 95 CI)	Sensitivity-Specificity	Intersection value	Youdens J index	p value
PSA at diagnosis	0.59 (0.43-0.75)	0.86-0.36	8.340	0.22	0.274
Postoperative PSA	0.64 (0.47-0.82)	0.50-0.83	0.185	0.33	0.094
Pre-RT PSA	0.68 (0.52-0.84)	0.64-0.39	0.460	0.39	0.036

Abbrevations: PSA: prostate specific antigen; AUC: area under curve; RT: radiotherapy

When the patients were grouped according to their PSA values at the time of diagnosis, postoperative PSA and pre-RT PSA values, and the effects of these parameters on progression-free survival was analyzed, median progression-free survival was higher in patients with postoperative PSA values ≤0.185 (135.6±24.4 vs 113.3±6.4, p:0.001).

Univariate Cox regression analysis showed that disease progression was 5.8 (1.81-18.599) times more frequent in patients with postoperative PSA values >0.185 ng/ml compared to those without. Progression was observed 3.73(1.29-10.78) times more frequently in patients with higher Gleason score compared to those with low-intermediate. Also, in the univariate Cox regression analysis, 9.51 (1.72-50.64) times higher mortality rates were observed in patients with a postoperative PSA values >0.235 ng/ml compared to those with lower PSA values. Mortality rates were observed 7.22 (1.39-37.42) times more frequently in cases with higher Gleason score than those withlower-intermediate (Table 4).

Table 4. Univariable Cox regression analysis

	Hazard ratio	95% confidence interval	p-value
Progressive disease			
Postoperative PSA			
≤0.185	1	1.81-18.59	0.003
>0.185	5.80		
Gleason score			
≤ 7	1	1.29-10.78	0.015
≥ 8	3.73		
Mortality			
Postoperative PSA			
≤0.235	1	1.72-52.64	0.010
>0.235	9.51		
Gleason score			
≤ 7	1	1.39-37.42	0.018
≥ 8	7.22		

Abbrevations: PSA:prostate specific antigen

DISCUSSION

In our retrospective study, we aimed to evaluate the factors affecting progression-free survival in patients with operated prostate cancer. In a systematic review Ohri et al.[20] evaluated 25 studies, and suggested that the application of salvage RT in patients with low PSA levels undergoing postoperative RT may improve the therapeutic success rate of salvage RT. Similarly, in our study, we obtained better results in progression-free survival in patients with operated prostate cancer having low pre-RT PSA values compared to those with higher pre-RT PSA values. Although salvage RT seems to be advantageous in postoperative RT applications, adjuvant RT is still recommended especially in patients with high Gleason scores.[21] Similarly, in our study, both disease progression and mortality rates were higher in patients with high Gleason scores compared to the low-moderate risk groups. In a retrospective series by Yoshida et al.[22] evaluating postoperative salvage RT, a Gleason score ≥8 was a significant predictor for PSA recurrence after salvage RT (hazard ratio: 4.531; 95% confidence interval 1.413-14.535; p=0.011) and 5-year PSA relapse-free survival rates were 62.7% and 15.4% in patients with Gleason scores ≤7 and ≥8, respectively. In a study on the results of 236 patients where prognostic factors in postoperative prostate cancer radiotherapy were analyzed, pre-RT PSA levels and T3 disease were found to be associated with an increased risk of progression, and the researchers found 5-year disease-free survival to be 86.9%.[23] Similar results were also obtained in our study.

Study Limitations

The fact that it was a retrospective study is the most important limitation of this study.

CONCLUSION

Postoperative RT can be applied as adjuvant or salvage therapy in cases with operated prostate cancer. Patient selection should be made based on all pathologic data. Gleason score can be considered as the most important prognostic factor for both progression-free survival and overall survival. However, prospective randomized trials with a greater number of patients should be planned for better evaluation of both the timing of RT and prognostic factors.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the University of Health and Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies and Ethics Committee (Date: 22.09.2022, Decision No: 2022-09/169).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Cytotoxic effect of *Centaurea solstitialis L. (Asteraceae)* on cell cultures

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ABSTRACT

Aims: The aim of this study was to investigate the cytotoxic effect of *Centaurea solstitialis* (*C. solstitialis*) L. (*Asteraceae*) plant extract on A-549 lung cancer cells. Cytotoxicity is an important parameter in evaluating the lethal effect of plant extracts on cancer cells.

Methods: In this study, plant specimens were collected from the campus area of Kırıkkale University during flowering in May–June and identified in the ADO Herbarium. Dried and crumbled plant leaves were mixed with 70% ethyl alcohol to form a paste, and this mixture was kept in a magnetic stirrer for at least 48 hours. It was then kept in a fume hood for at least 48 hours to dry, and the dried material was labeled and stored in eppendorf tubes. Cytotoxicity was determined by the WST-1 assay and evaluated by examining the morphological characteristics of the cells.

Results: Different doses of *C. solstitialis* plant extract (200 ug/ml, 100 ug/ml, 0.05 ug/ml, 0.025 ug/ml, 0.025 ug/ml, and 0.0125 ug/ml) were tested, and the percentage of cell viability was calculated relative to the control group. The results revealed that dose 1 exhibited a cell viability of 26%, with dose 2 showing the highest cell viability at 38%, dose 3 at 74%, dose 4 at 80%, and dose 5 at 96%. The toxicity levels of *C. solstitialis* plant extract was determined, and apoptotic and necrotic effects were examined at the observed toxic doses. According to these results, it was determined that *C. solstitialis* alcohol extract at a dose of 200 mg/ml caused 21.5% apoptosis and 7.56% necrosis in A-549 cancer cells. At a 100 mg/ml dose, these rates were determined as 16.2% apoptosis and 5.39% necrosis, respectively. At lower doses, apoptosis rates of 50 mg/ml and 25 mg/ml *C. solstitialis* extract in A-549 cells were 9.94% and 5.1%, respectively, while necrosis rates were 4.12% and 3.25%, respectively. At the lowest dose of 12.5 mg/ml, the apoptosis rate was 3.02% and the necrosis rate was 2.16%.

Conclusions: The results showed that *C. solstitialis* showed a cytotoxic effect, and accordingly, the percentage of viability decreased and as the dose applied to the cell decreased, the percentage of viability increased, and the cytotoxic effect decreased. Apoptotic and necrotic effects observed at toxic doses suggest that programmed cell death mechanisms are induced. Further studies are needed to elucidate the underlying molecular mechanisms and compare the cytotoxic effects of *C. solstitialis* with those of other Centaurea species.

Keywords: Lung cancer, apoptosis, *Centaurea solstitialis*, cell viability, necrosis, cytotoxicity

INTRODUCTION

Asteraceae is one of the largest families of Angiosperms, and according to the latest classifications, it consists of 1535 genera and about 26,000 species gathered under 3 subfamilies and 17 tribes. When the limited studies conducted in Kırıkkale are examined, it can be said that there are approximately 30 genera belonging to the family.[1-3] One of a country's most important natural resources is its flora. For this reason, each country identifies the plants belonging to its flora and carries out studies on them, such as antimicrobial, antioxidant, cell culture, identification and evaluation of gene resources, and protection of plants in their natural environment.[4] *C. solstitialis*, used in this study, is a plant species belonging to the family *Asteraceae* (Daisy family) and is commonly known as Yellowthorn. This plant usually grows in steppe areas, fields, roadsides, and vacant lots.[5] Humans have utilized plants in the treatment of diseases since time immemorial. Before the modern pharmaceutical industry, many plants were used as natural medicines. Today, people still use plants or drugs derived from plants in the treatment of various diseases. The killing effect of plants on microorganisms and their important

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properties for human health have been investigated in various laboratories in Turkey and other countries since 1926. It is known that naturally occurring plant extracts and essential oils exhibit antifungal activity against bacteria and fungi, and antimicrobial activities are the basis for many applications, such as food preservation, pharmacy, alternative medicine, and natural therapy.[6] Potential for plant-derived medicines There are approximately 120 plant-derived medicines available worldwide, derived from only 95 different plant species. Today, only 5,000 species out of approximately 250,000 flowering plant species have been evaluated for their pharmaceutical potential.[7] The lethal effects of plants on microorganisms and their important properties for human health have been investigated in Turkey since 1926, as well as in various laboratories in other countries.[7] The role of plants in cancer treatment Today, many different methods, such as radiotherapy, surgical methods, hyperthermia, gene therapy, and chemotherapy, are used in cancer treatment. Chemotherapy is the most widely used treatment method and is often combined with other methods. Chemotherapy uses a variety of chemical agents as well as natural compounds of plant origin. Cytotoxicity refers to the toxic effect of a substance or agent on cells.[8] This toxic effect can disrupt the structural integrity of cells, affect their metabolic activities, or cause cell death.[9] Cytotoxicity is an important concept in many fields, such as drug discovery and development, toxicology, cancer research, and biomedical applications.[10] Cytotoxicity is a consequence of changes observed in the viability, proliferation, metabolic activities, and morphological characteristics of cells.[11] These changes may manifest as cell death (necrosis or apoptosis) or cell damage.[11] When assessing cytotoxicity, measurements of cell viability or cell membrane integrity are usually used.[11] Cytotoxicity tests are used to assess cytotoxicity and determine the effect of a substance or agent on cells.[12] These tests are usually performed in vitro cell culture systems and evaluate cytotoxicity by measuring different parameters. Commonly used methods in cytotoxicity tests include the MTT assay, the WST-1 assay, the XTT assay, LDH release, and the use of apoptosis markers.[10,11] Besides cytotoxicity tests, other parameters such as morphological changes of cells, DNA damage, and genetic alterations can also be evaluated to determine the effects of cytotoxic substances.[10] Such tests are used to gain a more comprehensive understanding of the effect of a substance or agent on cells.[12] Lung cancer is a high mortality cancer that is the most common cause of cancer-related deaths worldwide, accounting for approximately 1.6 million deaths each year.[13,14] Lung cancers are traditionally divided into two main histologic groups (small cell lung cancer [SCLC] and non-SCLC [NSCLC]) according to the natural history of the disease and treatment approaches. NSCLC accounts for approximately 85% of all lung cancers, and the most common subtypes are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[15] In a study conducted in Turkey, lung cancer was observed in 90.5% of men and 9.5% of women.[16] According to the WHO 2014 report, 19.4% of cancer deaths are due to lung cancer.[17] The main aim of this research is to understand the effect of *C. solstitialis* plant extract on cancer tissues, and I think it will prioritize new treatment methods and existing treatments in the fight against cancer.

METHODS

Ethics

The study was conducted in a laboratory. No human or animal material was used, as this study did not require ethics approval. The approval of the institution was obtained. All procedures were carried out in accordance with the ethical rules and the principles.

Collection of Plant Specimens

C. solstitialis specimens were collected during the flowering period of May-June (2021–2022) in the campus area of Kırıkkale University. The collected plant specimens were identified in the ADO Herbarium. The plant specimens were washed with deionized water to remove dust and foreign debris and dried under room conditions in the shade. The leaves, which are the most commonly used part of the dried plants, were ground with a grinding device, and powders with a particle size between 0.50-1.00 mm were used to obtain plant extracts.

Preparation of Plant Extracts

Dried and crumbled plant leaves were mixed with 70% ethyl alcohol to form a paste. This mixture was kept in a magnetic stirrer for at least 48 hours. Then, the solution was kept in a fume hood for at least 48 hours and allowed to dry. The dried material was labeled and stored in eppendorf tubes for use.

Determination of Cytotoxicity

The WST-1 assay was used to determine cytotoxicity. Each of the cell lines to be used will be seeded in a separate 96-well plate with 5000 cells per well. The cells will be incubated for 24 hours. Then, the determined amounts of plant extracts will be prepared in ethanol, added to the cells, and incubated for 24, 48, and 72 hours. Only medium will be used as a positive control, and medium with H_2O_2 will

be used as a negative control. At the end of the incubation period, 15 µl of WST-1 solution will be added to each well and incubated at 37°C for 4 hours. Then, the absorbance intensity values of the 96-well plate will be measured at a wavelength of 440 nm in an ELISA plate reader to determine cell viability. Live cells will produce a yellow color, while dead cells will not show any color formation. Percent viability will be calculated based on the control group.[8]

Morphological Examination of Cells

The cells to be used in the study will be seeded with 10,000 cells per well of a 48-well plate. Then, the medium will be changed to apply plant extracts to the cells. After 24, 48, and 72 hours, the media will be removed and the cells will be fixed with 3% glutaraldehyde for 15 minutes, followed by fixation with 70% ethyl alcohol for 30 minutes. The cells will then be stained with Hematoxylin-eosin stain and examined under an inverted microscope to evaluate morphological changes such as cell membrane disruption and vacuoles. This evaluation will be done using the scoring method. Hematoxylin stains the nuclei blue (apoptosis appearance), while eosin stains the cytoplasm pink or red (necrosis appearance).[9]

Statistical Analysis

All experiments were performed in triplicate, and results were expressed as mean ± standard deviation (SD). Statistical analysis of the data was performed with the IBM SPSS Statistics 22 package program (IBM SPSS Statistics®, Chicago, IL, USA). Mean comparisons were obtained by analysis of variance followed by a one-sample Wilcoxon signed rank test.

RESULTS

When the WST-1 test was used for *C. solstitialis* plant extract, live cells formed a yellow color, while no color formation was observed in dead cells. The percent viability was calculated based on the control group. The findings regarding the cytotoxic effect of *C. solstitialis* alcohol extract on A-549 cancer cells are presented in Table 1.

Table 1. Cytotoxic effect of *C. solstitialis* alcohol extract on A-549 cancer cells

Centaurea solstitialis	
Doses	**% Vitality**
200 µg/ml	26.2±0.003^{d}
100 µg/ml	38.3±0^{c}
50 µg/ml	74.4±0.014^{b}
25 µg/ml	80.5±0.033^{ab}
12,5 µg/ml	96±0.00^{a}
Control	100^{a}

*Different letters in the same column indicate differences between means. (p<0,05).

According to Table 1, it was observed that *C. solstitialis* alcohol extract at a 200 µg/ml dose provided 26.2% viability in A-549 cancer cells. At a 100 µg/ml dose, this rate was 38.3%. Lower doses of 50 µg/ml and 25 µg/ml of *C. solstitialis* extract provided 74.4% and 80.5% viability rates in A-549 cells, respectively. The lowest dose of 12.5 µg/ml indicated a viability rate of 96%. In the control group, it is noteworthy that the cells showed 100% viability. It shows that the cytotoxic effect of *C. solstitialis* plant extract on A-549 cancer cells increases in a dose-dependent manner. In other words, it is seen that the plant extract has a stronger cytotoxic effect on cancer cells with increasing doses.

Table 2. Apoptotic and necrotic index results of *C. solstitialis* alcohol extract

Centaurea solstitialis		
Doses	**% Apoptosis**	**% Necrosis**
200 mg/ml	21.5^{a}	7.56^{a}
100 mg/ml	16.2^{b}	5,39^{b}
50 mg/ml	9,94^{c}	4.12^{bc}
25 mg/ml	5.1^{d}	3,25^{c}
12.5 mg/ml	3.02^{e}	2,16^{cd}

*Different letters in the same column indicate the differences between the means. (p<0,05).

According to Table 2, it was determined that *C. solstitialis* alcohol extract at a 200 mg/ml dose caused 21.5% apoptosis and 7.56% necrosis in A-549 cancer cells. At a 100 mg/ml dose, these rates were determined as 16.2% apoptosis and 5.39% necrosis, respectively. At lower doses, apoptosis rates of 50 mg/ml and 25 mg/ml *C. solstitialis* extract in A-549 cells were 9.94% and 5.1%, respectively, while necrosis rates were 4.12% and 3.25%, respectively. At the lowest dose of 12.5 mg/ml, the apoptosis rate was 3.02% and the necrosis rate was 2.16%. Table 2 shows that *C. solstitialis* alcohol extract has apoptotic and necrotic effects on A-549 cancer cells. Apoptosis refers to controlled cell death, while necrosis refers to sudden death by cell damage. These results show that the apoptotic effect of the plant extract on cells is more predominant. In other words, the plant extract shows its antitumoral effect by inducing controlled cell death in cancer cells. These findings suggest that *C. solstitialis* stimulates apoptosis and necrosis processes in cancer cells and has a potential antitumoral effect. However, more comprehensive and mechanistic studies are needed. It is also important to investigate the effect of these effects on normal cells and possible side effects. In this way, *C. solstitialis* could contribute to the evaluation of its potential use as a natural compound in the treatment of cancer. In Figure 1, images of A-549 cells treated with 100 µg/ml *C. solstitialis* extracts are presented.

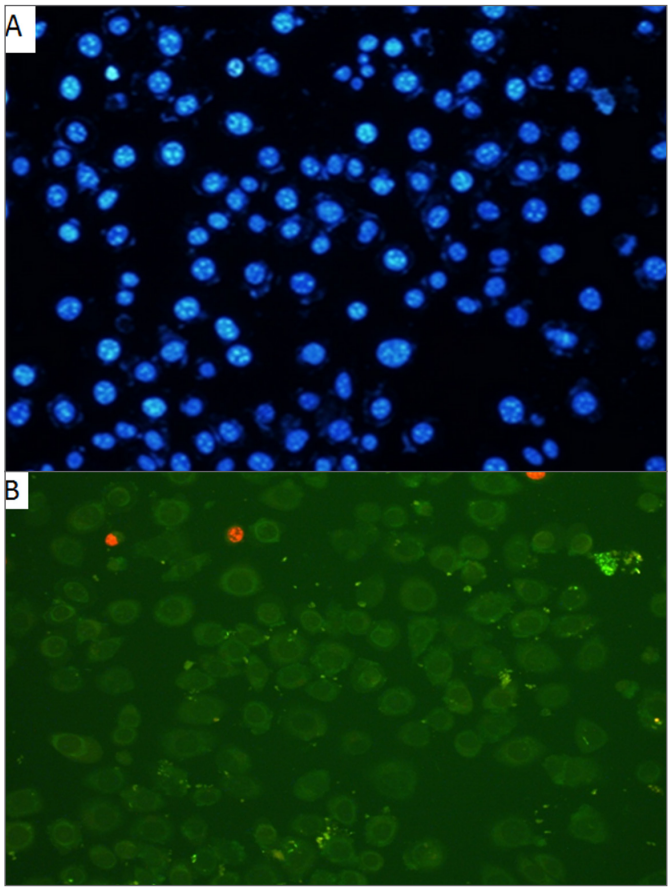

Figure 1. A-549 cells to which 100 ug/ml *C. solstitialis* extracts were applied

According to Figure 1, apoptotic cells are defined as having bright and fragmented nuclei, while necrotic cells are defined as having red nuclei. A: Apoptotic cells, B: Necrotic cells (Magnification of an inverted microscope image)

DISCUSSION

Various studies have revealed that *C. solstitialis* species may have various biological effects. In the study conducted by Akbar et al.[18] in 1995, they confirmed the hypothermic activity of repin isolated from *C. solstitialis* by using various pharmacological agents in rats and tried to explain its thermoregulatory effects and mechanisms of action. It was determined that repin induced dose-dependent and quite strong hypothermia in rats. Hypothermia caused by a 10 mg/kg dose of repin administration reached a maximum of 3 hours after injection, and the return to normal temperature was found to occur in more than 8 hours. Antimuscarinic agents such as atropine sulfate (10 mg/kg) and atropine methyl bromide (20 mg/kg), metergoline (non-selective serotonin receptor antagonist, 0.5 mg/kg), ketanserin (selective 5-HT2 receptor antagonist, 0.2 mg/kg), diphenhydramine (H1 receptor antagonist, 10 mg/kg), apomorphine (dopamine receptor antagonist, 0. 5 mg/kg) and propanolol (10 mg/kg), a non-selective β-adrenoreceptor antagonist and 5-HT1 receptor antagonist, 30 minutes before repin injection, did not directly antagonize the hypothermic effect of repin. In contrast, 2-4 hours after repin injection, hypothermia was partially but significantly reversed by atropine sulfate (20 mg/kg), metergoline, ketanserin, diphenhydramine, and apomorphine. According to the results obtained, it was stated that these late-onset effects may be due to secondary physiological mechanisms, and 20 mg/kg propanolol administration significantly increased the early and late-onset hypothermic effects of repin. The results of the study showed that cholinergic, serotonergic, histaminergic, and dopaminergic receptors were not involved in the hypothermic effects of repin.[18] In the study conducted by Yesilada et al.[19] in 1999, it was determined that the total extract prepared by mixing aqueous extracts (two extracts prepared at room temperature and with hot water) and methanol extract prepared from the aerial parts of *C. solstitialis* ssp. solstitialis provided 89.3% inhibition. In the results of the study, it was stated that the aqueous extract had a stronger antiulcerogenic effect compared to 100% inhibition of hot water extract prepared from 10 g of plant material, 80.1% inhibition of extract prepared from 5 g of plant material, and 81.6% inhibition of methanol extract prepared from 10 g of plant material.[19] In 2002, Arif determined the antibacterial effects of extracts and fractions of *C. solstitialis* and *C. depressa* species on Gram (+) (*Bacillus subtilis*) and Gram (-) (*Escherichia coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*) bacteria, and antifungal effects were determined by the microdilution method using *Candida tropicalis* strains.[20] The main extracts and fractions of both species showed an effect close to the control against *E. coli.* Chloroform fractions and ethanol extracts of the subsoil parts of the species were found to have a remarkable effect against Pseudomonas, and both species were found to have no antifungal effect.[20] In 2004, Yeşilada et al.[21] reported that fresh spiny flowers of *Centaurea solstitialis* ssp. (CSS) are used in the treatment of peptic ulcer in Turkey, and ethanol (80%) CSS extract exhibited a significant anti-ulcerogenic effect on an ethanol-induced ulcerogenesis model in rats. The ethanol extract was further fractionated by successive solvent extractions of n-hexane, chloroform, ethyl acetate, and n-butanol. All fractions showed significant anti-ulcerogenic activity, but the effect of the chloroform fraction was more pronounced with 99.5% ulcer inhibition. Bioassay-guided fractionation yielded sesquiterpene lactones as active components. The main components responsible for the activity of the chloroform fraction were identified as chlorojanerin and 13-acetyl solstitialin A, which were elucidated by HR-ESI and 1H, 13C, and 2D NMR spectroscopic techniques.[21] In 2009, Özçelik et al.[22] evaluated *Centaurea solstitialis* L. ssp. solstitialis

(*Asteraceae*) for antimicrobial and antiviral activities. Both standard and isolated strains of *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Candida albicans*, and *C. parapsilosis* were used for antimicrobial activity evaluation by the microdilution method. The antiviral activity of these three sesquiterpene lactones was determined using Vero cell lines of Herpes simplex type-1, a DNA virus, and Parainfluenza, an RNA virus. Ampicillin, ofloxacin, ketoconazole, fluconazole, acyclovir, and oseltamivir were used as reference drugs. 13-Acetyl solstitialin A was found to exhibit significant antibacterial activity against isolated E. faecalis strains at a concentration of 1 µg/ml, close to the effective concentrations of ampicillin. The same compound also showed significant activity against DNA viruses, which was as potent as the reference compound acyclovir at maximum and minimum concentrations of 16-<0.00006 µg/ml. This study is the first report proving that 13-acetyl solstitialin A has significant antiviral activity.[22] In 2016, Erenler et al.[23] reported that *Centaurea solstitialis* L. ssp. solstitialis (CSS) is used as a medicine for various diseases, and the root, stem, and flower parts of the plant were extracted separately with methanol for their isolation according to the bioassay guidance. The antiproliferative activities of each extract on C6 cells (rat brain tumor cells) and HeLa cells (human uterine carcinoma) were investigated in vitro. The methanol extract of the stem part of the plant exhibited the highest antiproliferative activity; therefore, isolation of active compounds for the stem part of the plant was carried out. The methanol extract of the stem part was boiled in water at 97°C for 2 h, followed by hexane and ethyl acetate extractions, respectively. Solstitialin A and 15-dechloro-15-hydroxychlorojanerin 2 were isolated from the ethyl acetate extract by column chromatography and identified by spectroscopic techniques. Solstitialin A 1 from CSS and 15-dechloro-15-hydroxychlorojanerin 2 were previously isolated from Saussurea lipschitz and Rhaponticum pulchrum. These two extracts exhibited very high antiproliferative activity on C6 and HeLa cells. The IC50 and IC75 values of extract 1 were 10.78 and 53.65 against C6 cells and 48.78 and 68.52 against HeLa cells, respectively. The IC50 and IC75 values of extract 2 were determined as 432.43 and 109.79 against C6 cells.[23] In 2019, Alper and Güneş evaluated the cytotoxicity of the crude ethanolic extract obtained from the flowering parts of *C. solstitialis* at seven different concentrations in A549, Daudi, HeLa, and Beas-2B cell lines to determine the IC50 value (µg/ml) causing 50% cell death.[24] According to the research findings, it was determined that the percentage of viable cells varied according to the cell lines used. It was reported that the viability of all cancer cells was significantly reduced by the extract in a concentration-dependent manner, as well as that the extract at concentrations of 15.6 and 31.2 µg/ml did not cause significant cytotoxicity in the normal BEAS-2B cell line, indicating that the extract has selectivity against cancer cells. The highest cytotoxicity was observed in HeLa cells with 63.18 µg/ml, while the IC50 values of A549 and Daudi cells were 252.5 µg/ml and 69.27 µg/ml, respectively. However, the extract exhibited a lower cytotoxic effect on normal BEAS-2B cells with an IC50 value of 75.25 µg/ml compared to the effects on HeLa and Daudi cancer cell lines. In other words, HeLa and Daudi cells were found to be the most sensitive cell lines in terms of cytotoxicity.[24] In 2021, Alper et al.[25] aimed to investigate the phenolic composition and antioxidant activity of *C. solstitialis* and Urospermum picroides and evaluate their possible cytotoxic effects. RP-HPLC analysis was used to elucidate the phenolic profiles of ethanolic extracts of the flowering parts of *C. solstitialis* and *U. picroides*. Both ethanolic extracts were evaluated for their antioxidant properties using DPPH, FRAP, phosphomolybdenum, and metal chelating assays. In addition, the effect of the extracts on cell viability was evaluated against MCF-7 and PC-3 cancer cells and the HEK293 cell line using the MTT assay. Caffeic acid was the most abundant phenolic compound in both extracts, and the amount of this compound was 24078.03 and 14329.59 µg/g in *C. solstitialis* and *U. picroides* extracts, respectively. Although the antioxidant activity of the extracts was similar, the *C. solstitialis* extract was found to have a higher potential for inhibition of cell viability compared to the *U. picroides* extract. The IC50 value of *C. solstitialis* on MCF cells was found to be 58.53 µg/ml. These findings suggest that *C. solstitialis* and *U. picroides* extracts can be considered as new and alternative natural antioxidant and anticancer sources.[25] In a study conducted in 2022 by Necip and Durgun, Mentha pulegium, *Lepidium draba*, and *Centaurea solstitialis* were traditionally used in different cultures for the treatment of various diseases. Total phenolic content analysis, chemical composition, and antioxidant activity of different solvent extracts, such as acetone, methanol, and n-hexane, obtained from the aboveground parts of *M. pulegium*, *L. draba*, and *C. solstitialis*, were investigated.[26] Total phenolic content was determined as gallic acid equivalent; the LC-MS/MS technique was used to determine the phenolic profiles of each extract; and the antioxidant activities of three extracts were determined by DPPH and ABTS methods. The highest total phenolic contents for acetone, n-hexane, and methanol extracts of *Centaurea solstitialis* were 99 507, 46 305, and 18 227 µg/mL, respectively. In the acetone extract of Mentha pulegium, the main component rosmarinic acid content was 128 195 µg/g extract, while this amount was determined as 780 383 µg/g extract in

the methanolic extract. The highest DPPH radical scavenging activity was found to be 77% and 79% in acetone and methanolic extracts of Mentha pulegium, respectively. ABTS radical scavenging activity was determined as 98% and 94% in acetone and methanolic extracts of Mentha pulegium, respectively. The antioxidant capacity of the extracts was found to be related to the total amount of phenolic substances.[26]

In 2023, Işık et al.[27] used nanoparticles obtained from the water extract of *C. solstitialis* leaves as green adsorbents for the removal of Reactive Red 180 (RR180) and Basic Red 18 (BR18) dyes in the Fenton reaction. Under optimum operating conditions, the nanoparticles showed high performance in the tested dye removal, with more than 98% elimination. Free radical capture, DNA nuclease, biofilm inhibition capacity, antimicrobial activity, microbial cell viability, and antimicrobial photodynamic therapy activities of iron oxide nanoparticles (FeO-NPs) obtained from water and methanol extracts of the plant were investigated. SEM-EDX, XRD, and Zeta potential were applied for the characterization of the prepared NPs and to explain their morphology, composition, and behavior in an aqueous solution, respectively. It was found that DPPH scavenging activities increased as the number of nanoparticles increased. The highest radical scavenging activity was obtained with FeO-NPs obtained from the water extract of the plant, with 97.41% at 200 mg/L. The new green synthesized FeO-NPs showed good DNA cleavage activity and good in vitro antimicrobial activity against human pathogens. As a result, both synthesized FeO-NPs showed 100% antimicrobial photodynamic therapy activity after LED irradiation. Water extract of FeO-NPs and methanol extract of FeO-NPs are also reported to have significant biofilm inhibition.[27]

When the literature findings were evaluated, hypothermic, antiulcerogenic, antibacterial, antiviral, antioxidant, and anticancer effects were found in studies with *C. solstitialis* extracts. The findings obtained from the study are similar to the literature findings and suggest that the effect of *C. solstitialis* extracts on A-549 cancer cells is due to the phenolic content that increases the antioxidant capacity of *C. solstitialis* extracts.

CONCLUSION

It was determined that alcohol extracts prepared from the leaves of *C. solstitialis* species showed an anti-carcinogenic effect that varied depending on the dose. Cytotoxicity and apoptosis-necrosis results show that *C. solstitialis* is a promising candidate for cancer treatment. It is thought that more comprehensive cancer studies on this plant species may be useful, and the phenolic compound that increases its antioxidant capacity should be further elucidated.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted in a laboratory. No human or animal material was used, as this study did not require ethics approval. The approval of the institution was obtained.

Informed Consent: Because the study was designed as a laboratory study and did not involve human or animal material, no written informed consent form was obtained.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Original Article

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Evaluation of changes in skin sebum and moisture content with treatment in children with atopic dermatitis

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ABSTRACT

Aims: Since the deterioration of the skin barrier plays a role in the development of atopic dermatitis, it is necessary to investigate the moisture and sebum content of the skin. In this context, our study aimed to evaluate the change of skin sebum and moisture content with treatment in children with atopic dermatitis.

Methods: This study is a cohort study. Patients aged 0-18 years, diagnosed with atopic dermatitis, and those who did not have any accompanying skin disease were included. Skin moisture and sebum levels were measured with a portable pen-shaped LCD Display Digital Skin Moist Oil Analyzer (Reyoung-Beauty, Guangdong, China) digital skin moisture and sebum measurement device from the cubital fossa before and 1 month after the treatment. Skin sebum and moisture were obtained as percentages.

Results: The median values of skin moisture and sebum content before treatment in 55 atopic dermatitis patients were 30.0% (10.0-55.0) and 24.0% (16.0-49.0), respectively. The percentages of skin moisture and sebum content after treatment were 38.0% (15.0-60.0) and 28.0% (18.0-50.0), respectively. In atopic dermatitis patients, the increase in skin moisture and sebum percentages was statistically significant for both ($p<0.001$ and $p=0.022$, respectively)

Conclusion: Skin moisture and skin sebum contents improved significantly with treatment in children with atopic dermatitis. This situation highlights the importance of adherence to treatment and continuity of selected treatments in patients.

Keywords: Atopic dermatitis, skin moisture, skin sebum, treatment

INTRODUCTION

Atopic dermatitis (AD) is one of the most common, inflammatory, chronic skin diseases and it has a recurrent feature.[1] The number of patients with AD is increasing.[2] In addition, the frequency of AD generally decreases with advancing age.[3] The prevalence of AD has been reported to be approximately 14% in adults and 20% in children.[4,5] According to a systematic review in the literature, 17.1% of adults and 22.6% of children have a diagnosis of AD.[6]

The skin has important functions such as reducing water loss. With this function, it contributes to the body's thermoregulation. The structure and cellular composition of the skin provide the protection from external physical and chemical exposures.[7] The most important function of the skin is to form a barrier between the internal and external environment of the body.[8] It is very important to protect the barrier function of the skin, as it prevents the entry of microorganisms, allergens, and mechanical and chemical irritants into the body.[8-10] There is an impaired skin barrier in the pathophysiology of AD.[8,11]

The barrier function of the skin is affected by features such as oil content in the skin, hydration of the epidermis, transepidermal water loss and skin pH.[10] Factors such as age, gender, race, amount of perspiration, skin and ambient temperature, and ambient humidity affect the amount of oil and moisture required for the barrier property of the skin.[12,13] When the sebum and moisture balance in the skin cannot be achieved, the symptoms of dryness and itching on the skin, which are common in AD, occur.[14] In a study conducted in children with AD in our country; the skin moisture and skin sebum ratios of

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children with AD were found to be lower than those of healthy children.[15] In a similar study, skin sebum in AD patients was reported to be lower than other individuals.[14]

Most treatments for AD focus on increasing skin moisture and protecting the skin from bacterial infections and irritation.[16] Topical and systemic treatments can be used in the pharmacological treatment of AD. Moisturizers, topical corticosteroids and calcineurin inhibitors are topical treatment options used in AD treatment.[17]

Since the deterioration of the skin barrier plays a role in the development of AD, it is extremely important to evaluate the moisture and sebum content necessary for the barrier function of the skin. In this context, our study aimed to evaluate the change of skin sebum and moisture content with treatment in children with AD.

METHODS

Ethics

The study was carried out with the permission of the University of Health and Sciences, Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 20/06/2023, Decision No: 196). All procedures were carried out in accordance with the ethical rules and the principles.

Study Type, Design and Population

The study is a cohort type study. Patients aged 0-18 years, diagnosed with AD, and those who did not have any accompanying skin disease were included in the study. Those who took a bath in the last 24 hours, who used drugs such as local steroids on the day of the examination, and those who used topical products such as moisturizer and additional products (soap, shampoo, detergent, etc.) on the examination day were excluded from the study as they may have an effect on the skin barrier. Considering the outpatient clinic appointment records, it was aimed to include 50 patients in the study.

Measures

Skin moisture and sebum levels were measured with a portable pen-shaped LCD Display Digital Skin Moist Oil Analyzer (Reyoung-Beauty, Guangdong, China) digital skin moisture and sebum measurement device from the cubital fossa before and one month after the treatment. The device measures moisture and sebum levels with the bioimpedance method, which is a non-invasive method. Measurements were made by placing the device probe on bare skin for a few seconds in the antecubital fossa of the non-dominant upper extremity. Sebum and moisture were obtained as percentages. Sebum and moisture content were considered as moist between 46% and 43%, normal between 42% and 38%, dry between 37% and 34%, and very dry between 33% and below.[15] In addition, children's sociodemographic characteristics (such as age, gender), eosinophils, total IgE values, allergy tests, SCORAD (SCORing Atopic Dermatitis) scores before and after treatment were also evaluated.

SCORAD (SCORing Atopic Dermatitis) is a scoring system used to measure the severity of AD and the response to treatment. It is the subjective evaluation of the patients' findings such as itching and the evaluation of the objective findings such as redness and dryness determined by physical examination. And it also evaluates the distribution of the lesions in the body. In other words, the SCORAD index contains three criteria: the distribution of the lesions (percentage of effected skin surface), intensity (redness, edema, papules, the outcome of itching, crust appearance, lichenification, dryness), and subjective symptoms (itching and insomnia).[18] SCORAD is scored with a numerical evaluation. A higher score reflects more severe disease. AD severity according to SCORAD is also categorized as mild, moderate, severe. If the total score is less than 25, it is classified as mild, between 25-50 as moderate and above 50 as severe AD.[19]

Patients with moderate or severe AD with a SCORAD score greater than 25 were included in our study. All patients were given medium or high potency topical corticosteroids in active therapy. In proactive treatment, patients who received pimecrolimus or tacrolimus treatment were included in the study. Treatments were chosen by the clinician in accordance with the guidelines according to the clinical features of the patients. In the study, skin moisture and sebum measurements were also evaluated according to the treatment groups.

Statistical Analysis

SPSS (Statistical Package for Social Sciences for Windows 25.0 program was used for data analysis and recording. Median, minimum, maximum values, numbers and percentages (%) were used for descriptive data. Conformity of continuous variables to normal distribution was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests). To evaluate the difference between two repeated measurements (pre- and post-treatment skin moisture, sebum, and SCORAD measurements) Wilcoxon test was used since the difference between the two measurements was not normally distributed. Analyzes with a p value below $0<0.05$ were considered statistically significant.

RESULTS

In our study, 55 children with AD were evaluated. While 50.9% (n=28) of the patients diagnosed with AD were female, 49.1% (n=27) were male. The median age

of patients with AD was 6 years (2-16). While 67.3% (n=37) of the atopic dermatitis patients had severe AD, 32.3% (n=18) had moderate AD. There were no patients classified as mild AD (Table 1).

Table 1. Gender, clinical classification and age distribution of atopic dermatitis patients

	Median (min-max)
Age (years)	6 (2-16)
	n (%)
Gender	
Female	28 (50.9)
Male	27 (49.1)
SCORAD classification	
Severe AD	37 (67.3)
Moderate AD	18 (32.3)

AD: Atopic dermatitis, SCORAD: SCORing Atopic Dermatitis

Eosinophil, total IgE values and allergy test positivity of AD patients were evaluated. The median values of absolute eosinophil and eosinophil (%) parameters were 405.0 103/µL (40.0-1840.0), 4.8% (0.5-23.7), respectively. The median total IgE value was 134.0 IU/mL (2.0-11052.0). The allergens to which the patients were sensitive were evaluated according to the skin prick test and/or the allergen-specific IgE values in the blood. House dust mite allergy was observed in 54.5% (n=30) of the patients. Egg and cat allergy positivity was 21.8% (n=12) for both. Pollen sensitivity was present in 14.5% (n=8) of the children. Nut and milk allergies were seen in 12.7% (n=7) and 9.1% (n=5) of children, respectively (Table 2).

Table 2. Eosinophil, total IgE values and allergy test positivity in atopic dermatitis patients

Laboratory parameters	**Median (min-maks)**
Eosinophil (absolute) (10^3/uL)	405.0 (40.0-1840.0)
Eosinophil (%)	4.8 (0.5-23.7)
Total IgE (IU/mL)	134.0 (2.0-11052.0)
Allergy test positivity	**N (%)**
House dust mite	30 (54.5)
Cat	12 (21.8)
Pollen	8 (14.5)
Egg	12 (21.8)
Nuts	7 (12.7)
Milk	5 (9.1)

The median values of skin moisture and sebum content before treatment in AD patients were 30.0% (10.0-55.0) and 24.0% (16.0-49.0), respectively. The percentages of skin moisture and sebum content after treatment were 38.0% (15.0-60.0) and 28.0% (18.0-50.0), respectively. In AD patients, the increase in skin moisture and sebum percentages after treatment was statistically significant for both (p<0.001 and p=0.022, respectively) (Table 3).

SCORAD scores of AD patients were also evaluated before and after treatment. The median SCORAD score before treatment was 67.7 (25.0-96.0) and 10.0 (5.0-40.0) post-treatment. The decrease in SCORAD score after treatment was statistically significant (p<0.001) (Table 3).

Table 3. Skin moisture, sebum and SCORAD score before and after treatment in atopic dermatitis patients

	Median (min-maks)	P value
Moist (%)- before treatment Moist (%)-after treatment	30.0 (10.0-55.0) 38.0 (15.0-60.0)	<0.001
Sebum(%)- before treatment Sebum (%)- after treatment	24.0 (16.0-49.0) 28.0 (18.0-50.0)	0.022
SCORAD- before treatment SCORAD- after treatment	67.7 (25.0-96.0) 10.0 (5.0-40.0)	<0.001

AD: Atopic dermatitis, SCORAD: SCORing Atopic Dermatitis

Moderate potency topical corticosteroid or high potency topical corticosteroid was used for active treatment in AD patients. While there were 27 patients using moderate potency topical corticosteroids, 28 patients used high potency topical corticosteroids. Skin moisture, sebum and SCORAD scores of patients using moderate potency and high potency topical corticosteroids were evaluated before and after treatment. The median percentage of skin moisture of patients using moderate potency topical corticosteroids was 31.0% (12.0-55.0) before treatment, while this value was 38.0% (16.0-60.0) after treatment. This increase in skin moisture after treatment was statistically significant (p<0.001). The median percentage of skin sebum before treatment was 25.0% (16.0-49.0), while this value was 26.0% (18.0-48.0) after treatment. This increase in skin sebum after treatment was not statistically significant (p=0.517). The SCORAD scores of patients receiving moderate potency topical corticosteroids were also compared. Median scores for SCORAD scores before and after treatment were 60.0 (25.0-89.6) and 10.0 (5.0-30.0), respectively. This decrease in SCORAD score after treatment was statistically significant (p<0.001) (Table 4).

The median percentage of skin moisture of patients using high potency topical corticosteroids was 30.0% (10.0-45.0) before treatment, while this value was 38.5% (15.0-59.8) after treatment. This increase in skin moisture after treatment was statistically significant (p<0.001). While the median percentage of skin sebum was 23.5% (16.0-49.0) before treatment, this value was 30.0% (19.1-50.0) after treatment. This increase in skin sebum after treatment was statistically significant (p<0.001). When the SCORAD scores of patients receiving high potency topical corticosteroids were also compared, the median SCORAD score values before and after treatment were 70.0 (25.0-96.0) and 17.5 (5.0-40.0), respectively. This decrease in SCORAD score after treatment was statistically significant (p<0.001) (Table 4).

Table 4. Pre- and post-treatment skin moisture, sebum and SCORAD values in moderate potency and high potency topical corticosteroids

	Moderate potency TC (n=27)	P value	High potency TC (n=28)	P value
	Median (min-max)		Median (min-max)	
Moist (%)- before treatment Moist (%)-after treatment	31.0 (12.0-55.0) 38.0 (16.0-60.0)	<0.001	30.0 (10.0-45.0) 38.5 (15.0-59.8)	<0.001
Sebum(%)- before treatment Sebum (%)- after treatment	25.0 (16.0-49.0) 26.0 (18.0-48.0)	0.517	23.5 (16.0-49.0) 30.0 (19.1-50.0)	0.012
SCORAD- before treatment SCORAD- after treatment	60.0 (25.0-89.6) 10.0 (5.0-30.0)	<0.001	70.0 (25.0-96.0) 17.5 (5.0-40.0)	<0.001

TC: Topical corticosteroids, SCORAD: SCORing Atopic Dermatitis

Pimecrolimus or tacrolimus was used for proactive treatment in patients with AD. While there were 28 patients using pimecrolimus, 27 patients used tacrolimus. Skin moisture, sebum and SCORAD scores of patients using pimecrolimus and tacrolimus were evaluated before and after treatment. The median percentage of skin moisture in patients using pimecrolimus was 30.5% (10.0-55.0) before treatment, while this value was 37.3% (15.0-60.0) after treatment. This increase in skin moisture after treatment was statistically significant (p<0.001). While the median skin sebum percentage in patients was 24.5% (16.0-49.0) before the treatment, this value was 26.0% (19.0-48.0) after the treatment. This increase in skin sebum after treatment was not statistically significant (p=0.170). The SCORAD scores of the patients receiving pimecrolimus were also compared. Median scores for SCORAD scores before and after treatment were 68.9 (25.0-90.0) and 15.0 (5.0-40.0), respectively. This decrease in SCORAD score after treatment was statistically significant (p<0.001) (Table 5).

The median percentage of skin moisture in patients using tacrolimus was 30.0% (11.0-45.0) before treatment, while this value was 40.0% (15.0-57.0) after treatment. This increase in skin moisture after treatment was statistically significant (p<0.001). While the median value of skin sebum percentage was 24.0% (16.0-49.0) before treatment, this value was 30.0% (18.0-50.0) after treatment. This increase in skin fat after treatment was not statistically significant (p=0.060). When SCORAD scores of patients receiving tacrolimus were also compared, the median SCORAD scores before and after treatment were 65.7 (25.0-96.0) and 10.0 (5.0-40.0), respectively. This decrease in SCORAD score after treatment was statistically significant (p<0.001) (Table 5).

DISCUSSION

With the treatments given in chronic diseases, it is aimed to control the clinical symptoms of the patients and to improve the prognosis. Atopic dermatitis is a chronic disease frequently seen in children accompanied by allergic mechanisms and inflammation. Uncontrolled symptoms constitute a significant burden of disease in children.[20] The clinical findings of AD can negatively affect the quality of life in children, causing sleep disorders and absenteeism from school.[21,22] For all these reasons, AD symptoms should be controlled with an effective treatment and skin moisture and sebum balances should be maintained in children with AD. In this context; according to the results of our study, the skin moisture and skin sebum values of the children increased significantly after the treatment. Besides, the SCORAD scores of our patients decreased significantly after treatment compared to before treatment.

Aerosol allergens originating from house dust mites can cause AD. House dust mite allergens, with their enzymatic activities, destroy tight junctions in the skin in patients with AD and impair the barrier function of the skin.[23] When the barrier function of the skin is impaired, allergen proteins penetrate the epidermis and then an allergic systemic inflammatory response begins. This situation causes the severity of AD to worsen.[24] In our study, house dust mite allergy was observed in more than half (54.5%) of AD patients. Cat allergy positivity was seen in 21.8% of the children, and pollen allergy positivity was observed in 14.5% of the children. The decreased skin sebum and moisture contents in our AD patients may also be due to the destruction of the skin barrier by aerosol allergens. In addition to

Table 5. Skin moisture, sebum and SCORAD values before and after treatment in patients receiving pimecrolimus and tacrolimus

	Receiving Pimecrolimus (n=28)	P value	Receiving Tacrolimus (n=27)	P value
	Median (min-max)		Median (min-max)	
Moist (%)- before treatment Moist (%)-after treatment	30.5 (10.0-55.0) 37.3 (15.0-60.0)	<0.001	30.0 (11.0-45.0) 40.0 (15.0-57.0)	<0.001
Sebum (%)- before treatment Sebum (%)- after treatment	24.5 (16.0-49.0) 26.0 (19.0-48.0)	0.170	24.0 (16.0-49.0) 30.0 (18.0-50.0)	0.060
SCORAD- before treatment SCORAD- after treatment	68.9 (25.0-90.0) 15.0 (5.0-40.0)	<0.001	65.7 (25.0-96.0) 10.0 (5.0-40.0)	<0.001

SCORAD: SCORing Atopic Dermatitis

pharmacological treatments such as moisturizers, topical steroids and calcineurin inhibitors, protection from environmental allergens is necessary for the control of the disease in AD patients. Necessary information should be given to families and children in this regard, and the awareness of the family and the child on environmental precautions should be increased.

The SCORAD score is frequently used in evaluating the clinical severity of the disease and following the prognosis of the disease in patients with AD.[25] All AD patients included in our study were moderate or severe AD patients. After the treatment, the SCORAD scores of the patients were significantly lower than before the treatment. A study in the literature showed a decrease in SCORAD scores of moderate to severe AD patients after topical corticosteroids, similar to our study.[26] In another study in the literature, a significant decrease in SCORAD scores was observed after methotrexate treatment in moderate to severe AD patients.[27] The results in the literature and the results of our study show that SCORAD is an important objective marker in evaluating response to treatment. In our study, the measurement of SCORAD scores before and after the treatment, apart from skin moisture and sebum, enabled us to associate the changes in the moisture and sebum content of the skin with the change in the clinic of AD. In other words, symptoms such as itching and dry skin, which developed with allergic and inflammatory mechanisms in AD patients, regressed in our patients after treatment, and this was reflected in SCORAD scores. At the same time, an increase in the skin moisture and skin sebum content of our patients was observed with the treatment. In this way, the barrier function of the skin can be improved and the function of the mechanisms that cause AD findings can be reduced.

Skin moisture and sebum in AD patients have been reported to be lower than those of healthy individuals.[28] In our study, it was possible to increase the amount of skin moisture and sebum with topical corticosteroid given to AD patients in the active period and then with topical calcineurin inhibitors given in the proactive period. In addition, while this increase was significant only in skin moisture in those receiving moderate potency topical corticosteroids in the treatment; statistically significant post-treatment increases in both skin moisture and skin sebum were seen in those receiving high potency topical corticosteroids. Topical corticosteroids show their effect in the treatment of AD by interacting with inflammatory cells and suppressing the release of pro-inflammatory cytokines.[29] It has been reported that higher potency topical corticosteroids heal faster in lesions.[30] In our study, it is expected to see a significant improvement in both skin moisture and skin sebum amounts in high potency topical corticosteroids.

Topical calcineurin inhibitors are used in the proactive treatment of AD. In our study, after the use of pimecrolimus or tacrolimus in proactive treatment in AD patients, an increase in skin moisture and skin sebum was observed. According to the literature, after the use of topical calcineurin inhibitors, the findings of AD patients improved.[31] Calcineurin inhibitors also act with mechanisms that suppress inflammation.[32] With the given treatment, inflammation as well as skin findings such as dryness, itching and skin damage are reduced in AD patients. Thus, it can be interpreted that the skin barrier, skin moisture and sebum content are also improved with the treatment.

Limitations and Strengths

The fact that our study was conducted in a single center creates a limitation in terms of the generalizability of the results. Another limitation of our study is that our patients with AD were moderate and severe patients according to the SCORAD score. For this reason, the change in skin moisture and sebum measurements of mild AD patients with treatment could not be evaluated within the scope of our study. This may be due to the fact that mostly moderate and severe AD patients applied to the hospital, since the clinic where the study was conducted was a tertiary hospital. The high probability of referral bias in our study also creates a limitation in terms of the generalizability of the study results. No study has been found in the literature evaluating the skin moisture and skin sebum changes in AD patients after treatment compared to before. This is the strength of our study. In our study, apart from skin sebum and skin moisture, the changes in SCORAD scores after treatment were also examined. Skin sebum and moisture were also evaluated according to the type of treatment received. Thus, our study contributes to the literature with a broad perspective.

CONCLUSION

According to the results of our study, the SCORAD scores of our patients with moderate and severe AD decreased significantly after treatment compared to before treatment. After the treatment, the skin moisture and skin sebum values of the children were statistically significantly higher than before the treatment. This increase was only significant in skin moisture in those receiving moderate potency topical corticosteroids in the treatment. There was a statistically significant increase in both skin moisture and skin sebum after treatment in high potency topical corticosteroids. While a significant increase in skin moisture was observed after the use of pimecrolimus and tacrolimus in proactive treatment, the increase in skin sebum was not statistically significant. According to the

results of our study, both the contents of skin moisture and sebum improved significantly after treatment in children with AD. This situation highlights the importance of adherence to treatment and continuity of selected treatments in patients. When the treatment is started by the physicians, the child and the family should be counseled with recommendations such as the importance of treatment and adherence to treatment, the use of medication, and avoidance of environmental allergens. There is a need for further multicenter studies with larger samples to support our study on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the University of Health and Sciences, Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 20/06/2023, Decision No: 196).

Informed Consent: Before participating in the study, participants and parents were informed about the study and their consent was obtained.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

TRANSLATIONAL&PRACTICAL MEDICINE

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Timing of adjuvant chemoradiation for pancreatic cancer with positive surgical margins

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ABSTRACT

Aims: Impact of adjuvant chemoradiation timing on the outcome of pancreatic cancer patients with positive surgical margins is unknown. The aim of this study was to evaluate the effect of adjuvant chemoradiation timing for margin positive pancreatic cancer patients.

Methods: A total of 36 pancreatic adenocarcinoma patients with positive surgical margins and received adjuvant chemoradiation were included in the study. The median radiation dose was 50.4 Gy in 28 fractions. The primary study variable was the timing of chemoradiation, grouped as immediate (after ≤ 1 cycle of chemotherapy) and delayed (after two or more cycles of chemotherapy) chemoradiation. Gemcitabine (n=16) and capecitabine (n=20) were chemotherapy regimens administered with radiation.

Results: Median follow-up time was 23.7 months. Thirteen patients (36%) received immediate and 23 (64%) received delayed chemoradiation. For immediate and delayed treatment groups, median overall survival was 13.5 and 42.5 months, and disease-free survival was 6.4 and 18.8 months, respectively. Disease-free survival and overall survival were better with delayed chemoradiation (p=0.02). However, the two groups did not significantly differ in locoregional control (p=0.96).

Conclusion: Delaying chemoradiation until completion of systemic therapy improves disease-free survival and overall survival without any difference in locoregional failure compared to early chemoradiation in pancreatic cancer patients with positive surgical margins.

Keywords: Pancreatic cancer, positive margin, chemoradiation timing, prognosis

INTRODUCTION

Surgery with clear resection margins has prognostic importance for the management of pancreatic cancer and positive surgical margin is associated with poor survival.[1] Incomplete surgical resection (R1) rates following pancreatoduodenectomy for pancreatic adenocarcinoma are reported to vary from below 14% to 85%,[2-4] and postoperative 5-year survival usually does not exceed 20% irrespective of margin status.[5,6]

In patients with pancreatic cancer, chemoradiation (CRT) is generally recommended after completion of systemic chemotherapy regardless of surgical margins,[7,8] in contrast to certain gastrointestinal malignancies.[9,10] However, there is no consensus on the timing of CRT in pancreatic cancer, and to our knowledge, the impact of CRT timing in the adjuvant setting of positive surgical margins in pancreatic cancer is not investigated before.

In this study, we investigated the impact of CRT timing on the outcome of pancreatic cancer patients with positive surgical resection margins.

METHODS

The study was carried out with the permission of Marmara University Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 09.2022.86). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Treatment results of 36 pancreatic adenocarcinoma patients with positive postoperative resection margins (R1 resection), treated with adjuvant CRT in addition to chemotherapy between January 2013 and September 2021 were evaluated. Patients with R0 resection

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(completely resected tumor with negative surgical margin) were not included in the study.

Baseline data on patients and tumor characteristics were recorded. All patients underwent surgical resection. Surgical procedures were distal pancreatectomy (n=3), total pancreatectomy (n=1), and pancreatoduodenectomy (Whipple Procedure) (n=32). Tumor (T) stage was T1 in 2, T2 in 17, T3 in 15, and T4 in 2 patients according to American Joint Committee on Cancer (AJCC, 8th edition) staging system.

Median radiotherapy dose was 50.4 (45-56) Gy in 1.8 Gy daily fractions, using intensity modulated radiation therapy or volumetric arc therapy. Tumor bed and regional (peripancreatic, celiac, superior mesenteric, porto-hepatic, and para-aortic) lymph nodes were included in the clinical target volume. Concurrent chemotherapy was either gemcitabine (n=16) or capecitabine (n=20). Adjuvant chemotherapy was gemcitabine-based in 27 patients and 5-flourourasil-based in 9 patients.

Patients were grouped according to the timing of CRT as immediate or delayed, consistently with Radiation Therapy Oncology Group (RTOG) 9704 11. Immediate CRT was defined as irradiation with or before the first cycle of adjuvant chemotherapy and delayed CRT was with or after the second cycle of adjuvant chemotherapy. The pathologic tumor (pT) stage was pT1 in 1, pT2 in 3, and pT3 in 9 patients in the immediate CRT group. In the delayed CRT group, number of patients with pT1, pT2, pT3, and pT4 tumors were 1, 14, 6, and 2, respectively. Pathologic nodal (pN) stage of the patients in immediate CRT group was pN0, pN1, and pN2 for 4, 8, and 1 patients, respectively. In delayed CRT group, number of patients with pN0, pN1, and pN2 stages were 3, 11, and 9, respectively. Patient characteristics are summarized in Table 1.

Follow-up visits were scheduled every 3 to 4 months. Disease recurrence was assessed by physical examination, computed tomography/ magnetic resonance imaging, and tumor markers.

Locoregional failure (LRF) was defined as recurrence at pancreatic bed or regional (peripancreatic, celiac, superior mesenteric, porto-hepatic, and para-aortic) lymph nodes. Metastases at liver, peritoneum, lung, bone or other distant sites were defined as distant failure.

Primary study endpoints were disease-free survival (DFS) and overall survival (OS). Secondary endpoint was locoregional control (LRC). OS was defined as the period (months) from the date of surgery until the last visit or death. DFS was defined as follow-up time (months) from the date of surgery to the first event.

Table 1. Baseline characteristics of patients

	Delayed CRT n (%)	Immediate CRT n (%)	p value
Age			
≤ 62	13 (56.5)	6 (46.2)	0.54
> 62	10 (43.5)	7 (53.8)	
Gender			
Female	9 (39.1)	6 (46.2)	0.68
Male	14 (60.9)	7 (53.8)	
Tumor Location			
Head	17 (73.9)	12 (92.3)	0.18
Body-Tail	6 (26.1)	1 (7.7)	
Stage			
1,2	12 (52.2)	12 (92.3)	0.05
3	11 (47.8)	1 (7.7)	
Grade			
1,2	14 (60.9)	12 (92.3)	0.06
3	9 (39.1)	1 (7.7)	
Adjuvant CT Agents			0.07
Gemcitabine based	15 (65.2)	12 (92.3)	
5-Flourouracil based	8 (34.8)	1 (7.7)	
Local Recurrence			
Yes	4 (17.4)	2 (15.4)	0.87
No	19 (82.6)	11 (84.6)	
Distant Metastasis			
Yes	7 (30.4)	9 (69.2)	0.02*
No	16 (69.6)	4(30.8)	
Local/Distant Recurrence			
Yes	11 (47.8)	11 (84.6)	0.03*
No	12 (52.2)	2 (15.4)	
Death			
Yes	9 (39.1)	10 (76.9)	0.02*
No	14 (60.9)	3 (23.1)	

CRT: Chemoradiation, CT: Chemotherapy

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows 23.0 (IBM SPSS Statistics, New York, USA). Descriptive statistics stratified by timing of adjuvant CRT were performed. The $\chi 2$ test was used to compare categorical variables, and the Kruskal-Wallis test was performed to compare the median values of continuous variables. Survival probabilities were estimated using Kaplan-Meier methodology and compared using log-rank statistics. Univariate and multivariate Cox regression models were used to generate hazard ratios. P-value < 0.5 was defined as statistical significance.

RESULTS

Median age was 62 (55-67) years. Median follow-up time was 23.7 (7-101) months. Median OS of the study population was 42.5 months (95% CI: 13.9-71.0) and median DFS was 16.1 months (95% CI: 13.2-19.0). Number of the patients received immediate and delayed CRT were 13 (36%) and 23 (64%), respectively. Median DFS for the patients treated with immediate and delayed

CRT was 6.4 and 18.8 months, respectively (p=0.02; Figure 1). Median OS was better in patients treated with delayed CRT (42.5 vs. 13.5 months; p=0.02) (Figure 2).

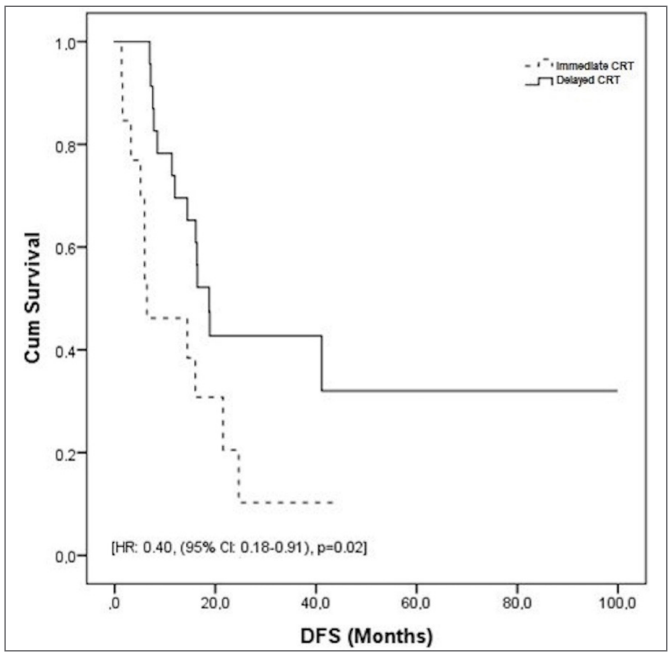

Figure 1. Disease free survival in patients treated with immediate and delayed chemoradiation

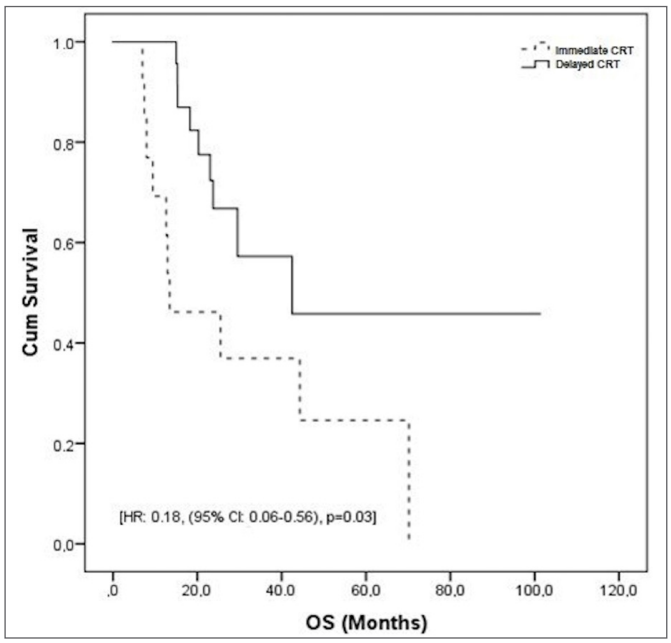

Figure 2. Overall survival in patients treated with immediate and delayed chemoradiation

Primary sites of distant failure were liver in 6 (17%) patients, peritoneum in 4 (11%), lung in 4 (11%), and bone in one (2%) patient. Median recurrence-free survival (RFS) of the study population was 7.2 months (95% CI: 0.2-14.8). Median RFS for delayed and immediate CRT groups was 11.95 and 11.38 months, respectively (p=0.96). Six (17%) patients developed local failure. Median time to LRF was 11.95 vs. 13.7 months for delayed and immediate CRT groups, respectively (p=0.96) (Table 2).

Table 2. Patients' outcome based on adjuvant CRT timing

	Immediate CRT	Delayed CRT	p-value
Median OS (Months)	13.5	42.5	
2-year OS (%)	38.5	47.8	0.02*
Median RFS (Months)	11.38	11.95	
2-year RFS (%)	38.5	39.1	0.96
Median time to LRF	13.7	11.95	
2-year LRC (%)	38.5	39.1	0.96

CRT: Chemoradiation, OS: Overall survival, RFS: Recurrence free survival, LRF: Locoreginal failure, LRC: Locoregional control

DISCUSSION

Results of our study showed that compared to immediate adjuvant CRT, OS and DFS were better with delayed adjuvant CRT in margin-positive pancreatic cancer patients.

Conflicting results are reported about the impact of CRT in the adjuvant setting of resected pancreatic cancer.[12-15] A meta-analysis by Butturini et al.[16] showed an increased survival benefit with adjuvant CRT in patients with R1 resection compared to R0 resection. In daily clinical practice, CRT is almost always delayed until completion of systemic therapy irrespective of margin status due to the aggressive nature of the disease and the importance of systemic control.[8]

Previous studies reported that timing of CRT in the adjuvant setting of pancreatic cancer did not significantly affect DFS or OS, regardless of the margin status.[17] However, the impact of adjuvant CRT timing on outcomes of patients with positive surgical margins has not been studied before.

Timing of adjuvant CRT after resection of pancreatic cancer was investigated by Wo et al.[17] and they reported that early or late adjuvant CRT for resectable disease did not significantly affect LRC or OS. They found that resection margin positivity was significantly associated with LRF but not OS. However, they did not analyze patients' survival and recurrence patterns in terms of immediate or delayed postoperative radiotherapy. In our study, delaying CRT after completion of systemic therapy in margin positive patients showed better DFS and OS, although the patients in these group had more advanced stages.

Early CRT is preferred in patients with margin positive gastric or gastroesophageal/esophageal cancers in adjuvant setting.[9,10] However, delaying CRT until completion of systemic chemotherapy is preferred in patients with margin positive pancreatic cancer, though there is no study conducting the effectiveness of early or late CRT.[8]

In our study, OS and DFS were better in the delayed CRT group. Surprisingly, LRR rates were not affected by the timing of CRT. This may be due to the low number of

patients in the immediate CRT group. Treating patients with systemic therapy first may result in the abandonment of early radiotherapy and this may explain the low number of patients in the immediate treatment group.

Our study has some limitations. It is a retrospective study and despite the collection of nine years of data, the patient number is very small due to strict selection criteria.

CONCLUSION

Treating margin-positive pancreatic cancer patients with adjuvant CRT following multi-agent systemic therapy increases OS and DFS compared to immediate treatment. LRC does not change with CRT timing. Further studies with larger patient numbers are needed to evaluate these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Marmara University Clinical Researches Ethics Committee (Date: 23.06.2022, Decision No: 09.2022.86).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

TRANSLATIONAL&PRACTICAL MEDICINE

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Frequency of night eating syndrome and its relationship with impulsivity in bariatric surgery candidates

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ABSTRACT

Aims: Eating attitude disorders are more common in obese individuals compared to the normal population and cause resistance to treatment. In our study, it is aimed to determine the frequency of night eating syndrome, which is an eating disorder, and to reveal its relationship with impulsivity, which is a personality trait, in bariatric surgery candidates with severe obesity .

Methods: Between May 2022 and December 2022, 93 patients aged 18-65 years who were planned for bariatric surgery were applied to Balıkesir University Health Practice and Research Hospital General Surgery outpatient clinic, Hamilton anxiety scale (HAMA), Hamilton depression scale (HAMD), Barratt impulsivity scale (BIS-11), Night Eating Questionnaire (ADL) were applied.

Results: 69 (74.2%) of the participants were women. There was no significant difference between genders in terms of ADL scores (p=0.683). h Night eating syndrome was detected in one third of the patients. (N=31). Barratt -not planning and total scale scores of patients with an ADL score above 25 were found to be higher than those with an ADL score of 25 and below (p=0.010, p=0.044, respectively).

Conclusion: Considering that night eating syndrome is associated with one third of obesity and it is associated with impulsivity, addressing the impulsivity of individuals with overeating in cognitive behavioral therapy before the operation will contribute to the success of the treatment.

Keywords: Night eating syndrome, bariatric surgery, obesity

INTRODUCTION

Obesity is an important public health problem that is increasing rapidly and negatively affecting life by causing disability. Investigating the factors that cause obesity gains importance in terms of detecting preventable conditions. For this reason, studies on detecting conditions that may provide psychiatric predisposition have increased in recent years.[1] The frequency of eating disorders is higher in obese individuals compared to the normal population. Although binge eating disorder draws the most attention for this situation; Other eating attitude disorders such as food addiction, emotional eating, restricted eating and night eating syndrome (NES) are also prominent.[2,3] In the DSM-5, NES is defined under the category of Other Specified Feeding or Eating Disorders, which includes nocturnal eating episodes defined as eating after waking up and/or binge eating after dinner.[4] In a study evaluating night eating syndrome in patients diagnosed with depressive and anxiety disorders, it was determined that the presence of depression and high body mass index were predictors of NES.[5] Another condition that is mentioned in eating disorders and obesity and often accompanies these disorders is impulsivity.[6,7] By definition; acting without thinking, regardless of the possible negative consequences of one's decisions Tendency or rapid response to stimuli was defined as a predisposition to unplanned movements. Although it is not a psychiatric diagnosis on its own, many psychiatric disorders are is one of the core symptoms.[8] There are studies indicating that impulsivity maintains faulty eating behavior in both obese individuals and individuals without obesity and with eating attitude disorders.[9,10] High level impulsivity is thought to be a risk factor contributing to increased, food intake and unhealthy diet.[11] In addition, impulsivity It is stated that obesity also contributes negatively to classical behavioral therapy. From a theoretical perspective Difficulty in adapting to the behavioral changes required for weight loss can be expected from

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impulsive individuals. Choosing smaller but shorter-term gains rather than long-term gains seen in impulsive individuals tendency may contribute to difficulties in the treatment of obesity in these individuals.[12,13]

Accompanied by this information in the literature; In our study, it is aimed to determine the frequency of night eating syndrome in bariatric surgery candidates with severe obesity and to reveal its relationship with impulsivity, a personality trait that we think may be related. We aim to detect these symptoms to help define the risk factors for post-operative weight regain and to contribute to increasing success in the post-op period.

METHODS

The study was carried out with the permission of Balıkesir University Health Sciences Non-interventional Researches Ethics Committee (Date: 17.05.2022, Decision No: 2022/56). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The universe of the research; patients between the ages of 18-65 who were planned for bariatric surgery by applying to the General Surgery Polyclinic of Balıkesir University Health Practice and Research Hospital between May 2022 and December 2022. The patients were evaluated in the Mental Health and Diseases outpatient clinic, and written consent was obtained for participation in the study; Hamilton anxiety (HAMA) and Hamilton depression (HAMD) scales were administered by the clinician. Scale scores of 5 and 7 and below, respectively; 93 patients suitable for the study constitute the sample of the study. To the participants; Sociodemographic data sheet, Barratt impulsivity scale (BIS-11), Night Eating Questionnaire (ADL) were applied. As exclusion criteria; mental retardation, pregnancy and accompanying alcohol/substance use disorder were determined.

Clinical Evaluation Scales

Night Eating Questionnaire (DL): It is a screening questionnaire consisting of 14 questions developed by Allison et al.[14] and adapted into Turkish by Atasoy et al.[15] Questionnaire morning appetite and first food intake of the day, evening and night eating, evening rate of food intake after dinner, cravings, night eating behavior The control included questions about difficulty falling asleep, frequency of waking up at night, awareness and mood during night eating. Items other than the 7th item in the questionnaire are five-dimensional. It is scored between 0 and 4 with a Likert- type measurement. Items 1, 4 and 14 are reverse scored. The total score can be between 0-52. Original night eating disorder for a score of 25 and above in the study and night eating disorder for below this score. is not envisaged.

Barratt Impulsivity Scale-11 (BIS-11): Barratt the impulsivity Scale-11 consists of thirty items and is self -contained. It has three, subscales.[16] These scales are; attention (inattention and cognitive disorder), motor (motor impulsivity, impatience) and lack of planning (control of inability to provide cognitive to the confusion intolerance). Barratt impulsivity scale 4 different sub-scores are obtained when evaluating; total score, non-planning, attention and motor impulsivity scores. The higher the total score, the higher the patient's impulsivity. the higher the level. Barratt Impulsivity-11 scale Turkish validity and reliability study made by Gülec, et al.[17]

Statistical Analysis

Package) for statistical analysis of data for the social Sciences) 25.0 package program was used. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where appropriate). Chi-square test was used to compare categorical expressions. Kolmogorow-Smirnov test was used to determine whether the parameters in the study showed normal distribution. Mann Whitney U test was used for the parameters that did not show normal distribution. In determining the relationship between continuous measurement parameters, Spearman's The rho correlation test was used. Statistical significance level was taken as 0.05 in all tests .

RESULTS

The mean age of the patients included in the study was 37.3±11.2 years; The mean preoperative BMI was calculated as 45.7±6.8.

69 (74.2%) of the participants are women. In terms of gender, the ADL score (mean±sd) of women was 22.6±9.9, and 22.9±9.1 for men; There was no significant difference between genders in terms of night eating questionnaire scores (p=0.683)

The total scale scores of the participants are given in Table 1.

Table 1. Mean scale scores of participants

Scales	Mean±SD
Night Eating Questionnaire (DL)	22.7±9.7
Barratt - Not Making a Plan	22.5±5.9
Barratt - Engine	18.0±3.8
Barratt - Caution	14.1±4.2
Barratt - Total	54.1±11.5

No correlation was found between night eating questionnaire scores and age and BMI index of the patients. (p=0.575, p=0.469). When the relationship between ADL scores and impulsivity is examined;

The patients' ADL scores and Barratt -Motor, Barratt -Attention and Total scores were positively (linear) weak (r=0.204; r=0.224; r=0.288); It was determined that there was a positive (linear) moderate correlation with the Barratt -Not Making a Plan score (r=0.314).

Table 2. The relationship between ADL and related parameters

	ADL score	
	r	p
Age	0.059	0.575
BMI preop	-0.076	0.469
Barratt - Not Making a Plan	0.314**	0.002
Barratt - Engine	0.204*	0.049
Barratt - Caution	0.224*	0.031
Total Barratt	0.288**	0.005

* p<0.05, **p<0.001, r: Spearman's rho correlation, +: Chi-square

When the patients were divided into two groups as 25 and above 25 points according to the 25 points accepted as the cut-off value in the original study; night eating syndrome was found in one third of the patients. (n=31). There was no statistically significant difference between the two groups in terms of gender, age and BMI. (p=0.615, p=0.308, p=0.483). It was determined that patients with an ADL score above 25 (the group with night eating syndrome) had higher Barratt -planning and total scale scores than those with an ADL score of 25 and below (p=0.010, p=0.044, respectively). No significant difference was found between the other parameters in Table 3 and the ADL groups (p >0.05).

Table 3. Analysis of clinical variables according to the presence of night eating syndrome

	GYA 25 and below (n =62)	GYA over 25 (n =31)	p
Gender (n(%))			
Woman	45 (72.6)	24 (77.4)	0.615+
Male	17 (27.4)	7 (22.6)	
Age (Mean±Sd)	36.7±11.3	38.6±11.1	0.308
BMI preop (Mean±Sd)	45.9±7.1	45.1±6.3	0.483
Scales	**(Mean±Sd)**	**(Mean±Sd)**	
Barratt -Plan (Av±Sd)	21.2±5.0	24.9±6.8	0.010*
Barratt -Engine (Av±Ss)	17.8±3.8	18.4±3.7	0.316
Barratt -Attention (Av±Sd)	13.5±3.9	15.2±4.6	0.130
Total Barratt (Mean±Sd)	52.1±10.1	58.2±13.1	0.044*

* p<0.05, **p<0.001, Mean±Sd : Mann Whitney U, +: Chi-square

DISCUSSION

After losing weight quickly after obesity surgeries, it becomes important to maintain this weight. In recent years; with the increase in surgery rates; on causes of weight regain (KGA) A lot study carried out, and possible factors were investigated. Lauti et al.[18] summarized the causes of CGA in five main, items : malnutrition; hormonal / metabolic imbalance; factors related to mental health; insufficient physical activity and anatomical surgical factors. Among the factors related to mental health, the continuation of depressive disorders, anxiety disorders and eating disorders are the first reasons that come to mind. Interest in other eating disorders has started to increase, especially after the data on the association of binge eating disorder and obesity. The frequency of night eating syndrome in bariatric surgery candidates can vary in a wide range such as 8.2%-55%, together with the evaluation of the diagnostic criteria and time factor. Baldofski et al.[19] found that the rate of meeting the criteria for night eating syndrome in surgical candidates was 8.2%. These individuals reported emotional eating, eating without feeling hungry, and food addiction symptoms more frequently than other individuals without an eating disorder. In our study, the night eating questionnaire score was found to be above 25 in approximately 1/3 of the surgical candidates, and these patients met the diagnostic criteria for night eating syndrome at the clinical interview. This situation is consistent with the literature. In addition, no difference was found in terms of frequency in men and women, nor was it associated with BMI. Sevinçer et al.[20] found the prevalence of NES to be higher in women in a study conducted with university students. Only the morbid The fact that it consisted of obese individuals may have caused the inability to reveal the relationship with gender and BMI. It is also important to know how much the frequency, which was determined at a rate of one third before the operation, continues after the operation and the related factors. In the flood study, it was observed that 27.6% of the patients experienced NES preoperatively and 10.3% postoperatively.[21] Chang's[22] systematic review _ pass found the rate of NES after surgery to be between 1.9% and 42%. In a study by Ünal et al.[23] those who experience weight regain after bariatric surgeries and those who do not compared to night eating was significantly higher. However, according to hierarchical linear regression analysis results, it was stated that night eating did not predict weight regain. In another study, it was stated that body perceptions were worse after bariatric surgery in people who continued to eat at night after surgery.[24]

Obesity and impulsivity studies have gained momentum in recent years. Significant relationship between impulsivity and disordered eating attitudes known to be impulsive It is associated with excessive food intake and compulsive eating. In rats; high with food addiction impulsiveness relationship between the level is; addiction of delicious foods features of high impulsiveness level of risk factor transferred.[25,26] In addition, impulsivity was interpreted as a predictor of losing weight with diet, gaining weight after treatment,

and discontinuing treatment. in the literature obesity and impulsivity women, obese patients with binge eating disorder, and obese kids over focused.[27-29] In a study evaluating both genders together morbid impulsivity in obese patients higher than healthy controls, no difference was found between non -morbidly obese patients and healthy controls. This result, impulsivity more morbid than non - morbid obese patients may be a condition specific to obese patients. suggests.[30] For this reason, this concept should be investigated more carefully in patients who apply for bariatric surgery with severe obesity. Ryden et al.[31] morbid impulsivity of obese patients after medical and surgical treatment unchanged, that this situation causes weight gain again has reported. Arias et al.[32] morbid binge eating disorder more impulsivity in obese than in those without binge eating disorder has determined. Carrard et al.[33] eating disorder exhibiting and meeting the symptoms of food addiction higher in people who do not meet symptoms impulsiveness indicated. its population In a study of bariatric surgery candidates, a significant relationship was found between food addiction and impulsivity scores. found.[34] Saraçlı et al.[35] Night eating syndrome was admitted to the psychiatry clinic with depression, impulse control disorder and nicotine addiction. applicant found to be common among obese patients. While a positive relationship was found between night eating and impulsivity in our study, individuals diagnosed with night eating had high scores on non-planning from the subscales. we saw. Impulsivity related to not making plans, being main oriented, future considers acting without thinking.[36] Inability to plan; your impulsiveness cognitive It is associated with a deterioration in the direction of gratification and people are more unsuccessful in delaying gratification. Immediate smallpox as a result of inability to plan rewards later, the future is bigger preferable to awards. Therefore, not making plans is obese. may play a key role in the process leading to morbidity.[30] In addition; Nasser et al.[37] a positive correlation between the scores of not planning and loss of control during binge eating in obese patients. has found. Neederkoorn et al.[38] reduce cognitive impulsivity leading to overeating in obese patients. behavioral therapy specifically. He suggested that he should focus on.

CONCLUSION

To summarize the important findings of our study, it was determined that one-third of bariatric surgery candidates had night eating syndrome and that these people had problems especially in the sub-title of impulsivity and not being able to plan. We conclude that future studies investigating the post-operative persistence rates of night eating syndrome and its relationship with impulsivity will contribute to the success of the surgery. However, the cross-sectional nature of our study and the fact that the scales are self-report scales are also limitations of the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Health Sciences Non-interventional Researches Ethics Committee (Date: 17.05.2022, Decision No: 2022/56).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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End-of-life decisions in the intensive care unit-exploring the knowledge and attitude of nurses and doctors: a national survey

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ABSTRACT

Aims: In Turkey, there is a growing awareness regarding end-of-life practices. It has become evident that treatments in intensive care to end-stage patients, instead of honoring their previously made end-of-life decisions, significantly diminishes patients' overall quality of life. The aim of study is drawing attention to end-of-life decision practices and to evaluate the knowledge and attitudes of intensive care physicians and nurses, who are decisive in end-of-life decision-making practices.

Methods: The study was planned as a multi-center, cross-sectional, descriptive questionnaire. There were 21 questions about demographic data, definitions, and end-of-life decisions. 259 of 760 intensive care physicians and nurses who filled out the questionnaire were included.

Results: Two hundred and fifty-nine participants were included. The rate of decision for terminal sedation and euthanasia was differentiating according to intensive care experience. Participants' knowledge was insufficient regarding withholding and withdrawal approaches. Intensive care physicians, and patients at the terminal stage of chronic disease were recommended as decision makers with the highest rate.

Conclusion: In this study, it was determined that the participants' knowledge about end-of-life decision concepts was not sufficient, and their approaches were differentiating due to experience. It is considered that there is a need for education and standardization about end-of-life decision-making process.

Keywords: End-of-life decision, terminal period, knowledge

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INTRODUCTION

Most of the deaths occur in hospitals, especially in intensive care units. It is known that 20% of deaths in the United States of America (USA) occur in intensive care units or the early period after intensive care.[1] In intensive care units (ICU), medical treatments involve using advanced life support systems, such as mechanical ventilation and dialysis, to provide organ support. These treatments utilize high technology and come with high costs.[2] In Turkey, some patients in the terminal stage of their chronic diseases are followed up in the ICU instead of applying end-of-life decisions and palliative care.[3] Integrating practices such as end-of-life decisions into the healthcare system is considered as an indicator of a country's level of development. Although our country's number of palliative care units is insufficient, it is gradually increasing.[4]

According to the American Academy of Hospice and Palliative Medicine and the American Medical Institute, palliative support is the care provided to patients with incurable, progressive diseases, considering their physical, social, religious, and existential needs. Palliative care aims to enhance the patient's quality of life.[5,6] Implementing end-of-life decisions is crucial for appropriately utilizing limited intensive care resources. With these decisions, it is known that end-stage patients experience this period more comfortably, and the period with pain is getting shorter.[3,7]

While some countries have legal regulations governing end-of-life decisions, and advanced directives, our country needs to develop and extend legislations in this regard.[8-10]

Treatments administered to trauma patients with

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irreversible severe injuries, patients in the terminal stage of chronic systemic diseases, or patients with medical conditions that cannot be effectively treated with current interventions often result in a low quality of life, futile treatments, or death. Factors such as legal regulations, cultural and religious beliefs, the opinions of patients and their relatives, as well as the approaches of the intensive care nurses and physicians who provide care, play a crucial role for applying end-of-life decisions.[8,11,12] In intensive care settings nurses and, more often, physicians are involved in this process.[13]

A literature review considering this information indicates a limited number of studies evaluating the knowledge and attitudes of nurses and physicians regarding end-of-life decisions and the individuals involved in the decision-making process. Therefore, this study aims to assess the level of knowledge among intensive care nurses and physicians regarding end-of-life decisions.

METHODS

The study was planned as a multi-center, cross-sectional, descriptive questionnaire study with the approval of Cukurova University Non-interventional Clinical Researches Ethics Committee (Date: 06.07.2018, Decision no: 79). All procedures were performed in our study by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and ethical standards.

Between August 2018 and August 2019, 259 of 760 intensive care physicians and nurses who accepted to participate to the study and filled out the study questionnaire sent by e-mail and multimedia message were included in the study. Responses were anonymous and non-traceable to individual participants.

The questionnaire included the demographic characteristics of nurses and physicians, the duration of experience in intensive care, the unit and the institution participants work in, and definitions and questions about end-of-life decisions. End-of-life decisions are defined as follows:

Withholding Approach

The concept of not performing necessary treatments and practices. Withdrawal approach: Abandoning supportive treatment decisions.

Terminal Sedation

Treatment of pain and symptoms (even if shortening surveillance). Euthanasia: Ending the life of a well-informed patient with unbearable and insoluble pain by a doctor.

Palliative Care

Improving patients' quality of life in the end-stage of chronic disease.

End-of-life care: Supportive treatment (comfort, symptom, support) of a patient in the last period of his life.

Futile Treatment

Treatment or practices in which medical intervention is useless or ineffective, has no or little benefit to the quality of life, and does not have the possibility of responding to patient expectations.

The questionnaire form was delivered to physicians and nurses via Google Forms® over the Internet.

Statistical Analysis

The statistical analysis of the data was made with the SPSS 20.0 (Chicago IL 20.00, USA) program. Descriptive data were expressed as arithmetic mean±standard deviation and percentages. After the continuous variables were evaluated with the Kolmogorov-Smirnov test regarding whether they were normally distributed, the T-test and Mann-Whitney U tests were used for comparison. Pearson's and Spearman correlation tests were used for the correlation between variables. Chi-square and Fischer Exact tests were used to compare categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Two hundred and fifty-nine participants were included in the study. Among the participants, seventy-three (28.2%) were male, and one hundred and eighty-six (71.8%) were female. The mean age was 33.9±8.4 years.

The participants were categorized based on their professions. One hundred and nineteen (45.9%) of the participants were doctors, and one hundred and forty (54.1%) were nurses. The hospitals where the participants worked were also evaluated. Education and research hospitals accounted for 48.3%(n=125) of the participants, while university hospitals accounted for 32.8%(n=85). Additionally 12.4, %(n=32) of the participants worked in a state hospital.

The participants were evaluated based on the ICU they worked in. The percentage of participants working in the surgical ICU was 16.6%(n=43). The percentage of participants working in the medical ICU was 13.9%(n=36). Most participants, 69.5%(n=180), worked in the surgical-medical mixed ICU. The participants' experience in intensive care field is indicated in Table 1.

Table 1. Experience in intensive care

0-5 Years	50% (n=129)
5-10 Years	31% (n=80)
10-15 Years	9% (n=23)
>15 Years	10% (n=27)

After introducing the end-of-life decisions to the participants, they were asked about their familiarity with the concept, and the difference in knowledge levels between nurses and physicians was evaluated (Table 2).

Table 2. Level of knowledge of end-of-life concepts - Assessment by profession

Terms	Those who say they know the concept		Those who say they don't know the concept		p
	Nurse	Physician	Nurse	Physician	
Withholding treatment	47 (0.18%)	72 (0.28%)	93 (0.36%)	47 (0.18%)	<0.001
Withdrawing treatment	64 (0.25%)	86 (0.33%)	76 (0.29%)	33 (0.13%)	<0.001
Terminal sedation	105 (0.41%)	102 (0.39%)	17 (0.28%)	35 (0.14%)	0.03
Euthanasia	136 (0.53%)	117 (0.45%)	4 (0.02%)	2 (0.01%)	0.53
Palliative care	137 (0.53%)	116 (0.45%)	3 (0.01%)	3 (0.01%)	0.84
End of life care	122 (0.47%)	107 (0.41%)	18 (0.66%)	12 (0.05%)	0.48
Futile treatment	115 (0.44%)	105 (0.41%)	25 (0.1%)	14 (0.05%)	0.17

The study examined the relationship between the knowledge levels of physicians and nurses and their duration of working in the ICU, as shown in Table 3.

Table 3. Knowledge level of the end of life concepts-Relationship with intensive care working year

Terms	Percentage of participants knowledge about the concept (according to the duration of intensive care unit)				p
	0-5 years (n=129)	5-10 years (n=80)	10-15 years (n=23)	>15 years (n=27)	
Withholding treatment	44 (34.1%)	43 (53.8%)	10 (43.5%)	22 (81.5%)	<0.001
Withdrawing treatment	62 (48.1%)	52 (65%)	12 (52.1%)	24 (88.9%)	<0.001
Terminal sedation	95 (73.6%)	67 (83.8%)	20 (87%)	25 (92.6%)	0.06
Euthanasia	124 (96.1%)	80 (100%)	22 (95.7%)	27 (100%)	0.22
Palliative care	126 (97.7%)	78 (97.5%)	22 (95.7%)	27 (100%)	0.78
End of life care	112 (86.8%)	71 (88.8%)	20 (87%)	26 (96.3%)	0.54
Futile treatment	101 (78.2%)	73 (91.2%)	19 (82.6%)	27 (100%)	0.08

In Table 4, participants were asked about the percentage of end-of-life decisions that should be applied to the patients they had been following up in the ICU during the last month, and their responses are provided.

Considering the necessity of implementing end-of-life decisions for the patients under the care of the study participants, it was observed that the proportion of those who believed that terminal sedation and euthanasia should be applied decreased as their duration of experience in the ICU increased. There was a statistically significant difference in the responses between those who worked in the ICU for less than five years and those who worked for more than fifteen years (Table 5).

Table 4. Answers to the question "What percentage of patients you followed up in the last month should be applied to the end-of-life decision?

	Nurse Median±SD	Physician Median±SD	p	Total
Withholding treatment	27.43±68.58	21.99±22.0	0.14	24.9
Withdrawing treatment	18.94±24.51	21.60±22.5	0.04	20.16
Terminal sedation	36.5±33.97	19.53±23	<0.001	28.70
Euthanasia	12.75±22.79	7.99±16.78	0.7	10.56
Palliative care	44.26±30.76	30.60±23.10	<0.001	37.91
End of life care	40.17±31.38	28.71±25.65	0.07	34.91
Futile treatment	30.49±28.74	24.07±22.02	0.31	27.53

Table 5. Intensive care experience-Thought of necessity to implement end of life decision

	0-5 years (n=129)	5-10 years (n=80)	10-15 years (n=23)	>15 years (n=27)	p
Terminal sedation	32.88	30.14	18.96	12.81	0.006
Euthanasia	14.56	7.63	7.04	3.15	0.012

The rate of end-of-life decision-making among the participants was evaluated based on the type of ICU they worked in, whether it was a medical, surgical, or mixed ICU. It was observed that there was no statistical difference between the different types of ICUs (Table 6).

Table 6. Rate of end-of-life decision making according to the intensive care unit worked in

	Median±Standart Deviation			p
	Surgical ICU	Medical ICU	Mixed ICU	
Withholding treatment	18.02±20.56	20.41±22.73	27.48±61.31	0.67
Withdrawing treatment	17.16±20.25	25.02±24.46	19.90±24.11	0.31
Terminal sedation	27.48±27.55	32.30±28.65	28.78±31.73	0.38
Euthanasia	9.86±16.11	14.80±23.49	9.87±20.59	0.32
Palliative care	38.53±27.56	44.50±30.94	36.42±27.79	0.37
End of life care	29.07±27.15	39.75±30.63	35.33±29.59	0.28
Futile treatment	22.26±22.12	31.36±26.22	28.02±26.76	0.35

The determinants for end-of-life decisions were assessed among the participants. The rate of patients approaching to the terminal stage of their chronic disease answer was 28.6% (n=74). The rate of patients in the terminal stage of their chronic disease was 56.8% (n=147). The rate of unconscious patients' families being followed up in ICU was 47.5% (n=123). The responsible physician who followed the patient in the ICU was determined as the determinant

by 89.6% (n=232) of the participants. On the other hand, only 23.2% (n=60) of the participants suggested the nurses following the patient in the ICU as the determinant.

DISCUSSION

It is recommended to implement end-of-life decisions to ensure the appropriately utilization of intensive care beds and providing a more comfortable last period to the end-stage patients.[3] In this process, the competence and approach of healthcare professionals, who are responsible for informing and guiding patients and their families regarding end-of-life decisions, become crucial.

Our study aimed to raise awareness about end-of-life decisions and evaluate the knowledge level of physicians and nurses involved in this process. It was observed that the participants' knowledge (46%, 58%) was insufficient regarding withholding and withdrawal approaches. However, in other questions, the percentage of participants who claimed to be familiar with the concepts ranged from 88% to 98%.

In a national report conducted by Sullivan et al.[14] in 2003 in the United States, it was highlighted that only 18% of medical school students and resident physicians received education on end-of-life decision practices, indicating insufficient knowledge in this area. Consequently, curriculum development and cultural change were emphasized.[15] Several studies have evaluated the knowledge level of nurses regarding end-of-life decisions. Schrerer et al.[16] conducted a study in New York in 2013, while Patti et al.[17] conducted a study in the United States in 1998. Both studies found that nurses had insufficient knowledge about end-of-life decisions. In a multinational study by Coffey et al.[18] in 2016, nurses' knowledge level about end-of-life decisions was evaluated in different countries. The study revealed that the percentage of nurses who knew end-of-life decisions was 49% in Hong Kong, 62% in Italy, 52% in Israel, 100% in the United States, and 75% in Ireland. Comparing the studies by Patti and Coffey, published 18 years apart, it was observed that the knowledge level in the United States reached 100% due to education on end-of-life decisions. Similar to our study, other studies conducted in different countries and at different times have reported insufficient knowledge levels. However, it has been demonstrated that knowledge about end-of-life decisions can be improved through education.

When participants were asked whether end-of-life decisions should be applied to the patients they were currently following up in the intensive care unit, it was found that a high percentage of participants believed that end-of-life decisions should be implemented. This could be attributed to our country's insufficient palliative care units. As a result, patients in need of palliative care are often provided medical support in intensive care units. The high rate of patients requiring end-of-life decisions among intensive care patients may be due to the limited availability of palliative care units for terminal-stage patients who are being followed up in the intensive care unit.[19-21]

The ratio of physicians and nurses who responded to the question regarding their belief in applying end-of-life decisions was evaluated according to the ICU they worked in, no statistically significant difference was observed between the groups (surgical/medical/mixed). According to profession groups, nurses showed a higher ratio in favor of applying supportive treatment withdrawal, terminal sedation, and palliative care to patients. Nurses are involved in the self-care of terminal patients, spend more time with patients and their relatives, and have access to detailed information about the patient's previous and current functional status, as well as the treatment expectations of the patients and their families.[22] It is believed that these factors may contribute to the different responses between the two professions.

Regarding the decision-maker for applying end-of-life decisions to the patient, the participants in our study indicated that the responsible physician following the patient in the ICU had the highest ratio, followed by the nurse who cared for the patient. The patient himself or his legal guardian was also considered a decision-maker, albeit to a lesser extent. Additionally, patients approaching the terminal stage of their chronic disease were mentioned as having some involvement in the decision-making process. Similar to the findings in our study, a prospective, multi-center cohort study by Esteban et al.[13] also found that physicians were more frequently involved in the decision-making process. However, the Australian and New Zealand Intensive Care Association (ANZIC) proposal and the study by McMillen et al.[23] suggested that nurses should play an active role in end-of-life decision-making. It was argued that decisions made solely by intensive care physicians might be one-sided and potentially misleading.[24] The studies by Ahrens et al.[25] and the review by Adams et al.[26] indicated that more positive outcomes were achieved when physicians and nurses were involved in end-of-life decisions.

Study Limitations

The use of an online survey format instead of face-to-face interaction is an important limitation of this study. In addition, the number of participants below the intended target can be stated as another limitation.

CONCLUSION

As awareness surrounding end-of-life decisions continues to expand, the capacity to implement these methodologies for end-stage patients will steadily gain relevance and applicability. In this case, it is necessary to review the

competence related to this issue. Based on this, our study evaluated ICU physicians' and nurses' knowledge and attitudes who are crucial in guiding patients and their families regarding end-of-life decisions. Unfortunately, this study demonstrated that the knowledge level of the participants in this regard was not sufficient. And significant differences were observed between the attitudes of participants based on their experience in the ICU. As a result, there is a need to enhance the level of knowledge and standardize the attitudes of intensive care physicians and nurses toward the end-of-life decision process. Therefore, we propose that issues related to end-of-life decisions should be integrated into the curriculum and included in postgraduate education programs.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Cukurova University Non-interventional Clinical Researches Ethics Committee (Date: 06.07.2018, Decision no: 79).

Informed Consent: A signed and free and informed consent form was obtained from all participants in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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The effects of etiological factors on timing of decortication

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ABSTRACT

Aims: Tube drainage is the primary method in the treatment of empyema with 80-90% cure rates. In patients with empyema who have not received adequate treatment, the result is pleural fibrosis. Decortication is the only treatment option for chronic empyema that has caused fibrothorax that prevents lung expansion. In our study, we aimed to determine the relations between etiological base of the disease, the consequences and the decision of decortication timing.

Methods: The patients who were admitted and hospitalized with pleural effusion between 1994 and 2000 were included in the study. We examined the duration of pretreatment, pleural thickness and the duration of postoperative hospital stay of these cases, with who have undergone decortication surgery.

Results: A total of 82 cases of decortication were enrolled, which consisted of 61 male (74.3%) and 21 female (25.6%). The cases were examined in two groups: tuberculosis [12 (25%) empyema, 27 (56.3%) tuberculous pachypleuritis, 9 (18.8%) pleurisy + parenchymal involvement] and non-tuberculosis [2 (5.9%) trauma, 5 (14.7%) pneumonia + empyema, 23 (%) 67.6% empyema, 4 (11.8%) hydatid cyst]. The effects of preoperative treatment durations on the thickness of the decortication materials and the duration of postoperative hospital stay were investigated. The preoperative treatment period of the tuberculosis group was significantly higher, the decortication pleural thicknesses were found to be greater. ($p<0.01$) There was no statistically significant difference in the duration of postoperative hospital stay between the tuberculosis and other group ($p>0.05$).

Conclusion: In cases that do not respond to closed tube drainage and appropriate antibiotic therapy, decortication should be performed without delay considering the etiological factors. If decortication is performed earlier than 2 weeks, the visceral pleura can be easily separated; parietal decortication is rarely needed which might be an advantage of the procedure.

Keywords: Tuberculosis, empyema, decortication, pleural thickness

This study was previously presented orally online in the 9th UTSAK Congress on 18 March 2022.

INTRODUCTION

Pleural effusions are the most common pleural disease and may develop due to many intrathoracic and systemic diseases. Thoracentesis is made for differential diagnosis; according to the nature of the effusion whether it is transudate or exudate. Transudates are formed because of an increase in hydrostatic pressure or a decrease in osmotic pressure in this barrier (such as congestive heart failure, nephrotic syndrome, atelectasis, hepatic hydrothorax, peritoneal dialysis effusions). They usually indicate that the pleural membranes themselves are not defective. Exudates, conversely, are formed due to the leakage of fluid and protein from an altered, increased permeability barrier. Pneumonia, pulmonary embolism, malignancies, esophageal rupture, chylothorax, ascites, and bacterial peritonitis are some courses in the exudate category. Lymphatic obstruction may accompany accumulation of effusion in both transudates and exudates.

As a result of the presence of fluid in the pleural space, the lung volumes decrease, being less than the volume of the pleural fluid, and restrictive ventilation disorder occurs. Pleuritic chest pain, cough, and dyspnea are the common symptoms. The prognosis varies according to the etiology of all pleural effusions. Exudative pleural effusions (tuberculosis, empyema, hemothorax) often result in pleural thickening. Empyema develop in three stages: exudation, fibrinopurulent, and organization.

Contrast-enhanced thorax computed tomography (CT) has an important role in detecting changes in the chest wall and parietal pleura in patients with empyema and influences therapeutic decisions. The thickened extrapleural fatty tissue layer is used as a basis for measuring the parietal pleural thickness in Thorax CT sections. It is also possible to show bronchopleural fistula tracts with Thorax CT.[1] Empyema is the presence of pus in the pleural space, 60%

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is the result of complicated parapneumonic effusion, 20% occurs after thoracic surgery, the remaining 20% occurs after thoracic trauma, thoracentesis, esophageal perforation, subdiaphragmatic infection. The most important point in the evaluation of complicated parapneumonic effusions is the decision of whether to apply tube drainage or not. The primary method in the treatment of empyema is tube thoracostomy with 80-90% cure rates.[2,3]

Fibrinolytic therapy can be tried in the organizational phase of empyema. In patients with empyema who have not got adequate treatment, the result is pleural fibrosis. Because of the thickened pleura, that hemithorax volume and its expansion decrease, and the mediastinum is pulled to that side.[2] The main functional disorder that occurs is not only the direct inhibition of the expansion of the lung, but also the contraction of the diaphragm, which is the most important muscle of inspiration. Insufficient contraction of the diaphragm on the one hand results in a restrictive ventilation disorder, on the other hand, it causes deterioration in mucociliary clearance and recurrent bronchitis with the deterioration of cough mechanism.[4,5] Tuberculous pleurisy accounts for approximately 10% of patients with tuberculosis and is still the most common cause of exudative pleurisy in many parts of the world. The precise distinction between tuberculous pleurisy and tuberculous empyema is essential before the decision of the treatment.

At the end of the 6-8 weeks of the disease course, varying amounts of fibrous tissue begin to form in the pleura in a significant proportion of these patients.[3] The degree of fibrosis changes depending on the extent of the inflammatory reaction in the pleura, the status of the infection in the lung parenchyma and the adequate medical treatment.[3] If the duration extends, fibroblasts proliferate and settle around the thickened pleura, tending to form a thick-walled loculated pleural collection. This is especially seen in patients with tuberculous pleurisy who had got inadequate treatment. Calcification and fibrothorax often develop in the parietal and visceral pleura in patients with chronic tuberculous empyema. In patients with tuberculous pleurisy, pleural fluid may resolve with medical treatment, so the decision for decortication should be left for 6-12 months after treatment. Approximately 1% of patients may develop fibrothorax after traumatic or iatrogenic hemothorax.

Although several months can be expected for spontaneous resolution of the pleural thickening, decortication is still the only treatment option in chronic empyema that prevents lung expansion, impairs respiratory functions, and causes fibrothorax. Lung tissue must not have remained under the thick pleural tissue for more than six months in order to expand after decortication6. Studies in the literature show that the results of early decortication are satisfactory in cases with closed tube drainage and empyema that do not respond to medical treatment.[6-9] The widespread use of video thoracoscopic surgery (VATS) has brought a new dimension to the treatment of thoracic empyema. While helping to differentiate between acute and chronic empyema by exploration of the pleural space, it also made it possible to treat acute empyema with thoracoscopic debridement and irrigation.[10-12] Several studies reveal that decortication with VATS gives good results for both the patient and the operator in localized empyema that are not located in the diaphragm.[9] The decortication procedure should be considered in patients who require additional drainage after tube thoracostomy or thoracoscopy. Decortication eliminates pleural sepsis and allows the underlying lung tissue to expand. However, it is a major thoracic surgery, and the risk of the operation, the age and the general condition of the patient should be under consideration for decision. Although the risk of complications in the early period is lower, no significant difference was observed between the operations performed in the early or late period in terms of affecting respiratory functions.[13,14]

METHODS

Since there was no Ethics Committee in our hospital in the year 2000 when the study was conducted, the study was carried out under the permission and supervision of the responsible Clinical Chief.

The study was conducted in a single center. The patients who had undergone decortication between January 1994 and July 2000, in Heybeliada Chest Diseases and Thoracic Surgery Center were enrolled. These patients were examined retrospectively from the database of the hospital. All the cases included in the study had preoperative contrast enhanced thorax CT.

According to the postoperative histopathological results of the cases, they were grouped into two groups specific (tuberculosis) and nonspecific (chronic pleuritis, intrapleural hydatid cyst rupture, diffuse malignant mesothelioma=non-tuberculosis).

The effects of the duration of preoperative treatment on the thickness of the decortication material and postoperative hospital stay were investigated in each group. Thorax CTs of all cases were reported by the same radiologist, and pleural thickening measurements in CT were compared with pleural thicknesses in postoperative histopathological evaluations.

Since there was no Ethics Committee in our hospital in the year 2000 when the study was conducted, the study was carried out under the permission and supervision of the responsible Clinical Chief.

Statistical Analysis

While evaluating the study data, besides descriptive statistical methods (mean, standard deviation), the t-Student test and Mann Whitney-u test were used to

compare quantitative data. Pearson correlation analysis was applied to calculate the correlation coefficients. The Chi-square test was used to compare qualitative data. The results were evaluated at the 95% confidence interval and the significance level at p<0.05.

RESULTS

A total of 82 cases between 18-71 years (average 33.79), were included in the study. It consisted of 48 cases with tuberculosis and 34 cases with non-tuberculosis etiology who had undergone decortication. In the group of tuberculosis cases, 12 (25%) were empyema, 27 (56.3%) had pachypleuritis, 9 (18.8%) had pleurisy + parenchyma involvement. The lesion distribution of non-tuberculosis cases is; 2 (5.9%) trauma, 5 (14.7%) pneumonia +empyema, 23 (67.6%) empyema, 4 (11.8%) hydatid cyst (Table 1).

Table 1. Distribution of tuberculosis and non-tuberculosis cases according to lesion types

Tuberculosis	**N**	**%**
Empyema	12	25
Tuberculosis pachypleuritis	27	56.3
Pleurisy + Parenchyma involvement	9	18.8
Total	48	100
Non-Tuberculosis group	**N**	**%**
Trauma	2	5.9
Pneumonia + Empyema	5	14.7
Empyema	23	67.6
Hydatid cyst	4	11.8
Total	34	100

While the mean age of the tuberculosis group was 29.21+12.20, the mean age of the non-tuberculosis cases was 40.26+19.46. While the tuberculosis group consisted of 35 male (72.9%) and 13 female (27.1%) patients, the non-tuberculosis group consisted of 26 male (76.5%) and 8 female (23.5%) patients. Most of the cases were male in both groups (72.9%, 76.5% respectively). While there was a statistically significant difference between the groups according to the mean age (p<0.05), there was no significant difference in the distribution according to the genders (p>0.05) (Table 2).

Table 2. Demographic data of the groups

		Tuberculosis group n=48	Non-tuberculosis group n=34	p
Age (mean±standard deviation)		29.21±12.20	40.26±19.46	0.02; p<0.05*
Gender	Male	35 (72.9%)	26 (76.5%)	0.716
	Female	13 (27.1%)	8 (23.5%)	p>0.05

The mean preoperative treatment duration of the tuberculosis group was 2.42±2.08 months for the tuberculosis group, and 0.63±0.29 months for the non-tuberculous cases. A statistically significant difference was found between the groups in terms of preoperative treatment duration (p<0.001). The number of untreated cases in the preoperative period was 1 (2.1%) in the tuberculosis group and 6 (17.6%) in the non-tuberculosis group; the number of cases who underwent tube thoracostomy was 4 (8.3%) in the tuberculosis group and 5 (14.7%) in the non-tuberculosis group, and they were not included in the statistical evaluations of treatment periods (Table 3).

Table 3. Distribution of groups according to duration of preoperative treatment

	n	**Mean±Standard Deviation (month)**	**p**
Tuberculosis	47	2.42±2.08	0.0001** p<0.0001
Non-tuberculosis	28	0.63±0.29	

**p<0,01 highly significant

There was a statistically significant difference between the two groups in terms of the time of decortication and pleural thickness (p<0.01). In tuberculosis cases, the time of decortication was found to be later and pleural thicknesses were found to be greater (Table 4).

Table 4. Distribution of groups according to the timing of decortication and pleural thickness

	Groups	**Mean±standard deviation**	**p**
Timing of decortication	Tuberculosis	4.58±4.39	0.008
	Non-tuberculosis	2.39±2.00	p<0.01**
Pleural thickness	Tuberculosis	14.73±5.37	0.005
	Non-tuberculosis	11.38±4.88	p<0.01**

**p<0,01 highly significant

There was no statistically significant difference between tuberculosis (Mean±Std. Deviation 15.81±13.6 days) and non-tuberculosis groups (Mean±Std. Deviation 18.17±16.9 days) in terms of hospital stay in the postoperative period (p>0.05) (Table 5).

Table 5. Distribution of groups according to postoperative hospital stay

	n	**Mean±Standard Deviation (day)**	**p**
Tuberculosis	48	15.81±13.6	0.777
Non-tuberculosis	34	18.17±16.9	p>0.05

When the relationship between the duration of preoperative treatment, the time of decortication, pleural thickness and postoperative hospital stay of the cases were examined: There was a positive, good, statistically significant correlation between the preoperative treatment periods of the tuberculosis cases and the decortication timing (r=0.601; p<0.01). There was no correlation between the duration of preoperative treatment and pleural thickness (r=0.032; p>0.05) and postoperative hospital stay (r=-0.165; p>0.05) (Table 6).

Table 6. Distribution of correlation between duration of treatment and timing of decortication, pleural thickness and postoperative hospital stay in tuberculosis cases

	Duration of treatment correlation coefficient (r)	p
Timing of decortication	0.601	0.0001; p<0.01**
Pleural thickness	0.032	0.829; p>0.05
Postoperative hospital stay	-0.165	0.268; p>0.05

While there was a positive, moderate and statistically significant correlation between the duration of preoperative treatment and the time of decortication in non-tuberculosis cases (r=0.385; p<0.05), there was no correlation between the duration of treatment, pleural thickness (r=0.104; p>0.05), and the patient's postoperative mortality (Table 7).

Table 7. Distribution of correlation between duration of treatment and timing of decortication, pleural thickness and postoperative hospital stay in non-tuberculosis cases

	Duration of treatment correlation coefficient (r)	p
Timing of decorticaiton	0.385	0.043; p<0.05*
Pleura thickness	0.104	0.829; p>0.05
Postoperative hospital stay	-0.017	0.268; p>0.05

There was no statistically significant correlation between pleural thickness and postoperative hospital stay in both groups (p>0.05) (Table 8).

Table 8. Distribution of correlation between postoperative hospital stay and pleural thickness according to groups

	Correlation of pleural thickness Coefficient: (r)	p
Postoperative hospital stay of Tuberculosis cases	-0.006	0.968; p>0.05
Postoperative hospital stay of Non-Tuberculosis cases	-0.238	0.175; p>0.05

A statistically significant difference was found between the pleural thickness measured in Thorax CT (Mean±Std. Deviation 7.7±3.76) and decortication material pleural thickness (mean±std. Deviation 13.34±5.4) in all cases (p<0.001) (Table 9).

Table 9. Distribution of relation between pleural thickness in thorax ct and pleural thickness of decortication material in all cases

	n	Mean±Standard Deviation	p
Pleural thickness in Thorax CT	82	7.70±3.76	0.0001 p<0.0001
Pleural thickness of decortication material	82	13.34±5.40	

3 cases (6.25%) in the tuberculosis group and 4 cases (11.7%) in the non-tuberculosis group developed postoperative complications.

DISCUSSION

Thoracic empyema is an ancient disease known since the Hippocratic period, and the most common cause is lung infections. Empyema still has significant morbidity and mortality rates; The development of modern antibiotic therapy has reduced the incidence of thoracic empyema.[10,11] The basic principle in treatment is drainage. Factors such as delay in drainage or insufficient drainage make the event chronic and reach more serious dimensions.[15-18] As exudative effusions can transform into multiloculated fibrinopurulent effusions within days timing is critical in the drainage of complicated parapneumonic effusion.[19] Considering the etiological factors, in cases where there is no response to closed tube drainage and appropriate antibiotic therapy, decortication should be performed without delay.[20,21]

The stages of the pleura are important in decortication surgery. While the decorticated tissue can be easily separated from the pleura between 2-4 months of the disease, fibrous bands develop between the fibrin layer on the visceral pleura and the septa of the parenchyma below it between 4-6 months. In the first months, these bands can be easily separated by blunt dissection in the operations. Since the parenchyma is also involved in late operated cases, the alveoli can also be peeled off together with the visceral pleura.[22,23]

Therefore, as the decortication decision is delayed, the frequency of complications such as postoperative bronchopleural fistula, infection, bleeding, and alveolar leaks increase; drainage and length of hospital stay are prolonged.[24,25] In 82 decortication cases that we examined retrospectively in our study; In terms of the effects of pleural thickening and the timing of decortication on morbidity and mortality, some of our results were similar to previous studies in the literature and some were not.

The main purpose of this study was to examine the effects of delay in surgical intervention and choice of operation on morbidity. In our study, the mean age of the tuberculosis group was (29.2) considerably lower than the non-tuberculous group (40.2) and consisted of young people. There was significant male gender dominance in both groups. Although the average age for pleural tuberculosis tends to increase both in our country and in developed countries, it is more common in young people (18-38 years old).[26,27] In another group's study to predict residual thickening in pleural tuberculosis, the mean age was found to be 35.8, and in Al-Kattan's tuberculosis empyema series,

the mean age was found to be 33.8.[26,28] In our study, the duration of preoperative treatment was found to be longer in the tuberculosis group than in the nontuberculous group.

The number of preoperative untreated cases was higher in the non-tuberculosis group. In the decortication series previously performed in our hospital, consisting of 140 men and 57 women, the preoperative treatment period of tuberculosis cases was found to be longer than the non-tuberculosis group, similar to our study.[15] Different researchers preferred to place a small thoracostomy tube with Thorax CT as an initial drainage option, and to add fibrinolytics when loculation develops.[29] VATS can be preferred in fibrinopurulent effusions. However, the opinion of the studies is that decortication is definitely indicated in patients with organized parapneumonic pleural effusion, who developed systemic symptoms and ventilatory disorder, and gradually increasing pleural thickening in these patients should not be forgotten.

It is observed that postoperative drainage times are longer and complications such as expansion defect and empyema reactivation are more common in patients receiving antituberculosis therapy for more than six months. It should not be forgotten that the condition of the underlying parenchyma is as important as the event in the pleura in pleural tuberculosis; If there is no clinical, radiological or bacteriological parenchymal tuberculosis or it has been cured, decortication should not be performed.[5,8] In our study, the thickness of the decorticated material was found to be significantly greater in the tuberculosis group than in the non-tuberculous group, which was associated with a more progressive course of the disease in tuberculosis. In the study of Sohaila et al.[20] no significant correlation was found between the duration of antituberculosis treatment received by patients and pleural thickening.

Thorax CT pleural thickness and mean hospital stay found in Al-Kattan's tuberculosis empyema series were similar to those in our study.[28] In the study of Martinez and Corderon,[29] in which they examined residual pleural thickening after parapneumonic effusion, the pleural thickness was found similar to our study. In our study, the time to decide on decortication was prolonged as the preoperative treatment time increased in both groups; however, no correlation was found between preoperative treatment times, decortication material thickness, and postoperative hospital stay. Similarly, in different series, it was shown that the postoperative drainage time gets longer as the pleural thickness increases in tuberculosis cases but no significant correlation was found in the non-tuberculous group.[30] In this present study, the pleural thickness measured in Thorax CT was smaller than the pleural thickness in the decorticated material.

Tube drainage and even thoracentesis alone may be sufficient in some empyema cases in the exudation phase; even tube drainage can still be tried in the fibrinopurulent phase, but only open drainage or decortication can be effective in the organization phase. Today, many data suggest that delay in surgical intervention in the organization phase increases morbidity. Burford et al.'s[31] study results support the effectiveness of early decortication, which showed low morbidity and mortality rates. In the decortication case series of Musgera et al.[32] in pachypleuritis, it was shown that the postoperative results deteriorate, when the duration of symptoms is prolonged and no correlation was found with the etiology. In our study, two mesothelioma cases preoperatively histopathologically diagnosed with chronic nonspecific pleuritis, differ from the others because of their pleural thickness and the nodular and irregular thickening. Again, the thickness of the decortication materials of the hydatid cyst cases in our study was found to be close to the group average, unlike the previous series. Early decortication of perforated hydatid cysts plays an important role in these results.

If tube drainage fails to expand the lung, early decortication is performed under appropriate antibiotic therapy. Here the main purpose is; the elimination of empyema, re-expansion of the lung, re-mobilization of the chest wall and diaphragm, normalization of respiratory functions, reduction of complications or the risk of chronicity, and shortening of hospital stay.

CONCLUSION

Tuberculous pleurisy, pyogenic empyema and traumatic hemothorax are the main causes of fibrothorax. Thickening and sticking pleural layers and the organized fibrin layer between them restrict the expansion of the lung and thorax, creating a restrictive type of respiratory disorder. Although thoracic CT is a good guide for pleural thickening, in the decortication decision the clinician's clinical and radiological evaluation is essential. There may be no need for decortication in a significant part of tuberculous pleurisy cases when they are followed up under medical treatment for a sufficient period. The opinion is that decortication should be performed in the early period in order to eliminate sepsis and provide expansion of the lung in pyogenic empyemas where pleural sepsis cannot be controlled with closed tube drainage.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since there was no Ethics Committee in our hospital in the year 2000 when the study was conducted, the study was carried out under the permission and supervision of the responsible Clinical Chief.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Evaluation of the causes of chest pain and its relationship with the cardiovascular system in COVID-19 patients

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ABSTRACT

Aims: Chest pain is one of the most common complaints of patients in the emergency departments during the pandemic and non-pandemic period. Because the cause of chest pain can range, from an ordinary, harmless muscle pull to serious cardiac complication ultimately leading to cardiac arrest. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects host cells through angiotensin converting enzyme 2 receptors, leading to coronavirus disease (COVID-19)-related pneumonia, and also causing acute cardiac injury and chronic damage to the cardiovascular system (CVS). COVID-19 contributes to the development of serious cardiovascular complications such as acute coronary syndrome, myocarditis, stress-cardiomyopathy, arrhythmias, cardiogenic shock, and cardiac arrest. In this study, it was aimed to determine the effects of COVID-19 on the cardiovascular system by evaluating the causes of chest pain in COVID-19 patients who applied to the emergency department with chest pain.

Methods: This retrospective study was conducted by examining the files of COVID-19 patients who applied to a district emergency department with chest pain.

Results: The files of 102 COVID-19 patients were reviewed. The most common causes of chest pain were musculoskeletal system (39.2%), respiratory system (23.5%), CVS diseases (20.6%), idiopathic causes (8.8%), gastrointestinal system diseases (7%, 9). Cardiac causes are non ST-segment elevation myocardial infarction (NSTMI), arrhythmia, ST-segment elevation myocardial infarction (STEMI) and unstable angina pectoris (USAP), respectively. Troponin value was higher in patients with cardiac chest pain (p=0.02), and ferritin value was higher in patients with pneumonia (p=0.01).

Conclusions: Chest pain or chest tightness is common in patients with active COVID-19. Although the causes of chest pain are due to musculoskeletal pathologies, both COVID-19 and cardiac origin chest pains due to direct cardiovascular system pathologies should be kept in mind.

Keywords: Chest pain, COVID-19, heart.

INTRODUCTION

In December 2019, a pneumonia outbreak caused by a new coronavirus in Wuhan, People's Republic of China, quickly spread across the world, causing the first pandemic of the 21st century. The causative virus was named "Severe Acute Respiratory Syndrome-Coronavirus-2" by the World Health Organization (WHO) (SARS-CoV-2) and the disease it causes was named COVID-19 (Coronavirus Disease 2019).[1,2] The first case was detected in Turkey on March 11, 2020, and the number of patients increased rapidly. Although the symptoms of COVID-19 disease are generally related to the respiratory system, symptoms related to the cardiovascular system (CVS) can also be observed. Patients with the highest mortality rate and most affected by the pandemic are elderly people with known cardiovascular diseases (CVD).[3] Cardiac diseases such as ischemic heart disease, HT, heart failure (HF), and atrial fibrillation are the most common conditions accompanying patients who die from COVID-19. Direct myocardial cell damage, myocardial oxygen supply/demand mismatch, acute plaque ruptures leading to acute coronary syndrome as part of systemic inflammation, catecholamine surges, and increased thrombosis have been reported as cardiac manifestations. While some of these are directly caused by the disease, others are associated with potential side effects of drugs used in the treatment of COVID-19.[1,4] In this study, we aimed to evaluate the causes of chest pain in COVID-19 patients who presented to the emergency department with chest pain and to determine the effects of COVID-19 on the CVS.

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METHODS

Approval was granted by the Ethics Committee of Kayseri City Hospital (Date: 09.2020, Decision No: 09.2020-146). This study was performed in line with the principles of the Declaration of Helsinki.

This retrospective study was conducted by examining the files of COVID-19 patients who presented to the emergency department of a district state hospital with chest pain between January 1, 2020, and December 31, 2020. Patients admitted to the emergency department with chest pain over the age of 18 and diagnosed with COVID-19 by PCR test were included in the study. Exclusion criteria were: age below 18 years; known as muscular and/or rheumatologic disease not diagnosed by PCR; mental-motor retardation; history of trauma; and incomplete file contents. General demographic characteristics (age, gender, comorbidities, smoking, etc.), vital signs (body temperature, pulse rate, arterial blood pressure (BP), oxygen saturation), type of pain, time of presentation, and time of onset of chest pain were evaluated from the patient files. Typical cardiac chest pain was considered to be a pressing, compressive chest pain behind the sternum lasting 5-15 minutes, relieved by rest and nitrate, not changing respirationally and positionally.[5] In addition, complete blood count (CBC), C-reactive protein (CRP), chest radiography, ferritin, lactate dehydrogenase (LDH), liver function tests, renal function tests, electrolytes, creatine kinase (CK), CK-MB, troponin I, electrocardiography (ECG), and echocardiography (ECHO) were evaluated. Chest pain of cardiac origin was compared with noncardiac chest pain.

Statistical Analysis

Data were evaluated using the statistical package program IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units (n), percentage (%), mean±standard deviation ($\bar{x}$±sh), median (M), minimum value (min), maximum value (max), first quartile (Q1), and third quartile (Q3). The log10 transformation was applied to variables with a wide distribution range. The normal distribution of the numerical variables was evaluated by the Shapiro-Wilk normality test and Q-Q graphs. The homogeneity of variances was evaluated by Levene's test. Comparisons between groups with categorical variables were evaluated with the Fisher exact test in the 2×2 and r×c tables. In cardiac and non-cardiac groups, the age variable was compared by an independent two sample t test, and the day variable was compared by a Mann-Whitney U test. Since the age variable differed between the groups, numerical variables were compared with one-way covariance analysis. A value of $P<0.05$ was considered statistically significant.

RESULTS

The study included 102 COVID-19 patients. The median age of the patients was 59.5 (24-78) years. The number of male and female patients was equal. Thirty-six of the patients (35.3%) presented with typical chest pain. The median body temperature was 36.9 (36.5-39.1) °C, the median systolic blood pressure was 120 (100-130) mmHg, the median diastolic blood pressure was 80 (70-80) mmHg, the median pulse rate was 79 (71.7-92) minutes, and the mean oxygen saturation was 93.5±5.7% (**Table 1**). The median interval between the onset of symptoms and hospital admission was 7 (1-12) days. 93.1% of the patients were admitted to the healthcare facility within the first 24 hours of experiencing chest pain. Fifty-two percent of the patients had comorbidities (Diyabetes Mellitus (DM), Hypertension (HT), Hyperlipidemia (HL), Coronary artery disease (CAD), Chronic obstructive pulmonary disease (COPD), Congestive heart failure (CHF)). 18 patients had one comorbidity, 17 patients had two, 5 patients had three, 7 patients had four, and 6 patients had five. The smoking rate was 17.6%. ECGs were normal (81.4%), T changes (7.8%), ST depression (6.9%), and ST elevation (3.9%), respectively (**Table 2**). White blood cell (WBC) median was 6.95 (5.9-9.25), hemoglobin median was 13.8 (12.3-15.2), ferritin median was 138.0 (62.7-337.2), CRP median was 8.0 (2.0-59.5), CK median was 141.5 (95.0-210.0), CKMB median was 26.0 (16.0-37.2), and 18.6% of patients had lymphopenia. Two patients died. The most common causes of GA in COVID-19 patients were musculoskeletal system (39.2%), respiratory system (23.5%), CVS diseases (20.6%), idiopathic causes (8.8%), gastrointestinal system diseases (7.9%). Cardiac causes were identified in 20.6% of chest pain and included Non ST-segment elevation myocardial infarction (NSTMI), arrhythmia, ST-segment elevation myocardial infarction (STMI), and unstable angina pectoris (USAP), respectively. 23 (28.4%) patients were diagnosed with pneumonia and 1 (1.2%) with pulmonary embolism. When patients with cardiac and noncardiac chest pain were compared, there was a significant difference between age ($p=0.01$), type of chest pain ($p<0.001$), comorbidity ($p=0.01$), and WBC count ($p=0.002$). There was a positive correlation between the number of comorbidities and the number of GA of cardiac origin ($p<0.001$). There was no significant difference between the two groups in terms of gender, day of illness, time of admission, smoking, liver and renal function tests, oxygen saturation, systolic and diastolic blood pressures, electrolytes, lymphocyte count, hemoglobin, LDH, CRP, CK, CK-MB, and troponin values (**Table 3**). There was no significant difference in age, gender, smoking, WBC, CK-MB, CK, LDH, but body temperature and

CRP values were significantly higher in patients with pneumonia (p<0.001). The troponin value was higher in patients with cardiac chest pain (p=0.02) and the ferritin value was higher in patients with pneumonia (p=0.01) (Table 4).

Tablo 1. Demographic and clinical characteristics of patients

Variables	Statistics
Age (year) M (min-max)	59.5 (24.0-78.0)
Gender, n (%)	
Female	51 (50.0)
Male	51 (50.0)
Pain type, n (%)	
Typical	36 (35.3)
Atypical	66 (64.7)
Application time, n (%)	
<12 hours	37 (36.3)
12-24 hours	58 (56.8)
>24 hours	7 (6.9)
Chest pain, n (%)	
Cardiac	21 (20.6)
Non-cardiyac	81 (79.4)
Cardiac causes, n (%)	n=21
STEMI	4 (19.0)
NSTMI	8 (38.1)
USAP	3 (14.3)
Aritmi	6 (28.6)
Non-cardiac causes, n (%)	n=81
Pneumonia	23 (28,4)
Pulmonary Embolism	1 (1.2)
Other	57 (70.4)

NSTMI: Non ST-Segment Elevation Myocardial Infarction, STEMI: ST-Segment Elevation Myocardial Infarction, USAP: Unstable Angina Pectoris.

Tablo 3. Patients' laboratory parameters according to chest pain

Variables	Chest Pain		Test statistics	
	Non-cardiac $\bar{x}$±sh	Cardiak $\bar{x}$±sh	F value	p value
WBC (10^3 /µL)	7.515±0.309	9.969±0.690	10.399	0.002
Hb (g/dL)	13.55±0.22	14.26±0.48	0.241	0.625
Lymphopenia, n (%)	16 (84.2)	18 (21.7)	0.329	0.757
logLDH(U/L)	2.408±0.027	2.513±0.061	0.847	0.360
logCRP (mg/L)	1.040±0.074	1.128±0.164	0.295	0.588
logFerritin (ml/ng)	2.104±0.073	2.198±0.163	0.151	0.04
logCK (ng/mL)	2.072±0.029	2.269±0.065	0.242	0.624
logCKMB (ng/mL)	1.407±0.037	1.591±0.081	0.283	0.596
Troponin (pg/ml)	0.012±0.118	1.260±0.262	2.403	0.124
Kreatinin (mg/dl)	0.897±0.076	0.919±0.169	0.060	0.806
AST (U/L)	34.8±1.6	39.3±3.6	0.067	0.796
ALT (U/L)	35.1±1.6	39.9±3.5	0.156	0.694

CK: creatine kinase, CRP: C-reactive protein, LDH: Lactate dehydrogenase, WBC: White blood cell, AST: Alanine aminotransferase, AST: aspartate aminotransferase. F: One-way analysis of covariance test statistics.

Tablo 4. Characteristics of patients according to inflammation parameters

Variables	Chest Pain			F value	p value
	Pneumonia $\bar{x}$±sh	Other $\bar{x}$±sh	Cardiac $\bar{x}$±sh		
CRP (mg/L)	2.041±0.077[a]	0.636±0.048[b]	1.128±0.089[c]	12.245	<0.001
Ferritin (ml/ng)	1.91±0.11[a]	2.03±0.74[b]	2.19±0.16[c]	12.160	<0.001

Superscripts a, b, and c indicate the difference between groups.

Tablo 2. Comparison of patient characteristics according to chest pain

Variables	Chest Pain		Test Statistics	
	Non-cardiac	Cardiac	Test value	p value
Age (year) $\bar{x}$±ss	54.1±15.7	63.1±13.2	t=2.665	0.011
Gender, n (%)			χ2=0.540	0.625
Female	42 (82.4)	9 (17.6)		
Male	39 (76.5)	12 (23.5)		
Type, n (%)			χ2=35.260	<0.001
Typical	17 (47.2)	19 (52.8)		
Atypical	64 (97.0)	2 (3.0)		
Starting day M (min-max)	7.0 (5.0-8.0)	8.0 (5.0-9.5)	z=1.470	0.142
Application time, n (%)			χ2=0.579	0.739
<12 hours	28 (75.7)	9 (24.3)		
12-24 hours	47 (81.0)	11 (19.0)		
>24 hours	6 (85.7)	1 (14.3)		
Additional illness, n (%)			χ2=6.220	0.015
No	44 (89.8)	5 (10.2)		
Yes	37 (69.8)	16 (30.2)		
Additional illness count, n (%)			χ2=13.939	0.016
No	44 (89.8)	5 (10.2)		
One	16 (88.9)	2 (11.1)		
Two	11 (64.7)	6 (35.3)		
Three	3 (60.0)	2 (40.0)		
Four	3 (42.9)	4 (57.1)		
Five	4 (66.7)	2 (33.3)		
Additional illness type, n (%)*				
DM	14 (53.8)	12 (46.2)	χ2=13.950	<0.001
HT	27 (71.1)	11 (28.9)	χ2=2.588	0.132
CAD	15 (65.2)	8 (34.8)	χ2=3.660	0.078
HL	10 (58.8)	7 (41.2)	χ2=5.289	0.043
CHF	6 (60.0)	4 (40.0)	χ2=2.555	0.209
COPD	7 (63.6)	4 (36.4)	χ2=1.877	0.231
Smoking, n (%)			χ2=0.206	0.759
No	66 (78.6)	18 (21.4)		
Yes	15 (83.3)	3 (16.7)		
EKG, n (%)			χ2=51.328	<0.001
Normal	76 (91.6)	7 (8.4)		
ST elevation	0 (0.0)	4 (100)		
ST depression	0 (0.0)	7 (100)		
T change	5 (62.5)	3 (37.5)		

COPD: Chronic obstructive pulmonary disease, CHF: congestive heart failure, CAD: coronary artery disease, HT: hypertension, DM:Diyabetes mellitus.

DISCUSSION

This study has shown that COVID-19 patients presenting to the emergency department with chest pain have more comorbidities, and approximately 1/5 of them have chest pain of cardiac origin. To our knowledge, our study is the first study in the literature investigating the causes of GA in COVID-19.

Chest pain is one of the most common reasons for admission to emergency departments, both before and during the pandemic. Chest pain is a common symptom in symptomatic COVID-19 patients.[6] The most common causes of chest pain in adults during non-pandemic periods are musculoskeletal system, CVS, respiratory system, psychiatric, and gastrointestinal system pathologies, respectively. In a study conducted in our country, the most common causes of chest pain were found to be the musculoskeletal system, gastrointestinal system, respiratory system, CVS, and psychological causes, respectively.[7] In our study, the most common causes of GA in COVID-19 patients were musculoskeletal system, respiratory, and CVS diseases, respectively. SARS-CoV2 virus enters the human body by attaching to angiotensin-converting enzyme-2 (ACE2) receptors in the cells of the lung and heart, esophagus, ileum, kidney, proximal tubule, and bladder.[8] ACE2 plays an important role in the neurohumoral regulation of CVS in various disease states and in normal health. The binding of SARS-CoV-2 to ACE2 leads to an alteration of ACE2 signaling pathways, which may primarily lead to acute myocardial and lung injury. As a result of the inflammatory effects of the SARS-CoV2 virus on cells, many clinical symptoms, including chest pain, can be observed.[9,10]

Cardiovascular system pathologies are the most common causes of chest pain in adults. Although the respiratory system is the system most affected by COVID-19, the highest mortality rate is due to CVS pathologies. In COVID-19, conditions such as advanced age, male gender, chronic lung disease, chronic heart disease, CRF, DM, HT, obesity, smoking, and malignancy are risk factors for mortality.[11] Especially those with advanced age and known CVD constitute the riskiest group. The mortality rate is also high in young COVID-19 patients with CVD.[3,12] The fact that advanced age and male gender are the main risk factors for CVD supports these results.[13] Similar to the literature, the patients who died in our study were male, over 65 years of age, and had comorbid diseases (DM, HT). In studies, COPD, CVD, DM, and HT were found to be comorbid risk factors.[14,15] In another study, the mean number of comorbid diseases in patients who died due to COVID-19 was found to be 2.7.[16] In our study, similar to the literature, 51.9% of our patients had comorbid diseases, and they were HT, DM, CAD, HL, COPD, and CHF, respectively.

The clinical presentation in COVID-19 patients, which is considered acute cardiac damage, has been reported as acute HF, acute myocardial infarction, myocarditis, arrhythmia and sudden cardiac arrest.[1,4] In COVID-19 infection, ECG changes and elevation in cardiac enzymes may be observed due to both direct damage of the virus to the myocardium and microvascular damage. Zhou et al.[6] found that 23% of the entire patient group and 52% of the patients who died had HF in their study. In our study, HF was detected in 9.8% of patients with chest pain and the most common ECG pathology in patients with cardiac involvement was T change, ST depression and ST elevation, respectively. Studies show that arrhythmic events are not uncommon in COVID-19 patients. Increased prevalence of arrhythmia has been found to be related to hypoxia, concomitant CVD, neurohumoral and inflammatory stress, and drugs used in treatment (18,19). One study showed that the incidence of cardiac arrhythmia was 9.3% (20). Sinus tachycardia, which occurs due to many reasons including fever, respiratory failure/hypoxemia, hemodynamic deterioration, fear/anxiety, pain, and some other physical and emotional symptoms, is the most common rhythm disorder in patients with COVID-19 infection (21). In our study, the arrhythmia rate was 28.6% of cardiac pathologies, and the most common arrhythmia was sinus tachycardia, respectively.

The most commonly used laboratory tests in COVID-19 disease include complete blood count, liver and kidney function tests, cardiac enzymes (CK, CK-MB, troponin), electrolytes, CRP, coagulation tests, procalcitonin, and LDH. Non-cardiac patients had significantly lower leukocyte counts than cardiac patients (p=0.002) and there was no difference in lymphopenia. Increased high-sensitivity cardiac troponin (hs-cTn) levels have been reported in a significant proportion of COVID-19 patients. Elevated troponin levels in these patients are considered an important indicator of poor prognosis and increased mortality (1,18). Because of the intense distribution of ACE2, the binding point of SARS-CoV-2, in cardiac myocyte cells, the high affinity of the virus to these cells and thus the destruction caused by the virus are held responsible for the elevation in troponin (1,22). In our study, the troponin values of patients with CVS involvement were higher than those of non-cardiac patients (p=0.02), but there was no significant difference in terms of CK and CK-MB. The limitation of our study is that it is retrospective and not multicenter.

CONCLUSION

Patients with a pre-diagnosis of COVID-19 presenting to the emergency department with chest pain should be considered to have more comorbid diseases. In addition, although the most common cause of chest pain is of musculoskeletal origin, it should not be forgotten that it may be caused by CAD.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Ethics Committee (Date: Date: 09.2020, Decision No: 09/2020-146).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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In vivo dynamic analysis of the bone–implant interface in cervical disc implants: a research article

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ABSTRACT

Aims: This study aimed to determine whether micro-motions occur at the bone–implant interface of UFO cervical disc prosthesis.

Methods: The sagittal range of motion of the functional spinal unit, which was defined as the angle formed by lines drawn at the superior margin of the upper vertebral body and the inferior margin of the lower body, was determined preoperatively and postoperatively. The presence of micro-motions at the bone-implant interface was also evaluated.

Results: We report the results of a dynamic computed tomography evaluation method to determine whether micro-motions occur at the bone–implant interface of cervical arthroplasty devices during the 1-year postoperative follow-up.

Conclusion: While significant motions could be observed in all our patients, in one level, significant (6°) segmental micro-motions at the bone–implant interface could be documented.

Keywords: Cervical disc disease, functional spinal unit, intervertebral disc prosthesis

INTRODUCTION

Anterior cervical discectomy with fusion is the gold standard in the surgical treatment of cervical degenerative disc diseases; however, a retrospective long-term study showed that approximately 3% of patients had adjacent-segment symptoms, with a predicted 10-year prevalence of approximately 25%, which is due to increased biochemical stresses and accelerated degeneration of neighboring spinal motion segments.[1] This novel concept of adjacent-segment disease is unproven, and the true incidence of this disease remains controversial. Moreover, little data in the literature support this theory.

The treatment of cervical spinal disorders is undergoing a paradigm change, from favoring fusion to motion preservation, since Goffin first reported treating cervical spondylotic radiculopathy with artificial cervical intervertebral disc prosthesis in 2002.[2] Artificial cervical intervertebral discs are intended to maintain the motion of the intervertebral space and theoretically slow down the degeneration of the adjacent space, allowing the restoration of the physiological curvatures and range of motion (ROM) of cervical vertebrae to the greatest extent possible. Intermediate follow-up studies, in which ROMs of the prosthesis were measured using dynamic plain X-ray images, have shown that cervical disc prostheses allow for the preservation of motions over time at index levels, and most of the adjacent segments are mobile.[3-6] Nevertheless, total cervical disc replacement (TCDR) is not free of complications. First, after the surgery, the normal mode of activity of the intervertebral space may not be restored. Specifically, the restoration of the transient axis of rotation when the cervical vertebrae are in motion is very challenging. In some cases, it may be impossible given that, after artificial cervical intervertebral disc replacement, the motion of the cervical vertebra is still unstable because of the asymmetric mechanical behavior between flexion and extension, probably due to the removal of the anterior longitudinal ligament and the preservation of posterior structures.[7] Second, although only a few reports about the radiologic outcomes following TCDR have been published thus far, heterotypic ossifications are responsible for the fusion of nearly 9% of the treated levels in these early follow-up studies, which leads to the suspicion of an even higher rate of spontaneous fusion after long-term follow-ups.[8,9] Third, because most of the artificial discs are not intended to restore lordosis, whether a preoperative kyphosis can be corrected while preserving motions remains unanswered. Given the passive design, most of

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the patients who underwent arthroplasty with cervical artificial discs experience a focal loss of lordosis following surgery at the treated levels, although the overall sagittal alignment can be maintained.[10-16] Finally, the degenerative conditions of the spine cause the sinking of the implant into the vertebral body.

Thus, this study aimed to determine whether micro-motions occur at the bone–implant interface of the cervical disc prosthesis.

METHODS

The study was carried out with the permission of Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Researches Ethics Committee (Date: 02/03/2022, Decision No: 03-07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

An arthroplasty with the UFO artificial disc (Pao Nan Biotech, Taiwan) was considered the most suitable choice for our patients because of several factors: first, the preservation and, if possible, the restoration of motions in the affected cervical spine segments appeared to be achievable using a multiaxially mobile construct of silicone. Second, the easy application of the device saved a considerable amount of time. Third, the overall sagittal alignment and lordosis could be better maintained with an implant having a nearly spherical shape. The posterior longitudinal ligament was not cut, so we tried to restore the natural disc height and functional spinal unit angle (if kyphotic) intraoperatively using an intervertebral distractor (Figure 1).

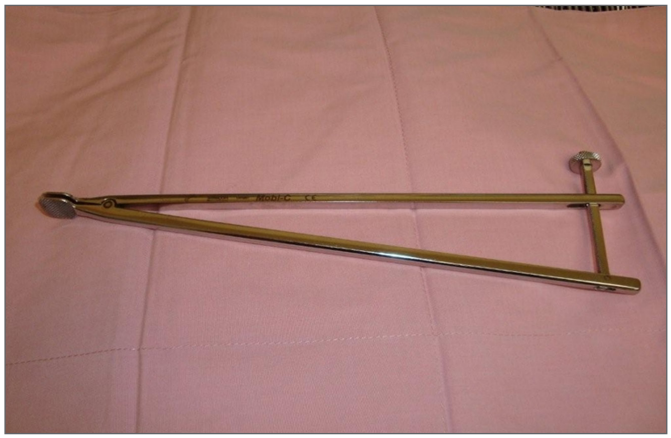

Figure 1. Intervertebral distractor used to restore the natural disc height and functional spinal unit angle (if kyphotic) intraoperatively.

The mobility of the implanted segments must be studied in detail, and we think that this is a more complex and unreported issue when more than one single level is operated upon. For this study, we examined six multilevel spondylotic cases among our patients with TCDR 1 year after the surgery, one female and six male patients aged 40–62 years without any osteoporosis (Table 1). Two and four patients underwent two- and three-level surgery, respectively. The sagittal ROM of the functional spinal unit, which was defined as the angle formed by lines drawn at the superior margin of the upper vertebral body and the inferior margin of the lower body, was determined preoperatively and postoperatively. Fine spiral computed tomography (CT) section of flexion and extension of the median sagittal plane were used for these measurements, which also visualized whether the disk–osteophyte complexes and calcified ridges were removed completely (Figure 2).

Table 1. Demographics Information of Patients'

Patients	Age	Gender	Level of disc Hernia	Osteoporosis	Systemic diseases
1	40	Male	C4-5, C5-6, C6-7	No	No
2	47	Male	C4-5, C5-6, C6-7	No	No
3	58	Male	C3-4, C4-5, C5-6, C6-7	No	No
4	62	Male	C3-4, C4-5, C5-6, C6-7	No	No
5	51	Male	C4-5, C5-6, C6-7	No	No
6	44	Female	C4-5, C5-6, C6-7	No	No
7	50	Male	C4-5, C5-6, C6-7	No	No

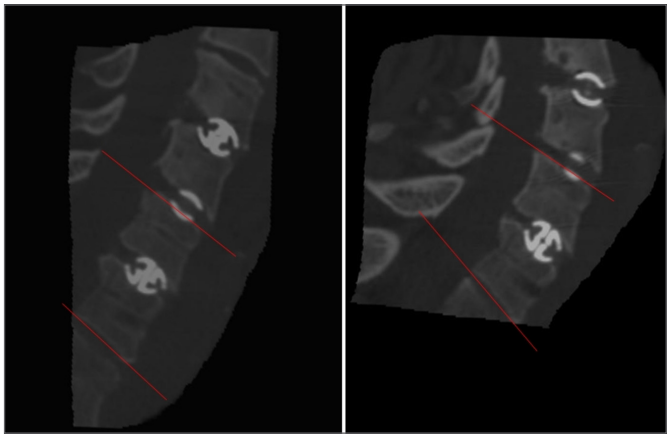

Figure 2. Sagittal 80° range of motion (ROM) of the functional spinal unit, which was defined as the angle formed by lines drawn at the superior margin of the upper vertebral body and the inferior margin of the lower body on fine spiral CT section of flexion and extension in the median sagittal plane.

Moreover, possible micro-motions at the bone–implant interface must be evaluated before drawing a conclusion. Thus, implant motion was also assessed simultaneously on the same CT sections at each level (Figure 3). For the motion of vertebral endplates, the Cobb method was used on flexion–extension CT images. As the landmark for prosthesis motion, the edge of the prosthesis was used. A digital anglometer was used and confirmed with a pencil perpendicular protractor. With a known intraobserver measurement accuracy of approximately +/−2°, to be 95% certain that an implanted prosthesis has any sagittal motion, an ROM of at least 4° must have

been observed. Movement at the bone–implant interface was documented by digitally subtracting the prosthesis ROM from the vertebral ROM.

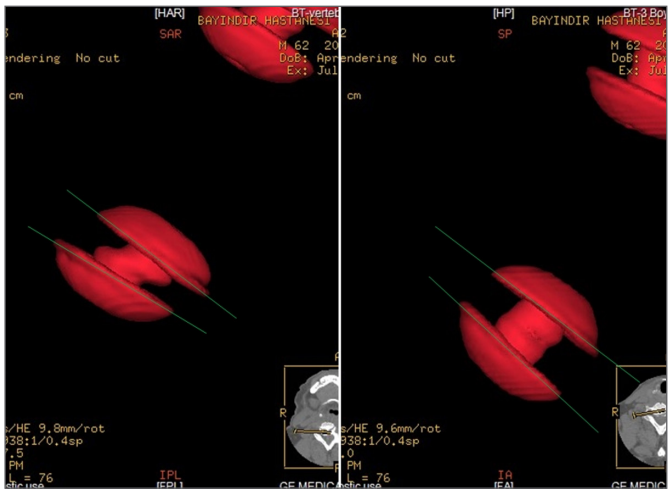

Figure 3. Sagittal 140° range of motion (ROM) of the prosthesis at the same level, which was defined as the angle formed by lines drawn at the edges of the prosthesis on the fine spiral CT section subtracted with the flexion and extension.

RESULTS

The study included patients aged 40–62 years, who had no osteoporosis and previous cervical disc surgery. Surgery was performed on a total of six patients (one female and five male), and 1 year later, six multilevel spondylotic cases were analyzed. Two and four patients underwent two- and three-level surgery, respectively. Some motions could be observed in all patients: in one level, significant (6°) segmental motions at the bone–implant interface could be documented (Figure 4). No adjacent-segment disease was observed in any patient at 1-year follow-up. No residual calcification or postoperative heterotopic calcification was found. No additional findings of radicular or central pathology secondary to a postoperative complication were noted. Cervical palpation revealed non-restricted neck ROM.

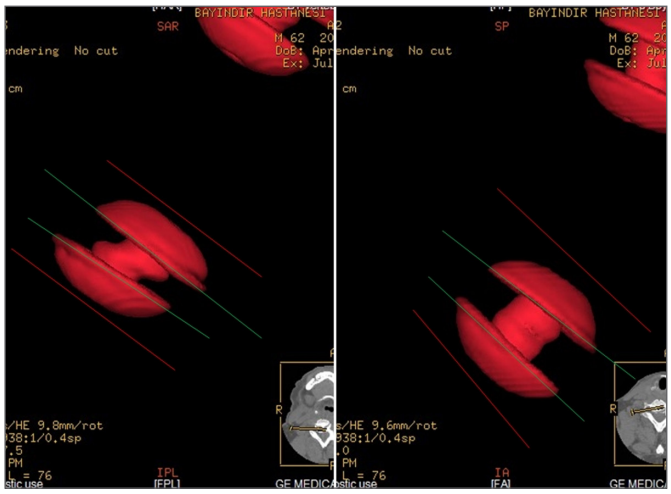

Figure 4. The 6° micromotion at the bone–implant interface was evaluated simultaneously on the same flexion and extension CT sections at the same level by digitally subtracting the prosthesis ROM from the vertebral ROM.

All patients had at least 2° of motion. Thanks to the preoperative endplate curettage and ideal placement of the prosthesis in the vertebra, no postoperative pathology related to prosthesis mobilization was observed in any patient.

DISCUSSION

Cervical disc prosthesis/cages are intended to maintain movements of the intervertebral space and theoretically slow down the degeneration of the adjacent space, allowing the restoration of the physiological curvatures and ROM of the cervical vertebrae to the greatest extent possible. Intermediate follow-up studies in which prosthesis ROMs were measured using dynamic plain X-ray images have shown that by cervical disc prostheses, movements are preserved over time at index levels, and most of the adjacent segments are mobile.[3-6]

This case series was exceedingly limited and heterogeneous, only evaluated six patients, and other more important attributes such as clinical outcomes and long-term durability with osseo-integration of the implant are still being evaluated; therefore, it was not possible to draw any statistically significant conclusions. Furthermore, it dealt specifically with a specific implant design that has a poor overall surface area and at high risk for subsidence, which is not generalizable to other implants that have specific design characteristics with regard to their articulation with the patient's host bone.

Surgical techniques have always been questioned since anterior cervical discectomy was performed. When simple discectomy is performed, the theory that the neural foramen narrows because of the closure of the intervertebral space and the root is compressed has been accepted.[13,14,18,19] Therefore, the excised pathological disc space should be filled with an implant. Since the mobility of the intervertebral discs was limited, fixing the distance to be excised with a material that would create interbody fusion was deemed appropriate, and different implants were placed here.[13] Adjacent-segment disease is one of the most important problems in the follow-up of interbody fusion, and the effectiveness of this method has also been questioned.[10]

Recently, the use of cervical prostheses has become widespread, and implants with different properties have been developed. Prostheses are widely used in cervical intervertebral pathologies, were thought to preserve mobility, albeit partially, and may be a remedy for the development of adjacent-segment disease.[10-14,17] Experimental studies have evaluated the motion efficacy of cervical prostheses; however, studies on patients proving motion efficacy in the late period are not enough.[14] This study aimed to address this scientific need.

The case series is extremely limited and heterogeneous, only six patients were evaluated, the clinical outcomes and other more important features such as osseo-integration, and long-term implant durability are still being evaluated. Therefore, drawing any statistically significant conclusions based on the present findings is not yet possible. We believe that this dynamic CT assessment method is possible at the 1-year postoperative follow-up to determine whether micro-motions occur at the bone–implant interface of this unique cervical arthroplasty device.

A study showed that cervical prostheses undergo heterotopic calcification in the long-term and lose-mobility in the late term.[13] The rate of heterotopic calcification is not very high, and the use of cervical prosthesis in most patients ensures the continuation of vertebral dynamics.[14] Although this study analyzed data from six patients in the early period, the desired dynamic movements continued to an acceptable extent. The findings are valuable in terms of the early maintenance of vertebral dynamics and the absence of adjacent-segment disease caused by immobility in the early period.

CONCLUSION

Given the presented findings, this study provides some preliminary evidence that the above-stated goal can be achieved to provide insight into the motions of surgically treated cervical spine segments under physiologic loads and the more important micro-motions at the bone–implant interface.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Researches Ethics Committee (Date: 02/03/2022, Decision No: 03-07).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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