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Adıyaman Üniversitesi Sağlık Bilimleri Dergisi
Journal of Health Sciences of Adıyaman University

A. KAPAK SAYFASI/*COVER PAGE*

B. DERGİ KÜNYESİ/*ISSUE MASTHEAD*

C. İÇİNDEKİLER/*TABLE OF CONTENTS*

i. ÖZGÜN ARAŞTIRMA/*RESEARCH ARTICLES*

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JOURNAL OF HEALTH SCIENCES OF ADIYAMAN UNIVERSITY

Research Article/Özgün Araştırma

Evaluation of the effect of a natural monoterpenic phenol on the cytotoxicity of carfilzomib

Doğal bir monoterpenik fenolün carfilzomibin sitotoksisitesine etkisinin değerlendirilmesi

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Abstract

Aim: The aim of this study was to reveal whether carfilzomib, proteasome inhibitor, and carvacrol, a natural monoterpenic phenol, causes cytotoxic and apoptotic effects and oxidative stress on A-549 cells.

Materials and Methods: Lactate dehydrogenase (LDH) activity test was used. Changes in caspase 3 and glutathione peroxidase enzyme activities in cells were determined.

Results: It was determined that carfilzomib alone and together with carvacrol caused a raise in the activities of lactate dehydrogenase (LDH), glutathione peroxidase and apoptotic enzyme, caspase-3 activity, compared to the control.

Conclusion: Our study showing that carfilzomib alone and together with carvacrol gave different responses may be guiding in determining new strategies to be applied in lung cancer treatment.

Keywords: Lung cancer; Carvacrol; Carfilzomib; Apoptotic effect.

Öz

Amaç: Bu çalışmanın amacı, bir proteazom inhibitörü olan carfilzomib ile doğal bir monoterpenik fenol olan karvakrolün A-549 hücrelerinde sitotoksik ve apoptotik etkilere ve oksidatif strese neden olup olmadığını ortaya koymaktır.

Gereç ve Yöntem: Laktat dehidrogenaz (LDH) aktivite testi kullanılmıştır. Hücrelerdeki kaspaz 3 ve glutatyon peroksidaz enzim aktivitelerindeki değişiklikler belirlenmiştir.

Bulgular: Carfilzomib'in tek başına ve karvakrol ile birlikte laktat dehidrogenaz (LDH), glutatyon peroksidaz ve apoptotik enzim olan kaspaz-3 aktivitelerinde kontrole göre artışlara neden oldukları belirlenmiştir.

Sonuç: Carfilzomib'in tek başına ve karvakrol ile birlikte farklı yanıtlar verdiğini gösteren çalışmamız, akciğer kanseri tedavisinde uygulanacak yeni stratejilerin belirlenmesinde yol gösterici olabilir.

Anahtar Kelimeler: Akciğer kanseri; Karvakrol; Carfilzomib; Apoptotik etki.

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Introduction

While lung cancer was a rare disease in the early twentieth century, it has become one of the most important health problems today and is one of the leading causes of cancer-related deaths worldwide.[1,2] Lung cancer, one of the most important health problems today, is the most common type of cancer that causes death in both women and men.[1-3] More than one million people die every year in the world due to lung cancer. It has been determined that the number of lung cancer cases has increased by 44% in men and 76% in women since 1985 worldwide.[3] While deaths from other cancer types have decreased over the years, 3-fold increase has been detected in lung cancer-related deaths.[4] The prognosis of lung cancer is worse than other types of cancer, with a five-year survival rate of less than 15%.[5]

Surgical methods, radiotherapy, chemotherapy, hormone therapy and new treatment methods such as immunotherapy, gene therapy, angiogenesis inhibitors and signal transduction system inhibitors are used to reduce the death rate and increase survival in cancer treatment.[6,7]

The proteasomal system is involved in many cellular processes, and changes in the regulation of these cellular events are directly related to cancer development.[8] Studies on the use of proteasome inhibitors in cancer treatment have been continuing for more than 20 years. Carfilzomib is one of the most studied and clinically used proteasome inhibitors *in vitro* and *in vivo*. However, these proteasome inhibitors, which are used very effectively in various cancers, have side effects such as diarrhea, constipation, thrombocytopenia and most importantly, peripheral type neuropathy.[9] These side effects can limit treatment and even lead to discontinuation of treatment. As a result, dose limitation, treatment plan changes or chemotherapy must be abandoned.[10,11]

Carfilzomib, which we used in our study, is a second generation proteasome inhibitor, causes irreversible proteasome inhibition and has an epoxyketone structure. Carfilzomib is structurally different from Bortezomib but similarly but more specifically inhibits the β5 subunit of the proteasome and does not affect other proteases.[12] In studies conducted with Bortezomib and Carfilzomib in cell culture, it was determined that Carfilzomib had a more cytotoxic effect than Bortezomib. Hematological cancer cells are more sensitive to Carfilzomib exposure than solid tumors and non-transformed cells. Proteasome inhibition with Carfilzomib is longer lasting than Bortezomib due to Carfilzomib covalently binding to the target protein.[11,13]

Essential oils obtained from various *Origanum* species have been widely used to flavor foods, alcoholic beverages, and wounds and burns since ancient times.[14-16] Essential oils of *Origanum* genus, the main component of which is carvacrol, have been scientifically demonstrated to have many specific biological effects such as antioxidant, analgesic, antifungal, antibacterial, insecticidal, antimelanogenic, anti-inflammatory and wound healing effects.[17-29] Carvacrol, a monoterpenic phenolic essential oil component, is known to have antibacterial, antioxidant, analgesic, antifungal, insecticidal, phytotoxic, antiviral, antiparasital and anti-inflammatory effects in different organisms, parallel to the effects of the essential oil.[17,22,30-40]

There are studies on the anti-cancer effect of carvacrol in some types of cancer in *in vivo* and *in vitro* conditions. The growth and tumorigenesis of chronic myeloid leukemia cells, N-ras transformed mouse myoblast cells, murine melanoma cells, and human cervical, lung, and breast cancer cells are known to be inhibited by carvacrol.[41-49] Although there is not much information about the mechanism of action of carvacrol, studies have shown that carvacrol specifically changes the cytoplasmic membrane surface and permeability and thus affects cells.[38,50] Although many studies have been carried out at the molecular level on the effect of carvacrol, especially on cancer cells, there is still not enough information today, so it is very important to investigate its anti-cancer effect mechanism.

Carfilzomib, known to be a second-generation proteasome inhibitor, may cause many side effects when used alone in treatment. New strategies in cancer treatment

may emerge as a result of the combined application of targeted cancer drugs such as carfilzomib and natural compounds such as carvacrol. By increasing the effectiveness of targeted drugs at low doses, their side effects can be reduced and the desired success in treatment can be achieved.

The results of this study revealed the cytotoxic, membrane-damaging, oxidative stress-inducing and apoptotic effects of carfilzomib, a targeted drug, alone and in combination with carvacrol, on lung cancer cells (A-549), which is the most common type of cancer that causes death.

Materials and Methods

Chemicals and drugs

Carfilzomib was supplied under the trade name as Kyprolis. The drug used in the experiments was diluted in appropriate proportions using the medium. Carvacrol is commercially available with 99% purity (Sigma Chemical Co.). The kit used for caspase activity was obtained from Elabscience Biotechnology Co., Ltd, USA. The kit used to determine Lactate Dehydrogenase Activity was purchased commercially from Sigma-Aldrich (St. Louis, MO, USA).

Cell Lines and culture

The cell line we used in the experiments, A-549 (human non-small cell lung cancer (NSCLC)), was purchased from the American Type Culture Collection (ATCC) and reproduced under suitable conditions. Cells were grown using Roswell Park Memorial Institute 1640 medium (RPMI 1640) and other medium components in appropriate proportions. After the cells reach sufficient density (more than 75%) in the culture vessel, experimental groups were created and then proteasome inhibitör (carfilzomib) ($<IC_{50}$), and natural monoterpenic phenol (carvacrol) ($<IC_{50}$), were applied to the cells for 48 h.

Cytotoxicity assay

After the cells grown in the flask were trypsinized, they were counted and planted in 96-well plates at 10^4 cells per well. The cytotoxicity of carfilzomib (250-2000 µg/mL) and carvacrol (20-70 µg/mL) on A-549 cells was determined for 48 h. Moreover, cells were treated with carfilzomib ($<IC_{50}$) and carvacrol ($<IC_{50}$) together for 48 h. 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) test was used to evaluate the cytotoxic effect after applications. In this test, tetrazolium salts such as MTT are metabolized by mitochondrial dehydrogenases to form a blue formazan dye that is used to measure cytotoxicity. Test reagents were added to the culture medium and incubated at 37 °C for 2 h. Then, solubilizing/stopping solutions (dimethyl sulfoxide) was added to each well for a 1 h incubation. The absorbance of all samples was measured at 490 nm.[51] Eight wells were replicated for each concentration.

Lower IC_{50} concentrations ($<IC_{50}$ values) were calculated separately for carfilzomib and carvacrol. Subsequent combination applications were continued using the calculated IC values ($<IC_{50}$).

According to the cytotoxicity results, the most effective combination concentration was determined after carfilzomib ($<IC_{50}$) and carvacrol ($<IC_{50}$) were applied together. The most effective combination concentrations were also used in other ongoing experiments. The combination index (CI) was calculated to determine whether the combined administration of carfilzomib and carvacrol in cells exhibited additive, synergistic or antagonistic effects.[52] Cells treated with only medium or 0.1% DMSO were considered as control cells.

Lactate dehydrogenase (LDH) assay

LDH activity were determined after the cells were exposed to carfilzomib alone (IC_{10}) and combination of carfilzomib (IC_{10}) and carvacrol concentrations (IC_{10}), showing the most effective cytotoxic effects, in A-549 cells for 48 h. Changes in LDH activity were determined to determine whether either application caused any membrane damages of lung cancer cells. LDH activity in each sample was determined by following the procedure included in the commercially available kit (MAK066, Sigma-Aldrich). The formula used to calculate LDH activity is given below.

LDH Activity = The amount of NADH that occurs between the first and last measurement (nmol) × Sample Dilution Factor/Reaction Time× Sample volume (mL)

Glutathione peroxidase (GPx) activity

After carfilzomib alone (IC_{10}) and combination of carfilzomib (IC_{10}) and carvacrol concentrations (IC_{10}), showing the most effective cytotoxic effects, were applied to the cells for 48 h, the cell supernatant to be used in GPx activity measurement was prepared. GSH-Px activity was determined according to the method using tert-butyl hydroperoxidase as the substrate. [53] The amount of protein was determined using the Bradford method, in which bovine serum was used as standard. [54] Tests were performed in triplicate.

Caspase-3 activity

Caspase-3 activity was determined after A-549 cells had been exposed to carfilzomib (IC_{10}) and combined with carvacrol (IC_{10}) (the most effective combination concentrations in cytotoxicity) for 48 h. Apoptotic enzyme activity were determined using commercially available colorimetric Caspase-3 Activity Assay Kit (Elabscience) according to kit protocol after application of carfilzomib alone and also together with carvacrol. The plates were read at 405 nm using the microplate reader. Tests were performed in triplicate. Results are given as Unit/mg protein.

Data analysis

The results of the replicates were pooled and expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) was carried out. The one-way ANOVA was used to determine whether there were any significant differences between the means of three or more independent (unrelated) groups on some variable. Tukey multiple comparisons tests were used. Statistical differences were considered significant at $p<0.05$.[55] Statistical analyses were performed using the Minitab program (http://www.minitab. com/products), release 13.0.

Results

Determination of cytotoxic effects of carfilzomib and carvacrol

The cytotoxic effect of both applications was measured using the MTT assay. IC_{10}, IC_{20}, IC_{30}, IC_{40} and IC_{50} concentrations (the concentration that kills 50% of cells) were determined for each of carfilzomib and carvacrol, which will be used in further experiments (Figure 1 and 2). After applying carfilzomib and carvacrol for 48 h, the cytotoxicity observed in A-549 cells was observed to be parallel to the increase in concentration (Figure 1 and 2).

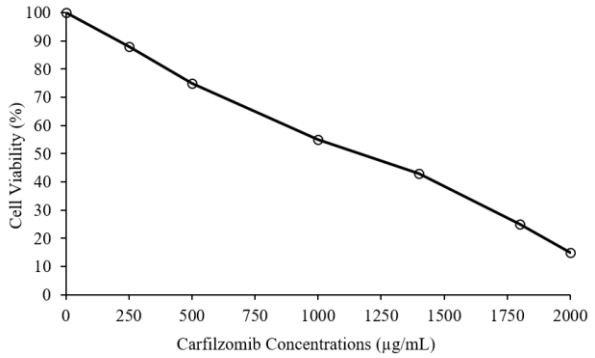

Figure 1. Dose-dependent cytotoxicity of carfilzomib.

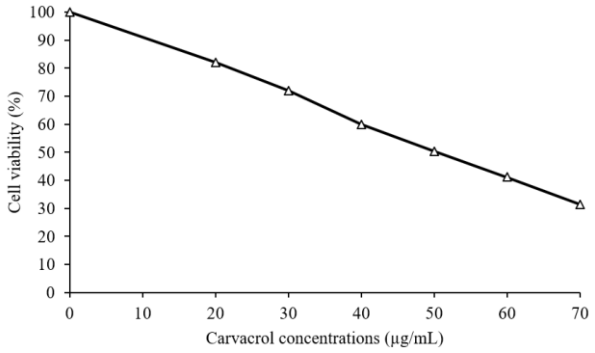

Figure 2. Dose-dependent cytotoxicity of carvacrol.

IC_{10}, IC_{20}, IC_{30}, IC_{40} and IC_{50} values of A-549 cells exposed to carfilzomib for 48 hours were calculated as 197, 440, 683, 927 and 1170 µg/mL, respectively. In this study, we also wanted to investigate whether carvacrol concentrations lower than IC_{50} increased the cytotoxic effect of carfilzomib ($<IC_{50}$). By applying carfilzomib and carvacrol together at concentrations lower than the IC_{50} concentration, it was determined at which combination concentrations they showed the most effective cytotoxic effect (Figure 3). When carvacrol (IC_{10}, IC_{20}, IC_{30}, IC_{40}) treated with carfilzomib ($<IC_{50}$) were ranked among

themselves, the concentrations showing the most effective cytotoxic effect were found to be IC_{10} carfilzomib + IC_{10} carvacrol. The synergistic effect of IC_{10} carfilzomib and IC_{10} carvacrol application in A-549 cells was also demonstrated by calculating the CI value of 1.75. Subsequent studies with cells continued using IC_{10} carfilzomib + IC_{10} carvacrol, which are the most effective cytotoxic combination concentrations.

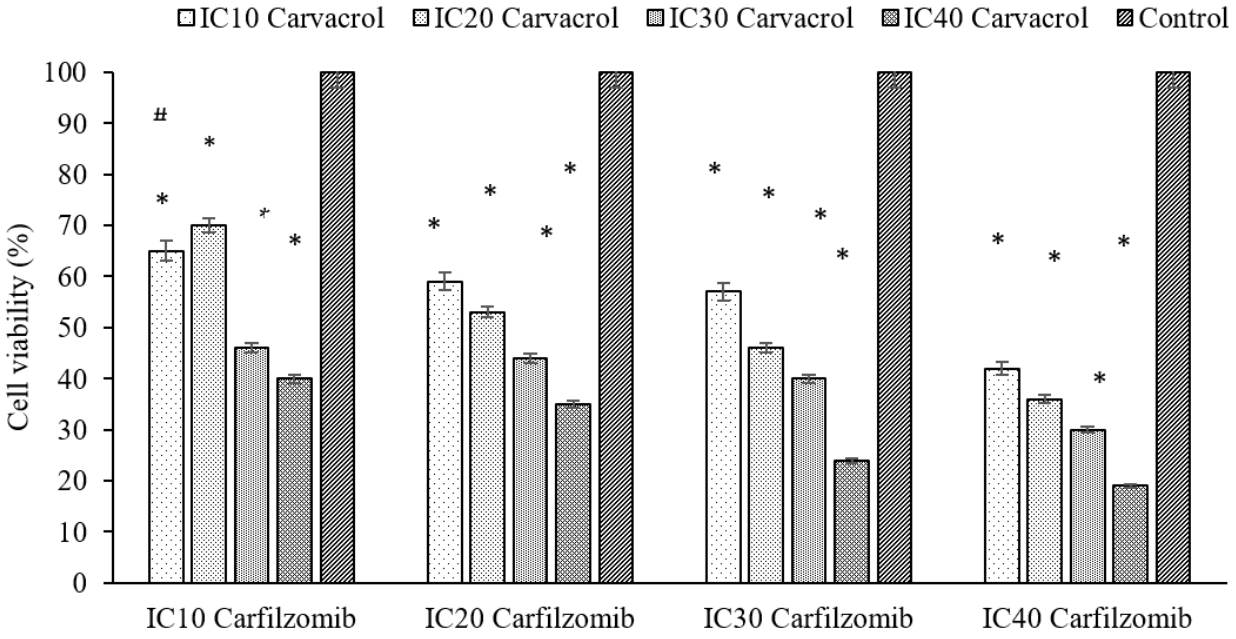

Figure 3. Combined cytotoxic effects of carfilzomib (IC_{10}, IC_{20}, IC_{30}, IC_{40}) and carvacrol (IC_{10}, IC_{20}, IC_{30}, IC_{40}) for 48 h on A-549 cells. Results are presented as viability ratio compared with the control group (treated with only the medium-untreated cells). Values are expressed as the mean of three separate trials with three replications ± standard deviation (SD). * Significantly different from control (untreated cells) (p<0.05). #Significantly different that IC_{10} carvacrol and IC_{10} carfilzomib combination treatment from all other combination treatments except IC_{10} carfilzomib + $IC_{2\ 0}$ carvacrol combination treatment in A-549 cells (p<0.05)

Lactate dehydrogenase (LDH) activity measurement

Since release of Lactate dehydrogenase (LDH) from the cells into the medium was measured, as an indicator of early cell apoptosis, we determined the changes in LDH activity to measure whether there was any damage to the membranes of A-549 cells when applied with carfilzomib alone (IC_{10}) and also combined with carvacrol (IC_{10} carfilzomib + IC_{10} carvacrol) (combination concentrations showing the most potent cytotoxic effect).[56]

After 48 h of applications, LDH enzyme activity rised approximately 2.1 times where combination concentrations (IC_{10} carfilzomib + IC_{10} carvacrol) were applied and approximately 1.6 fold in the cells where carfilzomib was applied only, relative to control group cells (cells present in medium containing only culture medium components). LDH enzyme activity in cells where combination concentrations and carfilzomib were applied alone was shown to be statistically different according to control (Figure 4).

Measurement of the effects of carfilzomib alone and combined with carvacrol on glutathione peroxidase activity in A-549 cells

Cells have a complex enzymatic and non-enzymatic antioxidant defense system. Antioxidant mechanisms develop a defense system against free radicals that have harmful effects on cells. Glutathione peroxidase (GPx) is one of the enzymes that constitute the basic line of defense against free radicals in the cell.

After treatment with carfilzomib alone (IC_{10}) and also with combination concentrations (IC_{10} carfilzomib + IC_{10} carvacrol) (the most potent cytotoxic effect) to A-549 cells for 48 h, changes in GPx activity, which is an important antioxidant that breaks down hydrogen peroxide into water in

mitochondria and sometimes in the cytosol, were determined (Figure 5).

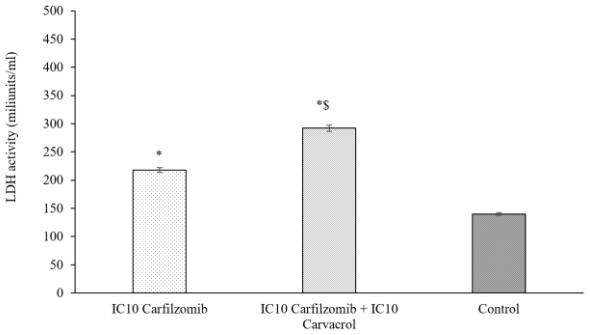

Figure 4. Changes in LDH activities after treated with carfilzomib alone and combine with carvacrol. *Significantly distinct from control (p<0.05). $Significantly distinct from carfilzomib alone treatment (p<0.05). One unit of LDH activity is defined as the amount of enzyme that catalyzes the conversion of lactate into pyruvate to generate 1.0 µmol of NADH per min at 37 °C.

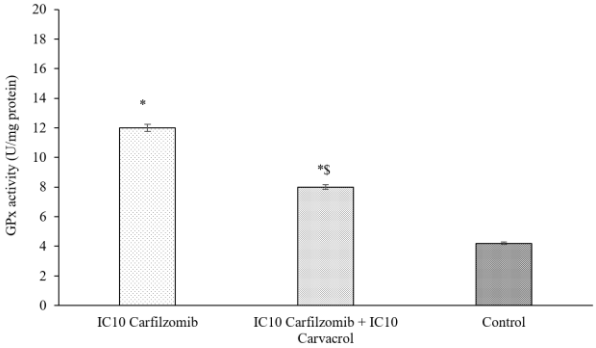

Figure 5. Effect of carfilzomib alone and combine with carvacrol on glutathione peroxidase (GPx) activity. *Significantly distinct from control (p<0.05). $Significantly distinct from carfilzomib alone treatment (p<0.05).

It was determined that GPx activity in A-549 cells applied only with carfilzomib (IC_{10}) was 90.5% higher than the glutathione peroxidase activity measured in the control group cells, and this excess was found to be statistically significant (p<0.05). It was found that GPx activity measured in the cells after the combination application (IC_{10} carfilzomib + IC_{10} carvacrol) was 2.9 fold higher than GPx activity measured in the control group cells. This difference was shown to be statistically significant. It was determined that the combination application was more effective in increasing GPx activity than the carfilzomib application alone, and the GPx activity measured in the cells after the combined application was 1.5 times higher than GPx activity measured after the application alone (Figure 5).

Measurement of the effect of carfilzomib alone and together with carvacrol on caspase-3 enzyme activity in A-549 cells

There are at least 12 caspases in mammals; It is divided into two groups: initiator (-8, -9, -10) and terminator (effector) (-3, -6, -7) caspases. Caspase-3, whose activity we determined through experiments after carfilzomib alone and also with carvacrol application, is also one of the effector caspases.

It was determined that after carfilzomib alone incubation, caspase-3 activity in A-549 cells was 1.8 fold higher compared to control, and after combined application, caspase-3 activity was increased 2.5 fold compared to control (Figure 6). While it was observed that the combined application was more effective in increasing caspase-3 activity than the application of carfilzomib alone, it was revealed that the combined application caused an increase in caspase-3 activity 1.4 fold more than the application alone. It was determined that caspase-3 activity in all applications was statistically different from each other and from the control (p<0.05).

Discussion

Approximately 2 million patients are diagnosed with lung cancer every year and 1.8 million people die due to lung cancer. Therefore, it is one of the cancer types with high cancer incidence and mortality in the world. It ranks second in frequency in women and men.[57] Survival rates after lung cancer treatment are very low. Although cancer survival rates are successful thanks to existing treatment methods (surgery, chemotherapy, radiotherapy), patients have begun to seek new methods other than existing methods. For this reason, cancer patients have turned to the use of complementary and alternative treatments.[58]

The development of new pharmacological strategies for cancer treatments is seen as a very important need today. In this context, there is an increasing interest in natural compounds day by day, thanks to the revealing of their promising therapeutic potential against cancer types such as lung, breast and colon.[59]

According to research conducted in recent years, new potential drugs have begun to be

produced for different pathologies that have important social impacts. For this purpose, studies have been conducted on biologically active species of medicinal plants.[60] Approximately 1/3 of the plants in Türkiye consist of medicinal and aromatic plants. The Lamiaceae family, which includes the thyme plant, has the widest distribution in the world and is a widespread plant family. Plants belonging to the Lamiaceae family; it is the source and main component of many essential oils used in medicine and perfumery. Its use for treatment and spice purposes shows that this family is important. One of the most important plants belonging to the Lamiaceae family is thyme. There are five species of thyme in Türkiye. These; *Thymus*, *Origanum*, *Satureja*, *Tymbra* and *Coridothymus*. With some exceptions, the main component of the essential oils of these genera is usually thymol or carvacrol or both.[61,62]

Carvacrol (2-methyl-5- (1-methylethyl)-phenol) is a monoterpenic phenol component that has an isomeric structure with thymol, an essential oil component found in many aromatic plants.[63] Carvacrol has antimicrobial, antioxidant, anticancer and anti-inflammatory effects.[64]

Oxidative stress occurs by detoxifying reactive intermediates with reactive oxygen species. Free radicals affect proteins, lipids and nucleic acids, causing oxidative damage to different molecules in cells. Essential oils, which can be obtained from many aromatic plants, can prevent or decrease oxidative damage by showing antioxidant effects. In addition, since essential oils have an antioxidant effect and scavenge radicals, they can prevent mutagenesis, carcinogenesis and aging, which are known to be effective in the formation mechanisms of radicals. It is known that different enzymatic antioxidants such as superoxide dismutase, catalase and glutathione peroxidase show activity within the cell. Carvacrol, which is an essential oil component and is known to show different biological activities, can also increase the activity of such antioxidant enzymes. It not only increases the activity of enzymatic antioxidants, but also increases the activity of non-enzymatic antioxidants such as vitamin C, vitamin E and reduced glutathione.[65] It has been demonstrated that carvacrol stimulates reactive oxygen-mediated apoptosis and arrests the cell cycle in human prostate cancer cells, and that it does this in the G0/G1 phase of the cell cycle.[65]

Since proteasome inhibition in multiple myeloma causes intracellular proteins to accumulate and cause cell death, the first generation Bortezomib has revolutionized the improvement of survival times of multiple myeloma patients. Second-generation carfilzomib provides a significant reduction in the risk of death by overcoming the resistance that occurs in bortezomib -resistant patients in the clinic.[66] Drug resistance developing under carfilzomib treatment currently limits therapeutic success in multiple myeloma, and furthermore, the mechanism of carfilzomib resistance is not fully understood to date.[67] Although carfilzomib is more effective than bortezomib, the desired treatment response rates are still not achieved from carfilzomib in patients. Additionally, drug resistance that develops in patients also affects the treatment response rates achieved by carfilzomib. Therefore, new combined treatment strategies are needed in which the drug doses used in treatment can be reduced. In this context, the combined application of existing proteasome inhibitors such as carfilzomib with naturally occurring essential oil components such as carvacrol may be a new strategy.

In one of the studies, carfilzomib was loaded into new nickel-based metal-organic frameworks (Ni-MOFs) and a drug delivery system that could be evaluated in targeted cancer treatment was created. The effects of drug delivery systems loaded with carfilzomib were investigated *in vitro* and *in vivo* by comparing them with standard drugs. After experiments, it has been shown that the drug delivery system releases the drug in a controlled manner and has a high loading efficiency. According to cytotoxicity results, it has been reported that carfilzomib-loaded drug delivery systems are more cytotoxic than free carfilzomib and show this effect more effectively on A-549 lung cancer cells. It has been shown that drug delivery systems not only increase cytotoxicity more effectively,

but also affect the mRNA level of TP53 and are more effective in increasing the level. It has been reported that when free and loaded carfilzomib was applied to rats, it affected various biochemical parameters and significantly increased serum alanine aminotransferase (ALT), serum creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST) and liver malondialdehyde (MDA). Ni-MOFs loaded with high doses of carfilzomib were also found to cause serious histopathological changes.[68] In another study, researchers investigated whether carfilzomib (proteasome inhibitor) and vorinostat (histone deacetylase inhibitor) had higher antitumor effects after co-administration in non-small cell lung cancer (NSCLC) cell lines by increasing endoplasmic reticulum stress. It has been reported that the co-administration of the two inhibitors showed a synergistic effect at the end of 48 and 72 h in all cell lines used. H520 and A-549 cell lines were used in this study to evaluate cell viability and apoptosis. It was found that co-administration of the two inhibitors caused more death and caspase-3 cleavage in both cell lines studied than the application of each inhibitor alone. Co-administration of the two inhibitors was observed to cause upregulation of endoplasmic reticulum stress-regulating proteins, activating transcription factor 4, GRP78/BiP and C/EBP homologous protein. After the application of the two inhibitors together, it was observed that there was an increase in the amount of reactive oxygen species in the cell and the level of oxidative stress-related proteins such as heat shock protein 70 in both cell lines.[69] In a different study, the anti-proliferative and cytotoxic effects of carfilzomib were evaluated using different lung cancer cell lines, and after the experiments, it was found that carfilzomib had strong anti-proliferative and cytotoxic activity. Carfilzomib-resistant cells were obtained by exposing A-549 and H520 non-small cell lung cancer (NSCLC) cells to increasing concentrations of carfilzomib. When IC_{50} value calculated for drug-resistant cells and parental cells was compared, it was shown that IC_{50} value in drug-resistant A-549 cells increased 2.5 times compared to the parental cells, and IC_{50} value in the drug-resistant H520 cells increased 122 times compared to the parental cells. It was observed that after carfilzomib application in resistant cells, cell deaths decreased compared to parental cells, and there was also a decrease in the expression of apoptotic and autophagy markers. When both resistant cells were compared with the parental cells, higher P-glycoprotein (Pgp) gene expression was observed to increase 1.2 times in A-549 drug-resistant cells and more than 9000 times in H520 drug-resistant cells. It has been observed that in drug-resistant cells, doxorubicin accumulates less intracellularly and cross-resistance develops against drugs such as bortezomib, doxorubicin and paclitaxel, except cisplatin (P-glycoprotein client drugs).[70]

In one of the studies, it was investigated whether fractional distillation had any effect on the physicochemical and biological properties of oregano essential oil obtained from *Lippia graveolens* H.B.K. It was observed that oregano essential oil was separated into two different fractions by dry vacuum fractional distillation.

When these two fractions were compared in terms of their content, it was determined that they consisted of different main components and the ratios of these components were different. According to the content analysis results, it was found that 45.32% of the first fraction was ρ-cymene and 19.14% was γ-terpinene, while 47.63% of the second fraction was phenolic thymol and 35.56% was carvacrol, approximately 83% of the content of the fraction was determined. It has also been shown that obtaining different fractions affects the biological properties of the essential oil. When the antioxidant activity of the fraction containing thymol and carvacrol as the main components was evaluated using the DPPH method, it was determined that it showed more antioxidant activity than the whole oregano essential oil and also the fraction containing ρ-cymene and γ-terpinene as the main components. It has been observed that the phenolic fraction has a cytotoxic effect on HeLa, Hep2 and A-549 cancer cell lines, and this effect increases with increasing concentration. When the cytotoxic activities of different fractions (phenolic and terpenic

fractions) and whole oregano essential oil were compared, it was determined that the phenolic fraction showed the highest cytotoxic activity.[71]

The results obtained from this study, in which carfilzomib was treated alone and together with carvacrol to human lung cancer A-549 cells for the first time, may may serve as a precursor to future clinical trials of combination therapies using carfilzomib.

Conclusion

The results obtained from our study may provide justification for future combined treatments with carfilzomib. Thus, lower doses of carfilzomib can be used in combined application compared to carfilzomib alone, and side effects caused by carfilzomib can be reduced or eliminated. In addition, greater response to treatment can be achieved, thus easing the economic burden of patients. Indirectly, profits can be made for the country's economy. Our study showing that carfilzomib alone and together with carvacrol gave different responses may be guiding in determining new strategies to be applied in lung cancer treatment.

Ethics Committee Approval

The study does not require ethics committee approval since it does not involve any human or animal subject.

Author Contributions

Concept – A.E.; Design – A.E.; Supervision – A.E.; Resources – A.E.; Materials – A.E; Data Collection and/or Processing – A.E.; Analysis and/or Interpretation – A.E.; Literature Search – A.E.; Writing – A.E.; Critical Reviews – A.E.

Conflict of Interest

There is no conflict of interest to declare.

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Research Article/Özgün Araştırma

Cytotoxic and antioxidant effects of paclitaxel and glutathione combination on breast cancer cell line

Paklitaksel ile glutatyon kombinasyonunun meme kanseri hücre hattında sitotoksik ve antioksidan etkileri

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Abstract

Aim: The aim of this study was to investigate the effects of glutathione (GSH) on chemotherapy-related toxicities in MCF-7 breast cancer cell line treated with paclitaxel (PTX) by cell viability and oxsidative stres parameters.

Materials and Methods: Cells were treated with glutathione (2.5-20 mM) and paclitaxel (0.001-100 µM) for 24, 48 and 72 hours, after which cell viability was determined by WST-1 assay. IC_{50} values were calculated from the data obtained. Following combination analyses, the combination index was calculated and the levels of glutathione, total oxidant species (TOS) and total antioxidant species (TAS) were measured in cell lysates exposed to the indicated combinations for 72 hours.

Results: In the study, it was determined that the cytotoxic effect of paclitaxel decreased as the amount of glutathion used in the combinations increased and glutathion concentrations above 10 mM showed antagonistic effect with paclitaxel.

Conclusion: In patients with breast cancer, the administration of appropriate doses of glutathione in combination with chemotherapy may prove beneficial in reducing the adverse effects associated with oxidative stress.

Keywords: Antioxidant, Glutathione, Cancer, MCF-7, Paclitaxel.

Öz

Amaç: Bu çalışmanın amacı Paklitaksel (PTX) ile tedavi edilen MCF-7 meme kanseri hücre hattında glutatyonun (GSH) kemoterapi ile ilişkili toksisiteler üzerindeki etkilerini hücre canlılığı ve oksidatif stres parametreleri ile araştırmaktır.

Gereç ve Yöntem: Hücreler 24, 48 ve 72 saat boyunca glutatyon (2,5-20 mM) ve paklitaksel (0,001-100 µM) ile muamele edilmiş, ardından hücre canlılığı WST-1 testi ile belirlenmiştir. Elde edilen verilerden IC_{50} değerleri hesaplanmıştır. Kombinasyon analizlerinin ardından kombinasyon indeksi hesaplanmış ve 72 saat boyunca belirtilen kombinasyonlara maruz bırakılan hücre lizatlarında glutatyon, toplam oksidan türler (TOS) ve toplam antioksidan türler (TAS) seviyeleri ölçülmüştür.

Bulgular: Çalışmada, kombinasyonlarda kullanılan glutatyon miktarı arttıkça paklitakselin sitotoksik etkisinin azaldığı ve 10 mM üzerindeki glutatyon konsantrasyonlarının paklitaksel ile antagonistik etki gösterdiği tespit edilmiştir.

Sonuç: Meme kanseri hastalarında, kemoterapi ile birlikte uygun dozlarda glutatyon uygulanması, oksidatif stres ile ilişkili olumsuz etkileri azaltmada faydalı olabilir.

Anahtar Kelimeler: Antioksidan, Glutatyon, Kanser, MCF-7, Paklitaksel.

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Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide and can also affect men, although less frequently. Breast cancer accounts for 31% of all new cases of cancer diagnosed in women and 15% of all deaths caused by cancer. It is the second most common cause of cancer-related deaths in women worldwide.[1,2] Despite the extensive research conducted on its treatment, the desired success in reducing its high mortality and morbidity rates has not been achieved. Common treatments for breast cancer include surgery (lumpectomy or mastectomy), radiation therapy, chemotherapy, hormone therapy, targeted therapy (such as HER2-targeted drugs), and immunotherapy.[3] Although treatment options for breast cancer depend on factors such as the type and stage of the cancer, as well as the patient's general health status and preferences, chemotherapy is currently the most effective and commonly used treatment.[1,4] Chemotherapy is used either alone or in combination with surgery and/or radiotherapy in treatment protocols.[4] Various chemotherapeutic agents, including doxorubicin (DOX), cisplatin (CP), docetaxel (DTX), and paclitaxel (PTX), have been developed and are widely used for cancer treatment.[5] These chemotherapeutic agents can induce apoptosis through both extrinsic and intrinsic pathways in the cell by inducing ROS production.[6]

The use of chemotherapeutic drugs can lead to the development of secondary (therapeutic-induced) malignancies, as well as nephro-, hepato-, neuro-, cardio-, and ototoxicity. It is important to consider and prevent these side effects, which can result in a decreased quality of life.[7,8] Although chemotherapy is the preferred treatment, its efficacy is often reduced due to the lack of drug selectivity and the development of drug resistance.[9] The ideal treatment aims to stop the growth of cancer cells, prevent invasion and metastation, and to eliminate uncontrolled cancer cells without harming healthy cells. Additionally, the goal is to prolong life and reduce the complications of treatment.[10,11] To avoid these disadvantages during treatment, many protocols have been and are being studied.[12]

The effects of antioxidants in minimising the toxicities caused by chemotherapy have been the subject of curiosity.[13] The combination of paclitaxel with curcumin reduced the side effects of treatment and increased the chemosensitivity of cancer cells to paclitaxel.[5,14]

Alterations in glutathione levels are known to be involved in the pathogenesis of many human diseases, including cancer.[12] It emphasises the importance of glutathione in cancer-related studies, especially because glutathione affects the growth and division processes of cells and plays a role in DNA repair processes.[15, 24]

Glutathione (L-γ-glutamyl-L-cysteinylglycine) is a tripeptide consisting of cysteine, glutamic acid and glycine that plays a central role in several cellular processes, including cell proliferation, death and differentiation. Due to its reducing properties, glutathione (GSH) is involved several metabolic and physiological processes, including the modulation of the immune response and detoxification of xenobiotics, in addition to protein synthesis.[16-18] GSH scavenges free radicals, which can damage cells and contribute to diseases and aging.[13] Glutathione functions as an antioxidant through various mechanisms, including direct interaction with reactive oxygen species (ROS), reactive nitrogen species (RNS), and electrophiles. Its thiol group, derived from the cysteine residue, is particularly important for these antioxidant functions.[16,19] It also regenerates other antioxidants, like vitamins C and E, which enhances the body’s ability to combat oxidative damage.[20] Some studies suggest that GSH may have potential benefits in preventing and treating cancer due to its antioxidant properties and its ability to support the immune system.[17,21-24] GSH levels can affect cell proliferation and apoptosis, both of which are dysregulated in cancer. Moderate levels of GSH are essential for cell survival and proliferation. However, excessively high levels may promote cancer cell growth by inhibiting apoptosis and supporting tumor progression.[25,26] Chemotherapy resistance is a significant challenge in cancer treatment, and GSH has been implicated in this process.

Cancer cells can increase GSH synthesis to counteract the cytotoxic effects of chemotherapy drugs, resulting in treatment resistance.[21,27,28] However, several studies have suggested that GSH plays a crucial role in chemotherapy by protecting healthy cells, enhancing treatment effectiveness, and reducing side effects.[29] Some studies suggest that antioxidants may work together with anti-cancer drugs, allowing for greater and longer uptake of anti-neoplastic agents, thereby increasing the effectiveness of treatment. According to a meta-analysis, using antioxidants in conjunction with chemotherapy enhances therapeutic potential and survival rates in cancer patients.[30,31]

Cancer patients use antioxidant supplements such as glutathione, an antioxidant mixture, melatonin, N-acetylcysteine, especially vitamin A and E, Co-Q10, selenium, ellagic acid and L-carnitine acid to alleviate the side effects of chemotherapies. However, glutathione is important both as an endogenous antioxidant and because of its role in chemotherapy resistance. For these reasons, it was aimed to investigate the determination of cell viability, oxidative stress balance and intracellular glutathione level in the simultaneous use of glutathione with chemotherapy.

Materials and Methods

Culturing the cell

The MCF-7 (human breast cancer) cell line used in the study was obtained from the Republic of Turkey Ministry of Agriculture and Forestry Şap Institute. MCF-7 cell lines were incubated in 25 cm^2 flasks under a constant 5% CO_2 flow at 37ºC. Dulbecco's modified Eagle's medium (DMEM, Sigma-Aldrich) F12 was supplemented with 10% fetal bovine serum (FBS) (Sigma-Aldrich, Burlington, MA, USA), 4 mM L-glutamine (Gibco), 0.02 M non-essential amino acid (Sigma, M7145), 1 mM sodium pyruvate (Sigma, P5280), 16 mg/dl gentamicin.

Preparation of materials and application of WST-1 analysis

In order to optimize cell numbers for WST-1 analysis, cells are seeded in 1:2, 1:4, 1:8 and 1:16 dilutions from $2x10^4$ cells. After 24 h, viability analysis is carried out by WST-1 assay (Roche-11644807001) and results are calculated in GraphPad Prism 8. The optimal number of cells for WST-1 analysis was determined to be $5x10^3$ cells per well.

In order to carry out cytotoxic analyses of PTX, 200 µl of the cell suspension was added to each well of a 96-well plate containing $5x10^3$ cells. The plate was then incubated in 5% CO_2 for 24 hours. Subsequently, different concentrations of PTX (ranging from 0.001 to 100 µM) in serially diluted medium were added to the cells. After 24, 48, and 72 hours of incubation, medium was removed and 100 µl of medium containing 10% WST-1 was added. Cells were incubated at 37ºC 5% CO_2 for 3 hours. At the end of the incubation period, the microplate reader (Thermo scientific multiscan go microdrop) was measured at 450 nm and the results were recorded.

Different concentrations of GSH (2.5, 5, 10, 15 and 20 mM; Sigma) were prepared from a 100 mM GSH stock solution in cell medium to study the effect of GSH on cell proliferation. The cells were treated with GSH and its viability was assessed using WST-1 after 24, 48, and 72 hours of incubation.

Determination of cytotoxicity levels with Trypan Blue

$1x10^6$ cells were seeded in 6-well plates and incubated for 24 h. followed by treatment with PTX ranging from 0.001 to 100 µM and different concentrations of GSH (2.5, 5, 10, 15 and 20 mM) and incubated for 24, 48 and 72 hours. At the end of the incubation period, cells were stained with trypan blue and counted. Cells were also treated with the determined combination doses for 72 hours and counted.

The trypan blue staining assay allows direct identification and counting of live (unstained) and dead (blue) cells in a given population. Prior to the trypan blue staining procedure, adherent cells were first trypsinised and suspended in PBS. After obtaining a homogeneous cell suspension, an appropriate amount (5-10 µl) of cell culture was mixed with an equal amount of trypan blue (0.4%). The cells were then counted in appropriate quantities in a haemocytometer. Cells that took

up the dye were considered dead and cells that did not were considered alive. The total percentage of dead cells in the suspension was thus determined.[32,33]

Determination of combination indexes

After obtaining cytotoxicity results for PTX and GSH at varying concentrations and time points in the MCF-7 cell line, we calculated the 72-hour cytotoxicity results for combinations using IC_{50} doses. These results were analysed using the CompuSyn programme 1.0 (ComboSyn Inc., Paramus, NJ, USA) to calculate combination indices (CI) for standard or different targeted drug combinations. The programme's CI analysis is based on the median-effect principle.[34]

WST-1 was analysed by applying the determined combinations individually and in combination by accepting only cells and medium containing cells and medium, without any agent as a positive control.

Determination of GSH levels

The cells were incubated for 72 hours with the combinations determined according to the results. After incubation, the cells were suspended in trypsin-EDTA (Sigma T4049) and washed with PBS (Invitrogen, 003002).

The lysate obtained from the cells, which were lysed by the freeze-thaw method, was deproteinised on ice using 5% sulfosalicylic acid. The supernatants were analysed for GSH after being freeze-thawed at -196ºC and 37ºC three times.[35,36]

Total oxidant species and total antioxidant species determinations

Total antioxidant species level (TAS) and total oxidant species level (TOS) analyses were performed in cell medium with REL Assay Diagnostic colorimetric kits. TAS is a method developed by Erel to measure the total antioxidant capacity of the body against powerful free radicals. Fe^{2+}-o-dianisidine complex forms OH radical by Fenton-type reaction with H_2O_2. This powerful reactive oxygen species (ROS) reacts with the colourless odianisidine molecule at low pH to form yellow-brown dianisidyl radicals. Dianisidyl radicals participate in further oxidation reactions and increase colour formation. However, antioxidants in the samples suppress these oxidation reactions and stop the colour formation. The samples are calibrated to Trolox, a vitamin E analogue.[37]

TOS is a colorimetric method developed by Erel. Oxidants in the sample oxidise the ferrous ion-o-dianisidine complex to a ferric ion. The presence of glycerol in the medium accelerates this reaction, increasing it approximately threefold. In an acidic medium, ferric ions form a coloured complex with xylenol orange.[38]

Statistical analysis

In the analysis of cytotoxicity and the examination of combination experiments, the studies were conducted with eight repetitions. Two analytical replicates were conducted for each of the GSH, TAS and TOS analyses, with a total of three biological replicates.

Data were collected and analysed using SPSS for Windows® Version 22 software. The conformity of the variables to normal distribution was analysed by Shapiro-Wilk test. Descriptive analyses were given using mean and standard deviation for normally distributed and non-normally distributed variables. Since the data obtained as a result of WST analysis did not conform to normal distribution was used by transforming the data (logarithm was taken in combination analyses). Whether there was a statistically significant difference between PTX, GSH and their combinations treated cell groups, and control groups in terms of inhibition of cell viability was determined by 2-way ANOVA, Tukey's test.

Results

WST-1 analysis and calculation of IC_{50}

In order to determine the effect of GSH on cell proliferation, GSH was prepared in concentrations of 2.5, 5, 10, 15 and 20 mM from a 100 mM stock solution in cell medium. Viability tests were performed with WST-1 after 24, 48 and 72 hours incubation. Upon evaluation of the results, it was determined that there was a maximum of 12% inhibition on cell viability in the first 24 hours, with 50% inhibition observed in the 48th hour following

the application of 15 mM GSH. However, when the results of 20 mM GSH application were evaluated in comparison to the control group, no inhibition on cell viability was observed. IC_{50} values could not be calculated with the viability results obtained in the first 48 hours. Upon evaluation of the results obtained at the 72-hour time point, it was determined that the viability rates in cells treated with 10 mM, 15 mM, and 20 mM GSH were 58.88%, 49.22%, and 52.3%, respectively. The 72-hour IC_{50} dose of GSH was found to be 7.5 mM (Figure 1). A series of dilutions of PTX (0.001-100 µM) were prepared in a medium and added to the cells. After 24, 48 and 72 hours of incubation, a cell proliferation assay was performed with WST-1. After 24 hours of incubation, a statistically significant cytotoxic effect was observed in cells treated with 10 µM and 100 µM PTX. After 48 hours of treatment, cell viability was significantly inhibited at all concentrations, with the exception of 0.001 and 0.01 µM. At 72 hours, no cytotoxic effect was observed, except the 0.001 µM PTX treatment. The IC_{50} dose of PTX was found to be 6 µM at 72 hours (Figure 2).

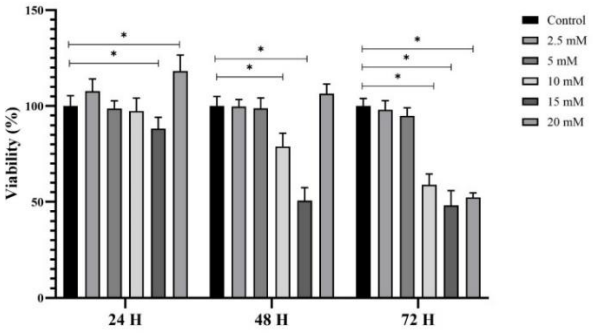

Figure 1. Results of GSH cytotoxicity in MCF-7 at 24, 48 and 72 hours (n=8, **p*<0.001).

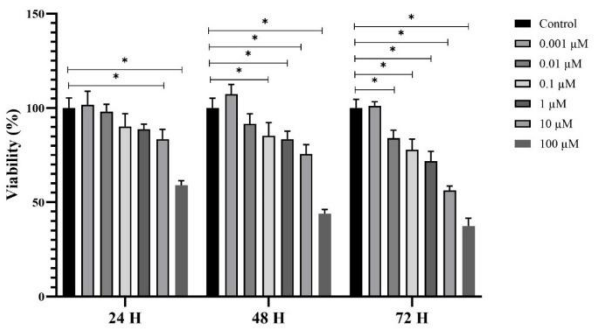

Figure 2. Results of PTX cytotoxicity in MCF-7 at 24, 48 and 72 hours (n=8, **p*<0.001).

Determination of cell viability by trypan blue staining

After 24, 48 and 72 hours of incubation, cells treated with GSH and PTX were stained with trypan blue and counted in a hemocytometer. When the results were analysed, all doses except 20 mM GSH in the first 24 hours showed an antiproliferative effect. At these doses, MCF-7 cells showed a maximum viability of 80%. In the first 48 hours, all other concentrations except 20 mM showed antiproliferative effect with a maximum cell viability of 50%. Similar results were observed at 72 h with a partial increase in antiproliferative effect (Table 1).

PTX treatment showed antiproliferative effect on cells depending on dose and duration (Table 2).

PTX and GSH combinations

Following the acquisition of cytotoxicity data for PTX and GSH at varying concentrations and time-dependent cytotoxicity data for the MCF-7 cell line, 72-hour cytotoxicity data for the combinations formed by considering IC_{50} doses were calculated (Figure 3, Table 3). 72 hours was preferred in combination applications because no significant cytotoxic effect was observed in the first 48 hours of GSH administration.

Table 1. Percentage expression of cell viability by trypan blue staining of GSH-treated MCF-7 cells after 24, 48 and 72 hours of incubation.

GSH concentration (mM)	24 H Cell viability (%) (n=8)	48 H Cell viability (%) (n=8)	72 H Cell viability (%) (n=8)
Control	100±1.52^{a}	100±2.79^{a}	100±3.15^{a}
2.5	110.84±2.45^{b}	98.74±2.35^{ab}	98.02±3.16^{a}
5	102.5±2.14^{a}	96.12±3.01^{b}	92.33±1.01^{b}
10	94.27±2.78^{c}	73.45±4.01^{c}	56.48±4.16^{c}
15	83.65±4.56^{d}	53.24±4.31^{d}	49.14±3.78^{d}
20	120.95±4.11^{e}	109.09±3.46^{e}	57.9±2.65^{c}

$^{a, b}$: Differences between means shown with different letters in the same column are statistically significant.

Table 2. Percentage expression of cell viability of PTX-treated MCF-7 cells by trypan blue staining after 24, 48 and 72 hours of incubation

PTX concentration (µM)	24 H Cell viability (%) (n=8)	48 H Cell viability (%) (n=8)	72 H Cell viability (%) (n=8)
Control	100±1.45[a]	100±3.45[a]	100±3.74[ab]
0.001	103.93±1.23[b]	109.05±2.03[b]	102.63±4.35[a]
0.01	96.38±2.47[c]	95.39±3.26[c]	86.67±4.03[b]
0.1	91.45±3.57[d]	89.14±2.97[d]	79.14±3.65[c]
1	87.17±1.69[e]	85.03±3.56[e]	69.46±3.25[d]
10	85.69±2.13[e]	71.79±4.03[f]	53.03±4.29[e]
100	53.31±3.45[f]	40.39±2.78[g]	35.13±2.38[f]

a, b: Differences between means shown with different letters in the same column are statistically significant

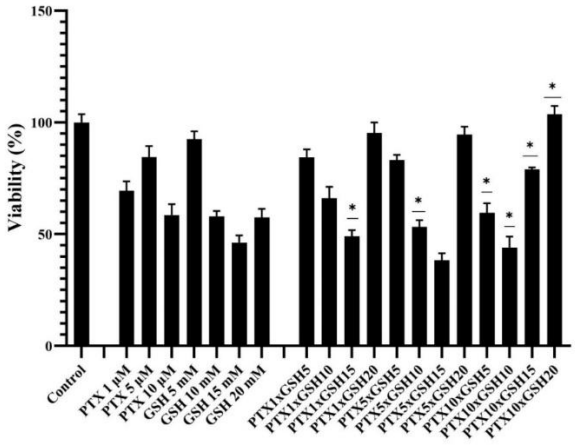

Figure 3. The results of the cytotoxic effect of PTX and GSH combinations in the MCF-7 cell line at 72 hours (PTX: Paclitaxel-µM, GSH: Glutathione-mM) (n=8, *p<0.001).

Table 3. Percentage expression of cell viability by trypan blue staining of MCF-7 cells treated with GSH and PTX combinations after 72 hours of incubation.

GSH and PTX combinations	Cell viability (%) (n=8)
Control	100±3.56
1 µM PTX	72.89±6.25
5 µM PTX	82.50±1.24
10 µM PTX	55.12±5.23
5 mM GSH	91.25±3.14
10 mM GSH	54.36±2.65
15 mM GSH	47.36±4.37
20 mM GSH	56.32±2.69
1 µM PTX + 15 mM GSH	47.39±4.25
5 µM PTX + 10 mM GSH	51.78±5.02
10 µM PTX + 5 mM GSH	57.85±2.48
10 µM PTX + 10 mM GSH	45.63±2.03
10 µM PTX + 15 mM GSH	76.78±2.74
10 µM PTX + 20 mM GSH	101.34±4.26

The data were entered into the CompuSyn programme, which automatically analyses the data of common or different targeted drug combinations, and CI was calculated. The CI analysis employed in this programme is based on the median-effect principle.[34] The CI values obtained were interpreted in accordance with the guidelines set out in Table 4. (CI<0.9=Synergism; 0.9-1.1=positive; CI>1.1= Antagonism).

Table 4. Combinations applied to MCF-7 cell culture line.

Concentrations	CI Value	Commentary*
10 µM PTX + 5 mM GSH	0.387	Strong synergism
1 µM PTX + 15 mM GSH	0.482	Synergism
10 µM PTX + 10 mM GSH	0.459	Synergism
10 µM PTX + 15 mM GSH	0.561	Synergism
5 µM PTX + 10 mM GSH	1.646	Antagonizm
10 µM PTX + 20 mM GSH	1.876	Antagonizm

* CI=1 indicates additive effect, CI<1 indicates synergistic effect and CI>1 indicates antagonism (Chou, 2010)

The combinations exhibiting a synergistic effect demonstrated a significant cytotoxic effect compared to the control (p<0.001). However, the proliferation of cells was observed in the combination with 20 mM GSH.

The effect of the determined combinations on cell viability was determined by both WST-1 and trypan blue staining. When the results obtained with the two methods were evaluated, no statistically significant difference was found between them (p>0.05).

Determination of GSH, total oxidant and total antioxidant levels

The analysis of the data revealed no significant difference in the levels of GSH in cell lysates treated with GSH and PTX (Figure 4A) (p>0.05). TAS was found to be lower in the cell line in which PTX was applied at 5 µM compared to the control (p<0.05). In contrast, GSH was found to be higher in other combinations, with the exception of the PTX10 x GSH5 combination, in which GSH was applied alone and in combination with PTX (p<0.05). The results demonstrated that GSH

levels above 5 mM had an effect on PTX toxicity (Figure 4B). PTX addition did not alter the TOS of MCF-7 cells, but it increased in cells treated with 15 and 20 mM GSH and in combinations containing GSH (p<0.05). A significant decrease was observed in the MCF-7 cell line treated with GSH10 and PTX10 x GSH10 compared to the control (p<0.05) (Figure 4C).

In summary, it was found that TAS levels increased significantly in all combination treatment groups except 5 mM GSH and 10 µM PTX combination treatment compared to the control (p<0.05). In addition, TOS levels increased significantly in all combination groups except 10 mM GSH and 10 µM PTX combination treatment compared to the control (p<0.05).

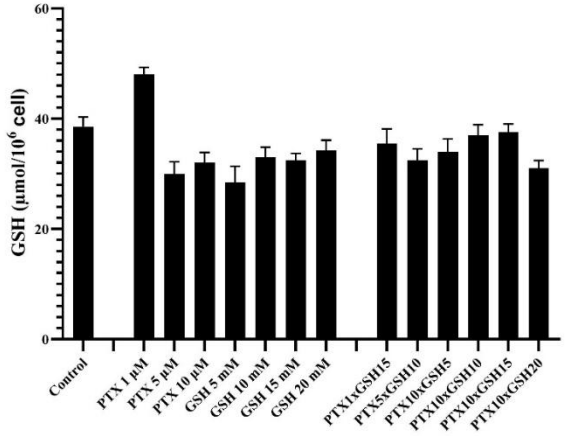

Figure 4A. GSH levels in MCF-7 cell line treated with GSH and PTX combinations for 72 hours (n=3, median ±SE).

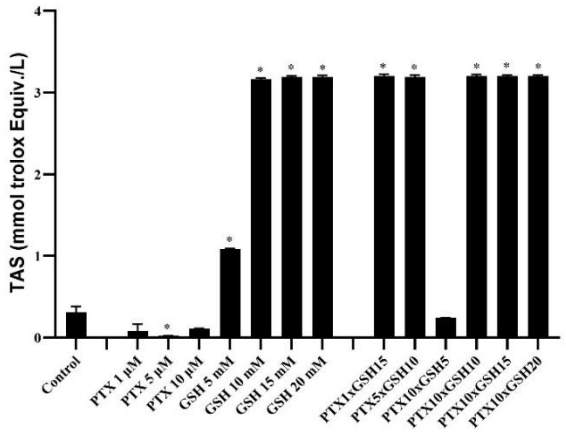

Figure 4B. TAS Level in MCF-7 cell line treated with GSH and PTX combinations for 72 hours (n=3, median ±SE). * p<0.05 different from control.

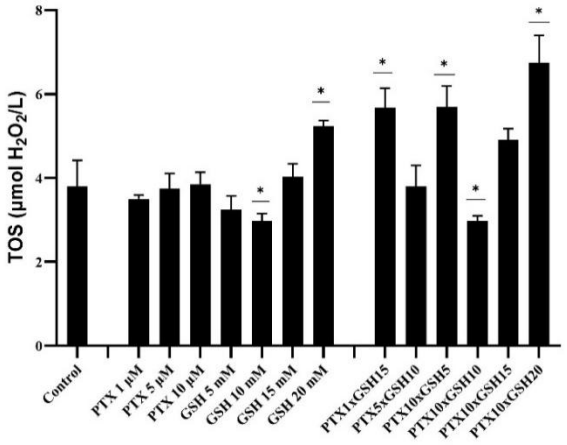

Figure 4C. TOS levels in MCF-7 cell line treated with GSH and PTX combinations for 72 hours (n=3, median±SE). * p<0.05 different from control.

Discussion

Despite the numerous new research studies and discoveries in the mechanisms of cancer and drug design, the incidence of cancer is expected to increase in the coming years. The search for natural, inexpensive treatments to prevent, treat and stop the progression of cancer has gained importance in recent years.

The objective of chemotherapeutic agents, which are currently the most effective in cancer treatment, is to destroy rapidly proliferating and growing cancer cells during the proliferative period. However, chemotherapy also affects normal cells while destroying cancer cells. Furthermore, these drugs cause an increase in ROS levels and disruption of the antioxidant balance of the cell. For this reason, the occurrence of side effects is attempted to be reduced and eliminated with the help of antioxidant substances in conjunction with chemotherapy. However, the literature still does not provide clear answers to questions such as whether the concomitant intake of antioxidants with chemotherapeutic drugs decreases the efficacy of the drug or develops drug resistance. Therefore, it is important to determine the synergistic additive and antigonistic effects of these combinations and to elucidate their mechanisms by cell culture studies. In our study, we investigated the combination of glutathione, which is important in the mechanism of chemotherapeutic drug resistance and whose intracellular concentration is controlled by many enzymes

as the same endogenous antioxidant, with paclitaxel, the most commonly used drug in breast cancer treatment.

Antioxidants, which reduce the damaging effects of free radicals, play an important role in the supportive treatment of cancer. GSH, which plays a dominant role in the antioxidant system, primarily as an intracellular radical scavenger and detoxifying molecule, is increasingly being investigated due to its potential role in the prevention and treatment of cancer.[31] This is due to the fact that the GSH system acts as a homeostatic redox buffer and is one of the primary cellular defences against free radicals.[39] GSH is crucial in the removal and detoxification of carcinogens and is thought to have a possible link with GSH deficiency in the development of cancer cells.[25,40,41] GSH deficiency or a decrease in the GSH/glutathione disulfide (GSSG) ratio leads to increased susceptibility to oxidative stress, which plays a role in cancer progression, whereas increased GSH levels increase antioxidant capacity and resistance to oxidative stress, as seen in many cancer cells.[27] The dual role of ROS in these processes further complicates the impact of GSH on oxidative stress and cancer initiation and progression.[25] The GSH system acts as a homeostatic redox buffer and is one of the first cellular defences against free radicals. Cellular redox potential is largely determined by GSH levels, which account for 90% of cellular non-protein thiols.[39] Furthermore, research has shown that increasing GSH levels in cancer cells may have anti-cancer effects by inhibiting tumour growth and promoting apoptosis or programmed cell death.[42] GSH has also been shown to increase the effectiveness of some chemotherapeutic drugs by protecting healthy cells from their toxic effects. Overall, there is growing evidence that GSH plays an important role in cancer and may have potential therapeutic effects.

In our study, PTX showed a dose- and time-dependent cytotoxic effect in MCF-7 cells. The viability assay results obtained are in parallel with similar studies.[43-45] In one study, it was observed that 1.6 mM GSH did not cause any change in the number of cells in A549 lung cells.[46] As a parallel result of this study, it was observed that GSH, which we applied at a lower concentration range (2.5-10 mM), had no significant effect on cell proliferation, but showed a cytotoxic effect similar to that of PTX as the applied dose and time increased. GSH applied at a concentration of 20 mM for 24 and 48 hours had a mitogenic effect on the cells. Alexandre et al.[46] observed that the accumulation of H_2O_2 and the cytotoxic activity of PTX against A549 cancer cells decreased with the addition of 1.6 mM N-acetylcysteine (NAC) and 1.6 mM GSH to the medium. Similarly, according to the results of the Compusyn programme in our study, GSH was found to reduce the cytotoxic effect of PTX as the amount of GSH increased in the combinations studied, and GSH above 10 mM showed an antagonistic effect with PTX.

Studies have shown that using antioxidants reduces the formation of some cancers caused by free radicals. However, as ROS have other important physiological functions, such as second messengers, it has been suggested that inhibition of apoptosis by antioxidants may prevent the destruction of unwanted (precancerous and cancerous) cells and may induce cancer in individuals with carcinogenic DNA damage.[47] Resveratrol treatment as an antioxidant caused GSH depletion in MCF-7 cells and GSH levels were found to be lower than controls.[48] A positive correlation was found between cellular levels of GSH and the growth of tumour cells in pancreatic and prostate cancer.[49,50] Studies have shown that the drug and radiation resistance of many tumours is associated with higher levels of GSH in cancer cells compared to normal tissue.[39,51] Despite an increase in ROS in MCF-7 cells treated with rose bengal, 100 mM GSH inhibited ROS generation but had no effect on toxicity.[52]

In contrast to the viability results, no significant difference was found between the intracellular GSH concentrations; GSH added to the cell media did not affect the intracellular GSH concentration. One of the limitations of our study was that we did not measure the activity of the enzyme g-glutamyl transpeptidase (GGT). While GSH synthesis occurs inside the cell, GSH degradation takes place with GGT expressed on the cell surface.

The glutamate, cysteine and glycine produced by GSH degradation are used for intracellular GSH synthesis. GGT enzyme activity is an important parameter that can provide information on the level of utilisation of GSH precursors in the extracellular fluid.[53,54].

PTX has been reported to induce the production of endogenous ROS.[45,55-57] In certain studies, it has been demonstrated that the application of PTX to cells results in an increase in ROS levels within the cell. The addition of antioxidants, such as NAC and GSH, to the medium has been shown to prevent the accumulation of ROS caused by PTX.[45,46]

A positive correlation was observed between total antioxidant capacity and PTX IC_{50} value in 16 cell lines, including MCF-7 cells. The higher the PTX IC_{50} value of tumour cells, the higher the total antioxidant capacity was found.[44] It was observed that taxol-induced apoptosis in chronic myeloid leukemia K562 cells treated with taxol, a taxane derivative, was associated with ROS production and GSH consumption. Adding NAC antioxidant to the medium was found to suppress taxol-induced apoptosis and ROS production.[58] Furthermore, in addition to the literature, it was found that TAS were considerably higher in cells and combinations that had been treated with GSH. There was also a significant increase in TOS levels. The high TAS levels indicate that GSH has a positive effect on the increase in antioxidant capacity.

Shen et al[59] investigated the effects of GSH on the chemotherapeutic efficacy of DOX in cancer cell models including MCF-7, HepG2 and Caco-2 cells. They reported that GSH administration dose-dependently decreased the anticancer efficacy of DOX both in vivo and in vitro. Therefore, they reported that the combination of GSH and DOX during chemotherapy can generally be considered contraindicated.

In the literature, many natural products have been combined with paclitaxel to reduce the side effects. The mechanisms of action of the combinations especially on cancer cell lines have been tried to be elucidated. Combinations of apigenin,[60] baicalein,[61] daidzein,[62] fisetin,[63] genistin[62] luteolin[64] have been examined and data have been obtained to reduce the side effects of apoptosis induction. However, since there are few publications with glutathione, which is an endogenous antioxidant, the results of our study make an important contribution to the literature.

Taxane family toxicity is associated with ROS production in cancer cells, leading to apoptosis activation. Cancer cells, in turn, induce an antioxidant response as a taxane resistance enhancing effect.[65] Therefore, an excess of antioxidants in the environment may actually minimize ROS production and cancer cell apoptosis. Our results show that the combination of exogenous GSH and PTX as treatment is dose dependent. It has been shown that appropriate GSH concentration increases treatment efficacy and sensitizes the cell to chemotherapeutic drugs. However, we can state that high concentrations decrease the treatment response.

Conclusion

The interactions between chemotherapeutic agents and antioxidants are complex and factors such as dose, localisation and metabolism of the drug influence the production of free radicals. Some antioxidants also have the potential to act as oxidative molecules, depending on their use and/or relative concentration. It is clear that monitoring all the enzymes and molecules involved in GSH metabolism will be more revealing in order to clearly see the antioxidant effect in cancer cells, and in this context studies are needed to investigate the multifaceted effect of GSH on cancer cells. The effectiveness of oral GSH supplements in supporting cancer treatment has not been fully established. Although GSH is an essential antioxidant, the body's ability to absorb it orally is limited and its effect on cancer treatment outcomes remains unclear.

Our results emphasise that antioxidants and chemotherapeutic agents should be used at appropriate doses and within a certain period of time. It should be kept in mind that the use of glutathione as an antioxidant in patients receiving paclitaxel chemotherapy is dose

dependent and high dose applications should be avoided.

Limitations

Although there is promising evidence suggesting a role for GSH in the prevention and treatment of cancer, most research to date has been limited to experiments using tumour cell lines or animal models. Further research is therefore needed, particularly through clinical trials in patients, to determine the efficacy and safety of using GSH as a preventive or therapeutic agent in cancer.

Ethics Committee Approval

Ethical approval was not required as this study did not involve animal or human experimentation.

Author Contributions

GSEA: Design and Conception, Resources, Materials, Analysis and/or Interpretation, Data Collection and/or Processing, Literature Review, Writing. IB: Data Collection and/or Processing, Literature Review, Analysis. AY: Literature Review, Analysis. AB: Idea/Concept, Supervision/Consultancy, Funding, Literature Review, Critical Review. PAU: Supervision/Counselling, Resources, Literature Review, Critical Review.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial Disclosure

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Statements

2nd International Cappadocia Scientific Research Congress, page 1185-1186 June, 2022, Cappadocia-Nevşehir/Türkiye.

Peer-review

Externally peer-reviewed.

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Research Article/Özgün Araştırma

Evaluation of incidental prostate cancer in patients who underwent radical cystectomy and its effect on survival

Radikal sistektomi uygulanan hastalarda insidental prostat kanserinin değerlendirilmesi ve sağkalım üzerindeki etkisi

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Abstract

Aim: Our study aimed to investigate the incidence of incidental prostate adenocarcinoma, its histopathological results and its effect on survival in patients who underwent radical cystectomy due to bladder tumor.

Materials and Methods: Patients who underwent radical cystectomy with a diagnosis of bladder tumor in our clinic in the last ten years and who had no preoperative suspicion or diagnosis of prostate cancer were included in the study. Patients were divided into two groups those with and without incidentally prostate cancer. Both groups were compared in terms of age, PSA value, histopathological features and overall survival.

Results: 15 (22.6%) of 79 patients who underwent radical cystectomy and were followed up for an average of 62 months were incidentally diagnosed with prostate adenocarcinoma. There was a significant difference between mean PSA value in patients with prostate cancer and the group without prostate cancer (p=0.004). When we evaluated it in terms of five-year overall survival, no significant difference was found between the two groups.

Conclusion: Although incidental prostate cancer does not seem to affect survival, it is necessary to follow up regularly in the presence of prostate cancer and be more careful, especially in the presence of locally advanced prostate cancer.

Keywords: Cystectomy, Survival; Incidental prostate adenocarcinoma; urotelial bladder carcinoma.

Öz

Amaç: Çalışmamızda mesane tümörü nedeniyle radikal sistektomi uygulanan hastalarda rastlantısal prostat adenokarsinomu görülme sıklığı, histopatolojik sonuçları ve sağ kalım üzerine etkisinin araştırılması amaçlandı.

Gereç ve Yöntem: Çalışmaya son 10 yıl içinde kliniğimizde mesane tümörü tanısıyla radikal sistektomi yapılan, ameliyat öncesi prostat kanseri şüphesi veya tanısı olmayan hastalar dahil edildi. Hastalar rastlantısal prostat kanseri saptanan ve saptanmayan grup olarak ikiye ayrıldı. Her iki grup yaş, PSA değeri, histopatolojik özellikler ve genel sağkalım açısından karşılaştırıldı.

Bulgular: Radikal sistektomi uygulanan ve ortalama 62 ay takip edilen 79 hastanın 15'ine (%22,6) insidental prostat adenokarsinomu tanısı konuldu. Prostat kanserli hastalar ile prostat kanseri olmayan grup arasında ortalama PSA değeri arasında anlamlı fark vardı (p=0,004). Beş yıllık genel sağkalım açısından değerlendirdiğimizde iki grup arasında anlamlı fark bulunamadı.

Sonuç: İnsidental prostat kanseri sağ kalımı etkilemiyor gibi görünse de prostat kanseri varlığında düzenli takip yapmak ve özellikle lokal ileri prostat kanseri varlığında daha dikkatli olmak gerekir.

Anahtar Kelimeler: Sistektomi; Sağkalım; Rastlantısal prostat adenokarsinomu; ürotelyal mesane karsinomu.

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Introduction

Prostate cancer is the most common cancer that causes death in men after lung cancer in the World.[1] The incidence of prostate cancer in the world is 30.6/100,000, and the incidence in Turkey is 10.9-28/100,000.[2] Bladder cancer is the ninth most common cancer worldwide and the seventh most common cancer in the male population, and there is male predominance in bladder cancer.[3] Bladder cancer and prostate cancer are genitourinary malignancies that cause serious morbidity and mortality.[4] Extended lymph node dissection along with radical cystectomy (RS) is the standard treatment for muscle-invasive bladder tumors. Some surgeons have preferred to preserve the prostate or prostate capsule apex during radical cystectomy, taking the risk of leaving cancer tissue behind, in order to avoid the urinary and sexual side effects of the operation, but as per the standard surgical procedure, all prostate tissue must be removed. The frequency of incidental prostate adenocarcinoma detected after RS varies in various series.[5] The majority of incidental prostate adenocarcinomas detected in patients undergoing RS are localized and clinically insignificant cancers.[6] In this study, the incidence, histopathological evaluation results and follow-up period of patients who underwent radical cystoprostatectomy due to bladder tumor and incidentally detected prostate adenocarcinoma were examined.

Materials and Methods

Type of the study

We planned our study as retrospective.

The sample size of the study

Patients who underwent radical cystectomy with a diagnosis of bladder tumor in our clinic between March 2013 and March 2023 and who had no preoperative suspicion or diagnosis of prostate cancer were included in the study. Patients who underwent radical cystoprostatectomy and bilateral extended pelvic lymphadenectomy were evaluated retrospectively. Patients who were histopathologically diagnosed with prostate cancer before RS, patients who underwent cystectomy for reasons other than bladder cancer, female patients were excluded from the study. Patients who received neo-adjuvant chemotherapy were also not included in our study because it would change the outcome of the article in terms of survival and affect the pathology results.

Data collection tools

Preoperative digital rectal examination (DRE), serum prostate specific antigen (PSA), chest radiography and whole abdomen imaging were performed on the patients to prove that there was no local or distant metastasis for the bladder tumor. Histopathological evaluation was performed by an experienced uropathologist. Serum PSA levels were checked in each patient every 3 months for prostate cancer follow-up in the postoperative period. Prostate cancer biochemical recurrence; It was defined as a PSA value >0.2 ng/mL measured at least twice. The patients were divided into two groups: those with incidental prostate cancer detection and those without detection. The two groups were assessed based on age, preoperative PSA value, bladder tumor stage, tumor grade, presence of concurrent carcinoma in situ, surgical margin positivity, lymph node involvement, and overall survival.

Data analysis

SPSS (IBM version 21, NY, USA) program was used in statistical analysis. Independent samples t-test was used for two-group comparisons of normally distributed quantitative variables, and Mann-Whitney U test was used for two-group comparisons of non-normally distributed quantitative variables. When comparing the tumor stages of the groups with and without prostate cancer, chi-square was performed by categorizing them. Pearson chi-square test and Fisher's exact probability test were used to compare qualitative data. Evaluation of overall survival was performed using Kaplan- Meier survival analysis. Statistical significance was accepted as $p<0.05$.

Ethics committee approval

The study protocol received scrutiny and approval from the Sivas Cumhuriyet University Clinical Research Ethics

Committee (decision no: 2023-07/02, date: 20.07.2023). Our study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent form were obtained from all patients.

Results

In the study, data of 102 patients who underwent radical cystectomy were examined. Of these patients, 9 were not included in the study because they had prostate cancer under follow-up, 8 because they received neo-adjuvant chemotherapy, 5 because metastasis was detected at the time of diagnosis, and 1 patient was female. Data from the remaining 79 patients were analyzed retrospectively. Inclusion in the study was indicated in the flow chart (Figure 1).

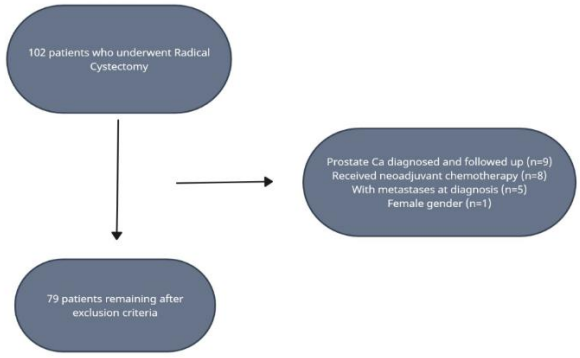

Figure 1. Study inclusion flow chart.

The remaining 79 patients after exclusion criteria were followed for an average of 62 months (4-148 months). 15 (22.6%) of the 79 patients included in the study were diagnosed with incidentally prostate adenocarcinoma. Demographic characteristics and histopathological findings of both groups are presented in Table 1. The average age of the patients with prostate cancer was 63.0±1.5, the group without prostate cancer was 65.1±1.4, there was no significant difference between the groups (p=0.312). In DRE performed on patients diagnosed with prostate cancer, it was determined that all patients had benign findings. The mean preoperative PSA value in patients with prostate cancer was 4.75 ng/ml, and the mean PSA value in the group without prostate cancer was 2.67 ng/ml (p=0.004). There was a significant difference between the groups (Table1).

In the histopathological examination of cysto-prostatectomy specimens of patients with prostate cancer, organ-confined tumor (≤ pT2) was detected in 8 (53.4%) patients, advanced stage (≥pT3) urothelial carcinoma was detected in 7 patients (46.6%), and there was no patient with no urothelial carcinoma detected and evaluated as T0. When we evaluated in terms of surgical margin positivity, surgical margin positivity was detected in 3 (20%) patients in the group with prostate cancer and in 11 (17.2%) patients in the group without prostate cancer (p=0.52). When evaluated in terms of lymph node metastasis, lymph node positivity was detected in 4 (26.7%) patients in the group with prostate cancer detected and in 16 (25%) patients in the group without prostate cancer, and this rate was similar between both groups (p=0.56) (Table 1).

The predominant histological stage for prostate cancer was observed to be T2 (46.7%). When patients with incidental prostate cancer were evaluated, 6 (40%) patients were found to have clinically significant prostate cancer (ISUP≥2), and when we analyzed these patients, the number of patients with Gleason score ≥ 7 was 6 (40%). There were no patients locally advanced stage (≥pT3a) (table 2). The average follow-up period in patients diagnosed with prostate cancer was 47 months (3-74) and biochemical recurrence was detected in 3 patients during this follow-up period. Pelvic radiotherapy was applied to two patients with biochemical recurrence, and one patient received hormonotherapy. No death was observed in any patient due to prostate adenocarcinoma, but in the group without prostate cancer, death occurred in 8 (12.5%) patients due to bladder tumor during an average follow-up period of 65 months (3-84).

Upon analyzing the five-year overall survival, we observed that patients with prostate cancer had an overall survival rate of 84%, while those without prostate cancer had a rate of 87.4%. The statistical analysis revealed no significant difference between the two groups, with a p-value of 0.691.

Table 1. Statistical comparison of patient groups.

	Prostate Cancer (+)	Prostate Cancer (-)	*p*
N	15 (23.4%)	64 (76.6%)	-
Age (years)	63.0 ± 1.5	65.1 ± 1.4	0.312
PSA (ng/ml)	4.75 ± 1.05	2.67 ± 0.29	0.004
Follow-up (month)	47.8 ± 8.6	65.3 ± 5.0	0.220
Bladder tm Stage			
pTa	1(6.7%)	3(4.7%)	0.767
pT1	0	8(12.5%)	
pT2	7(46.7%)	23(35.9%)	
pT3	4(26.7%)	18(28.1%)	
pT4	3(20%)	12(18.7%)	
CIS			
No	15	63	0.810
Yes	0	1	
Surgical Margin Positivity			
No	12	53	0.520
Yes	3	11	
Lymph Node Involvement			
No	11	48	0.560
Yes	4	16	
Metastasis			
No	13	59	0.390
Yes	2	5	
Ex	2 (13.3%)	8 (12.5%)	0.680

CIS: Carcinoma in situ.

Table 2. Pathological results and follow-up of prostate cancer patients.

Age	Bladder tm Stage	Psa	Surgical margin	Lymph node	Metastasis	Prostate Ca Stage	Gleason	ISUP	Follw-up	Ex
62	T2b	9.24	-	-	-	T2a	3+3	1	118	-
64	T4a	14.21	+	-	Lung	T2c	5+4	5	6	+
73	T3a	3.37	-	+	-	T2a	3+3	1	52	-
60	T4a	1.65	-	-	-	T2a	3+3	1	28	-
66	T3a	4.78	-	-	-	T2b	3+4	2	50	-
58	T3a	2.12	+	+	Lung	T2a	3+3	1	108	-
68	T2a	2.59	-	-	-	T2a	3+3	1	65	-
64	T2a	6.3	-	-	-	T2a	3+3	1	44	-
58	T2b	4.52	-	-	-	T2a	3+3	1	36	-
69	T4a	11.76	+	+	-	T2a	4+4	4	13	+
63	T2b	6.08	-	+	-	T2a	3+3	1	70	-
71	T3a	11.23	-	-	-	T2c	3+4	2	56	-
64	T2a	3.12	-	-	-	T2b	3+4	2	15	-
54	T2a	0.537	-	-	-	T2a	3+3	1	6	-
51	Ta	4.77	-	-	-	T2c	3+4	2	50	-

Discussion

The detection rates of simultaneous prostate cancer in patients who underwent radical cystectomy are seen between 4% and 61% in various series.[7-12] In our study, prostate cancer was detected in 15 (23.4%) of 79 male patients who underwent RS. On the other hand, rates reaching 60% have been reported in some studies.[13] The reason for this difference in prevalence may be epidemiological and racial differences in studies and differences in evaluation of pathology specimens. There are studies in the literature demonstrating that advanced age is an important independent marker in detecting prostate cancer concurrent with radical cystectomy.[11,13,14] Bladder cancer and prostate cancer reach their highest incidence rate over the age of 70.[15] Similarly, Bell et al. reported in an autopsy series that the incidence of prostate cancer increased with age.[16] Contrary to the literature, in our study,

the age of the group with incidental prostate cancer was found to be lower, and there was no significant difference between the group with and without prostate cancer. In their large-scale study, Fahmy et al. found that while advanced age was associated with the incidence of incidental prostate cancer, there was no age difference between clinically significant or clinically insignificant prostate cancer subgroups.[9] In our study, when the histopathological results of bladder cancer were evaluated between the groups with and without prostate cancer, no difference was detected in terms of tumor stage, presence of carcinoma in situ, lymph node metastasis and surgical margin positivity.

Although some previous studies on incidental prostate cancer stated that PSA could not be used as a predictor of prostate cancer, in our study, the PSA value was found to be statistically significantly higher in the prostate cancer group.[14] The clinical importance of PSA values should not be ignored in the preoperative evaluation of patients.

It was observed that the 3 patients with biochemical recurrence had high Gleason scores and/or locally advanced stage (pT3a) prostate cancer. In our study, no death due to prostate cancer was observed in any patient with biochemical recurrence. In their study, Pignot et al. observed biochemical recurrence in only 16 (1.9%) of the 931 incidental prostate cancer patients. Furthermore, no prostate cancer-related death was observed in any patient during the average follow-up period of 23 months.[15]

In patients with localized prostate cancer, the 5-year prostate cancer-specific survival after surgery is 100% and the 10-year survival rate is 99%.[16] Even in patients with pT3b disease who underwent radical prostatectomy, disease-related death may not occur within 6 years.[17] With these results, much longer follow-up periods will be required for incidental prostate adenocarcinoma in radical cystectomy to have a negative impact on cancer-related and overall survival. For muscle-invasive bladder cancer, the 5-year cancer-related survival rate is 55% in patients who undergo radical cystectomy without neoadjuvant chemotherapy. Recurrence may develop in these patients after a median follow-up of 12.5 months.[17] Cancer-related death rates in the older age group are lower than age and comorbidities-related death rates. If the prognosis is to be determined after cancer diagnosis in this age group, age and comorbidities should be taken into consideration as major causes of deat.

There are studies in the literature reporting that incidental prostate cancer has no effect on overall and cancer-related survival.[20,21] In contrast, Heidegger et al. observed that six of the 15 patients who developed biochemical recurrence died as a result of prostate cancer within a relatively short period, ranging from nine months to four years.[10] In a large series study, Fahmy et al. observed that the group with incidental prostate cancer had a relatively low 5-year overall survival rate (p=0.03).[9] In our study, the presence of prostate cancer did not have a negative effect on overall survival. Despite tumor aggressiveness remains high as age and tumor stage increases, these inconsistencies in studies indicate the need for prospective studies with larger and standardized study groups.

When we search in Urology literature in Turkey, we come across 8 articles on this subject. In these studies; The incidence of incidental prostate cancer in patients being treated RS has been reported to be between 9% and 30.2%.[19-26] When our study is compared to other studies, it is seen that there is an acceptable number of patients, a longer follow-up period, and a longer-term survival analysis (Table 3).

Previous multicenter studies have shown that the majority of prostate cancer accompanying bladder cancer is organ-confined (≤pT2) and non-aggressive, well-differentiated prostate cancer. The probability of developing non-aggressive prostate cancer has been found to be higher, especially in young age group men (under 60 and 70 years of age). For such reasons, it has been stated in studies that accompanying prostate cancer has no effect on the patient's survival.[18] The decrease in survival rates due to incidental prostate cancer may not be seen in the short-term follow-up due to reasons such as shorter

survival due to the pathological stage of bladder cancer, rapid recurrence, and older age of patients. However, the presence of locally advanced prostate cancer requires regular follow-up after surgery. The shortcomings of the study are that it has a retrospective evaluation and that the follow-up period is relatively short in terms of prostate cancer follow-up.

Table 3. Data from studies conducted on this subject.

Outhor	n	Follow-up (month)	Prostate Cancer(+). n (%)	Mean Age		Mean PSA ng/ml	
				Prostate Cancer (+)	Prostate Cancer (-)	Prostate Cancer (+)	Prostate Cancer (-)
Türk et al.[19] 2015	126	20	26 (20.6%)	67.1	65.8	4.2	3.9
Ceylan et al.[20] 2016	119	27.1	16 (13.4%)	62.3	-	2.13	-
Uğurlu et al.[21] 2010	149	22.8	14 (9.3%)	64.2	57.7	3.26	-
Sarı et al.[22] 2007	178	-	16 (9%)	-	-	-	-
Hızlı et al.[23] 2005	50	-	5 (10%)	70.2	62	-	-
Başpınar et al.[24] 2013	59	-	9 (15.3%)	71	65	-	-
Turan et al.[25] 2018	190	33	43 (22.6%)	70	63.7	5.38	2.72
Özer et al.[26] 2020	197	-	51 (30.2%)	62.9	66.4	3.5	2.6
Our Study	102	62	15 (23.4%)	63.0	65.1	5.75	2.67

Study limitation

The main limitation of our study is the small number of patients participating in the study. This can be explained by the fact that recent surgeries could not be included in the study in order to establish a 5-year follow-up rate. Although not specifying tumor volumes represents a classification in terms of survival, its absence in our study is among the limitations of the study.

Conclusion

As a result, it is common to detect prostate cancer in patients who underwent radical cystoprostatectomy, and in our study, this rate was found to be 23.4% and was consistent with the literature. Therefore, the pathologies of patients who underwent radical cystoprostatectomy should be evaluated carefully and in detail. Although prostate adenocarcinoma is limited to the organ in most patients, it is also important to follow up the patients in terms of this disease.

Ethics Committee Approval

The study protocol received scrutiny and approval from the Sivas Cumhuriyet University Clinical Research Ethics Committee (decision no: 2023-07/02, date: 20.07.2023). Our study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent form were obtained from all patients.

Informed Consent

All participants provided informed consent upon enrollment.

Authors Contrubituons

A.Ö.: Idea/Concept, Design, Audit/Consultancy, Materials, Data collectıon and/or processing, Analysis and/or comment, Literature review, Writing, Critical review. İ.E.E.: Idea/Concept, Design, Audit/Consultancy, Resources, Analysis and/or comment, Literature review, Writing. H.S.: Idea/Concept, Design, Audit/Consultancy, Resources, Materials, Data collectıon and/or processing, Critical review. A.A.: Idea/Concept, Design, Audit/Consultancy, Resources, Materials, Data collectıon and/or processing, Critical review.

Conflict of Interests

There is no conflict of interest to declare.

Financial Disclosure

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Statements

These research results have yet to be presented anywhere previously. Data related to the study is available on request.

Peer-review

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Özgün Araştırma/Research Article

İleri yaş mide kanserli hastalarda tedavi ve post operatif sonuçlarının değerlendirilmesi

Evaluation of treatment and postoperative outcomes in elderly patients with gastric cancer

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Öz

Amaç: Çalışmamız, 80 yaş üzeri mide adenokarsinom hastalarında cerrahi tedavi ile neoadjuvan ve adjuvan kemoterapi uygulanmasının, postoperatif komplikasyonlar ve bunların sağkalım üzerindeki etkilerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Adana Şehir Hastanesi'nde Eylül 2018 ile Eylül 2023 tarihlerinde mide adenokarsinomu teşhisi konmuş 44 hasta retrospektif olarak incelendi. Hastaların klinik ve patolojik verileri; cerrahi, neoadjuvan ve adjuvan kemoterapi kullanımı, kronik hastalıklar, postoperatif komplikasyonlar, hastanede kalış süresi ve sağkalım analiz edildi.

Bulgular: Hastaların yaş ortalaması 84,2±3,1 yıl olup, %59,1'i erkektir. Lenf nodu diseksiyonu %71 oranında yapılmış, tümör çapı ortalama 5,3±2,8 cm'dir. Neoadjuvan kemoterapi %65,9 ve adjuvan kemoterapi %68,2 oranında uygulanmış, kemoterapinin sağkalım üzerinde olumlu etkisi saptanmıştır (p<0,05). Postoperatif komplikasyonlarda anlamlı bir artış gözlenmiştir (p<0,05), bu komplikasyonların çoğunlukla akciğer kaynaklı olduğu belirlenmiştir.

Sonuç: Mide adenokarsinomlu yaşlı hastalarda cerrahi müdahalelerin güvenli olduğu görülmüştür. Ancak postoperatif komplikasyonların etkili bir şekilde yönetilmesi gerekmektedir. Neoadjuvan ve adjuvan kemoterapi kullanımının sağkalım üzerinde önemli bir etkisi olduğu bulunmuştur.

Anahtar Kelimeler: Mide adenokarsinomu; Yaşlı hastalar; Cerrahi tedavi; Kemoterapi; Postoperatif komplikasyonlar.

Abstract

Aim: To assess the impact of surgical treatment combined with neoadjuvant and adjuvant chemotherapy on postoperative complications and survival in patients aged 80 and older with gastric adenocarcinoma.

Materials and Methods: A retrospective analysis of 44 patients diagnosed with gastric adenocarcinoma between September 2018 and 2023 was conducted. Data included details of surgical procedures, chemotherapy administration, chronic diseases, postoperative complications, hospital stay duration, and survival rates.

Results: The mean patient age was 84.2±3.1 years, with 59.1% male. Lymph node dissection was performed in 71% of cases, and the average tumor size was 5.3 cm. Neoadjuvant chemotherapy was given to 65.9% and adjuvant to 68.2% of patients. Chemotherapy improved survival but increased pulmonary complications (p<0.05).

Conclusion: Surgical treatment is safe for elderly patients with gastric adenocarcinoma. However, careful management of postoperative complications is essential, as chemotherapy significantly improves survival outcomes.

Keywords: Gastric adenocarcinoma; Elderly patients; Surgical treatment; Chemotherapy; Postoperative complications.

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Giriş

Küresel nüfusun yaşlanmasıyla birlikte, mide kanserinin yaşlı bireylerde daha sık görülmesi beklenmektedir.[1] İstatistiklere göre, mide kanseri vakalarının %60'ından fazlası 65 yaş ve üzerinde görülmektedir.[2] Bu yaş grubunda uygun cerrahi kararlarının preoperatif dönemde detaylı bir şekilde değerlendirilmesi gereklidir. Yaşlılarda mide kanseri tedavi yönetimi, etkili tedavi seçeneklerinin yaş ve bireysel sağlık durumuna göre titizlikle değerlendirilmesini gerektirir. Yaşlı hastaların yaşı ve sahip oldukları diğer yandaş hastalıklar, postoperatif komplikasyon riskini artırabilir ve organ fonksiyon kapasitelerini olumsuz etkileyebilir. Bu da özellikle postoperatif dönemde, kanser dışı ölümlerin görülme sıklığını yaşlı hastalar için önemli bir sorun haline getirmektedir. Mide kanseri, küresel halk sağlığı açısından önemli bir tehdit oluşturmakta olup, özellikle yaşlı popülasyon için yüksek risk taşımaktadır. Bu grup, mide kanseri ile ilişkili ölümlerin %70'ten fazlasını oluşturmaktadır.[3] Mide kanseri hastalarının çoğu ileri evrelerde teşhis edilmekte olup, bu durum tedavi etkinliğini ve hasta prognozunu büyük ölçüde etkilemektedir. Son on yılda, neoadjuvan ve perioperatif tedaviler yeni umutlar getirmiştir; bu tedavilerin R0 rezeksiyon oranlarını artırdığı ve genel sağkalımı iyileştirdiği gösterilmiştir.[4]

Bu çalışma, 80 yaş üzeri hastaların preoperatif ve postoperatif dönemde titizlikle değerlendirildiğinde, genç yaş grubuna uygulanan kemoterapinin bu yaş grubuna da uygulanabileceğini vurgulamaktadır.

Gereç ve Yöntem

Araştırmanın tipi

Bu araştırma, retrospektif bir kohort çalışmasıdır. Eylül 2018-Eylül 2023 mide adenokarsinomu tanısı konmuş hastaların geçmiş verileri incelenmiş ve analiz edilmiştir. Çalışmada, bu hastaların cerrahi ve kemoterapi gibi tedavi yöntemlerinin sonuçları ve postoperatif komplikasyonları retrospektif olarak değerlendirilmiştir.

Araştırmanın evreni ve örneklemi

Adana Şehir Hastanesi'nde 01.09.2018 ile 30.09.2023 tarihleri arasında histolojik olarak kanıtlanmış mide adenokarsinomu teşhisi konmuş ve 80 yaş üzeri 44 hasta retrospektif olarak incelendi. Hastalar, açık cerrahi yöntemle distal gastrektomi (DG), total gastrektomi (TG) veya gastroenterostomi (GE) operasyonları geçirmiştir. Tümöral kitlenin pankreas, çöliak trunkus veya hepatoduodenal ligamenti invaze ettiği tespit edilen hastalarda, tümör rezeksiyon şansı bulunmadığından ve mide pasajında tıkanıklık oluştuğundan drenaj amacıyla GE uygulanmıştır. Gastrektomi yapılan hastalara D1 veya D1-2 lenf nodu diseksiyonu uygulanmıştır. Tüm hastaların histopatolojik incelemeleri AJCC 8. evreleme sistemine göre yapılmıştır. Neoadjuvan ve adjuvan tedavi kararları, tıbbi onkolog görüşü alınarak verilmiştir.

Çalışmaya dahil edilme kriterleri: Ameliyat öncesi ve sonrası klinik belgeleri eksiksiz olanlar, radyolojik ve patolojik verileri tam olanlar, histopatolojik olarak mide kanseri teşhisi almış 80 yaş ve üzeri hastalar oldu. Hariç tutulma kriterleri: Taburcu sonrası klinik verilere erişim imkânı olmayanlar, ameliyat öncesinde başka kanser türü taşıyanlar, operasyon geçirmeyenler ve non-adenokarsinom, GIST veya nöroendokrin tümör tanısı almış olanlar.

Çalışmanın verileri yaş, cinsiyet, TNM evresi, cerrahi türü, neoadjuvan ve adjuvan kemoterapi kullanımı, kronik hastalıklar, postoperatif komplikasyonlar, hastane kalış süresi, cerrahi alan enfeksiyonu ve mortalite gibi parametreler açısından incelendi. Hastalar operasyon sonrası bir yıl boyunca üç ayda bir, sonraki yıllarda ise altı ayda bir hastaneye kontrole çağrıldılar. Hastane kayıtları olmayan hastalar telefonla aranarak takip edildi. Her ziyarette rutin tüm laboratuvar testleri yapıldı. Hastalığın durumunu değerlendirmek için altı ayda bir abdominopelvik bilgisayarlı tomografi ve bir yıl sonra gastroskopi taramaları yapıldı.

Postoperatif komplikasyonlar Clavien Dindo sınıflandırma sistemine göre Grade II veya daha yüksek olarak tanımlandı. Operatif mortalite oranı, operasyondan sonraki 30 gün içindeki ölümler olarak hesaplandı. Hastane

taburculuğuna; intravenöz ilaç veya beslenme gereksinimi olmaması, komplikasyon belirtilerinin olmaması ve yardımsız tam olarak mobilize olabilme kriterlerine göre karar verildi.

Veri toplama araçları

Hasta Kayıtları ve Klinik Belgeler: Hastaların demografik bilgileri, mevcut hastalıkları, ameliyat öncesi ve sonrası durumlarına ilişkin detaylı klinik notlar. Radyolojik ve Patolojik Raporlar: Tümör boyutu, lokalizasyonu ve evresi. Histopatolojik incelemeler ve AJCC 8. evreleme sistemi kullanılarak yapılan değerlendirmeler. Tedavi ve Operasyon Kayıtları: Cerrahi prosedürler (Distal Gastrektomi, Total Gastrektomi, gastroenterostomi, lenf nodu diseksiyonu durumu). Neoadjuvan ve adjuvan kemoterapi uygulamaları. Postoperatif Komplikasyon Kayıtları: Postoperatif komplikasyonların türü ve ciddiyeti (Clavien-Dindo sınıflandırma sistemine göre). Hastane kalış süresi ve taburculuk sonrası izlem notları. Takip ve Sağkalım Verileri: Postoperatif dönemde hastaların üç ayda bir ve daha sonra altı ayda bir yapılan rutin kontrolleri. Telefon görüşmeleri ile yapılan izlemeler ve laboratuvar test sonuçları. Abdominopelvik bilgisayarlı tomografi ve gastroskopi taramaları.

Bu veri toplama araçları, çalışmanın amacı doğrultusunda gerekli bilgilerin sistematik ve güvenilir bir şekilde elde edilmesini sağlamıştır.

İstatistiksel Analiz

Postoperatif komplikasyonlarla değişkenler arasındaki ilişki, ki-kare ve Pearson korelasyon testi kullanılarak analiz edilmiştir. Genel sağkalım ise Cox regresyon yöntemi kullanılarak tahmin edilmiştir. İstatistiksel analizler, IBM SPSS İstatistikleri Windows sürüm 26 (IBM Corp.) kullanılarak gerçekleştirilmiştir.

Araştırmanın etik boyutu

Çalışmamız Adana Şehir Eğitim ve Araştırma Hastanesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'nun 28.09.2023 tarihli, 2852 protokol numarasıyla onaylanmıştır. Çalışma Helsinki Bildirisi'ne uygun olarak yapıldı.

Bulgular

Hastaların klinik ve patolojik özellikleri Tablo 1'de detaylandırılmıştır. Çalışmaya dahil edilen 44 hastanın yaş ortalaması 84,2±3,1 yıl olup, bunların %59,1'i (n=26) erkektir. Hastaların %68,2'sinde (n=30) en az bir kronik hastalık bulunmaktadır. Bunlardan 10 hastada iki veya daha fazla kronik hastalık mevcuttur. Kronik hastalıklar; diabetes mellitus (DM), hipertansiyon, koroner arter hastalığı ve kronik obstrüktif akciğer hastalığı (KOAH) olarak tanımlanmıştır. Yapılan istatistiksel analizde, kronik hastalıklar ve lenf nodu diseksiyonu uygulanan hastaların sağkalım açısından anlamlı bir fark göstermediği saptanmıştır (p>0,05). D1-2 lenf nodu diseksiyonu %71 (n=31) oranında, hiç diseksiyon yapılmayanların oranı ise %9,1 (n=4) olarak bulunmuştur. Neoadjuvan kemoterapi (KT) %65,9 (n=29) ve adjuvan KT %68,2 (n=30) oranında uygulanmıştır. Neoadjuvan ve adjuvan KT'nin sağkalım açısından olumlu yönde anlamlı bir etkisi olduğu saptanmıştır (p<0,05) (Şekil 1). Ancak hastaların evresi ilerledikçe ve tümör diferansiyasyon derecesi azaldıkça, sağkalım üzerindeki olumsuz etkilerin anlamlı derecede arttığı gözlemlenmiştir (p<0,05). Özellikle E4A evresinde belirgin bir yaşam süresi kısalması gözlenmiştir. E4A evresi %9,1 (n=4) ile en düşük oranı gösterirken, %43,3 (n=19) oranında E3 evresi mevcuttur. En fazla görülen tümör tipi %38,6 (n=17) ile az diferansiye olup, bu grubun yaşam süreleri belirgin olarak düşük tespit edilmiştir. Patolojik tanıda taşlı yüzük hücreli adenokarsinom %20,4 (n=9) oranında tespit edilmiştir. Tümör çapı ortalama 5,3±2,8 cm (1-12,1 cm) olup, çap arttıkça evrenin arttığı istatistiksel olarak anlamlı bulunmuştur (p<0,05). Ameliyat tipi olarak en sık uygulanan prosedür Total Gastrektomi (%56,8) iken, en az uygulananı ise Gastroenterostomi (%9,1) olmuştur. Total Gastrektomi sonrası postoperatif komplikasyonlarda anlamlı bir artış tespit edilmiştir (p<0,05).

Tablo 1. Hastaların demografik ve patolojik özellikleri.

		En az-En çok	Ortalama	±	sd/n-%
Yaş		80-92	84,2	±	3,1
Cinsiyet	Kadın		18		% 40,9
	Erkek		26		% 59,1
Tümör Çapı		1-12,1	5,3	±	2,8
Kronik Hastalık			30		% 68,2
Tümör Yerleşimi	Alt		19		% 29,5
	Orta		12		%27,3
	Üst		25		% 29,5
Ameliyat Tipi	Total gastrektomi		25		% 56,8
	Subtotal gastrektomi		15		% 34,1
	Gastroenterostomi		4		% 9,1
Tümör Farklılaşması	Az		17		% 38,6
	Orta		13		% 29,5
	İyi		14		% 31,8
Taşlı Yüzük Hücreli			9		%20,4
Lenf nod disseksiyonu	D1		9		% 20,4
	D1-2		31		% 70,5
	None		4		% 9,1
Evre	E1		13		% 29,5
	E2B		8		% 18,5
	E3		19		% 43,2
	E4A		4		% 9,1
Preoperatif Kemoterapi alan			29		% 65,9
Postoperatif kemoterapi alan			30		% 68,2

Postoperatif komplikasyonlar, Clavien-Dindo sınıflandırma sistemine göre %45,4 oranında grade II ve %18,1 oranında grade V olarak belirlenmiştir (Tablo 2). Postoperatif komplikasyon oranı %45,4 (n=20) olup, en sık görülen komplikasyon akciğerle ilgili olup %15,9 (n=7) oranında pnömoni saptanmıştır. Postoperatif komplikasyonlar, postoperatif yatış süresi ile pozitif yönde anlamlı bir korelasyon göstermiştir (Pearson korelasyon katsayısı r=0.67, p<0,05). Ortalama postoperatif yatış süresi 20,1±13,5 gün olarak bulunmuş olup, bu süreyi artıran faktörler arasında ameliyat tipi ve postoperatif komplikasyonlar yer almakta ve istatistiki olarak anlamlılık göstermektedir (p<0,05).

Tablo 2. Ameliyat sonrası komplikasyonlar.

	En az-En çok	Ortalama	±	sd/n-%
Pnömoni		7		% 15,9
Pulmoner Emboli		2		% 0,4
Atelektazi		1		% 0,2
Plevral effüzyon		2		% 0,4
Duodenum stump fistülü		1		% 0,2
Aritmi		2		% 0,4
Cerarhi alan enfeksiyonu		5		% 11,3
Clavien Dindo Sınıflaması				
II		20		% 45,4
V		8		% 18,1
Yatış süresi	6-67	20,1	±	13,5
Mortalite		8		% 18,1
Yaşam süresi	0,3-84,3	18,2	±	18,8

Tartışma

Bu çalışmada, mide kanseri olan yaşlı hastaların cerrahi tedavisi öncesinde ve sırasında uygulanan prosedürlerin ve patolojik özelliklerin hastalar üzerindeki etkilerini değerlendirdik. Mide kanseri, yüksek ölüm oranına sahip kötü huylu bir neoplazm olarak bilinmekte ve artan yaşam süresi ile yaşlı popülasyonda daha sık görülmektedir. Yaşlı hastalarda kanserin görülme sıklığı arttığı gibi, genellikle çeşitli kronik hastalıklarla birlikte seyreder. Bu nedenle, ileri yaş mide kanserleri için cerrahi müdahale seçeneklerinin preoperatif olarak dikkatli bir

şekilde değerlendirilmesi gerekmektedir. Yaşlı hastalarda postoperatif komplikasyonlar ve mortalitenin daha sık görüldüğü bilinmektedir.[5] Bu bağlamda, komplikasyonların azaltılması için geliştirilen tedavi stratejileri sadece olumlu sonuçları artırmakla kalmaz, aynı zamanda yaşam kalitesini ve sağ kalımı da artırabilir.

Yaşlı hastalar genellikle kronik hastalıklarla mücadele etmektedir. Çalışmamıza dahil ettiğimiz hastaların %68.2'si en az bir kronik hastalığa sahipken, %22.7'si ise iki veya daha fazla kronik hastalığa sahiptir. Bu durum, mortalite riskinin artmasına neden olabilir. Hastalarımızın %18,1'i mortalite ile sonuçlanmıştır. Ayrıca, postoperatif komplikasyonların mortaliteyi anlamlı derecede etkilediğini saptadık (p<0,05). Hastalarımızın %18,1'i mortalite ile sonuçlanmıştır. Postoperatif komplikasyonlar, Clavien-Dindo sınıflandırma sistemine göre %45,4 oranında grade II ve %18,1 oranında grade V olarak belirlenmiştir. Kronik hastalıklarla mortalite arasındaki ilişkiyi araştırdık. Yaptığımız analizde, kronik hastalıklar ile mortalite arasında anlamlı bir ilişki saptamadık (p>0,05). Kronik hastalıkları olan hastalarda düzenli medikal tedavi ve takiplerin yapılması, bu sonucun elde edilmesinde etkili olabilir. Kronik hastalıklar kontrol altında tutultuğunda, her yaş grubuna cerrahi müdahale ve KT güvenle uygulanabilir.

Birçok çalışmada; cerrahi işlemler, yaş, tümör evresi ve genel durum gibi faktörlerin postoperatif komplikasyon riskini artırdığı gösterilmiştir. Total gastrektomi sonrası özellikle akciğer komplikasyonlarının literatürle orantılı olarak arttığını gözlemledik.[6] Yaşlı gastrektomi hastalarında postoperatif pnömoni insidansı %2-16 arasında değişkenlik göstermektedir.[7] Bu geniş aralık, yaşlı hastalarda postoperatif pnömoni riskinin heterojen olduğunu ve bu alandaki çalışmaların çeşitliliğini göstermektedir. Clavien-Dindo sınıflandırma sistemine göre, postoperatif komplikasyonların oranı %45,4 (n=20) olarak saptanmıştır. Bu komplikasyonlar arasında en sık rastlananı %15,9 (n=7) ile akciğer pnömonisidir. Total gastrektomi geçiren hastaların cerrahi sonrası risklerinin ciddi olduğunu fakat titizlikle yapılan bakımlar sonucunda komplikasyonların azaltılabileceğini gözlemledik. Bu komplikasyonlar arasında literatürde en sık pnömoni geliştiği bildirilmektedir.[8] Pnömoninin sık görülen bir komplikasyon olması, cerrahi sonrası takipte solunum terapisinin önemini göstermektedir. Postoperatif komplikasyonlar ile mortalite arasında pozitif bir korelasyon saptamamız, hastaların yaşamını etkileyebileceğini göstermektedir (p<0,05). Postoperatif komplikasyonların; hastaların iyileşme süreci üzerindeki doğrudan etkilerinin, yatış süresini uzattığı (p<0,05) ve günlük yaşam aktivitelerini kısıtladığı gözlemlenmiştir.[6]

Hastalara uygulanan neoadjuvan ve adjuvan kemoterapi tıbbi onkoloji önerileri doğrultusunda yapılmıştır. Evre II ve III yaşlı hastalar arasında adjuvan kemoterapi alanlar ile almayanlar arasında belirgin bir prognoz farkı gözlemlenmemiştir.[3,7] Ancak, bazı çalışmalar kemoterapinin sağkalımı olumlu yönde etkilediğini göstermiştir.[3] Bizim çalışmamızda, adjuvan kemoterapinin sağkalımı olumlu etkilediği saptanmıştır (p<0,05). Bu nedenle, yaşına ve sahip olduğu kronik hastalığa bakılmaksızın cerrahi öncesi ve sonrasında Evre II-III hastalara kemoterapi önermekteyiz. Çalışmamızda hastaların %65,9'u neoadjuvan, %68,2'si ise adjuvan kemoterapi almıştır. En uzun yaşam süresi Evre I'de gözlemlenmiş, en kısa yaşam süresi Evre IV-A'da 5,3 ay olarak tespit edilmiştir. Evre I'den sonra en uzun sağkalım süresi Evre II-B'de 57,1 ay ve Evre III'te 48,1 aydı. Bu süreler uyguladığımız uygun cerrahi ve kemoterapiye bağlı olabilir. İstatistiksel olarak da pozitif anlamlılık saptadık. Literatürde yaşlı hastalarda kemoterapinin uygulanabilirliği düşük olduğu belirtilmiştir.[5] Çalışmamız özellikle yaşlı hastalarda kemoterapinin uygulanmasının yaşam kalitesini ve sağkalımı uzattığını göstermiştir. Kanser tedavilerinde, yaşlı hastaların genç hastalar gibi tedavi edilmeleri en az gençlerde olduğu kadar iyi sonuçlar elde edebilir. Yapılan çalışmalarda yaşlı hastalarda klasik kemoterapi tedavilerinin yüksek toksisite ve

komplikasyon riski taşımasına rağmen, kemoterapi alan yaşlı hastaların prognozunun kemoterapi almayanlara göre daha iyi olduğu bulunmuştur.[2] Yaşı 80 ve üzeri olan hastalarda neoadjuvan ve adjuvant kemoterapi güvenli bir şekilde uygulanabilir ve olumlu sonuçlar elde edilebilir.

Bazı literatürlerde D2 diseksiyonunun sağkalım üzerinde bir faydasının olmadığı vurgulanmakla birlikte[9], çalışmamızda, bazı literatürlerle uyumlu olarak, D2 diseksiyonunun yaşam süresini anlamlı derecede uzattığı tespit edilmiştir (p<0,05).[10] Tümör evresi ve lenf nodu diseksiyonunun postoperatif komplikasyonlarla anlamlı bir ilişkisi bulunmamıştır (p>0,05). Bu yüzden, cerrahi gerekliliğini ve etkinliğini değerlendirirken diseksiyon seviyelerinin tartışılması gerekmektedir. Hastaların evreleri ilerledikçe yaşam sürelerinin kısaldığı gözlenmektedir. Ne yazık ki, yaşlı hastalarda genellikle ileri evrelerde tanı konulduğu bilinmektedir.[2,5] Çalışmamızda en yüksek oranda Evre III (%43,2, n=19) saptanmıştır. Özellikle Evre IVA'da diğer evrelere göre anlamlı düzeyde yaşam süresinin kısaldığını bulmamız (p<0,05), evre IVA'daki hastalar için alternatif tedavi seçeneklerinin araştırılıp uygulanmasının ileri evre tümörlerde uygun tedavi seçeneklerinden biri olabileceğini düşündürmektedir. Kemoradyasyon ileri evre mide kanserleri için standart tedavi olarak kabul edilmektedir.[2,11] İleri evrelerde KT, yaşam süresi ve kalitesinin artırmasını sağlayabilir.

Yapılan analizler sonucunda, tümör çapı ile sağkalım arasında negatif bir korelasyon saptadık (p<0,05). Bunun nedeni muhtemelen daha büyük tümör boyutunun daha ağır tümör yüküne ve infiltratif büyüme olasılığının daha yüksek olmasına yol açabilmesidir.[2] Bu durum, daha büyük tümörlerin tedaviye yanıt verme olasılığının daha düşük olması ve hastalığın ilerlemesi açısından daha riskli bir profil sergilemesi ile açıklanabilir. Bulgularımız, tümör boyutunun prognostik bir gösterge olarak önemini vurgulamakta ve klinik uygulamalarda tümör çapının dikkate alınması gerektiğini göstermektedir.

Tümörün farklılaşma derecesi azaldıkça yaşam süresi olumsuz etkilenmektedir (p<0,05). Düşük farklılaşma dereceleri, tümör hücrelerinin daha agresif davranışlar sergilemesine ve tedaviye daha dirençli olmasına neden olduğundan kötü prognostik faktörler arasında yer alır.[12] Ayrıca, farklılaşma derecesi sadece tümörün agresifliğini değil, aynı zamanda lenf nodu yayılımını ve tümör evresini de etkileyebilir. Düşük dereceli farklılaşmaya sahip tümörler, daha yüksek metastatik potansiyele sahiptir ve bu da hastalığın ilerlemesine ve sağkalımın azalmasına yol açabilir. Dolayısıyla, farklılaşma derecesinin belirlenmesi, tedavi stratejilerinin planlanmasında ve hastaların prognozunun tahmin edilmesinde kritik bir rol oynamaktadır.

Araştırmanın sınırlılıkları

Bu çalışmanın bazı kısıtlılıkları mevcuttur. Retrospektif tasarım nedeniyle verilerin geçmiş kayıtlarına dayanması, eksik veya hatalı bilgi riski doğurabilir. Örneklem büyüklüğü nispeten küçük olduğundan, sonuçların genelleştirilebilirliği sınırlıdır ve daha büyük, çok merkezli çalışmalara ihtiyaç duyulmaktadır. Çalışma tek bir hastanede gerçekleştirilmiş olup, farklı merkezlerdeki uygulamalar ve hasta profilleri ile karşılaştırma yapmayı zorlaştırmaktadır. Ayrıca, hastaların, neoadjuvan ve adjuvan kemoterapi protokollerindeki farklılıklar, yaşlı hastaların tedaviye uyumu ve retrospektif çalışmaların doğası gereği seçici yanlılık riski gibi faktörler de sonuçların doğruluğunu etkileyebilir. Bu kısıtlılıklar göz önünde bulundurularak, elde edilen sonuçların dikkatle değerlendirilmesi ve daha geniş, prospektif, çok merkezli araştırmaların yapılması gerekmektedir.

Sonuç

Bulgularımız, neoadjuvan ve adjuvan kemoterapinin sağkalım üzerinde olumlu etkilerinin olabileceğini göstermektedir. Özellikle, cerrahi sonrası komplikasyonların sıklıkla gözlendiği ve pulmoner komplikasyonların belirgin olduğu tespit edilmiştir. Bu çalışma, cerrahi ve kemoterapinin entegre kullanımının güvenli ve etkili bir tedavi seçeneği olabileceğini desteklemektedir. Ancak, bu tedavi stratejisinin uygulanması sırasında dikkatli

hasta yönetimi ve komplikasyonların erken tanınması ve tedavi edilmesi gerekmektedir. Sonuç olarak, yaşlı hastalarda mide adenokarsinomu tedavisinde cerrahi ve kemoterapinin kombinasyonunun klinik pratikte değerlendirilmesi gereken önemli bir strateji olabileceği sonucuna varılmıştır.

Araştırmanın Etik Boyutu

Çalışmamız Adana Şehir Eğitim ve Araştırma Hastanesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'nun 28.09.2023 tarihli, 2852 protokol numarasıyla onaylandı. Çalışma Helsinki Bildirisi'ne uygun olarak yapıldı.

Bilgilendirilmiş Onam

Araştırmaya katılan bireylerden bilgilendirilmiş onam alındı.

Yazar katkıları

Fikir/Kavram Y.D., A.S., S.Ö., C.Y.; Tasarım ve dizayn Y.D., A.S., S.Ö., C.Y.; Denetleme/Danışmanlık Y.D., A.S., S.Ö., C.Y.; Kaynaklar Y.D., A.S., S.Ö.; Veri toplama ve/veya işleme Y.D., A.S.; Analiz ve/veya yorum Y.D., A.S., S.Ö., C.Y.; Literatür tarama Y.D., S.Ö., C.Y.; Yazıyı yazan Y.D., S.Ö.; Eleştirel inceleme A.S., C.Y.

Çıkar Çatışması Beyanı

Yazarların herhangi bir çıkara dayalı ilişkisi yoktur

Araştırma Desteği

Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur.

Beyanlar

Çalışma herhangi bir kongrede sunulmamıştır.

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Dış bağımsız.

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Research Article/Özgün Araştırma

Determination of symptoms and symptom clusters in breast cancer patients receiving adjuvant chemotherapy treatment

Adjuvan kemoterapi tedavisi alan meme kanserli hastalarda görülen semptomlar ve semptom kümelerinin belirlenmesi

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Abstract

Aim: To examine the symptom clusters in breast cancer patients receiving adjuvant chemotherapy treatment.

Materials and Methods: This descriptive study examined 128 female patients between February 2022-August 2023 using Memorial Symptom Assessment Scale, and EORTC QLQ-C30 Scale.

Results: In cluster analysis, 23 symptoms with a prevalence of >25% were selected, and six clusters were identified. First cluster is nausea, loss of appetite, and fatigue/loss of energy; second cluster is taste change, dry mouth, mucositis, vomiting, weight loss, and diarrhea; third cluster is worrying, feeling nervous, drowsy, and difficulty sleeping; fourth cluster is feeling bloated, shortness of breath, and difficulty swallowing; fifth cluster is alopecia, not look like herself, feeling irritable, sad; and last cluster includes problems with sexual interest, activity, pain, and sweating.

Conclusion: It may be recommended to plan and evaluate applications or interventions in breast cancer patients receiving adjuvant chemotherapy treatment for the six symptom clusters identified.

Keywords: Breast Cancer; Chemotherapy; Nursing; Symptom Cluster.

Öz

Amaç: Adjuvan kemoterapi tedavisi alan meme kanserli hastalarda görülen semptom kümelerini incelemektir.

Gereç ve Yöntem: Şubat 2022-Ağustos 2023 tarihleri arasında 128 kadın hasta ile gerçekleştirilen tanımlayıcı tipteki bu çalışmanın verileri Memorial Semptom Değerlendirme Ölçeği (MSDÖ) ve EORTC QLQ-C30 Yaşam Kalitesi Ölçeği kullanılarak toplandı.

Bulgular: Kümeleme analizinde >%25 prevalansı olan 23 semptom seçildi ve altı semptom kümesi belirlendi. *Birinci küme*; bulantı, iştahsızlık ve halsizlik/enerji kaybı, *ikinci küme*; yiyeceklerin tadını almada değişiklik, ağız kuruluğu, ağız yaraları, kusma, kilo kaybı ve ishal, *üçüncü küme;* endişelenme, kendini sinirli hissetme, uyumada zorluk ve kendini uykulu ya da sersemlemiş gibi hissetme, *dördüncü küme;* şişkinlik hissi, nefes darlığı ve yutma güçlüğü, *beşinci küme*; saç dökülmesi, kendine benzememe, hassas olma ve kendini üzgün hissetme iken *altıncı kümede*; cinsel istek veya aktivite ile ilgili sorunlar, ağrı ve terleme yer almaktadır.

Sonuç: Meme kanserli hastalardaki uygulamaların ya da girişimlerin belirlenen altı semptom kümesine yönelik planlanması ve değerlendirilmesi önerilebilir.

Anahtar Kelimeler: Hemşirelik; Kemoterapi; Meme Kanseri; Semptom Kümesi.

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Introduction

Breast cancer is the most common type of cancer among women in our country, as in the rest of the world. In the country under study, the age-standard breast cancer incidence rate is 46.6 in a hundred thousand.[1] Breast cancer treatment is carried out using various treatment approaches such as cytotoxic chemotherapy, endocrine therapy, and immunotherapy taking into account the size of the tumor, the absence of lymph node retention, and receptor expression. Chemotherapy, commonly used in cancer treatment, aims to stop cancer from spreading or eliminate it.[2] Chemotherapeutic drugs used in the treatment of breast cancer cause significant symptoms in patients such as pain, fatigue, nausea-breathing, anxiety, depression, sleep problems, and shortness of breath, thereby adversely affecting the quality of life of patients.[3] After treatment, the symptoms associated with chemotherapy have physical effects and have a biopsychosocial adverse effect on the individual.[5] Recent studies have concentrated on symptom clusters to enhance the understanding of how symptoms manifest together. Symptom sets are groups of related symptoms that occur together due to a common cause or similarity. Symptoms that also occur in cancer patients can in themselves affect each other negatively. According to Clark and Talcott, more than one synergistically associated symptom occurring at the same time causes treatment to be ineffective and unexpected therapeutic consequences to occur. One symptom causes other symptoms to appear or become more severe.[4] However, Dong et al.[5] conducted a systematic observational study of symptom sets identified in patients with various types of cancer. This systematic review assessed thirty-three articles and identified many symptom groups with four common groups, including anxiety-depression, nausea-coughing, nausée-loss of appetite, and fatigue-breathing-sleepiness-pain.[5] The major problem that patients undergoing chemotherapy experience is the failure to manage the concomitant symptoms, and as a result, the treatment is adversely affected. In patients receiving chemotherapy, one symptom affects another symptom and even increases its severity.

There is a synergistic interaction between many symptoms, which can increase the morbidity rate of patients. For example, patients with nausea-induced lack of appetite, undernutrition, and proteins deficit may occur.[3,4] In addition, patients with nausea and vomiting may develop sleep disturbances and fatigue problems. Sleep disorders can result in impaired immune functions and increase the risk of infection. Collaborative efforts to address synergistic symptoms in chemotherapy patients have the potential for improvement.[6] This research aims to identify symptom clusters in breast cancer patients undergoing chemotherapy to apply the findings in clinical practice. It is crucial to thoroughly assess the frequency, severity, and discomfort of individual symptoms in clinical studies. Studies of the literature[3-6] show that only the frequency of symptoms has been determined. Studies targeting the frequency of symptoms show that the intensity of the symptoms and the discomfort caused by the symptoms are skipped. Furthermore, since these symptoms can be seen in groups or clusters, the identification of the relationship between the symptoms for effective measurements improves compliance with therapy. To identify the set of symptoms, it is necessary to customize the situations. The methods of selection should include a specific stage of treatment, individuals with a similar diagnosis or sexual relationships, the type of relationships, and the duration of symptoms. It is based on previous single-symptomatic studies for the creation of symptom sets for specific conditions or for the prediction of symptom sets. Literature reviews[5,6] have not found a study covering the whole group of symptoms associated with stage I-IIIA breast cancer patients receiving adjuvant chemotherapy. The concept of symptom grouping is argued to advance the understanding of the synergistic side effects caused by cancer treatment and increase effective nursing efforts. Although they have different indicators and may occur at different stages of the course of the disease, the symptoms often have a common etiology, which is a potential target for intervention. Understanding the set of symptoms associated with breast cancer in the adjuvant

chemotherapy process can be useful in developing effective care plans for affected patients. Symptom groups in this study are thought to influence the evaluation of symptoms as a whole and minimize symptom severity. These results are transferable to the clinical environment in the care of patients with BC undergoing chemotherapy.

This study aimed to draw attention to the importance of identifying and evaluating the symptoms and symptom groups experienced by breast cancer, on the severity of chemotherapy symptoms seen in patients receiving adjuvant chemotherapy therapy.

Research questions

- What symptoms comply with breast cancer patient's experience during chemotherapy treatment?
- What are the symptom clusters experienced by cancer patients during chemotherapy treatment?

Materials and Methods

Type of research

This study was designed as a descriptive study. The study was conducted at the Medical Oncology Department of the University of Hacettepe's Oncological Hospital's Day-Treatment Unit between 01 February 2022 and 07 August 2023. The universe of this research was created by female patients receiving adjuvant chemotherapy treatment at the Day-Treatment Unit of the Department of Medical Oncology of the University of Hacettepe's Oncological Hospital. The sample of the study consisted of female patients between the ages of 18 and 65, who received the Adriamicin-Siclofosphamide (AC) chemotherapy protocol, who knew that they had received at least the first course of chemo, who could communicate, who were willing to participate in the research and who were volunteer. Patients were excluded if they were already receiving AC, ceased participation in the study, their chemotherapy protocol changed, or their treatment was postponed by the doctor because the blood values were not suitable for chemotherapy. A pilot study of 20 patients was carried out using the G Power package program to calculate the number of samples, and the minimum number of patients to be included with 85% force was set at 128.

The Ethics Committee for Non-Interventional Clinical Research at the University of Hacettepe, after receiving written permits from the Directorate of Health and Nursing Services of the University's Oncology Hospital, has evaluated patients who have applied the adjuvant chemotherapy protocol from 1st February 2022 to the Day-Treatment Unit of the Researchers' Oncological Hospital at Hacettebe University, as regards the criteria for inclusion in the study. Patients included in the study were informed by the researcher about the purpose, duration, and method of the study during the admission of the patient. After the information, patients who voluntarily agreed to participate in the study were included in the sampling group with written and verbal permission. The sampled patients were monitored in the hospital when they came to receive treatment throughout the AC protocol. Patients will be interviewed face-to-face in the area where they are being treated. The questions Patient Information Form, The Memorial Symptom Assessment Scale (MSAS), and EORTC QLQ-C30 Quality of Life Scale were addressed to patients by the researcher, and the patient's responses were recorded by him. The patients were evaluated based on their symptoms and quality of life scores during the first week after each cycle. Data collection tools were completed in approximately 30 minutes.

Data collection tools

Patient information form; the patient information form, created by the researcher by scanning the literature, consists of two parts.[3-6] The first part consists of eight questions about the patient's characteristics, such as age, body surface area, number of treatments, civilian condition, the status of having children, educational status, occupation, and cancer in the family, and the second part of the question, the condition of the patient having another disease, the medicines he uses outside of chemotherapy and the type of breast surgery he has undergone.

The Memorial Symptom Assessment Scale (MSAS) was developed by Portenoy et al a 32-

dimensional multidimensional scale used to evaluate the symptoms experienced by cancer patients in the last week.[7] The scale includes three sub-dimensions, which include the frequency, severity, and discomfort of the 22 symptoms in the last week, and two dimensions, including the severity of the 8 symptoms and the decomposition they cause in the patient. The "heat" and "violence" levels of the symptoms are answered in the form of a liqueur of 4, while the "difficulty" levels are replied in a liquéur of 5. The scale consists of “physical symptoms” (insomnia, numbness or loss of energy, pain, feeling asleep or numb, constipation, dry mouth, nausea, vomiting, changes in taste, weight loss, feeling swollen, dizziness), “psychological symptoms" (sickness, feeling sad, feeling nervous, feeling sleepy or numbing, feeling sensitive, difficulty gathering attention) and “general fatigue index” (sense of sadness, anxiety, feelings of self-irritation, sensitivity, lack of appetite, emptiness or energy loss, the sensation of pain, constipating, dryness, feeling somnolent or cumulative). The Memorial Symptom Evaluation Scale (MSAS), conducted by Yildirim et al.[8], was used to evaluate post-chemotherapy symptoms in patients with NHL. MSAS, Cronbach found the alpha ratios between 0.71 and 0.75 for sub-scales and 0.84 for the total.

EORTC QLQ-C30 life quality index (EORTC QLQ-C30) was developed by European Organization for Research Treatment of Cancer[9] and the Turkish validity and reliability was conducted of the by Güzelant et al.[10]. EORTC QLQ-C30, was designed to assess a range of cancer-specific QoL issues relevant to a broad spectrum of cancer patients. This questionnaire consisted of 30 cancer-specific questions with multiple-point scales, including a global health status/QoL scale, 5 functional scales (physical, role, emotional, cognitive, and social), 9 symptom scales (fatigue, nausea, and vomiting and pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulty). multiple-point scales were transformed into standard scores (from 0 to 100). High scores on global health status/QoL and functioning scales represented good QoL, while high scores on the symptom scales indicated more severe symptoms.

Analysis of data

Analyzes were evaluated in 25 package programs of SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). In the study, descriptive data are shown as n and % values in categorical data and mean ± standard deviation (mean ± SD) and median (minimum-maximum) values in continuous data.

There is no acceptance of the meaning of the association in determining the clusters of symptoms. Walsh and colleagues (2006) identified the symptoms, although symptoms with a frequency of less than 15% were not evaluated.[11] Kim et al.[12] investigated the connection of at least two symptoms to develop a set of symptoms. Cumulative analysis is a method for categorizing items (such as individuals) or variables (such as symptoms) into groups. Some similarity indicators should be applied to categorize the variables. Columns have been formed so that things in the same column are comparable while ones in separate columns are distinct. A cluster analysis of the symptoms was performed to identify symptoms that often occur together. For this study, each symptom was classed as either present or lacking. To keep the number of symptoms manageable, 23 symptoms with a prevalence of more than 25% were selected for cumulative analysis (Figure 1). A cluster hierarchical approach was applied, with each symptom treated as a single cluster of size one. Then, identical clusters were joined until a single cluster comprising all of the symptoms emerged. The average association approach was adopted, and the absolute value of correlation between symptoms was utilized to assess the similarity of symptom combinations. The final clusters were defined using a correlation score of ≥0.70. In our research, the collection of symptoms was determined using MVSP v.3.12 (Software Multi-Variate Statistical Package) and graphically represented using dendrograms. Dendograms are a type of data presentation that divides it into intrinsic parts at different levels. The vertical lines in the dendrogram refer to linked clusters. For

example, the location of the line on it indicates the distances where the clusters connect. The connection between items increases as their distance decreases.

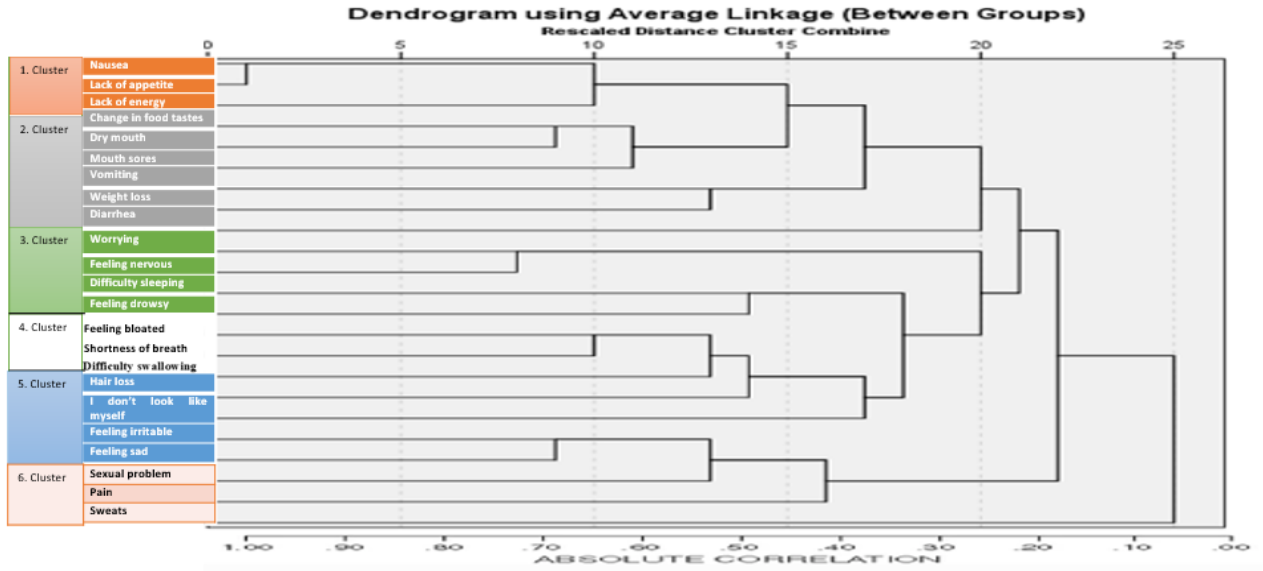

Figure 1. Dendogram.

Ethics committee approval

The ethics board of Hacettepe University Non-Interventional Clinical Research Ethics Committee (GO 21/1287) has authorized the study's conduct. The required permits have been obtained from the Administration of Health and Nursing at the University of Hacettepe Oncology Hospital, where the study was conducted, and material detailing what was learned from the research was submitted for approval. Furthermore, the study's participants provided both verbal and written permissions.

Results

Data on patient (n = 128) characteristics are presented as frequencies and percentages. The mean age of the patients in the study was 41.1 ± 5.3. 87.5% of patients were married. 53.1% of patients were 50 years of age or younger, and 64.9% of patients had a BSA of 1.60 to 1.79. While 67.2% of patients were primary school graduates, 67.2% were unemployed. While 75.0% of patients had a family history of cancer, 60.9% of them had no history of other diseases, and breast conservation surgery was performed in 51.6% of patients (Table 1).

Table 1. Demographic characteristics (n=128).

	n	%
Age		
Mean ± SD= 41.1 ± 5.3 (min: 32-max:58)		
≤50	68	53.1
>50	60	46.9
Chemotherapy Cycles= 1.3 ±1.1 (min:2-max:4)		
BSA		
1.40–1.59	28	21.8
1.60–1.79	83	64.9
1.80–1.99	17	13.3
Marital Status		
Married	112	87.5
Single	16	12.5
Education		
Primary education	86	67.2
High school	41	32.0
University	1	0.8
Occupation		
Unemployed	86	67.2
Public servant	12	9.5
Laborer	8	6.2
Other	22	17.1
A family history of cancer	96	75
Yes	32	25
No		
History of other diseases/Additional drugs	78	60.9
	50	39.1
Yes*		
No		
Surgery type		
Mastectomy	62	48.4
BCS	66	51.6

Abbreviation: BSA, Body Surface Area; BCS, Breast-Conservation Surgery; SD = Standard Deviation *Thyroid, , euthyrox

The number and percent of symptoms evaluated with the MSAS during treatment of first-time breast cancer patients (Table 2, Table 3). The most common symptoms during chemotherapy were nausea (93.2%), lack of appetite (85.1%), change in taste of food (79.6%), and dry mouth (70.3%). The symptoms with the lowest prevalence were coughing (15.6%), challenges focusing attention (14.1%), skin changes (14.1%), itching (14.1%), swelling of hands and feet (11.7%), drowsiness/deafness in hands and legs (11.7%), and problems urination (8.5%).

Table 2. Symptom frequency among patients in the study (n=128).

	Frequency				
Symptoms	**Yes** n (%)	**Rarely** n (%)	**Occasionally** n (%)	**Frequently** n (%)	**Almost constantly** n (%)
Nausea	120 (93.2)	4 (3.3)	2 (1.7)	10 (8.3)	104 **(86.7)**
Lack of appetite	109 (85.1)	1 (0.9)	1 (0.9)	98 **(89.9)**	9 (8.3)
Lack of energy	102 (79.6)	2 (2.0)	1 (1.0)	95 **(93.1)**	4 (3.9)
Change in food tastes	100 (78.1)	4 (4.0)	0 (0.00)	6(6.0)	90 **(90.0)**
Dry mouth	90 (70.3)	2 (2.2)	78 **(86.7)**	7 (7.8)	3 (3.3)
Mouth sores	85 (66.4)	5 (5.9)	10 (11.8)	60 (72.9)	8 (9.4)
Vomiting	85 (66.4)	12 (14.1)	5 (5.9)	62 (70.6)	8 (9.4)
Weight loss	81 (63.2)	1 (1.2)	5 (6.2)	20 (24.7)	55 (67.9)
Diarrhea	80 (62.5)	6 (7.5)	4 (5.0)	20 (25.0)	50 (62.5)
Worrying	76 (59.3)	1 (1.3)	0 (0.00)	55 (72.4)	20 (26.3)
Feeling nervous	76 (59.3)	6 (7.9)	9 (11.8)	50 (65.8)	11 (14.5)
Difficulty sleeping	74 (57.8)	6 (8.1)	10 (13.5)	48 (64.9)	10 (13.5)
Feeling drowsy	70 (54.6)	7 (10.0)	9(12.9)	44 (62.9)	10 (14.2)
Feeling bloated	66 (51.5)	3 (4.5)	6 (9.1)	35 (53.1)	22 (33.3)
Shortness of breath	66 (51.5)	13 (19.7)	0 (0.00)	35 (53.0)	18 (27.3)
Difficulty swallowing	63 (49.2)	0 (0.00)	17 (27.0)	31 (49.2)	15 (23.8)
Hair loss	60 (46.8)	0 (0.00)	8 (13.3)	22 (36.7)	30 (50.0)
I don’t look like myself	60 (46.8)	7 (11.7)	5 (8.3)	20 (33.3)	28 (46.7)
Feeling irritable	53 (41.4)	3 (5.7)	8 (15.1)	20 (37.7)	22 (41.5)
Feeling sad	50 (39.1)	0 (0.00)	8 (16.0)	22 (44.0)	20 (40.0)
Sexual problem	42 (32.8)	4 (9.5)	0 (0.00)	18 (42.9)	20 (47.6)
Pain	34 (26.5)	1 (2.9)	0 (0.00)	15 (44.2)	18 (52.9)
Sweats	34 (26.5)	3 (8.8)	0 (0.00)	13 (38.3)	18 (52.9)
Dizziness	32 (25)	1 (3.1)	0 (0.00)	13 (40.6)	18 (56.3)
Constipation	32 (25)	2 (6.2)	0 (0.00)	15 (46.9)	15 (46.9)
Cough	20 (15.6)	10 (50.0)	8 (40.0)	2 (10.0)	0 (0.00)
Difficulty concentrating	18 (14.1)	9 (50.0)	5 (27.8)	0 (0.00)	4 (22.2)
Skin Change	18 (14.1)	6 (33.4)	8 (44.4)	4 (22.2)	0 (0.00)
Itching	18 (14.1)	4 (22.2)	9 (50.0)	3 (16.7)	2 (11.1)
Swelling of arms or legs	15 (11.7)	7 (46.7)	4 (26.7)	3 (20.0)	1 (6.6)
Numbness/tingling	15 (11.7)	4 (26.7)	4 (26.7)	5 (33.3)	2 (13.3)
Problems with urination	11 (8.5)	2 (18.2)	5 (45.5)	3 (27.2)	1 (9.1)

The Memorial Symptom Assessment Scale, which examined the symptom frequency of breast cancer patients treated with adjuvant chemotherapy, identified that the symptoms experienced were "often" impotence or energy loss (93.1%) and appetite loss (89.9%), while nausea was experienced as "almost constant" (86.7%). Into the Memorial Symptom Assessment Scale, the symptom severity in breast cancer patients undergoing adjuvant chemotherapy included nausea categorized as "very severe" (91.6%), sores in the mouth (88.2%), and a change taste (84.0%).

When the Memorial Symptom Assessment Scale was applied to assess symptom lack in breast cancer patients undergoing adjuvant chemotherapy treatment, symptom nausea was regarded as "a little more" (85%), while symptom appetite loss was assessed as "too much" (77.3%).

Table 3. Symptom distress and severity among patients in the study (n=128).

Symptoms	Distress					Severity			
	Not at all n (%)	**A little bit** n (%)	**Somewhat** n (%)	**Quite a bit** n (%)	**Very much** n (%)	**Slight** n (%)	**Moderate** n (%)	**Severe** n (%)	**Very severe** n (%)
Nausea	1 (0.8)	0 (0.00)	0 (0.00)	102 (**85**)	17 (14.2)	1 (0.8)	3 (2.6)	6 (5)	**110 (91.6)**
Lack of appetite	0 (0.00)	0 (0.00)	0 (0.00)	10 (22.7)	55 (**77.3**)	3 (2.7)	7 (6.4)	**87 (79.8)**	12 (11.1)
Lack of energy	7 (6.8)	0 (0.00)	0 (0.00)	42 (54.9)	39 (38.3)	5 (4.9)	**81 (79.4)**	9 (8.8)	7 (6.9)
Change in food tastes	6 (6.0)	2 (2.0)	18 (18.0)	44 (44.0)	30 (30.0)	4 (4)	3 (3)	9 (9)	**84 (84)**
Dry mouth	2 (2.2)	1 (1.1)	35 (38.9)	38 (42.2)	14 (15.6)	6 (6.7)	**73 (81.1)**	5 (5.6)	6 (6.6)
Mouth sores	5 (5.9)	4 (4.7)	25 (29.4)	33 (38.8)	18 (21.2)	0 (0.00)	0 (0.00)	10 (11.8)	**75 (88.2)**
Vomiting	5 (5.9)	4 (4.7)	25 (29.4)	33 (38.8)	18 (21.2)	1 (1.2)	8 (9.5)	11 (12.9)	**65 (76.4)**
Weight loss	2 (2.5)	0 (0.00)	14 (17.3)	38 (46.9)	27 (33.3)	8 (9.8)	3 (3.8)	11 (13.6)	59 (72.8)
Diarrhea	0 (0.00)	0 (0.00)	12 (15.0)	24 (30.0)	44 (55.0)	6 (7.5)	4 (5)	12 (15)	58 (72.5)
Worrying	1 (1.3)	1 (1.3)	8 (10.5)	36 (47.4)	30 (39.5)	7 (9.3)	4 (5.3)	43 (56.5)	22 (28.9)
Feeling nervous	1 (1.3)	1 (1.3)	8 (10.5)	36 (47.4)	30 (39.5)	8 (10.5)	9 (11.9)	49 (64.5)	10 (13.1)
Difficulty sleeping	0 (0.00)	0 (0.00)	22 (29.7)	20 (27.1)	32 (43.2)	6 (8.2)	12 (16.2)	56 (**75.6**)	0 (0.00)
Feeling drowsy	3 (4.3)	2 (2.8)	0 (0.00)	38 (54.3)	27 (38.6)	9 (12.8)	9 (12.9)	52 (74.3)	0 (0.00)
Feeling bloated	3 (4.5)	3 (4.5)	3 (4.5)	35 (53.1)	22 (33.4)	4 (6.2)	7 (10.6)	30 (45.4)	25 (37.8)
Shortness of breath	3 (4.5)	3 (4.5)	3 (4.5)	35 (53.1)	22 (33.4)	3 (4.5)	6 (9.1)	35 (53.1)	22 (33.3)
Difficulty swallowing	0 (0.00)	0 (0.00)	5 (7.9)	34 (53.9)	24 (38.2)	14 (22.3)	6 (9.5)	34 (53.9)	9 (14.3)
Hair loss	1 (1.7)	4 (6.7)	6 (10.0)	34 (56.6)	15 (25.0)	3 (5)	4 (6.7)	43 (71.7)	10 (16.6)
I don't look like myself	1 (1.7)	4 (6.7)	6 (10.0)	34 (56.6)	15 (25.0)	7 (11.7)	5 (8.4)	25 (41.6)	23 (38.3)
Feeling irritable	11 (20.8)	3 (5.7)	8 (15.1)	8 (15.1)	23 (43.3)	12 (22.6)	7 (13.3)	25 (47.2)	9 (16.9)
Feeling sad	1 (2.0)	2 (4.0)	2 (4.0)	24 (48.0)	21 (42.0)	10 (20)	7 (14)	23 (46)	10 (20)
Sexual problem	0 (0.00)	0 (0.00)	19 (45.2)	19 (45.2)	4 (9.6)	4 (9.6)	5 (11.9)	12 (28.5)	21 (50)
Pain	2 (5.9)	0 (0.00)	0 (0.00)	22 (64.7)	10 (29.4)	6 (17.6)	5 (14.8)	12 (35.2)	11 (32.4)
Sweats	2 (5.9)	0 (0.00)	0 (0.00)	22 (64.7)	10 (29.4)	7 (20.5)	2 (5.8)	15 (44.2)	10 (29.5)
Dizziness	0 (0.00)	0 (0.00)	0 (0.00)	26 (81.3)	6 (18.7)	1 (3.2)	2 (6.2)	15 (46.8)	14 (43.8)
Constipation	0 (0.00)	0 (0.00)	0 (0.00)	26 (81.3)	6 (18.7)	2 (6.2)	0 (0.00)	15 (46.9)	15 (46.9)
Cough	2 (10.0)	0 (0.0)	2 (10.0)	13 (65.0)	3 (15.0)	1 (5)	4 (20)	4 (20)	11 (55)
Difficulty concentrating	3 (16.7)	4 (22.2)	0 (0.00)	9 (50.0)	2 (11.1)	7 (38.8)	6 (33.4)	0 (0.00)	5 (27.8)
Skin Change	3 (16.7)	4 (22.2)	0 (0.00)	9 (50.0)	2 (11.1)	7 (39)	8 (44.4)	3 (16.6)	0 (0.00)
Itching	3 (16.7)	4 (22.2)	0 (0.00)	9 (50.0)	2 (11.1)	4 (22.3)	8 (44.4)	6 (33.3)	0 (0.00)
Swelling of arms or legs	5 (33.4)	0 (0.00)	4 (26.6)	4 (26.6)	2 (13.4)	3 (20.1)	5 (33.3)	6 (40)	1 (6.6)
Numbness/tingling	2 (13.4)	0 (0.00)	6 (39.8)	5 (33.4)	2 (13.4)	3 (20.2)	4 (26.6)	7 (46.6)	1 (6.6)
Problems with urination	0 (0.00)	0 (0.00)	4 (36.4)	4 (36.4)	3 (27.2)	3 (13.7)	7 (49.9)	4 (36.3)	0 (0.00)

The Memorial Symptom Assessment Scale identified six separate groups of symptom clusters. A correlation of ≥0.70 was identified in determining a cluster (Figure 1). The table states that symptoms in each cluster have been grouped in decreasing order of total prevalence. The first group includes "nausea, appetite loss, and lack of weight/energy loss," the second group includes "changes in taste, dry mouth, mouth wounds, vomiting, weight loss, and diarrhea," the third group includes "depression, feeling nervous, difficulty sleeping, and feeling asleep or numb," the fourth group includes "sense of thirst, shortness of breath, and difficulty swallowing", the fifth group includes "hair loss, I don't like myself, feeling sensitive and sad", and the last group includes "problems with sexual desire or activity, pain, and sweating".

Discussion

Multiple symptoms in patients undergoing chemotherapy for breast cancer are different depending on what is causing the cancer. The patient's quality of life and the effect of the treatment have been impacted by symptom sets, whose effectiveness is following the particulars of the disease and the treatment strategy. Six clusters have been identified in the research we conducted based on the corresponding decrease in the patient's overall symptom prevalence. "Nausea, appetite loss, and intolerance/energy loss" are included in the first cluster. In literature studies, patients undergoing adjuvant chemotherapy commonly suffer from nausea, loss of appetite, or aggregation of energy loss. Moreover, ten symptoms that showed up in three of the six clusters strongly suggested the presence of digestive-related problems. The studies have shown that both before and during adjuvant therapy, there was negligible disparity between the quantity of symptoms and symptoms within a cluster in patients with breast cancer.[13-15] Kim et al. identified 10 symptoms using factor analysis. According to the research, a gastrointestinal (GI) cluster involving decreased appetite, nausea, and vomiting from the beginning of treatment until the fourth cycle has been identified in 44% of the women undergoing chemotherapy.[13] A three-point assessment was used in another research investigation to determine whether nausea is part of a set of symptoms. As a result of this, symptoms in the cluster that included nausea, dry mouth, drowsiness, lack of energy, and appetite loss were noted in the first measurement of chemotherapy. There is apprehension and a lack of energy at the end of the first treatment, and at the end of the second therapy, there is nausea and swelling along with a lack of energy.[14] The second and fourth clusters of gastrointestinal symptoms are also relevant to our study. It is consistent with the literature at this point.

The literature has shown that pain-fatigue-sleep occurs simultaneously with cancer treatments and as psychoneurological symptoms.[16-20] Differences in additional symptoms, such as nausea, that contributed to the psychoneurological symptom set were to be the result of differences in the number of symptomatic individuals used for the symptom clustering, the severity of the symptoms, the frequency of the symptoms, and the degree of symptom absence in an identifying-type study of 100 breast cancer patients undergoing stage I-IIIA chemotherapy treatment.[16] At least two of these psychological symptoms, known as psychological clusters, such as sadness, stress, and depression, occur before starting therapy. In addition, fatigue and/or insomnia have been associated with anxiety and sadness in this cluster.[21,22] Anxiety, sadness, worry, and anxiousness have all been linked to cancer treatment, and more than one of these symptoms may occur consecutively. These symptoms have the potential to result in a psychological cluster.[23-26] Since there are numerous symptoms in this psychological cluster, it becomes essential to thoroughly analyze these studies to verify consistency. Every cluster of these studies contains at least one of the psychological cluster symptoms. Our study in particularly, correlates the symptoms in the third cluster with the literature regarding "sickness, feeling anxious insomnia, and feeling asleep or fatigued." Although the underlying cause of these clusters of symptoms is unknown, pro-inflammatory cytokines, hyperactivation of the hypothalamic-hypofyse-adrenal (HPA) axis, and alterations

in the serotonin (5-HT) system might all contribute to psychoneurological symptoms.[27,28]

According to studies, women with breast cancer who accomplished treatment had a cluster known as the menopausal cluster, which included hot flashes, vaginal dryness, and at nocturnal sweats. Symptom sets were also brought about based on vasogenic symptoms with severity ranging from moderate to severe.[22,29] However, Li and Ark revealed that a collection of symptoms consisting only of hot flashes and nocturnal sweats does not include vaginal dryness.[30] In our study, the sixth category, known as vasomotor symptoms, has been identified as "problems with sexual desire or activity, pain, and sweating".

Known as adjuvant chemotherapy, women who have undergone surgery, specifically breast surgery, negatively influences their sexual behaviors throughout the treatment process. These adverse conditions could be influenced by changes in sexual development, changes in body image induced by cancer therapies (hair loss), and communication issues with the partner.[31,32] Our study's fifth cluster of symptoms, such as "hair loss, I don't look like myself, being sensitive and feeling sad about myself," are sexual life-related symptoms. An analysis comparing the sexuality of women with breast cancer with those without a history of cancer revealed that breast cancer patients had worse sexual functioning, decreased sexual desire, disliked sex, and other sexual issues.[33] Mastectomy is perceived as a loss of masculinity since the breast has become a symbol of beauty and sexuality in society, generating issues with body image and self-esteem.[34]

Symptom clusters are also considered crucial for clinical assessment the processes. If a particular treatment symptom impact is desired in a symptom control study, the other symptoms in that cluster should also be included as criteria for the result; otherwise, a meaningful therapy effect may be omitted. Our findings represent that it is indispensable and therapeutically relevant to investigate the association between symptoms not just among individuals, but also with other associated symptom features. The definition of symptom models is both intellectual and therapeutic, allowing us to get a better understanding of cancer's natural progression and offer more effective symptom management.

Limitations of the research

This study had certain limitations. Firstly, the data acquired in this research mainly represents the perspectives of patients at the hospital where the survey was conducted, therefore the conclusions cannot be generalized aside from sampling.

Second, this study was conducted in only patient receiving AC protocol. Therefore, other studies can determine the effect of the symptom clusters other chemotherapy protocols (oxaliplatin, taxol, etc.) and other cancer patients (stomach, lung, etc.).

Conclusion

The study we performed was conducted on a group of patients getting the same similar therapy to evaluate the set of symptoms, using female participants and standard tools. Clinical methods or initiatives emphasizing a particular symptom in breast cancer patients undergoing adjuvant chemotherapy could effectively manage multiple sub-symptoms within the six clusters to which the symptom belongs at affordable rates. It is additionally anticipated that the creation of individual therapies could supply the patient with vital information.

The assessment for specific biological stimulants during breast cancer therapy is advised based on subjective patient remarks and quantitative analytical data. Such research will assist us in identifying common biological pathways that underlie many reasons for symptom sets, as well as providing high-level information on efficient strategies for targeting these pathways. Our study results suggest the possibility of researching symptom clusters in different chemotherapy types and disease groups. The other studies can determine the effect of the symptom clusters on other chemotherapy protocols (oxaliplatin, taxol, etc.) and other cancer patients (stomach, lung, etc.).

Ethics Committee Approval

This study, approval was obtained from the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Number GO 21/1287). All interventions were carried out following institutional ethical standards and the national research committee, including the 1964 Declaration of Helsinki and subsequent amendments. Furthermore, the study's participants provided both verbal and written permissions.

Informed Consent

Informed consent was obtained from the individuals participating in the study.

Conflict of Interest

The authors report no actual or potential conflicts of interest.

Author Contributions

Responsibility for the study design: BK; Responsibility for supervising the study: BK; Responsibility for data analysis: Statistics expert; Provision of peer review during the analysis process: Statistics expert, BK; Responsibility for manuscript writing: BK.

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Research Article/Özgün Araştırma

The effect of death anxiety on orthorexia nervosa tendencies in type 2 diabetes patients

Tip 2 diyabet hastalarında ölüm kayısının otoreksiya nevroza eğilimleri üzerine etkisi

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Abstract

Aim: This study was conducted to investigate the effect of death anxiety on orthorexia nervosa tendencies in patients with Type 2 diabetes.

Materials and Methods: This study was conducted with 200 Type 2 diabetes patients who referred to internal medicine outpatient clinics of a university hospital in Elazığ, a city in the east of Turkey. The data were collected by using "Descriptive Information Form", "Death Anxiety Scale (DAS)" and "Orthorexia-11 Scale (ORTO-11)".

Results: The mean DAS score of the patients was 11.41±2.09, while their mean ORTO-11 score was found as 23.69±6.09. It was found that DAS total score was a significant and negative predictor (β= -.540, p<0.001) and explained 29 % of ORTO-11 total score.

Conclusion: Patients with Type 2 diabetes were found to have high level of death anxiety and moderate level of orthorexia nervosa tendency. It was found that orthorexia nervosa tendency increased as death anxiety increased.

Keywords: Diabetes mellitus; Death; Feeding and Eating Disorders; Nursing.

Öz

Amaç: Bu çalışma Tip 2 diyabetli hastalarında ölüm kaygısının ortoreksiya nervoza eğilimleri üzerine etkisini incelemek amacıyla yapıldı.

Gereç ve Yöntem: Bu çalışma, Türkiye'nin doğusunda yer alan Elazığ ilinde bir üniversite hastanesinin dahiliye polikliniğine başvuran 200 Tip 2 diyabet hastası ile gerçekleştirildi. Veriler "Tanımlayıcı Bilgi Formu", "Ölüm Kaygısı Ölçeği (DAÖ)" ve "Ortoreksiya-11 Ölçeği (ORTO-11)" kullanılarak toplandı.

Bulgular: Hastaların DAS puanı ortalaması 11,41±2,09, ORTO-11 puanı ortalaması ise 23,69±6,09 olarak belirlendi. DAS toplam puanının anlamlı ve negatif bir yordayıcı olduğu (β= -.540, p<0,001) ve ORTO-11 toplam puanının % 29'unu açıkladığı belirlendi.

Sonuç: Tip 2 diyabetli hastaların yüksek düzeyde ölüm kaygısı ve orta düzeyde ortoreksiya nervoza eğilimine sahip oldukları belirlendi. Ölüm kaygısı arttıkça ortoreksiya nervoza eğiliminin arttığı belirlendi.

Anahtar Kelimeler: Diabetes Mellitus; Ölüm; Beslenme ve Yeme Bozuklukları; Hemşirelik.

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Introduction

Diabetes Mellitus is a metabolic disease which affects all systems of the body and which is characterized by an increase in blood glucose level as a result of the inability to secrete insulin hormone or a decrease in the effect of insulin.[1,2] The disease has two types as Type 1 and Type 2 diabetes. Type 1 diabetes is usually seen among young people and accounts for 5-10% of diabetes patients. Type 2 diabetes is usually seen among adults and accounts for 90-95% of diabetes cases.[2] According to World Health Organization (WHO) data, it has been reported that there are approximately 422 million diabetes patients in the world today, the prevalence of type 2 diabetes has increased dramatically in the last three decades and diabetes is among the leading causes of death in the world.[3]

Due to the prevalence of the disease and its effects that may result in death, patients with diabetes may experience death anxiety.[4-6] Death anxiety includes anticipating death and being afraid of the process of dying.[7] The death anxiety experienced by diabetes patients can hinder the adoption of necessary behaviors for managing diabetes and increase the risk of complications arising from the disease.[5,6,8,9] Doğan et al. reported that high level of death anxiety in patients hospitalized for diabetes triggered depression.[5] Death anxiety can lead to complications in diabetes patients, such as cardiovascular diseases, nephropathy, neuropathy, and retinopathy, making it essential to prevent it and minimize its effects.[5,8,9] Regarding the importance of this concept in providing healthcare to patients, death anxiety is accepted as a nursing diagnosis by North American Nursing Diagnosis Association (NANDA).[10] For this reason, it is thought that nursing care is important in determining death anxiety and related factors and implementing interventions to decrease anxiety in patients with diabetes.[5,6]

In order to cope with the death anxiety they experience, patients may turn to healthy eating behaviors that are effective in symptom control and prevention of complications in diabetes.[11] Healthy diet, which is important in diabetes management, is an effective method to keep glycemic, lipid and blood pressure at normal levels.[12] For this reason, adherence to a healthy diet is an indispensable part of effective self-management of the disease process for patients with diabetes mellitus.[11,12] Since adherence to a healthy diet is essential in the disease, it is reported that patients with diabetes are often overly occupied with their diets.[13-15] This situation can turn healthy eating behaviors into an obsession in patients with diabetes. These obsessive behaviors may cause Orthorexia Nervosa, which is an eating disorder that is not commonly known in literature, in individuals.[14-16]

Orthorexia nervosa refers to the desire for healthy eating. Unlike patients with anorexia and bulimia who are concerned about the quantity of food, patients with orthorexia nervosa are concerned about the quality of food.[15,16] As in patients with obsessive compulsive disorder, occupational and social functionality may be impaired in patients with orthorexia nervosa as a result of spending a large part of the time with strict rules.[17] Orthorexia nervosa is currently not an official psychiatric diagnosis and it is not included in DSM-5 as an eating disorder. Research is helping to develop a new definition and to define diagnostic criteria for advanced versions of DSM.[18] Therefore, researches on orthorexia nervosa are important.[13]

There are limited numbers of studies examining orthorexia nervosa in patients with diabetes and there is not enough information on the effects of this disorder in patients with diabetes.[13,14] There are no research data on the prevalence of orthorexia nervosa in patients with diabetes in many countries.[13-15] According to the results of the limited numbers of studies conducted, it is emphasized that there is a concern that the rate of individuals with orthorexia nervosa tendencies will increase in the near future.[13,19] For these reasons, it is thought that there is a need for studies to be conducted in this field.

Patients with type 2 diabetes need to keep their blood sugar levels under control throughout their lives in order to maintain a healthy lifestyle. Therefore, these patients generally have to plan their meals, pay attention to portion sizes, and monitor their carbohydrate intake.[11,15,16] Consequently, it is

believed that the fear of death may influence eating behaviors, which are an important aspect of diabetes management. Due to this fear, patients might focus on consuming only healthy foods and avoid unhealthy ones.[11] It is thought that the desire to cope with the fear of death and the wish to sustain life may increase the likelihood of type 2 diabetes patients developing tendencies toward orthorexia nervosa. As a result, it is thought that death anxiety and thoughts of avoiding death may trigger orthorexia nervosa in patients with diabetes. When the literature was reviewed, no studies were found in which the components of death anxiety and healthy eating obsession were discussed together in diabetes patients.

This study was conducted to investigate the effect of death anxiety on orthorexia nervosa tendencies in patients with Type 2 diabetes. The data from the current study is expected to contribute to a better understanding of the concepts of fear of death in diabetes and orthorexia, which are not well known, and to demonstrate the relationship between these concepts. Additionally, since the research team did not encounter similar studies in the literature, this study is considered one of the pioneers in the field.

Research questions

- What is the level of death anxiety and orthorexia nervosa tendencies in type 2 diabetes patients?
- Is there a relationship between descriptive characteristics death anxiety, orthorexia nervosa tendencies in type 2 diabetes patients?
- Is there a relationship between death anxiety and orthorexia nervosa tendencies in type 2 diabetes patients?

Materials and Methods

Type of research

The study has a cross-sectional and correlational design.

Population and sample of the study

Population of the study consisted of patients with Type 2 diabetes who referred to internal medicine outpatient clinics of a university hospital in Elazığ, which is on the east of Turkey, between January 2022-January 2023. The convenience sampling method was used in the study. Sample of the study was calculated by considering the mean score of country variable in Özdemir et al. (2021)'s study (for the t test to compare two groups). As a result of prior power analysis in G*Power 3.1.9.2 program, effect size was calculated as 0.520 (high effect size), with 0.05 level of significance and 0.95 power.16 Thus, the minimum number of patients to be included in the study was found as 168. The study was completed with 200 patients who met the inclusion criteria and who agreed to participate in the study between the aforementioned dates.

Inclusion criteria

- Having been diagnosed with Type 2 diabetes at least 6 months ago
- Being ≥18 years of age
- Having no history of psychiatric disease
- Having no impairments (such as sight, speech and hearing) that will prevent the patient from communicating

Data collection tools

Study data were collected in 10-15 minutes through face-to-face interviews with the patients. Research data were collected in a waiting room at the institution where the research was conducted. "Descriptive Information Form", "Death Anxiety Scale" and "Orthorexia-11 Scale" were used to collect data.

Descriptive information form

This form prepared by the researchers includes a total of 10 questions on the patients' age, marital status, gender, educational status, income status, employment status, diagnosis time, the state of having information about the disease, the state of having complications and the presence of another chronic disease.

Death anxiety scale (DAS)

The scale was developed by Templer to evaluate individuals' anxiety and fears about their death and the risk of death.[20] Turkish validity and reliability study of the scale was conducted by Akça and Köse.[21] The scale is a 15-item scale that can be responded as right-wrong. Each "yes" response is scored as "1",

while each “no” response is scored as “0” in the first 9 items; in the remaining 6 items, each “no” response is scored as “1”, while each “yes” response is scored as “0”. Total score shows the death anxiety score. Higher score is interpreted as higher death anxiety. While the minimum possible score from the scale is “0”, the maximum possible score is 15. A score between 0 and 4 is evaluated as “mild level” death anxiety, a score between 5 and 9 is evaluated as “moderate level” death anxiety, a score between 10 and 14 is evaluated as “severe level” death anxiety, and a score of 15 is evaluated as “panic level” death anxiety.[21] Cronbach’s alpha value was 0.75 in the Turkish validity and reliability study.[21] Cronbach’s alpha was found to be 0.87 in the present study.

Orthorexia-11 scale (ORTO-11)

It was developed by Donini et al. to evaluate orthorexia nervosa tendency.[19] Turkish validity and reliability study was conducted by Arusoğlu et al. The scale is a 4-Likert type scale with 11 items.[17] The responses that are distinguishing for orthorexia are scored as "1", the responses that are distinguishing for normal eating behavior tendency are scored as "4"; minimum possible score is 11, while the maximum possible score is 55. Low scores indicate orthorectic tendency. The higher the scores get, eating behavior approaches from oversensitivity to normal.[17,19] Cronbach’s alpha value was 0.62 in the Turkish validity and reliability study.[17] Cronbach’s alpha was found to be 0.79 in the present study.

Data analysis

SPSS version 22.00 program was used for the analysis of data in the study. Percentage, mean and standard deviation were used in descriptive statistics. Kurtosis and Skewness coefficients were used to analyse the normality distribution of the data. Multiple linear regression analysis was used in data analysis. In multiple linear regression analysis, the 'ENTER' method was used to include the variables in the model. Multicollinearity and independence of residuals were tested in the regression model. The independence of factors was determined (none of the correlation coefficients between variables that influenced DAS and ORTO-11 was above 0.45). After verifying the error term's basic assumptions, the Durbin-Watson test statistic showed no autocorrelation. The tolerance limit of multicollinearities was ≥0.1, The variance inflation factor(VIF) was <10. The conditions for the error terms' normality and homoscedasticity were satisfied. Simple linear regression analysis was performed to investigate the effects of patients' DAS scores on ORTO-11 scores. Significance level was considered as $p<0.05$.

Ethics committee approval

Before starting the study, approval was taken from the Non-interventional Research Ethics Committee (29.09.2021 dated and E-97132852-050.01.04-90384 numbered) of a university and permission was taken from the institution where the study was conducted. The patients included in the study were provided with the required explanations about the purpose and method of the study and their verbal consent was taken. The study was carried out in line with the ethical standards of the Declaration of Helsinki. Individuals who volunteered to participate were included in the study and their personal identity information was kept confidential.

Results

Mean age of the patients was found as 52.59±17.84 years. It was found that 50.5% of the patients were female, 77% were married, 40% were illiterate, 71% had an income equal to expense, 78% were not working, 40% had a diagnosis year of 6 years and longer, 58.5% did not have sufficient information, 59% had a diabetes complication and 55.5% had another chronic disease (Table 1).

Mean DAS total score of the patients was found as 11.41±2.09, while their mean ORTO-11 total score was found as 23.69±6.09 (Table 2).

Multiple regression analysis was conducted to make estimations about the variables of age, gender, presence of another chronic disease, the state of having diabetes complications, diagnosis year, marital status, the state of having information about the disease, income status, employment status and educational

status and mean DAS and ORTO-11 total scores. When the analysis result for mean DAS total score was examined, the created model was found to be statistically significant F(15,184): 9.136, p<0.001. It was found that of the variables included in the model, age, having diabetes complication (yes), gender (female) were statistically significant and positive predictors of death anxiety (β= .260; β= .206; β= .213, p<0.05), while educational status (postgraduate) was a statistically significant and negative predictor of death anxiety (β=-.237, p<0.05). When the analysis result for mean ORTO-11 total score was examined, the created model was found to be statistically significant F (15,184): 4.458, p<0.001. It was found that of the variables included in the model, the state of having diabetes complication was a statistically significant and negative predictor of orthorexia nervosa tendency (β= -.239, p=.015) (Table 3).

Table 1. Descriptive characteristics of the patients.

Characteristics	**n** (n=200)	**%**
Gender		
Female	101	50.5
Male	99	49.5
Marital status		
Married	154	77
Single	46	23
Educational status		
Illiterate	80	40
Literate	23	11.5
Primary education	46	23
High school	40	20
Undergraduate and higher	11	5.5
Income status		
Income<expense	48	24
Income=expense	142	71
Income>expense	10	5
Employment status		
Employed	44	22
Unemployed	156	78
Diagnosis year		
0-2 years	62	31
2-6 years	58	29
≥6 years	80	40
The state of having information about the disease		
Adequately	83	41.5
Inadequate	117	58.5
The state of having diabetes complications		
Yes	118	59
No	82	41
Presence of another chronic disease		
Yes	111	55.5
No	89	44.5
	Mean±SD	
Age	52.59±17.84	

Table 2. Mean DAS and ORTO-11 scores of the patients.

	Mean±SD	**Min.**	**Max.**	**Skewness**	**Kurtosis**
DAS Total	11.41±2.09	7.00	14.00	-.37	-.91
ORTO-11 Total	23.69±6.09	11.00	40.00	.47	-.17

DAS: Death Anxiety Scale, ORTO-11: Orthorexia 11 Scale

Table 3. Regression analysis results in terms of descriptive characteristics.

Dependent variables	Model	Independent variables	B	S.E	Standard (Beta)	t	*p*	95% Confidence interval	
								Lower	Upper
DAS	1	Constant	8.977	.904		9.936	**.000***	7.195	10.760
		Age	.030	.013	.260	2.356	**.020****	.005	.056
		Diabetes Complication (Yes)	.874	.366	.206	2.392	**.018****	.153	1.596
		Gender (Female)	.890	.260	.213	3.421	**.001****	.377	1.403
		Education (Postgraduate)	-2.170	.710	-.237	-3.057	**.003****	-3.571	-.770
		R=.657,	R^2=.442		Durbin Watsın:0.667				
		$F_{(15,184)}$=9.136,	***p*=.000***						
ORTO-11	2	Constant	25.322	2.989		8.472	**.000***	19.425	31.220
		Complication (Yes)	-2.958	1.209	-.239	-2.446	**.015****	-5.344	-.572
		R=.516,	R^2=.267		Durbin Watsın:1.690				
		$F_{(15,184)}$=4.458,	***p*=.000***						

*p<0.001. **p<0.05 DAS: Death Anxiety Scale, ORTO-11: Orthorexia 11 Scale

As a result of the multiple regression analysis, the created model was found to be statistically significant (F(1.198)=29.130, p<0.001). It was found that independent variable DAS total score was a significant and negative predictor (β= -.540, p<0.001) and explained 29% of dependent variable ORTO-11 total score (Table 4).

Table 4. Regression analysis results.

Dependent variables	Model	Variables	B	S. Error	β	*t*	*p*	95%Confidence interval	
								Lower	Upper
ORTO-11	**1**	Constant	15.805	.503		31.453	**.000***	14.814	16.796
		DAS	-.186	.021	-.540	-9.030	**.000***	-.226	-.145
		R=.540,	R^2=.292		Durbin Watsın:1.606				
		$F_{(1.198)}$=81.541	***p*=.000***						

**p<0.000*, DAS: Death Anxiety Scale, ORTO-11: Orthorexia 11 Scale

Discussion

In the present study, it was found that patients with Type 2 diabetes mellitus had high levels of death anxiety. Although there are studies examining anxiety in patients with Type 2 diabetes in literature, there are limited numbers of studies examining death anxiety.[4,6] In the study they conducted in Turkey, Doğan et al. found that patients with diabetes experienced high levels of death anxiety.[5] An increase has been reported in the frequency and intensity of death-related thoughts in chronic diseases such as diabetes.[22,23] In this context, a large number of individuals with chronic diseases are actually not ready to die while they are facing with the truth that "death is inevitable".[23] Patients with diabetes may experience death anxiety more intensely due to the fact that diabetes does not have a definitive treatment and due to its serious complications.[6] It can be thought that after the COVID-19 epidemic, thoughts that individuals with chronic diseases have a higher risk of death in epidemics trigger death anxiety.[24]

In the present study, death anxiety was found to increase with advancing age. Different results can be seen in studies examining age and death anxiety in literature. Anxiety and death anxiety are expected to increase with age.[25,26] However, there are also studies reporting that death anxiety decreases with age.[4,27] The reason for this can be the fact that a large number of variables such as the patients' living conditions, psychosocial and cultural factors and individual differences affect death anxiety.

In the present study, diabetes complications were found to be a factor increasing death anxiety. Anxiety is traditionally associated with increased medical complications in individuals with Type 2 diabetes, Masmoudi et al. emphasized that diabetes patients who experienced complications had high levels of

anxiety.[8,9] However, Edwards and Mezuk found that complications were not associated with anxiety in Type 2 diabetes.[28] It can be thought that the severity of complications and the differences in coping skills of individuals might have caused this difference.

In the present study, death anxiety was found to be high in female patients. Women were found to have higher anxiety levels in studies conducted with Type 2 diabetes patients.[26,28] Russac et al. reported that women experienced death anxiety more frequently than men.[27] Missler et al. reported that women experienced more fear than men about their death and the death of their loved ones.[25] Traditional gender roles can influence how women experience and express their fear of death. In Eastern countries, both women and men are expected to suppress their health concerns and feelings about death. In our country, however, unlike in Western and Middle Eastern countries, it is considered normal for women to express their health concerns, fears of death, and thoughts related to death, while men are expected to be stronger.[29,30] Additionally, the caregiving responsibilities that come with traditional female identity can lead women to worry more about the futures of their loved ones and experience greater fear of death. Another factor is that women are generally more active than men in forming social support networks. This can provide women with more opportunities to share and express their fears of death.[29-31] All these gender-based factors are thought to contribute to women experiencing a greater fear of death.

In the present study, it was found that having postgraduate degree decreased death anxiety. Bjelland et al. reported that high level of education had a protective effect against anxiety that built throughout life.[32] Ganasegeran et al. found that Type 2 diabetes patients with high level of education experienced less anxiety.[33] Education enables individuals to understand the process and complications of disease correctly and makes it easier for them to manage the disease process.

In the present study, patients with Type 2 diabetes mellitus were found to have moderate level of orthorexia nervosa tendencies. In a systematic review they conducted, Grammatikopoulou et al.[13] pointed out that there were limited numbers of studies examining orthorexia nervosa tendencies in patients with diabetes.[13] There are studies in the literature investigating the relationship between eating disorders and diabetes.[34-37] Although these studies emphasize that eating disorders are a common problem in diabetic patients, the information about the relationship between diabetes and orthorexia nervosa is limited.[14-16,38,39] Barbanti et al. showed that 65.5% of the patients had orthorexic features in their study with 887 individuals with type 2 diabetes.[39] Despite this high rate of orthorexia nervosa in diabetic patients, the factors affecting it and its effects on the disease are not yet fully known.[38,39] The obsession to control food can put patients with diabetes at risk for orthorexia nervosa. In the present study, experiencing diabetes complications was found to increase orthorexia nervosa tendencies. Experiencing diabetes related complications may have a negative effect on individuals' life quality and mental health.[8,9] It can be said that this situation causes diabetes patients to tend to consume healthier foods to protect their health and healthy eating behaviors become an unhealthy obsession.

In the present study, death anxiety and orthorexia nervosa were found to be associated and patients' orthorexia nervosa tendencies were found to increase as their death anxiety levels increased. It has been emphasized in the literature that death anxiety can affect eating disorders.[40-42] Studies involving diabetic patients indicate that as anxiety levels increase, the prevalence of eating disorders also rises.[43,44] Swinbourne et al.[45] reported a high comorbidity rate of 65% for eating and anxiety disorders. However, there is a lack of literature examining the co-occurrence of death anxiety and tendencies toward orthorexia nervosa in diabetic patients. It has been reported that the foundation of orthorexia nervosa lies in perfectionistic and obsessive-compulsive attitudes towards nutrition.[15,16,40] Le Marne and Harris noted that death anxiety and general anxiety are associated with perfectionism and obsessive-compulsive disorder, which can

influence healthy eating obsessions.[40] Fitzsimmons et al.[46] found that as individuals' anxiety levels increase, their dieting behaviors also tend to rise, potentially triggering perfectionistic eating behaviors. Diabetic patients may engage in perfectionistic dieting as a way to cope with their anxiety related to disease management.[47,48] Menzies has indicated that death anxiety is linked to obsessive thoughts and behaviors.[49] The orthorexia nervosa examined in this study is thought to arise from perfectionistic and compulsive behaviors related to nutrition, suggesting that it may emerge as a coping mechanism for dealing with death anxiety. Another factor that may influence this finding is the health-related anxieties prompted by orthorexia nervosa.[50,51] Abramowitz et al.[50] emphasized that health-related anxieties and hypochondriasis are associated with anxiety. Maner et al.[51] reported that anxiety can lead to avoidance of risky health behaviors. In patients with Type 2 diabetes, anxiety can shape disease management behaviors and health-related quality of life.[52-54] Since the anxiety experienced by diabetic patients can influence their health behaviors, it is believed that death anxiety may lead to the development of orthorexia nervosa.

Study limitations

This study has several limitations. First, the data were collected using self-report scales, which raises the possibility of common method biases. Second, the study was conducted at a single center with a limited number of patients. Third, a limitation of the study is that it could not be determined which complications of diabetes are associated with fear of death. The fourth limitation is that probability sampling methods were not used in this study. Another significant limitation is the absence of research examining the relationship between orthorexia nervosa and death anxiety in patients with Type 2 diabetes. Additionally, the lack of studies investigating orthorexia nervosa and death anxiety in different groups has restricted our discussion. These challenges have made it difficult to interpret our findings comprehensively. However, this aspect of our research adds originality to it.

Conclusion

As a result of the study, patients with Type 2 diabetes were found to have high level of death anxiety and moderate level of orthorexia nervosa tendency. Orthorexia nervosa tendencies of patients were found to increase as their death anxiety levels increased. As a result of this study, it is recommended to examine death anxiety levels of diabetes patients periodically and to implement interventions on those who have high levels. It is recommended for healthcare professionals working with diabetes patients to train patients about healthy eating, to be aware of obsessive eating behaviors and to implement interventions to patients who show these tendencies. In addition, in line with the results of the present study, it is thought that conducting nursing interventions to decrease death anxiety of diabetes patients will be effective in decreasing their orthorexia nervosa tendencies. Methodological studies are needed to find out the factors that may affect death anxiety and orthorexia nervosa tendencies in diabetic patients and to establish a causal relationship.

Ethics Committee Approval

Before starting the study, approval was taken from the Non-interventional Research Ethics Committee (29.09.2021 dated and E-97132852-050.01.04-90384 numbered) of a university and permission was taken from the institution where the study was conducted. The patients included in the study were provided with the required explanations about the purpose and method of the study and their verbal consent was taken. The study was carried out in line with the ethical standards of the Declaration of Helsinki. Individuals who volunteered to participate were included in the study and their personal identity information was kept confidential.

Informed Consent

Informed consent was obtained from the individuals participating in the study.

Authors Contrubituons

All of the authors contributed at every stage of the study.

Conflict of Interests

There is no conflict of interest to declare.

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Peer-review

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Research Article/Özgün Araştırma

Religiosity, internalized sexism, and sexual attitudes in late female adolescents: A structural equality modeling

Geç dönem kadın ergenlerde dindarlık, içselleştirilmiş cinsiyetçilik ve cinsel tutumlar: Yapısal eşitlik modellemesi

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Abstract

Aim: Adolescence is a period marked by rapid physical and sexual changes, as well as the internalization of societal norms. However, while studies on sexual attitudes and religiosity yield inconsistent results, research on sexism remains limited. This study aims to examine the impact of religiosity on internalized sexism and sexual attitudes in late-adolescent women.

Materials and Methods: Conducted in Turkey, this study explores the effects of religiosity on internalized sexism and sexual attitudes among late-adolescent women. The sample consists of 670 women aged 18-25 years.

Results: Religiosity directly influences sexual attitudes and internalized sexism in late-adolescent women. Moreover, internalized sexism plays a mediating role in the relationship between religiosity and sexual attitudes.

Conclusion: Appropriately interpreting religious knowledge acquired from reliable sources positively influences adolescent women's attitudes toward sexism and sexuality. In this context, multidisciplinary collaborations among healthcare professionals are assumed to have a protective effect against risky sexual behaviors.

Keywords: Religiosity, internalized sexism, sexual attitudes, healthcare professionals, late adolescent women.

Öz

Amaç: Adölesan dönem pekçok alanda olduğu gibi fiziksel ve cinsel değişimlerinde hız kazanmasına ek olarak toplumsal normlarında içselleştirildiği bir dönem olmasına rağmen cinsel tutum ve dindarlığa ilişkin sonuçlar tutarsız iken, cinsiyetçilikle ilgili çalışmalar sınırlıdır. Bu araştırmanın amacı, geç ergenlik dönemindeki kadınlarda dindarlığın içselleştirilmiş cinsiyetçilik ve cinsel tutumlar üzerindeki etkisini belirlemektir.

Gereç ve Yöntem: Bu çalışma geç dönem ergen kadınlarda dindarlığın içselleştirilmiş cinsiyetçilik ve cinsel tutumlar üzerine etkisini belirlemek amacıyla Türkiye'de yürütülmüştür. Çalışmanın örneklemini 18-25 yaş arası 670 kadın ergen oluşturmuştur.

Bulgular: Geç dönem adölesan kadınlarda dindarlık, cinsel tutum ve içselleştirilmiş cinsiyetçiliği direkt etkilemektedir. Ayrıca dindarlık ile cinsel tutumlar arasındaki ilişkide içselleştirilmiş cinsiyetçilik aracı role sahiptir.

Sonuç: Doğru kaynaklardan edinilen din bilgisinin uygun yorumlanması ile kadın ergenlerin cinsiyetçiliğe ve cinselliğe yönelik tutumlarını olumlu etkilediği sonucuna ulaşılmıştır. Bu bağlamda sağlık profesyonellerinin ergenlere yönelik multidisipliner ekiple birlikte çalışmalar yapmalarının riskli cinsel davranışlara karşı koruyucu etkisinin olacağı varsayılmaktadır.

Anahtar kelimeler: Dindarlık, içselleştirilmiş cinsiyetçilik, cinsel tutumlar, sağlık profesyonelleri, geç dönem ergen kadınlar.

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Introduction

Sexuality, a vital indicator of the individual's physical, spiritual, and social well-being, is one of the critical health issues of adolescence, as it affects future life. Awareness of sexuality begins in childhood, and a sense of sexual identity develops during adolescence.

Adolescence is considered between the ages of 10-19 (WHO, 2003)[1] and is classified as early, medium, and late adolescence. Although it is reported that the early adolescence period covers the 11-14 age range, the middle adolescence period covers the 13-17 age range, the late adolescence period covers the 16-19 age range,[2] it is also emphasized that late adolescence continues until the age of 25.[3] Late adolescence is significant because the individual develops an identity by becoming autonomous. It is also of considerable importance in terms of internalizing sexual identity, sexual orientation, social norms, and roles and shaping moral values in this period.[4] Understanding the individual factors affecting sexual attitudes and beliefs is essential for adolescents to develop a sexual identity and orientation appropriate for their gender. In addition, the World Health Organization (WHO, 2017)[5] stated that concepts such as gender, sexual health, sexuality, and sexual rights are the main themes for reproductive health and sexual health. In this study, religiosity and internalized sexism are discussed as factors that can affect sexual attitudes. The results are expected to reference sexual and psychological education and activity development activities for adolescents.

Background

Developmental psychology considers the individual as a whole with its bodily, behavioral, sexual, cognitive, linguistic, emotional, and social dimensions. It evaluates the individual's development as a whole, consisting of separate periods. Adolescence, which has an essential place in the developmental periods, is the transition period from childhood to adulthood, where biological, psychological, physical, and social development and maturation are experienced. This stage is a period of very rapid physical and sexual changes.[6,7] Adolescents are a significant proportion of the total population in Türkiye and the world.[8,9] Late adolescence, which covers the ages of 18 to 24, is a developmental stage characterized by the individual's gradually becoming autonomous and gaining an adult identity.[3,4] In this period, adolescents entering university and professional life acquire new social roles and identities.[4] It is the most critical period in which sexual attitudes, social roles, and attitudes, religious values that are effective in forming moral values are shaped and affect each other.

Religious values, which are the reality of society and human beings, strongly influence the shaping of social phenomena. In this context, the influence of religion on constructing sexuality, which is a social phenomenon, and determining gender-related roles and principles is undeniable.[10] While sexuality is interpreted as coming together for reproduction and the continuation of the lineage in Judaism, celibacy and virginity are emphasized in Christianity. In Islam, on the other hand, it has been emphasized that sexuality experienced in appropriate (Halal) ways is worship and detailed information about sexuality has been given. Besides, there are some differences; it is stated that monotheistic religions emphasize the elimination of sexual desires and desires within legitimate limits.[11]

The desires and pursuits that increase in parallel with the emotional and cognitive skills developing rapidly during adolescence effectively shape the attitudes toward religious and sexual life in adolescents.[6,12] However, the findings on how these attitudes affect each other are inconsistent.[13-16] Although it is generally known that religiosity is a protective factor for risky sexual behaviors in adolescents,[14-16] it is emphasized that as the level of religiosity increases, sexual liberalization decreases as well as risky sexual behaviors increase.[13,17]

This period is also when adolescents strive to integrate with society, socialize, and adapt to social norms.[18] These norms shape the sexual and religious attitudes of the adolescent, as well as their perspective on gender. It is

known that social pressure against women has increased, and sexual attitudes have been negatively affected in Türkiye.[19] While sexuality is considered a task/activity that needs to be fulfilled rather than giving consent for men, it appears as a prohibited action for women.[20] These social attitudes and pressures make gender differences towards sexuality more apparent, and it is thought that women increase the potential for risky behavior in this regard. It is also reported that adolescents are sexually active. In addition, adolescents are inclined to dangerous behavior due to limited resources to protect or support them from unsafe sex, sexually transmitted infections, or pregnancy. It is stated that this situation increases even more in late adolescence.[21]

The influence of moral, economic, social, and religious conditions on individuals' sexual attitudes cannot be denied, and these conditions are closely related to the role assigned to women. Therefore, sexuality, in general, is taboo in Türkiye, and moral debates are likely to occur when the words "sexuality" and "woman" come together.[22] These discussions may lead to women's submission and a tendency to internalize all or some of the objectifying, humiliating, and oppressive attitudes about women who make up society.[23] This tendency causes women to increase their perceptions of worthlessness towards themselves and other women, that is, to experience internalized sexism.[24] In the formation of this negative perception towards women, it is seen that women are humiliated and devalued with the use of religion, which is the most decisive spiritual element in culture.[25] Women living in such a social environment are more likely to experience internalized sexism. Internalized sexism is a type of internalized oppression, and this oppression is a mechanism that is sustained not only by external control but also by subordinating the minds of individuals/groups.[26] Therefore, internalized sexism affects women's emotional[27] and relational health[28] as well as their perceptions of sexual attitudes.[29]

It is known that there is a relationship between the attitudes of adolescents towards sexual education and the attitudes of families towards sexism[30] and that families give answers to questions about sexuality based on religious beliefs.[31] How scientific these answers are is a matter of debate. In this context, it is essential for healthcare professionals who are responsible for providing holistic care to consider the sexual and religious beliefs and attitudes of individuals and families. It is also emphasized that healthcare professionals should increase their knowledge and awareness of these issues.[32] For this reason, it is thought that the present study will contribute to the literature in terms of realizing how the attitudes towards sexism and sexuality are affected by the religious beliefs and attitudes of healthcare professionals, who are an essential part of society and the health system.

In addition to the adolescents' search for their personality identity and social roles, research on this topic is considered necessary due to intense experiences of sexual emotions, sexual curiosity, and risky sexual intercourse. However, when the literature on this subject is examined, it is reported that research on women's sexuality is quite limited.[33] In addition, the effects of taboos and social perceptions on individuals have been virtually undiscovered, and it is expressed that it is essential to conduct such research.[33] It is thought that this research will contribute to the literature both in terms of religiosity and internalized sexism that affect women's sexual attitudes and in terms of the research method. Therefore, this study aims to investigate the effects of internalized sexism and religiosity levels on the sexual attitudes of late adolescent women (18-25 years old). The hypotheses established for this purpose are presented below:

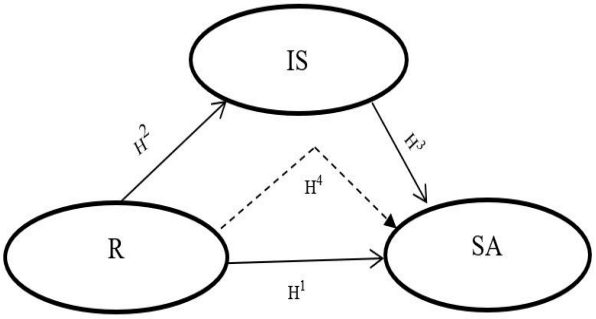

Figure 1. Hypothesis model
* SA: Sexual Attitudes; R: Religiosity; IS: Internalized Sexism
H1: The level of religiosity of late adolescent women affects their sexual attitudes.
H2: The level of religiosity of late adolescent women affects the level of internalized sexism.

H^3: The level of internalized sexism of late adolescent women affects their sexual attitudes.
H^4: Internalized sexism has a mediating role in the assumed relationship between the level of religiosity and sexual attitudes of late adolescent women.

Materials and Methods

Design and sample

This is a cross-sectional study aiming to investigate the effects of late adolescent (18-25 years old) women's internalized sexism and religiosity levels on their sexual attitudes by establishing structural equation modeling (SEM). A STROBE Statement for cross-sectional studies was used to report the study (https://www.strobe-statement.org/checklists/). The study inclusion criteria were adolescents between 18 and 25 who were female and had approved the informed consent form. Adolescents who had difficulties reading and understanding Turkish were excluded from the study. Data were collected between 30 December 2021 and 29 January 2022. Participants were selected by non-probability, convenience, and serial sampling; all female adolescents who met the inclusion criteria during the data collection process were invited to participate.

The research population consisted of female adolescents aged 18-25. Sample calculation was not made in the study, and theoretical information about the number of samples in SEM was considered. Structural equation modeling has no basic rule or standard for sample size.[34] Including three latent and 18 observed variables (all observed indicators and socio-demographic variables), the minimum sample size of 200 was calculated as a moderately effective (0.3) minimum sample size with a power value of 0.95 and an α value of 0.05 in this study, in a priori sample size calculator designed to calculate the sample size of SEM (Soper, 2015). In addition, attention was paid to the fact that the number of variables in the model should be between 10-20 times and not less than 200 in line with the recommendation of the literature.[34] The study forms created online were delivered to adolescents through WhatsApp groups. A group was not made for the study, and no additional information was requested. Adolescents were given 30 days to increase their willingness to participate in the survey at their appropriate time and to ensure the reliability of the answers to the questions. At the end of this period, the study was terminated with 670 adolescents who voluntarily participated. The details of the socio-demographic and sexual attitude characteristics are given in Table 1.

The data were collected with the information form containing the socio-demographic (age, gender, etc.) data of the individuals, the Hendrick Sexual Attitude Scale, the Religiosity Scale, and the Women's Internalized Sexism Scale.

Socio-demographic characteristics data form

This form consists of questions such as age, family type, marital status, talking about sexuality with the family, sexual intercourse experience, and opinions about pre-marital sexual intercourse.

Hendrick sexual attitudes scale

The Turkish validity and reliability of the scale, which was made by Karaçam et al.[35], consists of 23 items. It is in a 5-point Likert type. It comprises four sub-dimensions: Permissiveness, Birth Control, Communion, and Instrumentality. A score between 23 points and 115 points is obtained from the scale. High scores from the total of the scale indicate that the individual has an ideal, healthy, and balanced sexual attitude. In contrast, low scores indicate that the individual is in a self-centered sexual life and has a sex attitude far from an ideal sexual attitude. The total scale's Cronbach alpha internal consistency coefficient was 0.85.[35] In our study, this value was determined as 0.89.

Religiosity scale

It is a scale developed by Ayten and Hussain[36], has nine items and a 5-point Likert type. It consists of two sub-dimensions: Religious influence and religious faith and worship. A score between 9 and 45 points is obtained from the scale. Higher scores on the scale indicate an elevated level of religiosity. The Cronbach's alpha coefficient for the overall scale was 0.76.[36] The Cronbach's alpha of the scale was determined to be 0.89 in our study.

Table 1. Relationships between socio-demographic characteristics and variable scores.

Descriptive Characteristics	N(%)	SA	R	IS
		Mean±SD	Mean±SD	Mean±SD
Family type				
Nuclear family	559 (83.4)	80.38±15.80	32.61±8.06	91.53±15.73
Extended family	92 (13.7)	78.23±14.38	34.20±7.23	95.13±15.55
Broken family	19 (2.9)	77.26±16.37	30.10±9.61	94.05±14.19
p		*0.359*	*0.072*	*0.108*
Marital status				
Unmarried	660 (98.5)	80.02±15.68	32.72±8.00	92.01±15.61
Married	10 (1.5)	78.70±12.84	35.20±9.21	97.90±20.45
p		0.791	0.334	0.239
Talking about sexual matters with family				
Yes	113 (16.9)	74.29±14.81	29.88±8.51	88.67±16.33
No	557 (83.1)	81.15±15.55	33.34±7.79	92.79±15.48
p		**0.001**	**0.001**	**0.011**
Education status with sexuality				
Yes	319 (47.6)	79.18±13.99	33.15±7.45	91.70±14.97
No	351 (52.4)	80.74±16.97	32.41±8.49	92.45±16.33
p		*0.199*	*0.231*	*0.540*
Sexual intercourse status				
Yes	46 (6.9)	68.80±15.04	24.02±8.96	83.23±16.34
No	624 (93.1)	80.82±15.36	33.40±7.56	92.75±15.46
p		**0.001**	**0.001**	**0.001**
Opinions regarding pre-marital sexuality				
I am against any pre-marital sexual intercourse for religious reasons.	378 (56.4)	85.09±15.05[a]	36.65±6.01[a]	94.90±15.47[a]
Pre-marital sexual intercourse should be limited.	167 (24.9)	76.35±12.45[b]	30.05±6.01[b]	90.22±14.19[b]
Pre-marital sexual intercourse is natural.	105 (15.7)	67.26±13.67[c]	23.22±7.38[c]	85.12±17.16[c]
Other	20 (3.0)	80.00±15.63[ab]	31.95±7.91[b]	91.25±9.84[abc]
p		**0.001**	**0.001**	**0.001**

(a,b,c,d: Superscript shows the differences within the group. There is no difference in the measurement in the same letters.) SA: Sexual Attitudes; R: Religiosity; IS: Internalızed Sexism

Internalized sexism scale for women

Bozkur[37] developed the scale to measure various aspects of internalized sexism in women with questions such as "Some women deserve violence" and "I don't like to be tantalizing like some women." The scale consists of 35 items and is in a 5-point Likert type. It comprises five sub-dimensions: Self-Objectification, Derogation, Internalized Powerlessness, Self-Separation and Male Prioritization. A score between 35 and 175 points is obtained from the scale. The scale can be used based on sub-dimensions and by taking the total score. The high score obtained from the scale indicates that the internalized sexism of women is high. The Cronbach's alpha coefficient for the overall scale was 0.84.[37] In our study, Cronbach's alpha on the scale was determined to be 0.81.

Ethics committee approval

The data forms were sent to the adolescents via Google Forms, and they were asked to fill them in. The "Informed Consent Form" was placed on Google Forms, and the volunteering tab was mandatory. In addition, approval was obtained from the Social and Human Sciences Ethics Committee (Approval No:473/Date:28.12.2021).

Statistical analysis

Data were evaluated using IBM SPSS Statistics Standard Concurrent User version 25. An independent sample was used to assess binary variables in evaluating score differences in socio-demographic data. ANOVA test was applied for three or more variables. A Pearson correlation test was used to determine the correlation between variables.

Structural equation modeling applies a two-stage method, measurement and hypothetical model. First, exploratory factor analysis was performed for all scales, and it was found that KMO>0.83 and Bartlett/df<0.05. When the exploratory factor analysis results were found suitable, confirmatory factor analysis was

performed in the LISREL 8.71 program to measure whether the measurement models met the good fit index values. The fit of the model was taken as CMIN/df (<5) root mean square error of approximation (RMSEA)<0.08, Goodness Index fit Index (GFI), Adjusted Goodness Adjustment Index (AGFI), and Comparative Fit Index (CFI)>0.90[34] (Table 2). These values reflect a good model fit. It is reported that for sample size >300, normality of data is acceptable with skewness value ≤2 and kurtosis value ≤4.[38] Since multivariate normality could achieved, the bootstrap method was applied, and a bias-corrected bootstrap approach based on 2000 samples was used to test the standardized sum and the direct and indirect effects of each variable. This method studies a resampling technique that is thought to represent the original data. Multiple subsamples of the same size as the original sample are randomly drawn and replaced, providing data for empirical analysis of parameter estimation and fit indices. In the bootstrap approach, parameters, standard errors, and model test statistics are estimated by empirical sampling distributions from many produced samples.[34]

Table 2. Structural equation modeling fit index and normal distribution (skewness-kurtosis) values of the study.

Index name	Test value	Threshold value[34]		Variables	Normality[38]	
		Good fit	Acceptable		Skewness	Kurtosis
CMIN/df	4.62	<3	3< CMIN/df<5	**SA**	-0.080	0.030
RMSEA	0.074	<0.05	<0.08	**R**	-0.603	-0.091
GFI	0.96	>0.95	>0.90	**IS**	0.557	1.298
AGFI	0.90	>0.95	>0.90			
CFI	0.93	>0.95	>0.90			

SA: Sexual Attitudes; R: Religiosity; IS: Internalızed Sexism

Finally, the hypothetical structural equation modeling based on the theoretical infrastructure was evaluated. First, Chi-square, df, and Probability level (*p*) were used to assess the model, and then the fit indicators listed above were examined. The corrections depending on the modification indices ensured the hypothetical model's frugality. The final model is given in Figure 2.

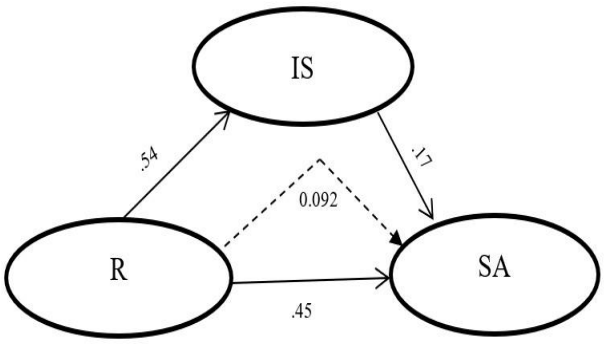

Figure 2. Structural equality modeling established between sexual attitude, religiosity, and internalized sexism

* SA: Sexual Attitudes; R: Religiosity; IS: Internalized Sexism

Results

A total of the participants 98.5% were single and 83.4% stated that they had a nuclear family type. Furthermore, of the participants 83.1% said that they did not talk to their families about sexual matters. In addition, of the participants 52.4% said that they did not receive any training on sexuality during their education. Of the participants 93.1% stated that they did not have any sexual intercourse experience. Lastly, of the participants 56.4% indicated that they were against any sexual intercourse before marriage due to religious reasons.

The mean scores of the scale variables and the multiple correlation analysis values of the adolescents are given in Table 3. It is seen that the mean scores of sexual attitudes and religiosity of the adolescents participating in our study are higher than the mean score of the scale. Still, the mean score of internalized sexism is close to the middle level. In addition, a statistically significant positive correlation was found between the sexual attitude levels of the adolescents and the levels of religiosity (r (670) =.419, p<0.01) and internalized sexism (r (670) =.095, p<0.05). A negative and statistically significant relationship was found with the age variable (r (670) =-.085, p<0.05). It is seen that there is a positive and significant relationship between religiosity and internalized sexism (r (670) =.208, p<0.01).

Table 3. Average, standard deviation, min-max, and correlation values of adolescents' ages and scores obtained from the scales

Variables		*X*± *SS*	Min-Max	1.	2.	3.	4.
1.	SA	80.00±15.63	23-115	-			
2.	R	32.76±8.01	9-45	.419**	-		
3.	IS	92.09±15.69	50-167	.095*	.208**	-	
4.	Age	20.24±1.62	18-25	-.085*	-019.	-.063	-

Spearman'a rho (** p<.01, * p<.05); SA: Sexual Attitudes; R: Religiosity; IS: Internalızed Sexism

Results related to structural equation model analysis

In this section, structural equation model analyses were conducted to reveal the effects of religiosity and sub-factors and internalized sexism and its sub-factors on sexual attitudes.

The test results of the first structural equation model established did not meet the recommended values in some indices of the statistics suitable for the model (CMIN/*df*= 12.09, RMSEA = 0.129, GFI= 0.87, AGFI = 0.79, CFI=0.76). For this reason, modifications were made to the established model. Theoretical backgrounds and the statistical significance of the modification index values were considered while modifying the model. The standardized parameters of the final model are presented in Figure 2. The effect of each variable on sexual attitude values is summarized in Tables 3 and 4.

When the fit statistics of the structural equation modeling in Figure 2, obtained as a result of the modifications created depending on the theoretical background and modification index values, were examined, it was seen that df=30 and p<0.05. Since df >0, it was seen that the model was fully saturated. Since p<0.05 was small, model fit indices were examined. Model fit index values were determined as CMIN/df=4.62, RMSEA=0.074, GFI=0.96, AGFI=0.90, CFI=0.93. These values show that the data support the model and that the fit indices are acceptable.[34]

Figure 2 and Table 4 show the results of the structural equation model analysis established to determine how much religiosity and internalized sexism predict sexual attitudes in late adolescent women. It is seen that religiosity affects internalized sexism and sexual attitudes in late adolescent women, and this effect is statistically significant (p<0.001). It was determined that internalized sexism has a substantial impact on sexual attitudes (p<0.05). A one-unit increase in the level of religiosity of late adolescent women causes an increase of 0.260 in the level of internalized sexism and an increase of 1.417 in the level of sexual attitudes. In addition, a one-unit increase in the level of internalized sexism results in an increase of 1,108 units in the level of sexual attitudes. Similarly, one standard deviation change in religiosity causes a standard deviation of 0.542 in internalized sexism and 0.452 in sexual attitudes. In addition, a one standard deviation change in internalized sexism in late adolescent females creates a 0.170 standard deviation in sexual attitudes. In addition, it is seen that 29.3% of the changes in internalized sexism and 31.7% of the changes in sexual attitudes are explained by this model (Table 4).

Table 4. Regression weights, standardized regression weights, and squared multiple correlations of the model.

Variables			Estimate		S.E.	t	*p*
			Unstandardized β	Standardized β			
IS	<---	R	0.260	0.542	0.070	3.708	**0.001**
SA	<---	IS	1.108	0.170	0.436	2.542	**0.011**
SA	<---	R	1.417	0,452	0.170	8.342	**0.001**
SMC							
IS			0.293				
SA			0.317				

* SA: Sexual Attitudes; R: Religiosity; IS: Internalızed Sexism; S.E.:Standard Error; SMC: Squared Multiple Correlations

It is seen that religiosity has a substantial and statistically significant effect on internalized sexism (effect value = 0.54) and sexual attitudes (effect value = 0.45)

(p<0.001). In addition, it was determined that internalized sexism has a direct (effect value = 0.17) effect on sexual attitudes (p<0.05). Finally, it was determined that religiosity has a direct impact on sexual attitudes, as well as through internalized sexism (effect value = 0.09) (p<0.01). In this context, internalized sexism is a significant mediator between religiosity and sexual attitudes (Table 5).

Table 5. Standardized estimates of direct and indirect effects on sexual attitudes.

		Bias-adjusted 95% (Confidence interval))	
		R	IS
Total Effect	IS	0.578 (0.468/0.706)***	
	SA	0.544 (0.328/0.569)***	0.181 (0.012/0.338)*
Direct Effects	IS	0.542 (0.448/0.680)***	-
	SA	0.452 (0.165/0.486)***	0.170 (0.087/0.337)*
Indirect Effects	IS	-	-
	SA	0.092 (0.029/0.218)**	-

* SA: Sexual Attitudes; R: Religiosity; IS: Internalızed Sexism; * p < 0.05, ** p < 0.01,*** p < 0.001. (Maximum Likelihood Test)

Discussion

Sexual attitudes and behavior, which are considered most important determinants of sexual health, affect many social problems, such as sexually transmitted infections, family planning, sexual abuse, and adolescent pregnancy.[39,40] This causes adolescence and adolescent sexuality to attract researchers, where sexual tendencies are shaped, and problematic sexual orientation is high. It is known that one of the factors affecting sexual attitudes in adolescence is religiousness.[16] However, the findings on this subject are inconsistent.[13-16] In a study by Miller and Gur[17], it was determined that although there was a positive relationship between religiosity and sexuality, personal conservatism, which is a sub-dimension of religiosity, negatively affected risky sexual attitudes and behavior. In general, it is reported that the importance given to religion is the most critical deterrent to starting sexual intercourse at an early age and having multiple sexual partners and that religiosity is a protective factor for risky sexual behaviors in adolescents.[14-16]

In our study, it was found that religiosity affects the sexual attitudes of late adolescent women (effect value=0.45; p<0.001), which is consistent with the literature in general (Figure 2; Table 4; Table 5). Accordingly, of the hypotheses investigated in the study, the H^1 hypothesis stating that religiosity affects the sexual attitudes of late adolescent women was accepted. This finding can be interpreted as an elevated level of religiosity in late adolescent women has a protective feature against risky sexual attitudes and behavior such as random, multiple partners and may contribute to the individual's ideal, healthy, and balanced sexual attitude.

Another issue closely related to religiosity in adolescent sexuality is gender differences.[41] It has been emphasized that religiosity has a predictive effect on sexual attitudes, and this affects women more[16]. It is essential to investigate the mechanisms that cause this in women[16] In our study, internalized sexism was assumed to be an essential variable in the interaction between religiosity and sexual attitude in late adolescent women. It was determined that individuals were affected by their level of religiosity (effect value=0.54; p<0.001) and sexual attitudes (effect value=0.17; p<0.05). According to these findings, the H^2 and H^3 hypothesis was accepted. In addition, it has been determined that religiosity has a direct effect on sexual attitudes, as well as through internalized sexism (effect value = 0.09), and internalized sexism is a mediator (Figure 2; Table 4; Table 5). With this finding, the H^4 hypothesis was accepted.

In light of this, it can be interpreted that internalized sexism, which includes negative situations such as self-objectification, loss of self, or male prioritization, will evolve into a positive and have a positive effect on sexual attitudes as a result of correctly interpreting religious knowledge. It is also reported that while patients want reliable and non-judgmental access to sexual health education during their care processes, healthcare professionals frequently ignore sexual health issues in this process. One of the most

important reasons for ignoring sexuality in care processes is healthcare professionals' attitudes and beliefs that sexual health services are private and not a priority.[32] It can be said that internalized sexism and religiosity may have influenced these attitudes and beliefs.

As with all Muslim societies, sexuality, culture, and gender are historically linked to religion in Turkish society. It is known that the Turkish community has a patriarchal structure and that the majority of its population is Muslim.[22] The two primary sources of Islam are the words of Allah (Qur'an) and the words and practices of the Prophet Muhammad (hadith/Sunnah), which shape people's thoughts, behavior, and values.[42] In this context, sexuality is a necessity for human survival, but it is a phenomenon that must be managed according to Islamic rules. According to Islamic regulations, sexual intercourse outside of marriage is accepted as adultery and prohibited. In addition, sexuality is considered legitimate with marriage and includes protective measures such as compensation and alimony.[43]

Although the spiritual existence of women in Islam has been elevated, the patriarchal structure has not been destroyed. Of course, the current cultural order has a significant impact on the occurrence of this situation. In addition, although worship and rituals in Islam are determined according to gender, the Qur'an addresses men and women together in every religious issue, such as faith, worship, morality, halal, and haram. Women are included in general addresses such as "O people" and "O believers" in the Qur'an, and the fundamental rights and freedoms granted to men are equally recognized for women.[44] In this context, individuals who understand and interpret the religion of Islam correctly cannot be expected to be adversely affected by gender differences or internalized sexism.; because the belief that "female or male individuals do not have superiority over each other, superiority is only in taqwa" prevails in Islam. In addition, there are no significant differences between other monotheistic (Judaism, Christianity) religions, such as Islam, and all divine religions have a common discourse on the perfection and development of human beings. It can be stated that when superstitions are excluded, all religions have a positive perspective on women and sexuality.[45]

Limitations

Since some conditions limit the generalizability of the study, the findings should be interpreted within these limitations. The study was a cross-sectional study based on self-reporting to obtain variable data from an appropriate sample. Therefore, the data obtained are limited to the scales used. In addition, since the study group consists of female adolescents of Turkish ethnicity who adopt the religion of Islam, it cannot be generalized to adolescent populations other than this group or samples with different ethnic and religious structures. Finally, the use of only internalized sexism as a mediator variable was accepted as a limitation in terms of revealing mediator variables between religiosity and sexual attitude. Therefore, future research can apply a longitudinal design to evaluate more variables at different time points, thus contributing to the literature regarding increasing knowledge on sexual attitudes.

Conclusion

In this study, it was determined that internalized sexism and religiosity had an effect on sexual attitudes in late adolescent women and that internalized sexism had a mediating effect on the interaction between religiosity and sexual attitudes. Religiosity has a relatively sizeable direct impact (effect value = 0.54) on internalized sexism. In addition, it was determined that religiosity has a direct effect on sexual attitude (effect value = 0.45). In addition, internalized sexism has a direct impact (effect value = 0.17) on sexual attitudes. Finally, it was determined that religiosity had a direct effect on sexual attitudes as well as internalized sexism (effect value = 0.09), and internalized sexism was the mediator between these variables. It is thought that the study conducted in light of these findings will contribute to the literature in terms of determining the source of taboos regarding the sexual behavior of women who are affected by social and cultural values. In addition, it is assumed that this study will

enable healthcare professionals to understand why they have difficulty assessing the sexual dimension of the patients they care for.[32]

Additionally, late adolescent women need to learn and interpret religious information from suitable sources and internalize the religious perspective towards women through a cognitive filter to have positive sexual attitudes. In this context, it can be stated that sexual attitudes to be acquired will have a protective effect on adolescent women against risky sexual situations.

The well-being of adolescents' health indicators, which is one of the health achievements of nations, has deficiencies in developing countries, especially in terms of sexuality and sexism. In addition, physical growth, sexual development, and psychological changes in adolescence are essential factors in shaping risky behaviors such as unprotected sexual intercourse, early marriages, early or unwanted pregnancies, and sexually transmitted diseases. Therefore, in addition to focusing on healthcare, health protection, and health promotion, the quality of training given to healthcare professionals should also be considered.[46] During the planning of healthcare professionals' training, factors such as religiosity and sexism that may affect sexual attitudes should be considered, and the training content should be determined accordingly. In addition, the usefulness of including a multidisciplinary team (clergy, social worker, etc.) in training planning should not be overlooked.

It is important to note that sexuality is an essential component of physical and mental health, which may affect the future life of the individual. For this reason, the correct healthcare practices in the adolescent period, in which sexual, religious, and social trends are shaped, will protect individuals in the future stages of development. Finally, it is thought that healthcare professionals should be aware of their perspective on sexuality and which factors, such as religion and sexism, affect this perspective to be able to implement correct and effective practices.

Ethics Committee Approval

Ethics committee approval for our study was received from Erciyes University, Social and Human Sciences Ethics Committee (Approval No:473/Date:28.12.2021). All procedures were utilized in accordance with the Declaration of Helsinki.

Informed Consent

Informed consent form was obtained from all participants

Author Contributions

M.E.: Idea/Concept, Design, Audit/Consultancy, Data collectıon and/or processing, Analysis and/or comment, Literature review, Writing, Critical review.

Conflict of Interest

There is no conflict of interest to declare.

Financial Disclosure

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Declarations

The study was presented as an oral presentation at the Black Sea Summit 8th International Social Sciences Congress, 05 March 2022, Ordu, Türkiye

Peer-review

Externally peer-reviewed.

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Research Article/Özgün Araştırma

Comparison of countries in European region according to risk factors of noncommunicable diseases by APLOCO method

Avrupa bölgesindeki ülkelerin APLOCO yöntemiyle bulaşıcı olmayan hastalıkların risk faktörlerine göre karşılaştırılması

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Abstract

Aim: The aim of the study was to compare countries in the WHO European Region according to key risk factors of NCDs.

Materials and Methods: Target population of study consists of 37 European Region countries. Weights of key risk factors were determined by Shannon Entropy and NMV weighting methods. APLOCO, one of the MCDM methods, was used to evaluate countries according to decision criteria.

Results: There is a significant and very strong positive monotonic relationship between score rankings obtained from NMV-based APLOCO and Shannon Entropy-based APLOCO methods. According to both the NMV-based and Shannon Entropy-based APLOCO methods, 14 European countries have above-average while 23 have below-average scores.

Conclusion: NCD risk factors are more prevalent in countries of the European Region with below-average NCD prevalence. NCDs may increase in countries of this region due to high risk factor prevalence.

Keywords: NMV; Shannon Entropy; MCDM, APLOCO; NCD risk factors.

Öz

Amaç: Çalışmanın amacı, DSÖ Avrupa Bölgesi'ndeki ülkeleri bulaşıcı olmayan hastalıkların temel risk faktörlerine göre karşılaştırmaktır.

Gereç ve Yöntemler: Çalışmanın hedef popülasyonunu Avrupa Bölgesi'ndeki 37 ülke oluşturmaktadır. Karar kriteri olarak kullanılan temel risk faktörlerinin ağırlıkları Shannon Entropi ve NMD objektif ağırlıklandırma yöntemleri ile belirlenmiştir. Ülkeleri karar kriterlerine göre değerlendirmek için ÇKKV yöntemlerinden biri olan APLOCO kullanılmıştır.

Bulgular: NMD tabanlı APLOCO ve Shannon Entropi tabanlı APLOCO yöntemlerinden elde edilen puan sıralamaları arasında anlamlı ve çok güçlü pozitif monoton bir ilişki vardır. NMD tabanlı APLOCO ve Shannon Entropi tabanlı APLOCO yöntemlerine göre Avrupa Bölgesi'nde ortalamanın üzerinde puana sahip ülke sayısı 14, ortalamanın altında puana sahip ülke sayısı ise 23'tür.

Sonuç: Bulaşıcı olmayan hastalık risk faktörlerinin prevelansı, ortalamanın altındaki Avrupa Bölgesi ülkelerinde daha yüksektir. Bulaşıcı olmayan hastalık risk faktörlerinin yüksek prevalansı, bu bölgedeki bulaşıcı olmayan hastalıkların prevalansını artırabilir.

Anahtar Kelimeler: NMD; Shannon Entropi; ÇKKV, APLOCO; BOH risk faktörleri.

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Introduction

Noncommunicable diseases (NCDs) pose a significant health challenge on a global scale, and their impact continues to grow as a result of shifting demographic trends such as longer life expectancy, changing fertility rates, and evolving causes of death. In the WHO (World Health Organization) European Region, NCDs are responsible for 90% of all deaths and contribute to 85% of years lived with disability.[1,5]

A significant number of deaths in the WHO European Region occur before the age of 70 and are attributed to four major NCDs: cancers, chronic respiratory diseases, cardiovascular diseases, and diabetes. It is concerning that approximately 85% of the NCD burden is linked to preventable and controllable risk factors. Notably, the European Region has the poorest performance regarding two critical risk factors: alcohol and tobacco use.[2]

Proper healthcare can prevent a significant number of NCDs. The primary culprits behind most NCDs are four changeable behavioral risk factors: tobacco use, poor diet, insufficient physical activity, and the harmful consumption of alcohol. These behavioral risks contribute to biological risk factors, with obesity, high blood pressure, high glucose, and elevated cholesterol being the most prevalent. When combined, preventable risk factors account for more than two-thirds of the NCD burden in the region.[3]

The relationships among air pollution, various environmental elements, psychological, social, and economic hazards, as well as NCDs, have gained greater recognition in recent times. Premature mortality from NCDs serves as an appropriate gauge for evaluating the region's efforts to curb unhealthy behaviors and risk factors on the one hand, as well as the efficacy of its healthcare systems on the other. It's important to note that premature mortality captures only a fraction of the NCD burden in the region, as the majority of deaths occur after the age of 70. Progress on SDG 3.4 will significantly influence the success of at least nine other SDGs (Sustainable Development Goals), necessitating a unified approach across multiple sectors and leveraging effective economic tools such as price policies and insurance. NCDs disproportionately affect individuals with low socioeconomic status and are a leading cause of medical impoverishment. Besides causing health and well-being challenges, NCDs also impose significant economic losses. [4]

The study used APLOCO (Approach of Logarithmic Concept), one of the MCDM methods, to compare countries in the WHO European Region based on key risk factors of NCDs. Weights of key risk factors determined as decision criteria were calculated by Shannon Entropy and NMV (Normalized Maximum Values) methods, which are objective weighting methods. With the study, APLOCO was used for the first time in solving multi-criteria decision making problems in the field of health. In addition, an updated version of the APLOCO method application algorithm was developed by revising the application algorithm with the R programming language in order to produce instant solutions in small and especially large-scale data sets.

Materials and Methods

Type of the study

The study was cross-sectional.

Universe and sample of the study

The population of the study consists of 53 European Region countries determined by WHO. However, the number of countries with complete observations in the variables used in the evaluation of the countries is 37. Therefore, 37 countries constitute the target population of the study.

Data collection tools

The data set of the study consists of the data set of noncommunicable diseases and key risk factors publicly published by WHO. The dataset was published on the https://ncdportal.org/ web page called “Noncommunicable Diseases Data Portal”.[6] The values of all variables were taken as total without differentiation according to gender or rural and urban settlements. The R programming language was used to make the

data suitable for analysis and for data analyses.[7] The number of decision criteria used in the comparison of the countries of the European Region according to key risk factors is 16, and the key risk factors are coded according to categories and given in Table 1. The years to which the values of the decision criteria belong are given on the far right of the table.

Table 1. Decision criteria and direction of decision criteria.

Category	Decision Criteria	Code	Direction of Criteria	Year
Air pollution	Mortality rate attributed to household and ambient air pollution	c1	Minimum	2019
	Exceedance of WHO PM guidelines (by a multiple of)	c2	Minimum	2019
Harmful alcohol use	Total alcohol per capita consumption	c4	Minimum	2019
	Heavy episodic drinking, adults aged 15+	c5	Minimum	2016
Obesity / Unhealthy diet	Overweight, adults aged 18+	c6	Minimum	2022
	Obesity, adults aged 18+	c7	Minimum	2022
	Overweight, adolescents aged 10–19	c8	Minimum	2022
	Obesity, adolescents aged 10–19	c9	Minimum	2022
	Overweight, children aged 5–9	c10	Minimum	2022
	Obesity, children aged 5–9	c11	Minimum	2022
	Mean population salt intake, adults aged 25+	c12	Minimum	2019
Physical inactivity	Physical inactivity, adults aged 18+	c13	Minimum	2022
	Physical inactivity, adolescents aged 11-17	c14	Minimum	2016
Tobacco use	Current tobacco use, adults aged 15+	c15	Minimum	2022
	Current tobacco smoking, adults aged 15+	c16	Minimum	2022

Data analysis

NMV and Shannon Entropy methods were used for the objective weighting of the decision criteria within NCD key risk factors, and the APLOCO method, one of the MCDM methods, was used to compare the countries of the European Region according to the decision criteria. The APLOCO,[8] which was developed as a MCDM method, was previously used in calculating node weights in complex networks and determining the central metrics of networks,[9-10] and determining vital nodes in terrorist networks.[11] In the study where the APLOCO and other decision-making methods were used, the APLOCO method showed higher performance than other methods and was recommended for analysis of terrorist networks.[11] Within the scope of this study, the APLOCO application algorithm,[12] which was previously developed and published in the R environment, was revised and updated and used in the analyses. Spearman rank correlation test was used to measure monotonic relationship between the score rankings obtained from APLOCO combinations based on weighting methods. Spearman's rank correlation test,[13] which is used to compare whether two rankings are statistically different from each other, is also widely used to compare the rankings obtained from MCDM methods.[14-17] The alternative hypothesis (H_A) established in correlation tests are as follows:

- H_A: There is a monotonic relationship between NVM Method and Entropy Method weight rankings.
- H_A: There is a monotonic relationship between the rankings of NMV-Based APLOCO method and Shannon Etropy-Based APLOCO method.

The decision matrix used for weighting the decision criteria and comparing the countries of the European Region (N = 37) according to the key risk factors according to the decision criteria is presented in Table 2.

Since NMV and Shannon Entropy methods are known in the literature, mathematical equations used in application steps of these methods are not included. On the other hand, since APLOCO is a relatively new approach to solving MCDM problems, the method's application steps and the mathematical equations involved in those steps are provided.

Table 2. Decision matrix.

Country	c1	c2	c3	c4	c5	c6	c7	….	c13	c14	c15
Albania	92.5	3.2	5.1	24.6	62.2	23.4	20.7	….	21.9	24.3	73.9
Armenia	74.6	6.8	5.0	11.5	55.4	24.5	22.0	….	24.9	26.6	77.7
Austria	17.5	2.3	12.0	37.7	45.0	15.4	29.4	….	24.9	19.8	77.8
Belgium	15.3	2.3	10.3	36.6	51.1	20.0	21.6	….	24.8	25.4	83.5
Bulgaria	62.9	3.4	11.9	38.7	51.9	20.6	26.9	….	39.5	32.3	73.3
Croatia	31.3	7.3	8.5	32.1	64.2	30.6	25.0	….	37.0	28.4	76.8
Czechia	32.5	2.9	13.3	47.0	59.5	26.0	14.4	….	29.9	23.4	77.4
Denmark	12.9	1.9	9.4	34.0	44.9	13.3	18.4	….	16.2	12.1	84.5
Estonia	12.8	1.2	11.3	47.4	57.2	22.2	27.9	….	25.9	15.9	84.1
Finland	7.4	1.1	9.2	33.3	55.3	21.5	31.2	….	17.1	9.6	75.4
France	10.0	2.1	11.3	36.0	34.3	9.7	16.1	….	34.6	23.2	87.0
Germany	14.7	2.1	12.2	39.7	53.8	20.4	26.3	….	21.3	12.0	83.7
Greece	23.1	3.0	7.1	28.2	61.4	28.0	32.0	….	32.8	35.2	84.5
Hungary	42.3	2.8	10.6	37.9	62.2	31.7	31.7	….	32.2	29.4	79.5
Iceland	8.2	1.1	8.1	30.6	57.4	21.2	24.2	….	9.4	25.9	80.3
Ireland	12.8	1.6	11.7	40.5	64.7	28.3	25.2	….	19.3	21.9	71.8
Israel	15.1	3.9	3.0	18.4	54.3	22.5	23.5	….	20.4	26.6	84.7
Italy	15.0	2.7	8.0	25.0	49.1	17.3	24.2	….	22.4	40.1	88.6
Latvia	40.1	2.3	13.1	50.2	59.3	24.3	19.0	….	30.4	14.5	80.1
Lithuania	38.8	2.0	11.8	54.9	58.7	25.4	17.0	….	29.1	20.2	80.1
Luxembourg	12.5	1.8	11.5	51.2	51.5	18.4	21.1	….	23.0	13.9	79.2
Malta	20.9	2.5	8.5	25.6	64.7	32.3	25.5	….	24.7	40.7	81.4
Netherlands	13.2	2.1	9.3	31.6	45.9	14.5	16.7	….	21.3	9.4	80.2
Norway	7.9	1.3	6.8	35.4	57.5	19.1	23.1	….	14.2	35.1	83.5
Poland	40.9	3.7	11.6	38.9	62.7	27.5	21.8	….	23.6	37.0	78.8
Portugal	10.0	1.5	10.5	31.3	54.7	21.8	18.5	….	25.6	51.7	84.3
Moldova	68.9	2.4	11.4	28.6	61.2	23.0	16.8	….	28.2	10.8	75.7
Romania	67.8	2.6	17.0	39.0	65.1	34.0	20.4	….	29.4	36.8	79.5
Russian Federation	67.1	1.7	10.4	38.8	58.8	24.2	15.7	….	29.2	18.1	84.5
Slovakia	30.3	3.1	10.5	39.2	60.6	26.8	23.7	….	32.4	23.3	71.5
Slovenia	18.8	2.8	11.0	42.3	54.8	19.4	27.6	….	20.1	19.0	80.0
Spain	10.1	1.8	10.9	29.7	49.9	15.7	28.2	….	28.4	21.8	76.6
Sweden	8.1	1.1	9.3	32.4	50.6	15.3	25.3	….	12.6	8.7	84.7
Switzerland	10.4	1.8	10.4	39.9	40.6	12.1	23.7	….	25.5	19.0	85.7
Türkiye	45.5	4.6	1.8	1.5	67.6	33.3	32.8	….	30.5	44.4	81.3
Ukraine	78.9	2.6	8.7	20.2	56.1	23.6	13.1	….	24.9	12.8	76.7
United Kingdom	13.4	1.9	10.8	33.7	61.4	26.8	30.4	….	14.2	19.0	79.9

Objective weighting methods

This section provides the application steps for the NMV and Shannon Entropy weighting methods, which are objective weighting methods used to weigh decision criteria.

NMV weighting method

The NMV method, which functions as an objective weighting technique, is executed through four distinct steps. These steps include the following:[18-19]

1. Creating decision matrix
2. Obtaining ratio matrix
3. Determination of normalised values
4. Calculation of weights

Shannon entropy weighting method

Shannon Entropy represents an unbiased weighting approach used to calculate the weights of decision criteria.[20] In simpler terms, it does not incorporate the subjective opinions of the decision maker.[21] The steps for implementing Shannon Entropy are as follows:[22-23,29]

1. Creation of decision matrix
2. Normalizing decision matrix
3. Determination of entropy values
4. Determining the degrees of differentiation and weights

APLOCO MCDM method

This section provides both the APLOCO method's application steps and the revised

APLOCO application algorithm using the R programming language.

APLOCO Application Steps

In the APLOCO method developed as an MCDM method, the application steps are completed in 5 steps:[8]

1. Creating decision matrix: The decision matrix includes decision alternatives in columns and decision criteria in rows.
2. Determination of starting point criteria (SPC) values: When the criterion value needs to be maximized, we determine the maximum value among the relevant criterion values in that row. Conversely, when the criterion value needs to be minimized, we identify the minimum value among the relevant criterion values in that line. If the desired criterion condition is maximum, we subtract the criterion values in the row from the maximum value. Conversely, if the desired criterion condition is minimum, we subtract the minimum value from the criterion values in the corresponding row. These operations are given in equation (1). The matrix formed after these operations is given in Equation (2).
   $X_{ij} - \min_i p_{ij}$ where P_{ij} is minimum, and $\max_i p_{ij} - X_{ij}$ where P_{ij} is maximum. (1)

$$P_{ij} = \begin{bmatrix} p_{11} & p_{12} & \dots & p_{1r} \\ p_{21} & p_{22} & \dots & p_{2r} \\ \dots & \dots & \dots & \dots \\ p_{c1} & p_{c2} & \dots & p_{cr} \end{bmatrix} \quad (2)$$

3. Creating logarithmic conversion (LC) matrix: At this stage, P_{ij} matrix is normalised by taking inverse of each element of P_{ij} matrix according to multiplication by natural logarithm as shown in equation (3). With this operation, logarithmic transformation (LC) matrix (L_{ij}) is obtained.

$$L_{ij} = \begin{bmatrix} l_{11} & l_{12} & \dots & l_{1r} \\ l_{21} & l_{22} & \dots & l_{2r} \\ \dots & \dots & \dots & \dots \\ l_{c1} & l_{c2} & \dots & l_{cr} \end{bmatrix} \quad \text{where} \quad L_{ij} = \frac{1}{\ln(P_{ij}+2)} \quad (3)$$

4. Creating weighted logarithmic conversion (WLC) matrix: The weights (wj) of the decision criteria obtained by weighting methods are multiplied by the LC matrix (L_{ij}) to obtain the WLC matrix. This matrix (T_{ij}) is given in equation (4). This step is not mandatory and depends entirely on decision maker and nature of multi-criteria decision making problem.

$$T_{ij} = \begin{bmatrix} t_{11} & t_{12} & \dots & t_{1r} \\ t_{21} & t_{22} & \dots & t_{2r} \\ \dots & \dots & \dots & \dots \\ t_{c1} & t_{c2} & \dots & t_{cr} \end{bmatrix} \quad (4)$$

5. Determination of optimal alternative: In this stage, the optimal solution values (β_j) are determined as the maximum values of the criteria in each row, and β_{sj} scores are obtained by taking the sum of these values. The scores for each alternative (θ) are determined by dividing the total scores of criteria values for alternatives (α_{si}) by the sum of the optimal solution values (β_{sj}). Equations (5) and (6) are used to perform these operations, respectively. The theta scores obtained from Equation (6) range from 0 to 1 and allow an evaluation within this range. The theta scores are then ranked from largest to smallest, and the top ranked alternative is considered the most optimal alternative.
   $a_{si} = \sum_{j=1}^{n} tj$ where decision criteria for WLC matrix are weighted or
   $a_{si} = \sum_{j=1}^{n} lj$ where decision criteria for LC matrix are not weighted (5)
   $\theta = \frac{a_{si}}{\beta_{sj}}$ where $0 \le \theta \le 1$ (6)

APLOCO application algorithm in R

The aploco() function, which represents the application algorithm of APLOCO, was created using the R programming language. You can directly copy and run this application algorithm within R without needing to install it as a package in an R environment. The aploco() function provides instant evaluation results across all sectors for both large-scale and small-scale data sets. The aploco() function's output is defined as a data frame in a list. Below is the code block for the APLOCO application algorithm in the R environment:

```
aploco<-function(dm=as.matrix(NULL), dc=NULL, w=NULL){
        dm2 <- dm
        dc1=ifelse(dc=="max", 1, 0)
        for (r in 1:nrow(dm))
          for (c in 1:ncol(dm))
            if (dc1[r])
            {
                dm2[r,c] <- max(dm[r,]) - dm[r,c]
            } else

            {
                dm2[r,c] <- dm[r,c] - min(dm[r,])
            }

            dm3 <- 1 / logb(dm2 + 2)
            weights <- w
            dm4 <- dm3 * weights
            beta_j <- apply(dm4, 1, max)
            beta_sj <- sum(beta_j)
            a_si <- apply(dm4, 2, sum)
            theta_scores <- a_si / beta_sj

return(list(Decision_Matrix=as.matrix(dm), SPC_Matrix=dm2, LC_Matrix= dm3, WLC=dm4, Alpfa=a_si, Beta=beta_sj, Theta_Scores=theta_scores))
          }
```

The arguments listed in the aploco() function are as follows:

- dm refers to decision matrix. The rows of dm contain decision criteria, while columns contain decision alternatives.
- w shows weights of decision criteria. If decision criteria are not weighted, value of w will be 1.
- dc represents direction of decision criteria, which is expressed in vector format. Put simply, “max” stands for maximum and “min” stands for minimum in argument dc.

The aploco () function provides a list of outputs. Outputs are structured in a list format and include the following:

- Decision_Matrix indicates decision matrix in the first step.
- SPC_Matrix indicates starting point criteria (SPC) values in the second step.
- LC_Matrix indicates logarithmic conversion (LC) matrix in the third stage.
- WLC indicates weighted logarithmic conversion (WLC) matrix in the fourth stage. If decision criteria are not weighted, WLC matrix is equal to LC matrix in the third step.
- Alpha shows total scores of criteria values for decision alternatives (a_{si}) in the fifth stage.
- Beta shows sum of optimal solution values (β_{sj}) in the fifth stage. It is expressed as Beta scores.
- Theta_Scores shows final scores in the fifth stage.

Ethics committee approval

As the data used for the study has been publicly published by WHO, there is no need for ethics committee approval.

Results

Descriptive statistics of NCD key risk factors determined as decision criteria in the study are given in Table 3. The decision criterion with the highest mean value in the European Region countries is c13 (Physical inactivity, adolescents aged 11-17) (Mean = 80.2) in the physical inactivity category. Bu bulgu Avrupa Bölgesi ülkelerinde ortalama risk prevelansının “Physical inactivity, adolescents aged 11-17” risk faktöründe diğer risk faktörlerine göre daha yüksek olduğunu göstermektedir. The decision criterion with the highest standard deviation (Sd) and range value is c1 (Mortality rate attributed to household and ambient air pollution) (Sd = 49.1, Range = 196.4) in the air pollution category. In determining the weights of the decision criteria and evaluating the countries in the European Region according to the decision criteria, countries with no missing

observations in all decision criteria were taken into account. Therefore, 37 countries were included in the analysis in the weighting of the decision criteria and in the evaluation of the countries according to the decision criteria. Table 4 shows the weights of the decision criteria according to the objective weighting method. According to NMV method, the first three decision criteria with the highest weights are as follows: c2 (Exceedance of WHO PM guidelines (by a multiple of)) (w_j = 0.105), c1 (Mortality rate attributed to household and ambient air pollution) (w_j = 0.078) and c15 (Current tobacco use, adults aged 15+) (w_j = 0.078). On the other hand, according to Shannon Entropy method, the first three decision criteria with the highest weight values are as follows: c1 (Mortality rate attributed to household and ambient air pollution) (w_j = 0.317), c2 (Exceedance of WHO PM guidelines (by a multiple of)) (w_j = 0.123) and c14 (Current tobacco use, adults aged 15+) (w_j = 0.105).There is a statistically significant strong positive monotonic relationship between the rankings obtained from NMV and Shannon Entropy weighting methods ($r_s(35)$ = 0.682, p<0.05, N = 37). Therefore, the alternative hypothesis (H_A) was accepted. The correlation between the two weighting methods is given in Figure 1.

Table 3. Descriptive statistics of decision criteria.

Criteria	Description	N	Mean	Sd	Min	Max	Range
c1	Mortality rate attributed to household and ambient air pollution	50	49.1	44.7	7.4	203.8	196.4
c2	Exceedance of WHO PM guidelines (by a multiple of)	53	3.2	1.9	1.1	10.3	9.2
c3	Total alcohol per capita consumption	51	8.9	3.5	0.9	17.0	16.1
c4	Heavy episodic drinking, adults aged 15+	51	30.4	11.9	1.5	54.9	53.4
c5	Overweight, adults aged 18+	52	56.2	6.7	34.3	67.6	33.3
c6	Obesity, adults aged 18+	52	23.0	5.7	9.7	34.7	25.0
c7	Overweight, adolescents aged 10–19	52	22.7	5.8	9.9	32.8	22.8
c8	Obesity, adolescents aged 10–19	52	7.3	2.9	1.3	13.7	12.4
c9	Overweight, children aged 5–9	52	26.8	6.6	8.1	38.8	30.7
c10	Obesity, children aged 5–9	52	10.7	3.9	1.8	18.4	16.6
c11	Mean population salt intake, adults aged 25+	53	9.2	2.2	5.2	14.1	8.9
c12	Physical inactivity, adults aged 18+	52	24.7	10.2	8.7	51.7	43.0
c13	Physical inactivity, adolescents aged 11-17	38	80.2	4.2	71.5	88.6	17.1
c14	Current tobacco use, adults aged 15+	49	26.2	7.5	5.6	39.5	33.9
c15	Current tobacco smoking, adults aged 15+	49	25.4	7.9	5.4	39.5	34.1

Table 4. Weights of decision criteria by weighting methods.

NMV			Shannon Entropy		
Decision Criteria	**w_j**	**Rank**	**Decision Criteria**	**w_j**	**Rank**
Exceedance of WHO PM guidelines (by a multiple of)	0.105	1	Mortality rate attributed to household and ambient air pollution	0.317	1
Mortality rate attributed to household and ambient air pollution	0.078	2	Exceedance of WHO PM guidelines (by a multiple of)	0.123	2
Current tobacco use, adults aged 15+	0.078	2	Current tobacco use, adults aged 15+	0.105	3
Total alcohol per capita consumption	0.075	3	Obesity, adolescents aged 10–19	0.070	4
Obesity, adolescents aged 10–19	0.068	4	Heavy episodic drinking, adults aged 15+	0.064	5
Mean population salt intake, adults aged 25+	0.067	5	Total alcohol per capita consumption	0.055	6
Overweight, children aged 5–9	0.065	6	Obesity, children aged 5–9	0.054	7
Physical inactivity, adolescents aged 11-17	0.064	7	Physical inactivity, adolescents aged 11-17	0.043	8
Physical inactivity, adults aged 18+	0.063	8	Obesity, adults aged 18+	0.040	9
Current tobacco smoking, adults aged 15+	0.060	9	Physical inactivity, adults aged 18+	0.038	10
Heavy episodic drinking, adults aged 15+	0.059	10	Mean population salt intake, adults aged 25+	0.033	11
Obesity, children aged 5–9	0.058	11	Overweight, adolescents aged 10–19	0.028	12
Obesity, adults aged 18+	0.057	12	Overweight, children aged 5–9	0.020	13
Overweight, adolescents aged 10–19	0.054	13	Overweight, adults aged 18+	0.010	14
Overweight, adults aged 18+	0.048	14	Current tobacco smoking, adults aged 15+	0.002	15

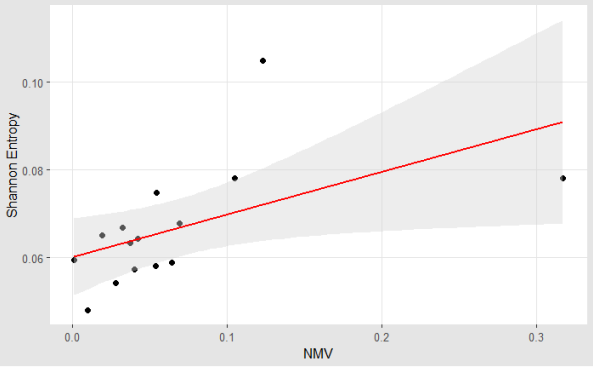

Figure 1. Correlation between NMV and shannon entropy weighting methods.

The comparative results of key risk factors for 37 European Region countries of APLOCO based on NMV and Shannon Entropy are presented in Table 5. Due to space constraints, the findings of the application steps preceding the final step of APLOCO method are not included. According to NMV-based APLOCO method, the number of countries with above average theta score (θ = 0.353) in the European Region is 14 and the number of countries with below average score is 23. The 14 countries with above average scores are as follows: France (θ = 0.520), Iceland (θ = 0.493), Sweden (θ = 0.460), Finland (θ = 0.449), Netherlands (θ = 0.429), Norway (θ = 0.427), Ukraine (θ = 0.417), Türkiye (θ = 0.405), Denmark (θ = 0.401), Moldova (θ = 0.386), Switzerland (θ = 0.385), Ireland (θ = 0.379), Estonia (θ = 0.370) and Luxembourg (θ = 0.357). These countries are also the top 14 countries with the highest theta (θ) score according to risk factors.

Table 5. NMV and shannon entropy based APLOCO scores.

NMV-Based APLOCO					Shannon Entropy-Based APLOCO				
Country	**a_{si}**	**β_{sj}**	**θ**	**Rank**	**Country**	**a_{si}**	**β_{sj}**	**θ**	**Rank**
France	0.751	1.443	0.520	1	Finland	0.919	1.443	0.637	1
Iceland	0.711	1.443	0.493	2	Sweden	0.851	1.443	0.590	2
Sweden	0.664	1.443	0.460	3	Iceland	0.811	1.443	0.562	3
Finland	0.648	1.443	0.449	4	Norway	0.785	1.443	0.544	4
Netherlands	0.618	1.443	0.429	5	France	0.703	1.443	0.487	5
Norway	0.616	1.443	0.427	6	Netherlands	0.631	1.443	0.437	6
Ukraine	0.601	1.443	0.417	7	Switzerland	0.592	1.443	0.410	7
Türkiye	0.585	1.443	0.405	8	Denmark	0.587	1.443	0.407	8
Denmark	0.578	1.443	0.401	9	Portugal	0.575	1.443	0.399	9
Moldova	0.557	1.443	0.386	10	Estonia	0.560	1.443	0.388	10
Switzerland	0.556	1.443	0.385	11	Spain	0.551	1.443	0.382	11
Ireland	0.547	1.443	0.379	12	Luxembourg	0.542	1.443	0.376	12
Estonia	0.533	1.443	0.370	13	Ukraine	0.531	1.443	0.368	13
Luxembourg	0.515	1.443	0.357	14	Ireland	0.527	1.443	0.365	14
Portugal	0.505	1.443	0.350	15	Türkiye	0.516	1.443	0.358	15
Russian Federation	0.496	1.443	0.344	16	Germany	0.512	1.443	0.355	16
Belgium	0.495	1.443	0.343	17	United Kingdom	0.509	1.443	0.353	17
Germany	0.492	1.443	0.341	18	Moldova	0.502	1.443	0.348	18
United Kingdom	0.492	1.443	0.341	18	Belgium	0.495	1.443	0.343	19
Spain	0.488	1.443	0.338	19	Israel	0.476	1.443	0.330	20
Israel	0.481	1.443	0.334	20	Russian Federation	0.467	1.443	0.324	21
Czechia	0.473	1.443	0.328	21	Austria	0.461	1.443	0.319	22
Lithuania	0.474	1.443	0.328	21	Italy	0.457	1.443	0.317	23
Latvia	0.471	1.443	0.326	22	Latvia	0.448	1.443	0.310	24
Slovakia	0.469	1.443	0.325	23	Lithuania	0.447	1.443	0.310	24
Austria	0.463	1.443	0.321	24	Czechia	0.437	1.443	0.303	25
Albania	0.455	1.443	0.316	25	Slovenia	0.436	1.443	0.302	26
Italy	0.441	1.443	0.306	26	Malta	0.422	1.443	0.292	27
Slovenia	0.43	1.443	0.298	27	Greece	0.410	1.443	0.284	28
Armenia	0.422	1.443	0.292	28	Slovakia	0.399	1.443	0.277	29
Malta	0.422	1.443	0.292	28	Albania	0.399	1.443	0.276	30
Poland	0.421	1.443	0.292	28	Poland	0.392	1.443	0.272	31
Greece	0.412	1.443	0.285	29	Romania	0.380	1.443	0.263	32
Romania	0.407	1.443	0.282	30	Armenia	0.375	1.443	0.260	33
Bulgaria	0.406	1.443	0.281	31	Hungary	0.374	1.443	0.259	34
Hungary	0.389	1.443	0.270	32	Croatia	0.366	1.443	0.254	35
Croatia	0.386	1.443	0.267	33	Bulgaria	0.361	1.443	0.250	36
Average			**0.353**		**Average**			**0.360**	

On the other hand, according to Shannon Entropy-based APLOCO method, the number of countries with a theta score above the average theta score (θ = 0.360) in the European Region is 14 as in the NMV-based APLOCO method, and the number of countries with a theta score below the average is 23. According to Shannon Entropy based APLOCO method, 14 countries with above average scores are as follows: Finland (θ = 0.637), Sweden (θ = 0.590), Iceland (θ = 0.562), Norway (θ = 0.544), France (θ = 0.487), Netherlands (θ = 0.437), Switzerland (θ = 0.410), Denmark (θ = 0.407), Portugal (θ = 0.399), Estonia (θ = 0.388), Spain (θ = 0.382), Luxembourg (θ = 0.376), Ukraine (θ = 0.368) and Ireland (θ = 0.365). However, as can be seen, score rankings of the countries are different in the Shannon Entropy based APLOCO method. There is a statistically significant and very strong positive monotonic relationship between score rankings obtained from NMV-based APLOCO and Shannon Entropy-based APLOCO methods ($r_s(35) = 0.938$, $p<0.05$, N = 37). Therefore, the alternative hypothesis (H_A) was accepted. The correlation between NMV-based APLOCO and Shannon Entropy-based APLOCO methods is given in Figure 2.

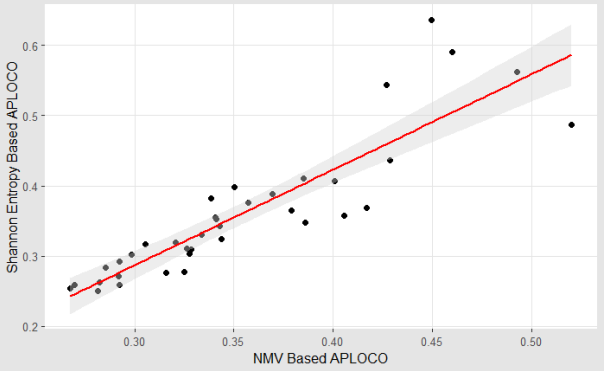

Figure 2. Correlation between NMV based APLOCO and shannon entropy based APLOCO methods.

Discussion

NCDs represent a major risk to global public health, leading to elevated rates of mortality and morbidity. These diseases are linked to common behavioral risk factors such as smoking, excessive alcohol consumption, physical inactivity and an unhealthy diet. Moreover, they are also associated with modifiable risk factors like hypertension, elevated total cholesterol, obesity, and diabetes. NCDs can be avoided by making healthy lifestyle choices that affect modifiable risk factors such as physical inactivity, smoking, and poor diet, as well as their physical outcomes like elevated cholesterol levels, obesity, high blood pressure, and diabetes.[24-26]

From a more regional perspective, ninety percent of deaths in the WHO European Region are caused by NCDs, and risk factors are directly responsible for about two thirds of these deaths.[5] For this purpose, initially, it is necessary to objectively determine weights of NCD key risk factors determined by WHO in the context of WHO European Region and to determine the prominent countries in this region in terms of risk factors by evaluating the WHO European Region countries relatively according to NCD risk factors. In this context, firstly, NCD key risk factors were weighted by NMV and Shannon Entropy methods, which are objective weighting methods. Subsequently, the WHO European Region countries were evaluated by APLOCO method and the relative prevalence of NCD risk factors of the countries was revealed.

There is a strong monotonic positive relationship between the rankings obtained from NMV and Shannon Entropy weighting methods. Similarly, a very strong monotonic relationship was found between NMV-based APLOCO and Shannon Entropy-based APLOCO methods. However, the scores and rankings of the countries obtained from both combinations are not the same. This is because the theoretical concept of NVM and Shannon Entropy weighting methods are different from each other. This is because the theoretical concepts of NVM and Shannon Entropy weighting methods are different from each other.

According to NMV-based APLOCO method, the top three European Region countries with the lowest prevalence of NCD risk factors (closest to the optimal solution) are France, Iceland and Sweden, while the top three European Region countries with the highest prevalence (furthest from the optimal solution) are Croatia, Hungary and Bulgaria. Among the 37 countries in the European Region, the country with the lowest prevalence of NCD risk factors is France and the country

with the highest prevalence of risk factors is Croatia.

On the other hand, according to Shannon Entropy-based APLOCO method, the top three European Region countries with the lowest prevalence of NCD risk factors are Finland, Sweden and Iceland, while the top three European Region countries with the farthest distance from the optimal solution are Bulgaria, Croatia and Hungary. Unlike the country rankings obtained from NMV-based APLOCO method, according to the Shannon Entropy-based APLOCO method, Finland has the lowest prevalence of NCD risk factors, while Bulgaria has the highest prevalence of NCD risk factors.

In both NMV-based and Shannon Entropy APLOCO methods, the prevalence of NCD risk factors is higher in European Region countries below the average theta (θ) score compared to other European Region countries. The high prevalence of NCD risk factors can increase the prevalence of NCDs in the countries of the European Region.[5] High NCD prevalence opens the door to many problems. Human development is severely hampered by NCD pandemic in social, cultural, and economic spheres. NCDs cause poverty and lower productivity. Health systems are significantly impacted by NCDs, and their financial cost on national economies is only increasing.[27] Patients with multiple NCDs often have high out-of-pocket health expenditures due to both non-medical and medical expenses.[28]

Limitations

All European Region countries could not be included in the study due to the lack of observations and data on the key risk factors determined as decision criteria. Since the study is a cross-sectional study, it is aimed to take a snapshot of the current situation. Therefore, the study does not aim to forecast the future.

Conclusion

The NMV-based APLOCO method ranks France, Iceland, and Sweden as the top three European countries with the lowest NCD risk factors, while Croatia, Hungary, and Bulgaria rank highest. In the European Region, France has the lowest prevalence, while Croatia has the highest. The Shannon Entropy-based APLOCO method places Finland, Sweden, and Iceland as the lowest risk countries, with Bulgaria, Croatia, and Hungary as the highest. Finland has the lowest prevalence according to this method, while Bulgaria has the highest. According to both the NMV-based and Shannon Entropy-based APLOCO methods, countries in the European Region with below-average theta scores have more NCD risk factors than other countries in the European Region.

In this study, furthermore, an updated version of the APLOCO application algorithm was developed by revising the APLOCO application algorithm using the R programming language. Thus, with the application algorithm, in solving multi-criteria decision making problems, decision makers and field workers are provided with the opportunity to produce instant solutions in small and especially large-scale data sets in all sectors, regardless of the health sector.

Ethics Committee Approval

As the data used for the study has been publicly published by WHO, there is no need for ethics committee approval.

Informed Consent

Author have approved the manuscript and consent for publication.

Author Contributions

T.B. contributed 100% to the entire process of writing the manuscript.

Conflict of Interest

The author declared no potential conflicts of interest.

Financial Disclosure

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Peer-review

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Research Article/Özgün Araştırma

Attitude scale towards the use of cryptocurrency among nursing students: A Turkish validity and reliability study

Hemşirelik öğrencilerinde kripto para kullanımına yönelik tutum ölçeği: Türkçe geçerlik ve güvenirlik çalışması

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Abstract

Aim: This research was conducted to realize the validity and reliability of the Turkish version of the attitude scale towards the use of cryptocurrency in nursing students.

Materials and Methods: This research is a methodological research. Language validity, content validity, construct validity, factor and reliability analyzes were performed for the validity and reliability of the scale.

Results: After language validity using the translation-back translation technique, content validity was performed and the content validity index score was determined as 0.80. In confirmatory factor analysis, the Cronbach's alpha coefficient for the whole scale was found to be 0.853, 0.893 for the first sub-dimension, and 0.864 for the second sub-dimension.

Conclusion: As a result of the research, it was determined that the scale was similar to the original scale and the Turkish version of the scale was a valid and reliable measurement tool in evaluating nursing students' attitudes towards the use of cryptocurrencies.

Keywords: Nursing student, Cryptocurrency, Validity, Reliability.

Öz

Amaç: Bu araştırma, hemşirelik öğrencilerinde Kripto Para Kullanımına Yönelik Tutum Ölçeği'nin Türkçe formunun geçerlik ve güvenirliğini gerçekleştirmek amacıyla yapılmıştır.

Gereç ve Yöntem: Bu araştırma metodolojik bir araştırmadır. Ölçeğin, geçerlik ve güvenirliği için dil geçerliği, kapsam geçerliği, yapı geçerliği, faktör ve güvenirlik analizleri yapılmıştır.

Bulgular: Çeviri-geri çeviri tekniği kullanılarak yapılan dil geçerliğinin ardından kapsam geçerliği yapıldı ve kapsam geçerlik indeksi puanı 0,80 olarak belirlendi. Doğrulayıcı faktör analizlerinde ölçeğin tamamına yönelik Cronbach alfa katsayısının 0,853, birinci alt boyutu için 0,893, ikinci alt boyutu için 0,864 olduğu bulundu.

Sonuçlar: Araştırma sonucunda, ölçeğin orijinal ölçekle benzer yapıda olduğu ve ölçeğin Türkçe formunun hemşirelik öğrencilerinin kripto para kullanımına yönelik tutumlarını değerlendirmede geçerli ve güvenilir bir ölçüm aracı olduğu belirlendi.

Anahtar Kelimeler: Hemşirelik öğrencisi, Kripto para, Geçerlik, Güvenirlik.

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Introduction

Cryptocurrencies are system-specific digital assets that have a wide variety of purposes in the economic coordination mechanisms of blockchain systems.[1] Blockchain, the technology underlying most cryptocurrencies, is a technical infrastructure centered around a distributed database that is jointly managed, maintained and secured by network participants.[2,3] The increasing prevalence of cryptocurrency and blockchain technology has a growing interest in many segments of society, from economics to politics.

Due to this increasing interest, it has been reported that cryptocurrency users tend to gamble, and it has been stated that these people tend to have lower self-esteem, a history of hyperactivity and impulsivity, and have higher alcohol use rates than their peers.[4] It has also been reported that cryptocurrency users are mostly young, male, better educated and wealthier than their peers, and have knowledge and confidence about cryptocurrency.[3] In addition, it has been reported that there are always scenarios for cryptocurrencies in the minds of crypto money users.[3] Griffiths classified cryptocurrency trading addiction as a subtype of online day trading addiction.[5] According to Nower the hope of gaining high profits has brought to the agenda that it is similar to a kind of gambling addiction.[6] In a study conducted by the UK Financial Executive Authority (FCA) on cryptocurrency users, the majority of respondents stated that buying cryptocurrencies is a type of gambling, designed for those who diversify their portfolio or expect quick earnings.[7] Similarly, it has been reported that cryptocurrency trading increases commitment to gambling.[3] In a different study on those who follow cryptocurrency trading, it was conducted to determine how sudden fluctuations in the exchange rate cause a change in mood on users. The participants stated that they suffer from sudden drops and fluctuations, make them unhappy, have difficulty sleeping at night, have a constant sense of anxiety, and negatively affect their work performance.[7] It has been emphasized that large fluctuations in the crypto money market can have negative effects on the mental health of users such as anxiety, distress and demoralization.[3,7] It has been reported that many negative processes such as constant arguments about debts, neglect of family members, violence and divorce are more common in the family life of crypto currency users.[8,9]

Nursing encompasses holistic care practices that potentially improve the health and well-being of patients. Nursing offers opportunities beyond the more traditional health approaches typically emphasized in basic and graduate nursing education programs and encouraged in acute care settings. Nurses are instilled in the holistic value of the individual "physically, mentally and spiritually" and practices that include this value in the "art and science" of nursing.[10] It includes management and decision-making processes rather than individualized care practices that include physical, nutritional, emotional, social, spiritual, intellectual and even financial well-being in addition to a situation where patient care settings often give priority to physical well-being, technology-oriented care.[11] In this context, it is very important to determine the habits of nursing students, who climb the intensive education and training steps to step into the nursing profession, which includes all processes of care, which takes care of the patient in every sense, and which can harm themselves, their families and, of course, their patients before they start the profession is important. Although it is not a payment instrument according to the current legal system in Turkey, Turkey ranks 4th in the world and 1st in Europe in cryptocurrency investment with 16%.[12,13] It also ranks 6th among the countries that make the most profit from cryptocurrencies.[14] Therefore, the interest in cryptocurrencies, which are described as electronic money, attracts great interest from the population in Turkey.[15] While the state approaches cryptocurrencies with a distance, citizens show great interest in cryptocurrencies.[16,17]

By determining the attitudes of nursing students towards crypto money trading, which is a new trend today, they will not experience problems such as stress, anxiety, worry, suicidal thoughts, thoughts of divorce, family

violence, loss of work and performance, sleep disorders, rhythm disorders that they may encounter in the future both in their family life and in their professional lives. In this study, it is aimed to make the validity and reliability of the scale developed by Gagarina et al.[18]

Materials and Methods

The study form prepared by the World Health Organization for scale development was translated and adapted for this study.[19] The Attitude Scale Towards Cryptocurrencies was translated from English to Turkish by two linguists who are academically fluent in both Turkish and English. In order to determine the inadequacies and inconsistencies in the expressions in the translation, the translations of the scale were translated from Turkish to English by 5 PhD graduates who are fluent in both English and Turkish languages. Afterwards, it will be rejected by the first author to ensure that the translation is conceptually and linguistically appropriate for item-by-item comparisons. The suitability of the scale adaptation between the original text and the English text was investigated. Experts examined the scope validity of the Crypto money scale and suggested some changes in the Turkish version of the Crypto money scale. All of the changes to the cryptocurrency scale were made under expert review.

Research design

In this study, a methodological research design was preferred to test the Turkish version of the Attitudes Towards Cryptocurrencies Scale.

Sample of the research

The population of the study consisted of Nursing students of Adıyaman University Faculty of Health Sciences in Adıyaman. There are 500 nursing students in total in the institution. The number of participants was determined as at least ten times the number of items in the scale used. The data collection phase of the research was carried out between 20.11.2022 and 20.12.2022.

Data collection tools

In this study, as a data collection tool; "Introductory Information Form", "Attitude Scale Towards Cryptocurrencies" developed by Gagarina et al. was applied.[12]

Information Form, It includes questions about gender, age, monthly income of their families, whether they work in a job, the type of residence their families live in, their knowledge of cryptocurrencies, whether they have bought or are considering buying crypto money.

Attitude Scale Towards Cryptocurrencies (ASTC), Gagarina et al. as 10 items and a triple likert scale. The lowest score that can be obtained from the scale is 10 and the highest score is 50. As the score obtained from the scale increases, the concerns of individuals about crypto money increase. The original Cronbach alpha coefficient of the Attitudes Towards Cryptocurrencies Scale was α=0.90.[12]

Data Collecting, the research was applied to nursing students who accepted to participate in the study. Written and verbal consent was obtained from the students before starting the study. Before starting the research, a pilot study was conducted with 10 students to determine the clarity of the questions. Based on this, 163 students were reached in this study. According to the COSMIN guide,[20] it is stated that between 50 and 99 participants are sufficient for retesting. Therefore, for test-retest purposes, the test was re-administered two weeks later to 58 individuals in the group to which the scale was applied.

Criteria for inclusion in the research students;

- Studying in the department of nursing,
- Complete research questions,
- Participating in the research voluntarily.

Data analysis

SPSS 16.0 and LISREL 8.7 programs were used for the validity and reliability analyzes required during the development of the scale. In order to determine the construct validity of the scale, KMO and Bartlett test analyzes were performed, and it was decided whether factor analysis would be performed within the scope of the value found. In the light of the data obtained, exploratory factor analysis and confirmatory factor analysis were performed.

In order to determine the reliability of the scale, internal consistency coefficients will be examined and Cronbach's Alpha reliability coefficient was calculated to determine the level of internal consistency.

Ethics committee approval

Permission was obtained from Adıyaman University Social and Human Sciences Ethics Committee (No: 28.10.2022-336) and Adıyaman University Faculty of Health Sciences Department of Nursing to collect data in the study.

Results

The students participating in the research, 112 (68.7%) were female and 51 (31.3%) were male. The ages of the participants ranged between 18 and 33, with a mean age of 19.88±1.92. Demographic data are given in Table 1.

Table 1. Demographic characteristics of the participants (n = 163).

Demographic characteristics		n	(%)
Age		19.88±1.92	
Gender	Female	112	68.7
	Male	51	31.3
Your family's monthly income	0-5000	99	60.7
	6000-10000	39	23.9
	11000-15000	19	11.7
	16000-20000	4	2.5
	210000-Over	2	1.2
Do you work in any job other than your education?	Yes	8	4.9
	No	155	95.1
Where your family lives	Province	93	57.1
	Town	50	30.7
	Village	20	12.3
Do you know about crypto money?	Yes	52	31.9
	No	111	68.1
Are you considering buying cryptocurrencies?	Yes	22	13.5
	No	141	86.5

Validity test

Internal validity

It was sent to five experts who were informed about the concepts of the ASTC and the purpose of the scale. Experts were asked to rate the necessity of each item of the ASTC on a five-point Likert scale. As a result of the evaluations of the experts, the content validity index (CVI) of the scale was calculated as 0.80. The fact that the CVI value for this study is above the acceptable (0.70) value indicates that the ASTC has acceptable content validity.

Construct validity

In the factor analysis of the research, varimax was used as principal component extraction. Barlett test score of ASTC was 944.771 (p<0.001) and KMO value was 0.849, which is in the appropriate range for the global test. After this stage, exploratory factor analysis (EFA) was performed. As a result of the analysis, two values with the screeplot eigenvalues greater than 1.0 were found. The sub-dimension of Beliefs in the potential of cryptocurrency as a payment instrument and willingness to use cryptocurrencies consists of 7 items (items 1-7) and its eigenvalue was found to be 4.613, explaining 46.128% of the variance. Worries about the introduction of cryptocurrency, its sub-dimension consists of 3 items (items 8-10), explains 22.160 of the variance and its eigenvalue is calculated as 2.216.

The factor load of all the items of the ASTC is higher than 0.30 (Table 2). After the factor structure was obtained by EFA, analysis was performed with a different sample with LISRELL 8.7 and confirmatory factor analysis (CFA). The model obtained after the modification indices were made for the model mismatch in the research is shown in Figure 1. ASTC has 10 items and two factors and acceptable fit values as a result of CFA (x^2 (N = 163) = 72.60, p<0.001; x2/df=2.268). The

acceptable fit values of the two-factor structure of the scale valid for nursing students are shown in Table 3. Also, the correlation between the scale items is given in Table 4.

Table 2. Construct validity of the ATCQ: individual item loadings from the exploratory factor analysis (n = 163)

Items	Factor 1	Factor 2	Total item correlation
10. I discuss cryptocurrency news with my friends and acquaintances	0.875		0.576
4. I caught myself thinking about cryptocurrency mining	0.850		0.577
7. After 5 years, most of the stores in which I shop will accept payments in bitcoins	0.839		0.643
1. I follow the news about the value of bitcoin and the development of cryptocurrencies	0.809		0.673
2. The development of cryptocurrency is as inevitable as scientific and technical progress	0.730		0.576
5. In 10 years, cryptocurrencies will be issued by the state and will replace the money	0.679		0.626
8. After 5 years, most of the stores in which I shop will accept payments in bitcoins	0.636		0.656
6. I worry that cryptocurrency opens up unlimited possibilities for financial fraud		0.900	0.452
9. I am concerned about the fact that cryptocurrencies are not provided with anything, except for the greed of people		0.872	0.518
3. I am worried that bitcoin and other cryptocurrencies are most profitable for criminals and terrorists, as they allow money laundering and tax evasion		0.851	0.375
Eigenvalue	4.613	2.216	
Percent total variance	46.128	22.160	

Note. Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 5 iterations

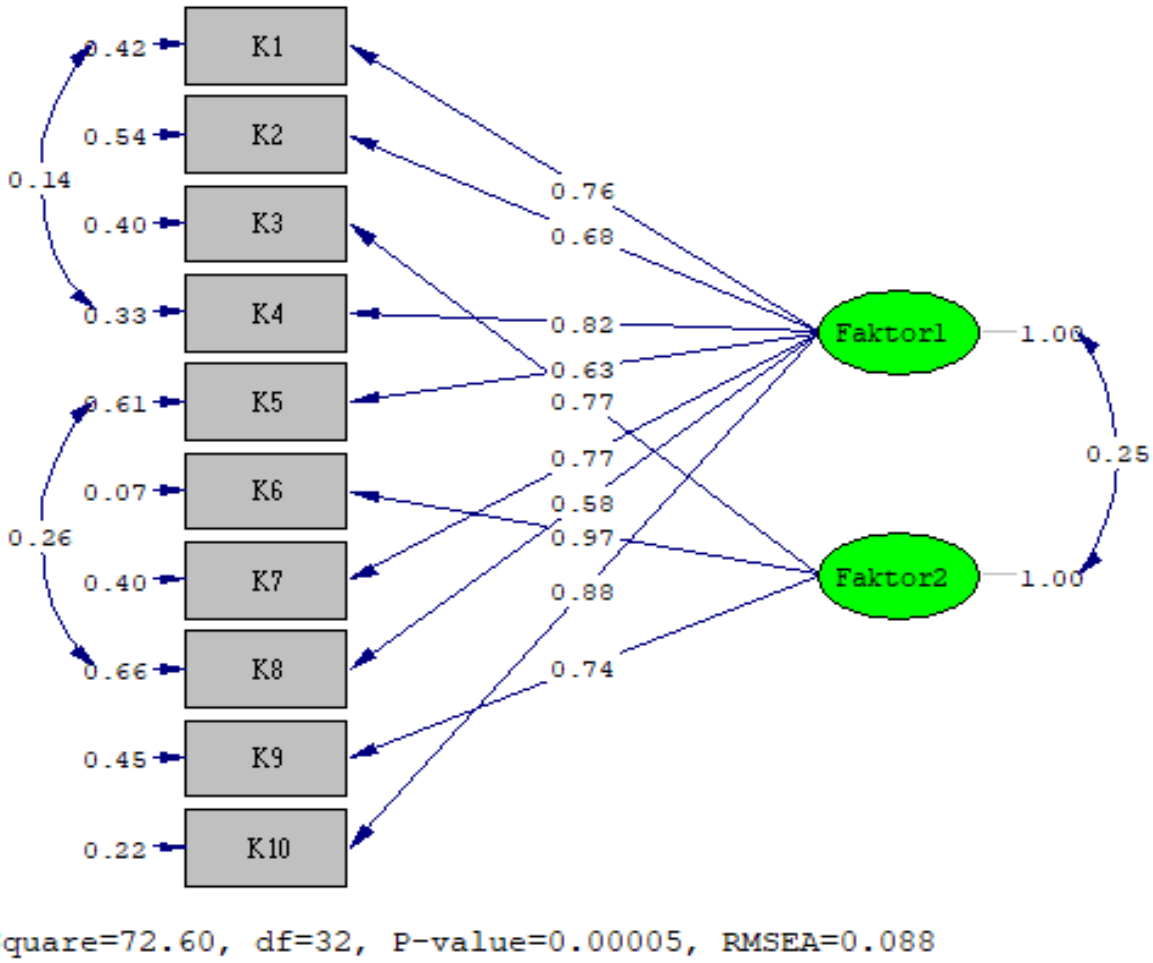

Figure 1. The final structural model of ATCQ among nursing studies (n = 138)

Table 3. Fit indices of five-component structure model of the ATCQ

Fit Index	Value
Comparative fit index (CFI)	0.97
Normed Fit Index (NFI)	0.95
Non- Normed Fit Index (NNFI)	0.96
Incremental Fit Index (IFI)	0.97
Goodness of Fit Index (GFI)	0.92
Adjusted Goodness of Fit Index (AGFI)	0.86
Root mean square error approximation (RMSEA)	0.088

Table 4. Concurrent validity coefficients of the ATCQ.

Scale	1	2	3	4	5	6	7	8	9	10
1	-	0.482**	0.152**	0.761**	0.460	0.175	0.550	0.339	0.014	0.718
2		-	0.205**	0.544**	0.476	0.200	0.571	0.448	0.097	0.576
3			-	0.160*	0.298**	0.744**	0.055	0.270**	0.580	0.142
4				-	0.477**	0.207**	0.605**	0.429**	0.077	0.758**
5					-	0.348**	0.565**	0.621**	0.281**	0.507**
6						-	0.093	0278**	0.714**	0.197**
7							-	0.582**	0.005	0.665**
8								-	0.313**	0.480**
9									-	0.048
10										-

Note: All coefficients are significant at $p< 0.01$

Reliability Analysis

Cronbach alpha values were examined to determine the internal consistency of the ASTC, and as a result of the analyzes performed, it was determined that the Cronbach alpha values were in the acceptable range. Cronbach's alpha value was 0.853 for the whole ASTC, and the Cronbach's alpha coefficient of the sub-dimensions was calculated as 0.893 for the first sub-dimension and 0.864 for the second sub-dimension (Table 5). It is seen that ASTC has acceptable internal consistency with these values. In order to determine the test-retest reliability of ASTC, it was applied to 58 students two weeks later. The test-retest reliability of ASTC was calculated as 0.826, and the scale is reliable according to this value.

Table 5. Internal consistency of the ATCQ (Cronbach's a coefficient, n = 163).

Subscales (no. of items)	Composite scores	Cronbach's a coefficient
Factor 1 (7)	13.37±6.51	0.893
Factor 2 (3)	8.99±3.83	0.864

Discussion

Around 300 million people worldwide use cryptocurrencies, which is a socially significant ratio.[21] Turkey has twice the average of Europe and the USA (16-25%) cryptocurrencies.[22-24] In particular, high inflation in the Turkish lira has led to an alternative option for individuals in Turkey to maintain their purchasing power and make their payments, even though cryptocurrencies are volatile.[25,26] This has made Turkey a top priority for studying cryptocurrency holders and their motivations. All items of the scale were validated with the results obtained in this research, which was planned to determine the anxiety status of cryptocurrency holders. According to the results from the scale, the desire to use cryptocurrencies, concerns about cryptocurrencies, and beliefs about cryptocurrencies are an inevitable consequence of young students' views on cryptocurrencies due to scientific and technological advances. It is seen that individuals willing to use crypto money do it for investment purposes. Participants see cryptocurrencies as promising for their future.

The ASTC was developed to determine the attitudes of young people towards cryptocurrency, which has gained significant popularity recently. ASTC was developed in Russia and its Turkish validity and reliability has not been established before.[18] ASTC was translated into Turkish in our research. According to the literature review, this research is the first to confirm the ASTC in Turkish in a sample of nursing students.

EFA was used to determine the factors of ASTC and a two-factor structure was obtained. EFA explains 46.128% of the variance in the first stage. In our study, the Cronbach alpha coefficient for the whole scale was 0.853, for the Beliefs in the potential of cryptocurrency as a payment instrument and willingness to use cryptocurrencies factor, it was 0.893 and the Cronbach alpha coefficient of the Worries about the introduction of cryptocurrency factor was calculated as 0.864. These results show similar results with the Cronbach alpha coefficients of the original three-dimensional scale (0.827, 0.884, 0.900, respectively).[18]

ASTC is a valid and reliable tool for Turkish with 10 ıtems and 2 sub-dimensions. ASTC has high reliability with a Cronbach alpha value of 0.853.

Conclusion

As a result of the validity and reliability analyzes, it was concluded that the Attitude Scale Towards Cryptocurrencies Questionnaire is a valid and reliable measurement tool in evaluating the attitudes of nursing students in Turkish society towards the use of cryptocurrencies. Attitude scale towards the use of cryptocurrency consist of Belief in the potential of cryptocurrency as a payment instrument (Factor 1) and Willingness to use cryptocurrency (Factor 2) subscales. Belief in the potential of cryptocurrency as a payment instrument consist of 1, 2, 4, 5, 7, 8, 10 ıtems. Willingness to use cryptocurrency consist of 3, 6 and 9 ıtems. As a result of the research, it was determined that the content validity, model fit and reliability of this scale were high and it consisted of two sub-dimensions. It is recommended to use the scale with nursing students studying in different institutions, to evaluate the attitudes of nursing students towards the use of cryptocurrencies at regular intervals through this scale, and to compare the results. In addition, it is thought that it will be important to adapt the validity and reliability of different measurement tools examining the attitudes towards the use of crypto money in nursing students and thus to determine the most appropriate measurement tool.

Limitations

The limitation of the study is that the study was conducted in a single center and only for nursing students.

Ethics Committee Approval

Ethical approval was received from the Adıyaman University Social and Human Sciences Ethics Committee (28/10/2022 & 336) for the carrying out of this study. By explaining the purpose and benefits of the study, written and verbal consents of all the participants were obtained.

In addition, this scale, which we have validated and verified, includes questions about whether users follow current information about crypto money, constantly think about crypto money, the direction and applicability of crypto money in the future, whether current systems are open to fraud for crypto money users, whether they are used in tax evasion or money laundering. When we look at the studies conducted on crypto money use in the literature, it has been determined that the scales used in a similar way examine topics such as anxiety-addiction-worry-lifestyle of the users.[12,27,28]

Informed Consent

The study was explained to the participants and their consent was obtained.

Author Contributions

All authors contributed to the conception and design of the study. M.S., and Y.C. performed data collection. M.S. and Y.C., made substantial contributions to analysis and interpretation of data. M.S. drafted the manuscript. M.S., and Y.C. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final version of the manuscript.

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Conflict of Interest

The authors have no funding or conflicts of interest to disclose.

Financial Disclosure

Not applicable.

Statements

The results of this study were not published or presented anywhere previously.

Peer-review

Externally peer-reviewed.

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Research Article/Özgün Araştırma

Brain drain in health professionals: a bibliometric study

Sağlık profesyonellerinde beyin göçü: bibliyometrik bir çalışma

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Abstract

Aim: The research was carried out to identify, visualize and reveal the trends in the studies conducted between 1988-2023 in the field of health workers and brain drain.

Materials and Methods: Performance analysis, scientific mapping and bibliometric analysis were performed with VOSViewer (1.6.15) software program. When the findings were limited to publication language, WoS category, countries, institutions, authors, publication type, indexes and publication year 1988-2023, the sample was found to be 2.247.

Results: As a result of the analysis, the most used keywords in the WoS category were "health professional", "mental health", "brain drain", "education", the most published in the USA as a country, the number of publications in "University of London" as the institution with the highest number of publications.

Conclusion: According to the results of this analysis, the most broadcasts were made in 2022 and the most broadcasts were made in the USA.

Keywords: Brain drain; Health workers; Health professional.

Öz

Amaç: Araştırma, 1988-2023 yılları arasında sağlık çalışanları ve beyin göçü alanında yapılan çalışmalardaki eğilimleri belirlemek, görselleştirmek ve ortaya koymak amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem: VOSViewer (1.6.15) yazılım programı ile performans analizi, bilimsel haritalama ve bibliyometrik analiz yapılmıştır. Elde edilen bulgular yayın dili, WoS kategorisi, ülkeler, kurumlar, yazarlar, yayın türü taranan indeksler ve yayın yılı 1988-2023 ile sınırlandırıldığında örneklem 2.247 olarak bulunmuştur.

Bulgular: Analiz sonucunda WoS kategorisinde en çok kullanılan anahtar kelimeler "health professional", "mental health", "brain drain", "education", ülke olarak en çok yayın ABD'de, yayın sayısı olarak en çok yayın yapılan kurum "University of London" olmuştur.

Sonuç: Bu analiz sonuçlarına göre en çok yayının 2022 yılında yapıldığı ve yayınların en çok ABD'de olduğu belirlendi.

Anahtar Kelimeler: Beyin göçü; Sağlık çalışanları; Sağlık profesyonelleri.

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Introduction

Brain drain is caused by unfavorable economic conditions, especially the lack of scientific and academic opportunities in the country of residence. In addition, high scientific and technological conditions in the destination country are also among the attractive factors.[1-3] Today, advances in information, transportation and communication enable people to move faster, more practically and cheaper in terms of employment, education, career opportunities and quality of life. In the face of all these attractive opportunities, as well as adversities such as conflict, unemployment, poverty and inequality in their home countries, individuals seek a better future for themselves and their families.[1]

In recent years, not only academics but also businessmen, entrepreneurs and highly educated people have turned to brain drain due to high unemployment rates, low budget jobs and high living standards abroad. Countries such as Germany, the USA and the UK have been preferred for education and investment purposes, and visa applications have increased. Statistics provided by organizations such as the Dutch Immigration and Naturalization Agency (IND), the Council for At-Risk Academics and New World Wealth confirm the increase in brain drain abroad. The most common occupational group experiencing brain drain is health personnel.[2,4]

In countries with brain drain, loss of qualified manpower can lead to increased workload of other employees, limitations in access to quality health services and inequalities in access to health services. According to the UNESCO Institute of Statistics (UIS) (2023), there are 51,146 Turks abroad in terms of education.[5] It is seen that qualified health workers are needed all over the world, brain drain is increasing, and it is an issue that needs to be carefully considered considering the problems experienced by brain drain countries.[6] The factors that cause the migration of health workers are divided into two as repulsive and attractive factors. While the driving factors are characterized as internal factors that force migration, attractive factors can be defined as external factors that make migration attractive. Internal factors (driving or repulsive factors); low wages, unfavorable working conditions, limited career opportunities, political difficulties, violence, and torment, etc. External factors (attractive or attracting factors); higher income, better working conditions, political stability, career opportunities and a better future, etc.[7] Although the programs and projects carried out by TUBITAK for scientists in Turkey in order to ensure a reverse brain drain are successful,[8] no work is being done for healthcare personnel.

The worldwide shortage and under distribution of healthcare workers are at a critical stage and threatens the sustainability of health systems.[9,10] The World Health Organization (WHO) estimated that there was a global shortage of 7.2 million health care providers in 2013[11] with some sources predicting that this number could reach 15 million by 2030.[12] The insufficient number of health workers in the global framework for effective service delivery is a growing concern for states and policymakers working to achieve the United Nations Development Goals, which prioritize meeting the universal and sustained nature of health services and the equitable delivery of health services to the whole society by 2030. At the core of achieving these goals and improving health outcomes is a threshold for the number of physicians, nurses, midwives, and all other healthcare professionals to support an effective health care delivery system.[10,13]

Bibliometric analysis is a type of analysis that uses statistical methods to analyze articles, scientific studies and other publications. Bibliometric analysis uses statistical analysis to identify, evaluate and monitor the published literature in relation to bibliometric data, including information on authors, publications, institutions, journals and countries. Studies using bibliometric methods in the field of health are increasing day by day.[14]

Çelikkaya and Atila[15] analyzed 1586 studies in the Web of Science database between 1980-2019 in their study on the relationship between migration and development. According to the results of the analysis, it was observed that the number of

studies started to increase after 2006. In a study that considers international migration literature more generally, Arslan[16] analyzed the bibliometric analysis of studies on migration in international field indexes between 1975 and 2020 with the help of Orange program. Although brain drain among health workers is a common global condition, there is no bibliometric analysis of studies in this field. Based on this direction and rationale, the research was carried out in order to identify, visualize and reveal the trends in the studies conducted between 1988-2023 in the field of health workers and brain drain.

Materials and Methods

Design

The research was carried out in order to identify, visualize and reveal the trends in the studies conducted between 1988-2023 in the field of health workers and brain drain. For this purpose, answers were sought to the following questions.

- How are relevant publications distributed by year?
- Who are the authors who publish and contribute the most in the field?
- Which institutions, funding organizations and journals contribute the most to the field?
- Which countries produce the most publications?
- What are the most used keywords in publications?
- What are the most cited publications?
- What are the publications that stand out in the network map of the data set in the citation analysis?

The aim of the research is to examine and reveal the current status of research published in the field of healthcare workers and brain drain in the "Web of Science Core Collection (WoS) database from a bibliometric perspective.

Nowadays, there are multiple databases from which the data set can be obtained in bibliometric analysis.

There are currently more than one database for bibliometric analysis. PubMed, Embase, Scopus, SpringerLink, Google Scholar, ScienceDirect are among the most frequently used databases. Databases used in bibliometric analyzes have different features. [19]

WoS database was the database used to obtain the data set in the research.[16]

Setting

The study data were collected on November 27, 2023, from publications in the WoS database spanning the years 1988-2023.

At the end of the search using the keywords "brain drain" and "health workers" or "health professional" to create the data set, 13.865 publications were reached.

The database is limited to Science Citation Index Expanded, Social Sciences Citation Index, Emerging Sources Citation Index.

Criteria for inclusion in the database were limited to Publications between the years 1988-2023, WoS category, publishing institutions, countries, journals, authors, publication language English, publication type article.

The research dataset consisted of 2.247 articles retrieved from the WoS database. The publication selection flow diagram is given in Figure 1.

Data analysis

In this research, VOSViewer (1.6.15) software program was used to visualize and map the bibliometric analysis method.

Using VOSViewer, data-based maps can be created and visualizations are made.[17] The VOSViewer program is one of the most preferred programs in bibliometric analysis due to its features. Bibliometric analysis is a powerful statistical analysis method used in the numerical and content examination of articles.[20]

In the bibliometric analysis, the language of publication, distribution of publications by years, prominent countries, journals, co-authors, partner institutions, country collaborations, leading researchers and most used keywords were analyzed.

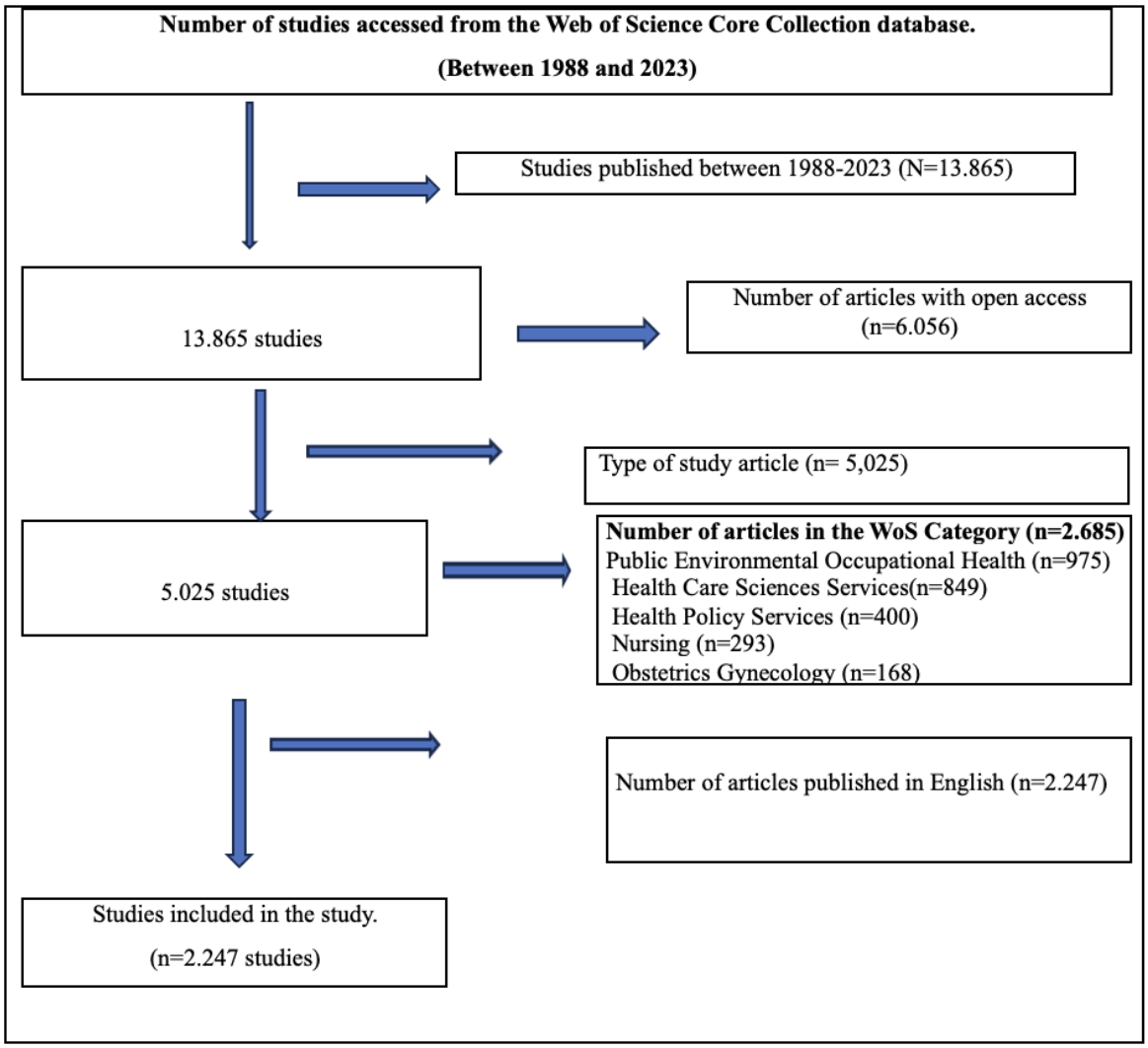


Figure 1. Publication selection flow diagram.

In the bibliometric analysis method of this study, VOSViewer (1.6.15) package program was used for visualization.

The data was shown graphically to better understand the results.[19] Analysis and graphical interpretation are invaluable for researchers to understand issues in this field.

One of the software that analyzes bibliographic data in different databases such as WoS, Scopus and PubMed is VOSViewer.[21] The VOSViewer provides density and visualization and network maps of data based on a variety of techniques, including citation analysis, bibliographic matching, co-authorship, and keyword usage.[22]

Network analysis is a visualization method used to examine the relationships of individuals, institutions or objects, and changes in relationships over time, from a social and structural perspective.[23,24] For network analysis, clusters, which are the units of analysis and constitute the total sample, and the relationships of the edges connecting the clusters are visualized and modeled.[24,25]

This method was chosen because it effectively presents the holistic and temporal dimension that is difficult to grasp due to the continuous and cumulative nature of the literature.

For this reason, bibliometric analysis has been preferred in many studies investigating new trends.[19,26] The frequency of use of concepts is determined in the first stage of analysis.

This is simply based on the principle of counting one unit of data set. The first basic data consists of the findings obtained as a result of frequency analysis. Data expressed as clusters in network analysis are also represented as circles on maps. The lines

connecting the clusters represent the connections, and their thickness and sum represent the strength of the connections.

The presence of each concept, person, or object in the literature is expressed by the number of clusters, the number of relations, and the total strength of the concept it represents.

In this research, concepts that were repeated at least twice and had terminological value were accepted as hypotheses for the unit of analysis.

The threshold value is determined by trial and error method to ensure that the maps created by the researchers for the purpose of the research can be read.[27,28]

When the concepts used at least once are included in the network analysis when determining the threshold value, independent concepts consisting of a single cluster without establishing a relationship with other concepts will be seen more on the map.

Therefore, the threshold value is limited to two. In the research, an attempt was made to determine the direction in which the discipline is moving and the frequently used concepts, rather than the concepts used in individual studies.

Results

The most publications were made in 2022 (n=256, 11.393%) and second in 2021 (n=243, 10.814%). It was determined that the first publications were made in 1988 (n=1) (Table 1).

Table 1. Distribution of publications by year (1988- 2023).

Publication Years	Record Count	% of 2.247
2023	123	5.474
2022	256	11.393
2021	243	10.814
2020	228	10.147
2019	184	8.189
2018	176	7.833
2017	168	7.477
2016	138	6.142
2015	123	5.474
2014	116	5.162
2013	93	4.139
2012	71	3.160
2011	56	2.492
2010	52	2.314
2009	43	1.914
2008	38	1.691
2007	28	1.246
2006	18	0.801
2005	15	0.668
2004	15	0.668
2003	13	0.579
2002	8	0.356
2001	9	0.401
2000	7	0.312
1999	10	0.445
1998	1	0.045
1997	3	0.134
1996	2	0.089
1995	2	0.089
1994	2	0.089
1993	2	0.089
1992	2	0.089
1991	1	0.045
1988	1	0.045

It was determined that the author who contributed the most to the field of health workers and brain drain was “Grimshaw JM” (n=14). It was determined that the institution providing the most funding support was the 'United States Department of Health Human Services' (n=163) and the most publications were published in the journal 'BMC Health Services Research' (n=129). The USA (n=594) was the country with the highest number of publications, and most publications were made in “University of London” (n=115) (Table 2).

Table 2. Top 10 authors with the most contributions to the field, countries, institutions, funding institutions, journal.

Author	Number of articles	Country	Number of articles	Affiliation	Number of articles	Funding support institution	Number of articles	Journal	Number of articles
Grimshaw JM	14	USA	594	London University	115	United States Department of Health Human Services	163	BMC Health Services Research	129
Francis JJ	12	Australia	524	Sydney University	106	National Institutes of Health NIH USA	140	BMC Public Health	87
Johnston M	9	England	406	N8 Research Partnership	102	National Health and Medical Research Council Nhmrc of Australia	77	Journal of Medical Internet Research	80
Butow P	8	Canada	279	Monash University	87	Canadian Institutes of Health Research Cihr	62	International Journal of Environmental Research and Public Health	72
Eccles MP	8	Brazil	125	Melbourne University	76	National Institutes of Health Research Nihr	57	Human Resources for Health	54
Legare F	8	Scotland	90	Toronto University	66	Uk Research Innovation Ukri	51	Academic Medicine	46
Neusy AJ	8	Netherlands	81	Queensland University	58	Australian Government	38	Frontiers In Public Health	41
Wensing M	8	Spain	59	Harvard University	57	European Union Eu	37	Bmc Pregnancy and Childbirth	37
Brown A	7	New Zealand	57	White Rose University Consortium	56	Medical Research Council UK MRC	37	Implementation Science	32
Michie S	7	South Africa	55	California University	54	NIH National Cancer Institute NC	27	Healthcare	28

As a result of the analysis, the most cited first place was the publication titled "The PHQ-9- Validity of a brief depression severity measure", "Kroenke, K; Spitzer, RL; Williams, JBW" in 2001, published in the Journal of General Internal Medicine, with an average of 981.09 citations, a total of 22.565 citations, followed by "Effectiveness and efficiency of guideline dissemination and implementation strategies", "Grimshaw, JM; Thomas, RE; MacLennan, G; Fraser, C; Ramsay, CR ; Valet, L ; Whitty, P; Eccles, MP; Matowe, L; Shirran, L; Wensing, M; Dijkstra, R; Published by Donaldson, C in 2004 and published in the journal "Health Technology Assessment", it received an average of 96.5 citations, for a total of 1.930 citations (Table 3).

Table 3. Top 10 most cited publications (1988-2023).

	Publication	Author	Year	Journal	Average Citation	Total Citation
1	The PHQ-9- Validity of a brief depression severity measure	Kroenke K, Spitzer RL, Williams JBW	2001	Journal of General Internal Medicine	981.09	22.565
2	Effectiveness and efficiency of guideline dissemination and implementation strategies	Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C	2004	Health Technology Assessment	96.5	1.930
3	Factors Associated with Smoking Behavior among University Students in Syria	Al-Kubaisy W, Abdullah NN, Al-Nuaimy H, Kahn SM, Halawany G, Kurdy S	2012	Asia Pacific International Conference on Environment -Behavior Studies (Aıce-Bs)	83.08	997
4	Cognitive load theory in health professional education: design principles and strategies	van Merrienboer JJG and Sweller J	2010	Medical Education	48.07	673
5	Smartphones for Smarter Delivery of Mental Health Programs: A Systematic Review	Donker T, Petrie K, Proudfoot J, Clarke J, Birch MR, Christensen H	2013	Journal of Medical Internet Research	60.45	665
6	A checklist for identifying determinants of practice: A systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice	Flottorp SA, Oxman AD, Krause J, Musila NR, Wensing M, Godycki-Cwirko M, Baker R, Eccles MP	2013	Implementation Science	48.09	529
7	Coproduction of healthcare service	Batalden M, Batalden P, Margolis P, Seid M, Armstrong G, Opipari-Arrigan L, Hartung H	2016	Bmj Quality & Safety	63.63	509
8	Do self-reported intentions predict clinicians' behavior: a systematic review	Eccles MP, Hrisos S, Francis J, Kaner EF, Dickinson HO, Beyer F, Johnston M	2006	Implementation Science	26.28	473
9	Determinants of innovation within health care organizations - Literature review and Delphi study	Fleuren M, Wiefferink K and Paulussen T	2004	International Journal for Quality in Health Care	21.45	429
10	Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome	Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ	2018	Fertility and Sterility	68.33	410

When the co-author analysis was limited to a minimum of 2 publications and 2 citations per author, the total number of authors was found to be 10.963. Based on the minimum number of publications and minimum citations per author, the number of authors meeting the threshold values was found to be 813. The number of publications of "Univ Sydney" (n=95), the number of citations (n=2171), the total connection power was 219, the number of publications of "Univ Toronto" (n=57), the number of citations (n=1047), the total connection power was 152, the number of publications of "Univ British Columbia" was 152, the number of citations (n=977), the total connection power was 105. In the co-author country cooperation analysis, when the threshold value per country was limited to a minimum of 2 publications and 2 citations and analyzed, the number of countries doing joint work was found to be 130. The number of collaborating countries that met the threshold values was found to be 95 (Figure 2).

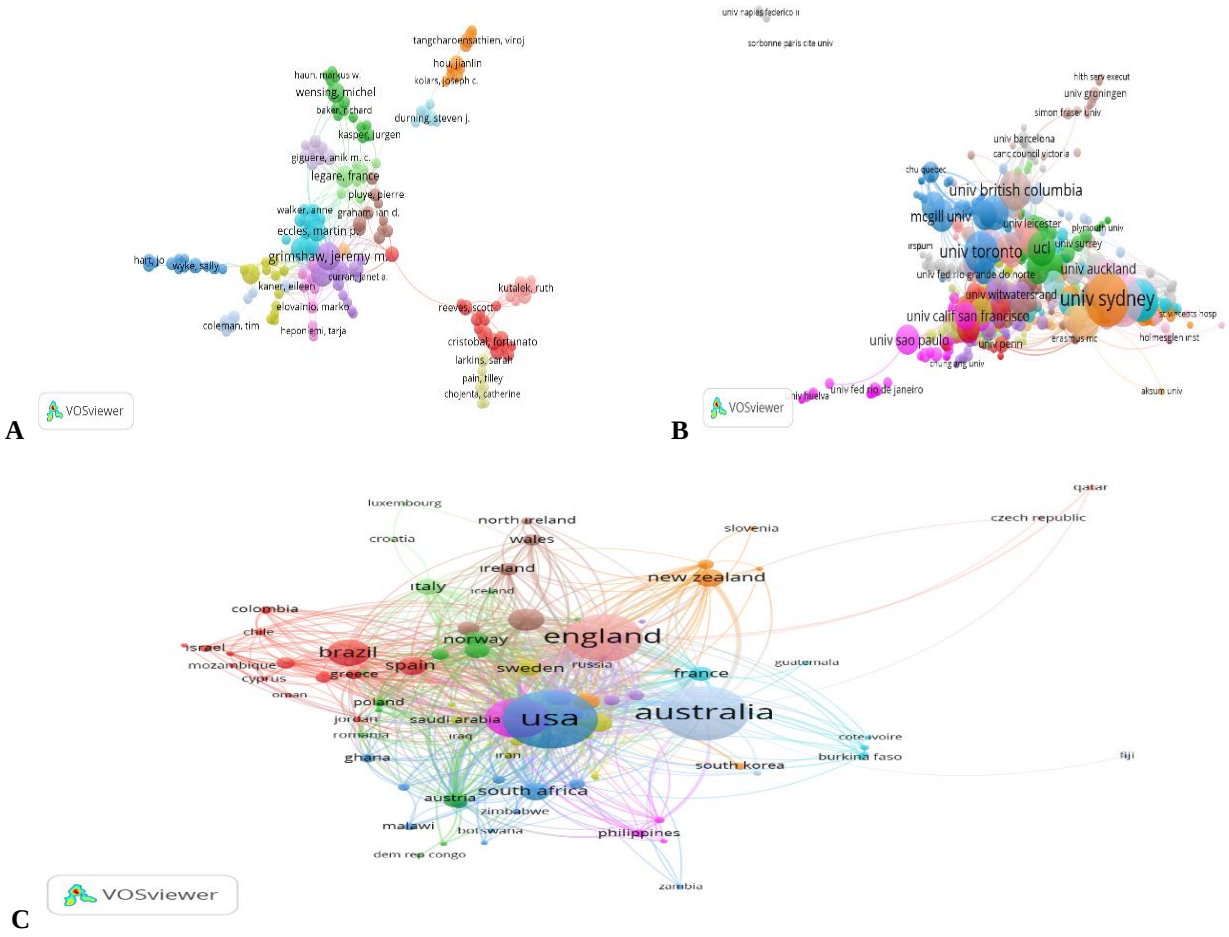


Figure 2. Co-author- author, institution, country analysis network map: A. Co-author-author collaboration network consists of 155 authors, 16 clusters, 537 links. The total connection strength is 905. B. In co-author-institution cooperation, the network consists of 755 institutions, 23 clusters, 4224 connections. The total connection strength is 5650. C. In co-author-country cooperation, the network consists of 95 countries, 12 clusters, 764 connections. The total connection strength is 2068

When the threshold value of the network was limited to 5, it was seen that it consisted of 341 keywords, 12 clusters, 3780 links that passed the threshold value, and the total connection strength was 4803. In the field of health workers and brain drain, the common keyword in the field of network map analysis is that the keyword "health professional" is 9 clusters, 122 formations, 148 links, 274 total connection strength, the keyword "mental health" is 7 clusters, 70 formations, 91 links, 147 aggregate link strength, the keyword "brain drain" is 3 clusters, 7 formations, 15 links, the total connection power is 19, the keyword "education" is 19, 2 clusters, 67 formations, 94 connections were found as a result of the analysis of 178 total connection strengths (Figure 3).

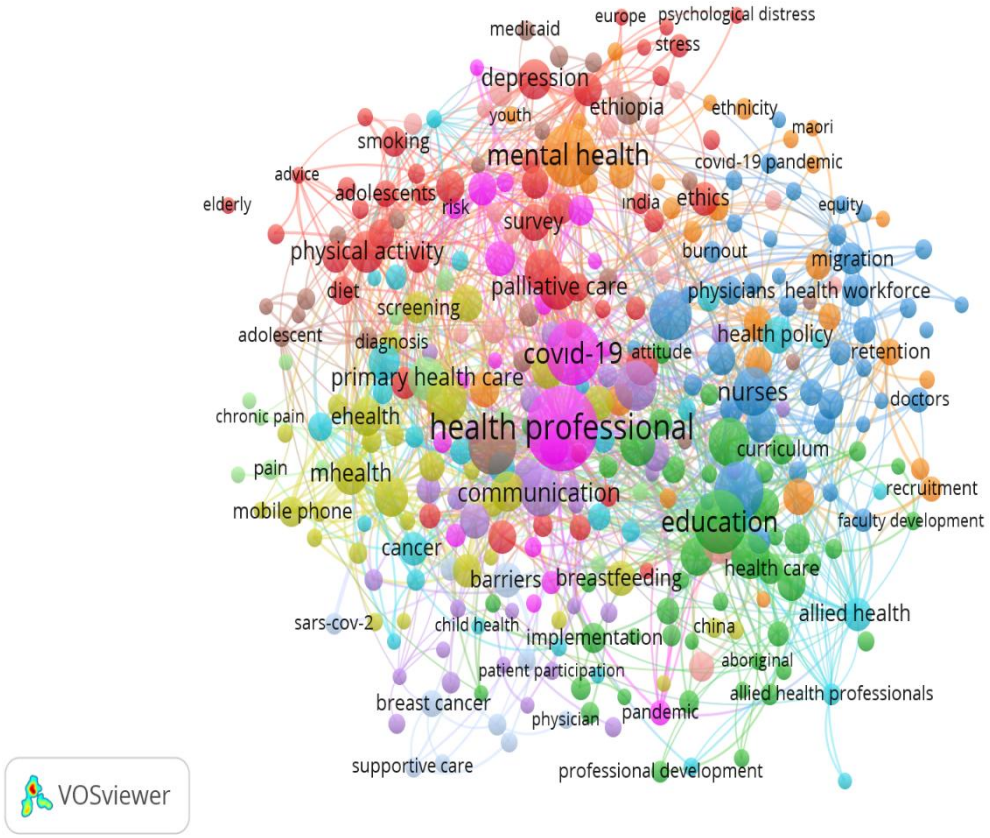


Figure 3. Common keyword analysis network map.

When the threshold value per article for citation analysis of articles was limited to a minimum of 10 citations and analyzed, the total number of publications was found to be 2247. Based on the minimum number of citations, the number of publications that met the threshold values was found to be 941 (Figure 4B).

When the number of articles related to the number of citations received by the institutions was limited to 2 and the citation threshold value was 2, it was seen that the total number of institutions was 3139 and the number of institutions meeting the threshold value was 789 (Figure 4C).

When the number of citations received by the countries was limited to the number of articles and the citation threshold value was 2, it was seen that the total number of countries was 130 and the number of countries meeting the threshold value was 96. According to the country citation analysis, USA received 36275 citations, Australia received 12208, England received 12268, Canada received 8311 citations (Figure 4D).

In the common citation analysis of the articles, when the number of citations per study was limited to a minimum of 10, it was seen that there were 74 articles in the data set that exceeded the threshold value and received a minimum of 10 citations per article. It was found that a total of 6 clusters were formed in the data set, there were 518 connections, the total connection strength was 983 (Figure 5A).

In the common citation analysis of journals, it was seen that when the number of citations per journal was limited to a minimum of 20, the minimum number of journals exceeding the threshold value was 595. The dataset showed a total of 7 clusters, 78678 links, 646609 total link strength (Figure 5B).

In the joint analysis of the authors, it was seen that when the number of citations per author was limited to a minimum of 20, the minimum number of journals exceeding the threshold value was 89. In the data set, it was seen that there was a total of 5 clusters, 1254 links, 5175 total connection strength (Figure 5C).

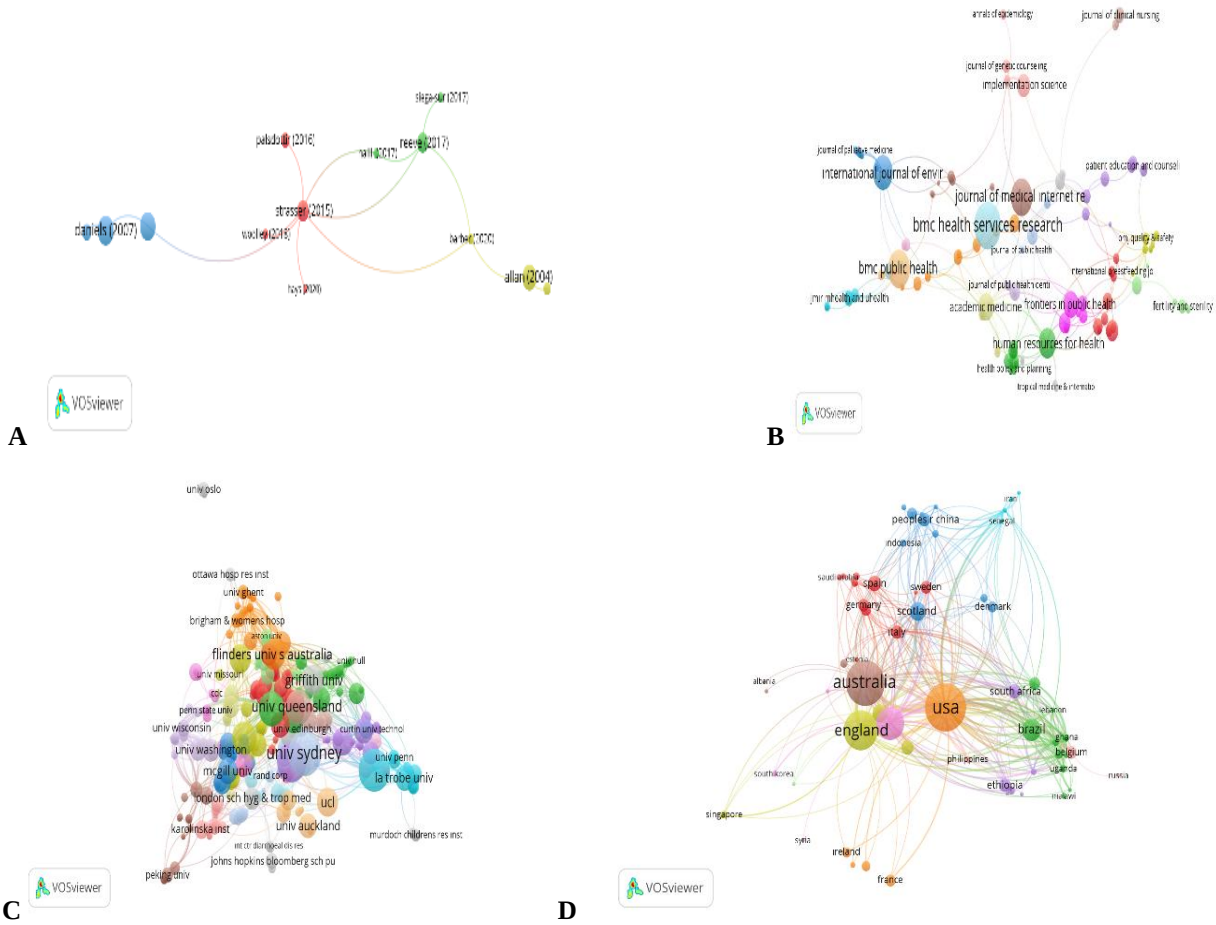
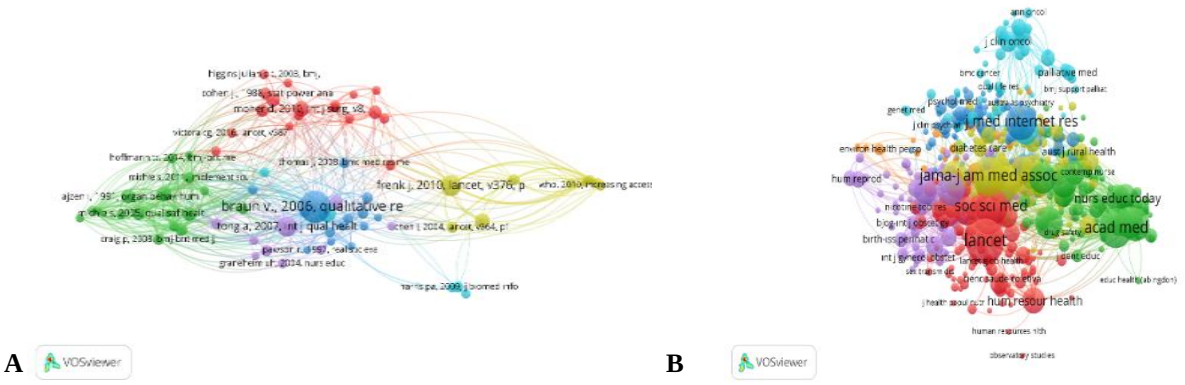


Figure 4. Article, journal, institution, country network map according to citation analysis



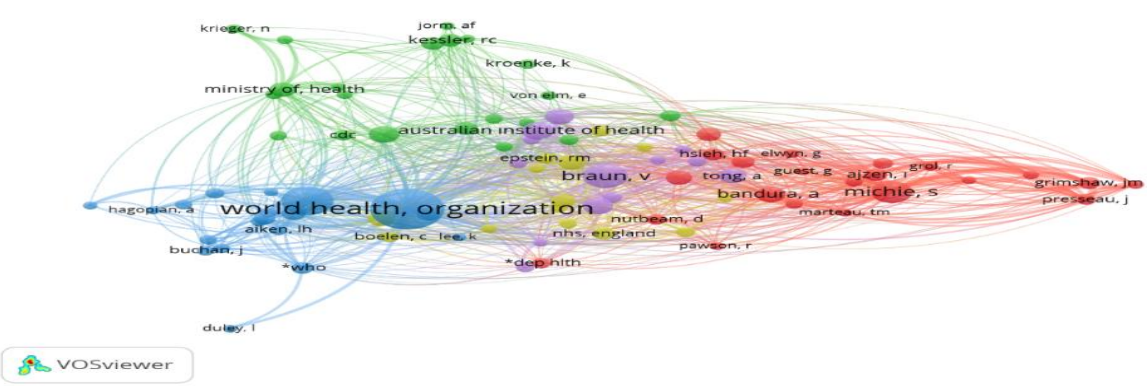


Figure 5. Common-citation article, journal, author analysis network map

Discussion

This research is the first bibliometric analysis carried out in order to identify and visualize the studies in the field of health workers and brain drain, to reveal the trends, to point out the gaps in the literature and to provide researchers with a literature-based perspective. According to the results of this analysis, the most broadcasts were made in 2022 and the most broadcasts were made in the USA.

According to the results of the analysis, the studies on employees and brain drain have gradually increased since 2013 and reached the highest number in 2022. As a result of the analysis, it was found that the most used keywords were "health professional", "mental health", "brain drain", and that the USA published the most as a country. This may be due to the fact that the US, as a general human resources policy, has policies to offer various opportunities to qualified healthcare professionals worldwide in terms of working life, and the number of publishers and the number of journals may have determined the results of the research in this direction. In addition, it may be due to the fact that the publications are published in English. In the review of 17 studies conducted in West Africa, which gives a lot of brain drain, it was reported that physicians especially preferred the USA.[14] In Nigeria, a sub-Saharan African country, it is reported that 44.5% of those with a medical degree emigrate to the United States.[31] Between 2005 and 2015, there was an increase of over 70% in the number of African-trained physicians entering the U.S. workforce.[30] In 2016, non-U.S.-born medical graduates accounted for about one-fifth of general practitioners in the United States, and that number is projected to continue to grow.[29] The findings of the analysis overlap with the literature, and especially the USA and high-income countries receive brain drain from health personnel. It may be recommended to develop policies to address this issue in order to eliminate global inequality.

The need for more staff trained in evidence-based medicine is increasing by the day, and it is reported that it fails to meet the basic minimum threshold for the employment of 23 trained health professionals per 10.000 people in 83 countries globally. This condition is particularly severe in low- and middle-income countries.[12,13,32] The picture is exacerbated by the migration of large numbers of trained health workers from low- and middle-income countries, whose current numbers are already insufficient, to high-income countries.[12,13,32,33] Similarly, studies have found that the need for financial security, especially in doctors, is the main driver of doctor migration, and in addition, factors related to self-actualization, such as educational opportunities and the desire for professional development through research, are also among the reasons for major migration.[31] In a study on migration and development, 1586 studies in the Web of Science database were examined and it was reported that the number of studies started to increase after 2006.[15] Due to the health policies implemented in line with the results of this analysis, the lack of health workers in developed countries due to the rapid aging of the world population and the variable picture in the global economy, it is clear that the mobility of brain drain in health workers will increase from developing countries to developed countries and this will be reflected in the number of publications in the literature. The findings of the analysis and the literature are similar, and the brain drain of health workers is a global problem, and the gap between unequal distribution continues to grow rapidly.

Since the results of this analysis are evaluated based on quantitative data, the findings in the field of health workers and brain drain are important in terms of giving an overview in terms of contributing to the literature. In order to reveal the causes of brain drain of health workers and the reasons for mobility in this field, the planning of qualitative research in the field can be recommended to researchers interested in the field. Since these research results were limited to quantitative data from the WoS database, publications in other databases could not be evaluated. In the future, the research in which the data to be obtained from other databases are studied together will be important as it reveals the general picture.

It is thought that the brain drains of health personnel to developed countries will increase rapidly day by day and it is recommended to create and adopt policies on the subject. When the literature in the field of health workers and brain drain is examined, it is seen that more studies are needed in this area. It is thought that the results obtained from this study will contribute to new research and literature in providing a more general perspective to researchers.

Conclusion

According to the results of this analysis, it was found that the most publications were made in 2022 and the publications were mostly in the USA, the population density in the countries receiving brain drain was low, the population density was less in the developed countries, there was more health personnel brain drain in developed countries, and employment and economic reasons were the triggering force in terms of brain drain in health personnel. It is known that the sector that experiences the highest brain drain is health professionals. Migration from countries with poor conditions to countries with more advantageous conditions continues to increase day by day. This situation needs to be addressed in terms of country policies.

Ethics Committee Approval

There was no data obtained from animal or human experiments for this article.

Informed Consent

The consents were obtained from all of the authors for this article.

Author Contributions

All of the authors contributed at every stage of the study.

Acknowledgments

None

Conflict of Interest

The authors declare that they have no conflict of interest.

Financial Disclosure

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Statements

These data have not been presented or published anywhere previously.

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