ANKARA MEDICAL JOURNAL

Vol. 23 / Num. 3, 2023
www.ankaramedj.com
e-ISSN: 2148-4570

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

Organization, Preparation and Correspondence

- Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Family Medicine, 06800 Bilkent / Ankara / TURKEY

Date of Issue: 29.09.2023

Ankara Medical Journal is an international peer-reviewed journal and is published quarterly.
The responsibility of the published articles belongs to the authors.

Ankara Medical Journal is indexed / abstracted in Scopus, DOAJ, ULAKBIM TR Index, Google Scholar, Index Copernicus, ROAD, ResearchBib, SHERPA/RoMEO, Turkish Citation Index and Turkish Medline.

ANKARA MEDICAL JOURNAL

From the Editor

Dear Esteemed Readers,

We are delighted to present the third edition of 2023, encompassing an array of articles designed to captivate healthcare professionals, particularly primary care physicians. Our foremost objective is to furnish an invaluable compass for healthcare practitioners; hence we have curated nine research articles spotlighting groundbreaking advancements in critical healthcare domains.

Within the pages of this publication, our research articles traverse diverse subjects, ranging from the cutting-edge applications of artificial intelligence in the medical realm to the profound influence of healthcare reforms on overall well-being, and the implications of specific gene polymorphisms on vitamin D levels. We trust that these articles, among others, will both intrigue and exhilarate you.

As the most widely recognized primary care journal in Turkey, we are deeply honored to persist in our role as an indispensable resource for healthcare professionals within the region. We sincerely appreciate your ever-growing interest in our journal and eagerly anticipate the privilege of continuously delivering the latest research findings and evidence pertinent to primary care.

Anticipate our upcoming edition, which we are confident will be equally enlightening and thought-provoking.

Prof. Dr. Ahmet Keskin

ANKARA MEDICAL JOURNAL

Contents

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):256-268 // 10.5505/amj.2023.89990

IDENTIFYING FACTORS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN THYROID DISORDERS AND PREDICTION OF RISK USING MACHINE LEARNING APPROACH: A COMPREHENSIVE STUDY

Bhavya Poojary[1], Merlin Maria Wilson[1], Riya Jose[1], Sona P Sam[1], Ann Elizabeth George[2], Mallikarjuna V Jeeragi[3]

[1]Department of Pharmacy Practice, Bapuji Pharmacy College, Davangere, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India
[2]Bapuji Pharmacy College, Davangere, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India
[3]Department of Endocrinology, SSIMS&RC, Davangere, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India

Correspondence:
Riya Jose (e-mail: riyajosemoolan333@gmail.com)

Submitted: 07.07.2023 // Accepted: 26.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: Thyroid disorders are a significant health concern in India and globally, being the second most common disease. Cognitive impairment associated with thyroid disorders is often neglected by healthcare providers, necessitating improved awareness and screening to identify neurocognitive changes in affected individuals. This study aimed to determine the prevalence of cognitive impairment in thyroid disorders and identify the associated risk factors. This study also predicted the risk of the development of cognitive impairment using a machine learning algorithm and was conducted in a tertiary hospital in South India.

Materials and Methods: A prospective observational study was conducted among 202 patients with thyroid disorders over six months. In order to achieve primary and secondary goals, tools such as the M-ACE questionnaire and XGBoost algorithm were used. Data were collected using a validated form and analyzed using standard statistical methods.

Results: Among the studied population, 29.21% were cognitively impaired, with an average M-ACE Score of 22.56± 2.62. Age, duration of illness, BMI, comorbidities, and tobacco chewing were significant contributors when factors were analyzed for their association with cognitive impairment. A similar number of people with hypothyroidism and hyperthyroidism had a >75% risk of developing cognitive impairment in the near future.

Conclusion: This study revealed that thyroid disorders have significant effects on the cognitive status of individuals and were also successful in predicting future risk.

Keywords: Thyroid disorders, cognitive impairment, machine learning, XGBoost

ANKARA MEDICAL JOURNAL

Introduction

In the Indian population, endocrine disorders are prominent, and thyroid problems comprise a significant subset of these conditions.[1,2] Globally, as in India, thyroid disorders are the second most common disease.[3] The term "thyroid disorder" refers to a broad category of medical conditions that prevent the thyroid gland from producing the appropriate amount of hormones. The levels of triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) in the blood indicate a spectrum of diseases that present as either hypo or hyperfunctioning of the thyroid gland.[4] Thyroid hormone abnormalities may result from conditions affecting the thyroid gland itself (primary), pituitary conditions (secondary), or conditions affecting the hypothalamus (tertiary).[2]

Cognitive impairment is a frequently experienced problem among individuals with thyroid disorders, but it may be overlooked by healthcare providers if patients do not specifically report any changes in their neurocognitive functioning.[5,6] Various factors, including sociodemographic variables (such as age, sex, marital status, educational status, and job status), comorbid medical conditions (such as hypertension, cardiovascular diseases, diabetes mellitus, and chronic kidney disease), behavioral factors such as tobacco chewing, drinking alcohol, and cigarette smoking, and disease-related factors such as duration of illness and thyroid hormone levels, contribute to future cognitive functions.[5] In particular, low thyroid hormone is a common risk factor for the occurrence of cognitive impairment in aged females.[7] According to studies determining the prevalence of cognitive impairment in thyroid disorders, the prevalence of cognitive impairment in hypothyroid patients was 27.3%.[5] In hyperthyroidism, cognitive impairment was noticed as a common issue.[8] People diagnosed with hyperthyroidism were having a major decline in their cognitive health compared to euthyroid patients.[9] In hospitalized elderly hyperthyroid patients the prevalence of cognitive impairment was 52% with 33% dementia and 18% confusion.[8,10]

Artificial intelligence (AI) is being used more frequently, which will probably alter how clinical evaluations and training are conducted. To ensure the potential of AI to improve medical care dramatically, doctors can collaborate in developing this technology for its application in medical care. This process generally entails gathering data, creating effective methods for using them, showing precise or approximate conclusions, and self-corrections/adjustments. AI is typically used to analyze machine learning to mimic human cognitive function. AI technology is used to conduct more accurate analyses and to achieve helpful interpretations.[11] This technology was used as a predictive model in this study.

This study aimed to determine the prevalence of cognitive impairment in patients with thyroid disease and identify the associated risk factors. Extreme gradient boosting (XGBoost) was also used to predict the risk of cognitive impairment.

Materials and Methods

A prospective study was conducted for six months in a research and training hospital with 202 diagnosed thyroid patients. The selected participants were of both genders, within the age range of 18 to 85 years. They displayed diverse clinical profiles, including comorbidities, educational levels, and social behaviors. Additionally, our sample had individuals from rural and urban areas, ensuring a comprehensive representation of thyroid patients across various demographic backgrounds.

Further, strict measures were taken to confirm that the selected participants had no prior history of seizure, epilepsy, stroke, schizophrenia, major depressive disorder, bipolar disorder, obsessive-compulsive disorder (OCD), brain tumor, head injury, or neurosurgery. Additionally, patients in critical condition, unable to communicate verbally or previously diagnosed with hearing impairments were excluded from the study. Notably, the study focused solely on diagnosed and under-treatment thyroid patients, meaning individuals with subclinical thyroid conditions were not part of our investigation. Therefore, the impact of subclinical conditions on cognitive health was not assessed in this study. This approach ensured a participant cohort with distinct clinical characteristics, providing a focused foundation for our study.

The data collection form was designed such that it contained separate sections for demographic details, patient history, lab values, and Mini Addrenbrooke's Cognitive Examination (M-ACE) scores. Patients' consent to participate in the study was obtained using an informed consent form in Kannada or English. First, the patient's demographic details were collected using a case sheet or direct patient interviews. The prevalence of cognitive impairment in thyroid patients was assessed using the M-ACE Questionnaire, and factors associated with cognitive impairment were collected, analyzed, and entered into an Excel sheet. Patients without any cognitive impairment were assessed for the risk of developing cognitive impairment using the XGBoost machine learning algorithm. XGBoost, which stands for extreme gradient boosting, is a machine learning algorithm. It is an optimized distributed gradient-boosting library designed to be highly efficient, flexible, and portable. It provides parallel tree boosting and is the leading machine-learning library for regression, classification, and ranking problems. It also has additional features for cross-validation and identification of important variables. The XGBoost model has the best combination of prediction performance and processing time compared to other algorithms.

The collected data were entered into Microsoft Excel Professional Plus 2016 and analyzed using the International Business Machine Statistical Presentation System Software (IBM SPSS) Version 25 for Windows. Categorical data are presented as frequencies and percentages. Quantitative data are represented as the mean and standard deviation (SD), and associations between categorical variables were assessed using the chi-

square test. Quantitative variables were compared using unpaired t-tests and analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

Results

A total of 202 thyroid patients with an average age of 45.92 years participated in this study, with a predominance of females (77.23%) (Table 1). In addition, 14.36% of patients admitted to engaging in substance abuse habits, including 5.94% of smokers, 5.45% of drinkers, and 2.97% of tobacco chewers. When the body mass index (BMI) was calculated, 50.99% of the population was identified as having a healthy weight, 33.66% was overweight, 9.90% was obese, and the remaining population was underweight. Comorbidities were present in 59.90% of the patients; the majority had diabetes (24.75%) and hypertension (22.77%), and the remainder had other comorbidities. Hypothyroidism (80.69%) was the major thyroid disorder among the participants, followed by hyperthyroidism (12.38%), and the rest were diagnosed with other thyroid conditions (6.93%). When the duration of illness was considered, 66.34% of the patients had thyroid disorders for ≤5 years (Table 2).

Table 1. Sociodemographic data of thyroid patients

Variables	Category	n	%
Age	18-28	34	16.83
	29-38	31	15.35
	39-48	49	24.26
	49-58	42	20.79
	59-68	33	16.34
	69-78	8	3.96
	79-88	5	2.48
Sex	Female	156	77.23
	Male	46	22.77
Residential area	Rural	91	45.05
	Urban	111	54.95
Educational status	≤ 8	64	31.68
	9 – 12	89	44.06
	> 12	49	24.26
Job-status	Employed	89	44.06
	Unemployed	107	52.97
	Retired	6	2.97

Table 2. Social behavior and clinical characteristics thyroid patients

Variables	Category	n	%
Social Habits	Smoking	12	5.94
	Alcohol	11	5.45
	Tobacco Chewing	6	2.97
	Nil	173	85.64
BMI	Underweight	11	5.45
	Healthy weight	103	50.99
	Overweight	68	33.66
	Obese	20	9.90
Comorbidities	Yes	121	59.90
	No	81	40.10
Thyroid disorders	Hypothyroidism	163	80.69
	Hyperthyroidism	25	12.38
	Other thyroid conditions	14	6.93
Duration of illness	≤5	134	66.34
	6-10	52	25.74
	11-15	13	6.44
	>15	3	1.48

Prevalence of cognitive impairment

In this study, the prevalence of cognitive impairment in patients with thyroid disorders was 29.21%. The severity of cognitive impairment was also tested according to the M ACE scores gained by the cognitively impaired patients, where 89.83% had mild cognitive impairment (MCI) and 10.17% had dementia. Of the 59 cognitively impaired patients, 72.88% had hypothyroidism, 15.25% had hyperthyroidism, and the rest had other thyroid conditions (Table 3).

Risk factors associated with cognitive impairment in thyroid patients

The chi-square test assessed many sociodemographic, social-behavioral, and clinical characteristics for their association with cognitive impairment. Among these factors, age ($p<0.010$), duration of illness ($p=0.030$), BMI ($p=0.040$), tobacco chewing ($p=0.040$), and comorbidities ($p=0.002$) were significantly associated with cognitive impairment in patients with thyroid disorder (Table 4).

Table 3. Prevalence of cognitive Impairment

Variables	Category	n	(%)
Cognitive Impairment	Present	59	29.21
	Absent	143	70.79
Severity of Cognitive impairment	Mild	53	89.83
	Dementia	6	10.17
Cognitive impairment in thyroid disorders	Hypothyroidism	43	72.88
	Hyperthyroidism	9	15.25
	Other thyroid conditions	7	11.86

Table 4. Risk factors associated with cognitive impairment in thyroid patients

Variables		Cognitive Impairment No. of Cases (%)		Normal No. of Cases (%)		Chi-Square Test, p-value
		n	%	n	%	
Age						
18-28		4	6.78	30	20.98	**p<0.010**
29-38		10	16.95	21	14.69	
39-48		13	22.03	36	25.17	
49-58		10	16.95	32	22.38	
59-68		14	23.73	19	13.29	
69-78		5	8.47	3	2.10	
79-88		3	5.08	2	1.40	
Gender						
Male		15	25.42	31	21.68	p=0.564
Female		44	74.58	112	78.32	
Education						
≤ 8		19	32.20	45	31.47	p=0.948
9-12		25	42.37	64	44.76	
> 12		15	25.42	34	23.78	
Residential area						
Rural		29	49.15	62	43.36	p=0.452
Urban		30	50.85	81	56.64	
Employment Status						
Employed		24	40.68	65	45.45	p=0.817
Unemployed		33	55.93	74	51.75	
Retired		2	3.39	4	2.80	
Body Mass Index						
Underweight		6	10.17	5	3.50	**p=0.040**
Healthy weight		22	37.29	81	56.64	
Overweight		24	40.68	44	30.77	
Obese		7	11.86	13	9.09	
Social Habits						
Tobacco Chewing	Yes	4	6.78	2	1.40	**p=0.040**
	No	55	93.22	141	98.60	
Smoking	Yes	3	5.08	9	6.29	p=0.740
	No	56	94.92	134	93.71	
Alcohol	Yes	2	3.39	9	6.29	p=0.410
	No	57	96.61	134	93.71	
Comorbidities						
Present		45	76.27	76	53.15	**p=0.002**
Absent		14	23.73	67	46.85	
Duration of illness						
0-5		32	54.24	102	71.33	p=0.030
6-10		20	33.90	32	22.38	
11-15		7	11.86	6	4.20	
> 15		0	0.00	3	2.10	

(Significant values are shown in bold)

Due to differences in the reference values of the thyroid function test, patients were segregated into age groups ≤60 years and >60 years to determine the relationship between thyroid hormones and cognitive impairment. When normal vs. below normal and normal vs. above normal levels of T3, T4, and TSH were compared individually, hypothyroidism was significantly associated with T3 (below normal), T4 (below and above normal), TSH (above normal), in patients with cognitive impairment aged ≤60 years, whereas T3 (below normal), T4 (below normal), and TSH (above normal) showed a significant association with cognitive impairment in patients aged >60 years ($p < 0.001$). Meanwhile, in hyperthyroidism, when comparison of normal vs. below normal and normal vs. above normal levels of T3, T4, and TSH were done individually, a significant association was found between T3 (above normal), T4 (above normal), TSH (below normal), in patients with cognitive impairment aged ≤60 years ($p < 0.001$) (Table 5).

Table 5. Thyroid function test

Hypothyroidism				
Age (in years)		**T3 (in ng/dL) Mean (SD)**	**T4 (in µg/mL) Mean (SD)**	**TSH (in µIU/dL) Mean (SD)**
≤ 60 years	Normal	0.98 (0.24)	6.94 (2.12)	2.88 (0.91)
	Below	0.29 (0.22)	1.42 (1.7)	0.05
	Unpaired t-test, p-value	<0.001*	<0.001*	-
	Normal	0.98 (0.24)	6.94 (2.12)	2.88 (0.91)
	Above	2.54	13.91(1.3)	17.56 (11.24)
	Unpaired t-test, p-value	-	<0.001*	<0.001*
> 60 years	Normal	0.92 (0.35)	7.29 (2.29)	4.82 (5.64)
	Below	0.2 (0.05)	2.54 (1.06)	-
	Unpaired t-test, p-value	<0.001*	<0.001*	-
	Normal	0.92 (0.35)	7.29 (2.29)	4.82 (5.64)
	Above	1.96	11.15	18.8(5.35)
	Unpaired t-test, p-value	-	-	<0.001*
Hyperthyroidism				
Age (in years)		**T3 (in ng/dL) Mean (SD)**	**T4 (in µg/mL) Mean (SD)**	**TSH (in µIU/dL) Mean (SD)**
≤ 60 years	Normal	1.14 (0.28)	9.62 (0.55)	1.52 (0.91)
	Below	-	-	0.09(0.13)
	Unpaired t-test, p-value	-	-	<0.001*
	Normal	1.14 (0.28)	9.62 (0.55)	1.52 (0.91)
	Above	4.18 (1.29)	19.7 (9.67)	-
	Unpaired t-test, p-value	<0.001*	<0.001*	-
> 60 years	Normal	1.84	-	2.25
	Below	0.11	1.03	0.19 (1.13)
	p-value	-	-	-
	Normal	1.84	-	2.25
	Above	7.25	15.6 (11.84)	-
	p-value	-	-	-

Cognitive impairment risk in thyroid patients with normal cognition during the study was predicted using the XGBoost machine learning algorithm (accuracy = 96.40%). Among 143 thyroid patients with normal cognition (M-ACE score > 25), 66 (46.15%) had a ≤25% risk of cognitive impairment, 15(10.49%) had a 26-50% risk, 34 (23.78%) had a 51-75% risk, and 27 (18.88%) had more than a 75% risk of developing cognitive impairment in the near future (Table 6). Table 6 also depicts the risk prediction of cognitive impairment in each thyroid disorder, where patients with hyperthyroidism (18.75%) and hypothyroidism (18.33%) showed almost similar results in more than 75% risk of developing cognitive impairment when compared to other thyroid conditions.

Discussion

The main focus of this study was to assess the relationship between thyroid disorders and cognitive impairment and to predict the future risk of cognitive impairment in thyroid patients. All participants were previously diagnosed with a thyroid condition and were 18 to 85 years old. Their compliance with inclusion and exclusion criteria was also verified. The overall prevalence of cognitive impairment in patients with thyroid disorders was approximately one-fourth (29.21%) of the total participants. Among those with cognitive impairments, nine out of ten (89.83%) exhibited mild cognitive impairment (with M-ACE scores ranging from 19-25), while the rest (10.17%) had dementia (with M-ACE scores of ≤18). Slightly over a quarter of the hypothyroid patients (26.38%) demonstrated cognitive difficulties, aligning with the findings of the study conducted by Mulat B et al., showing a prevalence of 27.3%.[5] Conversely, approximately one-third (36.00%) of hyperthyroid patients demonstrated cognitive impairment.

After considering sociodemographic data, social behavior, and clinical factors associated with cognitive impairment, increased age, increased duration of illness, abnormal BMI, tobacco chewing, and comorbidities were found to be significantly linked. These findings were supported by the study conducted by Mulat B et al.[5]

Regarding sociodemographic variables, increased age was significantly associated with cognitive impairment, which agreed with the study conducted by Osterweil et al., which demonstrated a significant correlation between age and cognitive impairment in adult hypothyroid patients.[12] According to Zhang et al., age-dependent thyroid insufficiency encourages exosomal transfer of peripheral ApoE4 into the brain, which causes cognitive impairment.[13] Other factors such as gender, education, residential area, and employment status were not significantly associated with cognitive impairment. Behavioral variables, such as social habits (tobacco chewing, smoking, and alcohol consumption) and sleep status, were also analyzed, causing a significant association between tobacco chewing and cognitive impairment. This aligns with the notion of the

study by Mohammed T et al., except for smoking and alcohol.[14] Disease-related factors such as increased duration of illness and abnormal T3 were positively associated with cognitive impairment, which resembles the results of Mulat B et al.[5] Various studies collectively imply that there may be a continuum describing the relationship between thyroid function and cognition, where cognitive dysfunction is caused by either increased or decreased thyroid hormone concentrations.[15] Some evidence shows that mild hypothyroidism causes reduced cerebral blood flow in the areas of the brain that control attention, motor speed, memory, and visuospatial processing.[16] In cases of clinical hypothyroidism, high TSH levels may also reduce cerebral blood flow and glucose metabolism.[17,18] Patients with hyperthyroidism were found to have higher levels of oxidative stress, lower levels of antioxidant metabolites, and increased levels of thyroid hormonal exposure, leading to increased neuronal death.[19]

While our findings underscore the significant impact of hypo- and hyperthyroidism on cognitive decline, it is important to consider the broader context presented in the study by van Vliet et al. Their comprehensive analysis, involving a large participant cohort from 23 cohorts, found no significant association between subclinical thyroid dysfunction and cognitive function, cognitive decline, or dementia. While our results affirm the influence of hypo- and hyperthyroidism on cognitive decline, it is evident that further research is warranted to fully elucidate the complex interplay between thyroid function and cognitive health. Additionally, the implications of these findings for clinical practice necessitate a careful reevaluation of existing guidelines, particularly those advocating for the screening of subclinical thyroid dysfunction to prevent cognitive decline or dementia. That underscores the need for a balanced and evidence-based approach to managing thyroid disorders in the context of cognitive health.[20] Additionally, a meta-analysis by Ye Y et al. implies that comorbidities may influence the association between hypothyroidism and cognitive dysfunction.[21] When comorbidities were not considered, no significant link was found. However, upon accounting for comorbidities related to vascular disease, hypothyroidism was associated with a lower risk of cognitive dysfunction. This finding contradicts our study results. The authors also emphasize the need for further prospective observational studies to better understand this relationship in the future.[21]

James C et al. assessed the ability of a machine learning algorithm by comparing two existing models for dementia risk prediction (Brief Dementia Screening Indicator- BDSI and Cardiovascular Risk Factors, Aging, and Incidence of Dementia - CAIDE) with four different machine learning algorithms (Logistic Regression-LR, Support Vector Machine-SVM, Random Machine-RF, XGBoost), which proved that machine learning algorithms were superior, in which XGBoost was the most powerful and accurate machine learning approach.[22] Thus, our study used the XGBoost machine learning algorithm with an accuracy of 96.40% for risk prediction.

A risk assessment of 143 patients with no cognitive impairment (NCI) for cognitive impairment was performed, in which 18.88% had a more than 75% risk of developing cognitive impairment. Patients with hyperthyroidism

(18.75%) and hypothyroidism (18.33%) showed similar results in terms of more than 75% risk of developing cognitive impairment compared to other thyroid conditions. Thyroid hormones have many target genes that are important for many brain functions, and numerous genes acquire important functions in the nervous system, such as T3, which plays a crucial role in cerebral cortex development.[23,24] One such example of a gene regulated by thyroid hormones is Reelin, which is produced by the RELN gene and has many functions, such as neuronal migration regulation, dendritic growth, dendritic spine formation, dendritic branching, and synaptic plasticity. Therefore, Reelin is related to many brain disorders, such as autism, depression, schizophrenia, and Alzheimer's disease.[23,25] Moreover, brain-derived neurotrophic factor (BDNF) is involved in cognitive features. These levels are increased in the hippocampus, where the highest concentration is observed in the amygdala, cerebral cortex, and cerebellum. In the case of severe hypothyroidism due to the decrease in protein expression of BDNF, developmental and cognitive issues have been observed, in which memory is the one seen as most damaged.[26] The habit of loss in decision-making was observed in hyperthyroid patients, possibly because of metabolic disorders in the frontal cortex and limbic system.[27] The factors that can lead to an increased risk of developing cognitive problems in the future can be established from the data of this study. To the best of our knowledge, this is the first analysis to predict the risk of cognitive impairment in thyroid patients using the XGBoost machine learning algorithm.

While our study offers crucial insights into the link between thyroid disorders and cognitive function and enhances the awareness about the overlooked aspect of cognitive health in thyroid patients, it's important to acknowledge some limitations. Though carefully chosen, the sample size may be considered modest, particularly when accounting for potential subgroup variations within the population. Additionally, excluding participants with specific medical histories may limit the generalizability of our findings, and the potential presence of undiagnosed medical conditions could have influenced our outcomes. Focusing on diagnosed patients receiving treatment may not fully represent those with milder thyroid conditions, including subclinical thyroid conditions. Combining the M-ACE test with ACE III and other cognitive assessment tools could strengthen our results. Finally, we could not capture long-term trends due to the six-month duration and cross-sectional nature. Despite these constraints, our study provides a foundational insight into this critical area of research.

In conclusion, thyroid dysfunction is a key factor in the development of cognitive impairment. Significant risk factors for the development of cognitive impairment in patients with thyroid disease include advanced age, prolonged disease duration, abnormal BMI, comorbidities, altered T3, T4, and TSH levels, and tobacco chewing. Therefore, early screening of cognitive status in patients with the abovementioned risk factors is advised to ensure timely diagnosis, prevent disease progression, reduce financial burden, and improve quality of life.

Moreover, as AI programs continue to find their place in clinical practice, it is foreseeable that AI will take on a prevalent and influential role in evaluating cognitive function among patients with thyroid disorders. Thus, the incorporation of AI technologies holds the potential to streamline and enhance the accuracy of cognitive assessments, revolutionizing the way of diagnosis and management of cognitive impairment in this patient population.

Ethical Considerations: The study received ethical clearance from the BPC Institutional Ethics Committee on Human Subjects, identified by reference number BPC/IEC/75/2021-22.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Nagarkar R, Roy S, Akheel M, Palwe V, Kulkarni N, Pandit P. Incidence of thyroid disorders in India: An institutional retrospective analysis. *Int J Dent Med Specialty*. 2015;2(2):19-23 (doi: 10.5958/2394-4196.2015.00012.6).
2. Singh A, Purani C, Mandal A, Mehariya KM, Das RR. Prevalence of thyroid disorders in children at a tertiary care hospital in Western India. *J Clin Diagn Res*. 2016;10(2):1-4 (doi: 10.7860/JCDR/2016/16315.7189).
3. Bose A, Sharma N, Hemvani N, Chitnis DS. A hospital based prevalence study on thyroid disorders in Malwa region of Central India. *Int J Curr Microbiol App Sci*. 2015;4(6):604-11.
4. Vissenberg R, Manders VD, Mastenbroek S, et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. *Hum Reprod Update*. 2015;21(3):378-87 (doi: 10.1093/humupd/dmv004).
5. Mulat B, Ambelu A, Yitayih S, et al. Cognitive impairment and associated factors among adult hypothyroid patients in referral hospitals, Amhara region, Ethiopia: Multicenter cross-sectional study. *Neuropsychiatr Dis Treat*. 2021;17:935-43 (doi: 10.2147/NDT.S299840).
6. Rajesh CH L, Reddy Endreddy A, Shaik S, S S. A study of cognitive dysfunctions in patients with thyroid disorders. *Int J Med Res Rev*. 2017;5(11):933-42 (doi: 10.17511/IJMRR.2017.I11.03).
7. Ribeiro FS, de Oliveira Duarte YA, Santos JLF, Leist AK. Changes in prevalence of cognitive impairment and associated risk factors 2000-2015 in Sao Paulo, Brazil. *BMC Geriatr*. 2021;21(1):609 (doi: 10.1186/s12877-021-02542-x).
8. Rubin DI. Neurologic manifestations of hyperthyroidism and Graves' disease [Internet]. 2022; https://www.medilib.ir/uptodate/show/4836 [Accessed: 03.06.2022].
9. Yudiarto FL, Muliadi L, Moeljanto D, Hartono B. Neuropsychological findings in hyperthyroid patients. *Acta Med Indones*. 2006;38(1):6-10.
10. Martin FIR, Deam DR. Hyperthyroidism in elderly hospitalised patients: Clinical features and treatment outcomes. *Med J Aust*. 1996;164(4):200-3 (doi: 10.5694/j.1326-5377.1996.tb94135.x).
11. Das S, Dey R, Nayak AK. Artificial intelligence in pharmacy. Indian J Pharm Educ Res. 2021;55(2):304-18 (doi: 10.5530/ijper.55.2.68).
12. Osterweil D, Syndulko K, Cohen SN, et al. Cognitive function in non-demented older adults with hypothyroidism. *J Am Geriatr Soc*. 1992;40(4):325–35 (doi:10.1111/j.1532-5415.1992.tb02130.x).
13. Zhang M, Gong W, Zhang D, et al. Ageing related thyroid deficiency increases brain-targeted transport of liver-derived ApoE4-laden exosomes leading to cognitive impairment. *Cell Death Dis*. 2022;13(406):1-13 (doi: 10.1038/s41419-022-04858-x).

14. Muhammad T, Govindu M, Srivastava S. Relationship between chewing tobacco, smoking, consuming alcohol and cognitive impairment among older adults in India: a cross-sectional study. *BMC Geriatr*. 2021;21(85):1-14 (doi: 10.1186/s12877-021-02027-x).
15. Begin ME, Langlois MF, Lorrain D, Cunnane SC. Thyroid function and cognition during aging. *Curr Gerontol Geriatr Res*. 2008;2008:1–11 (doi: 10.1155/2008/47486824).
16. Krausz Y, Freedman N, Lest er H, et al. Regional cerebral blood flow in patients with mild hypothyroidism. *J Nucl Med*. 2004;45(10):1712–5.
17. Constant EL, de Volder AG, Ivanoiu A, et al. Cerebral blood flow and glucose metabolism in hypothyroidism: A positron emission tomography study. *J Clin Endocrinol Metab*. 2001;86(8):3864-70 (doi: 10.1210/jcem.86.8.7749).
18. Duntas LH, Maillis A. Hypothyroidism and depression: salient aspects of pathogenesis and management. *Minerva Endocrinol*. 2013;38(4):365-77.
19. Hu Y, Wang ZC, Guo QH, Cheng W, Chen YW. Is thyroid status associated with cognitive impairment in elderly patients in China?. BMC Endocr Disord. 2016;(1):1-7 (doi: 10.1186/s12902-016-0092-z).
20. van Vliet NA, van Heemst D, Almeida OP, et al. Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. *JAMA Intern Med.* 2021;181(11):1440–50 (doi:10.1001/jamainternmed.2021.5078).
21. Ye Y, Wang Y, Li S, Guo J, Ding L, Liu M. Association of Hypothyroidism and the Risk of Cognitive Dysfunction: A Meta-Analysis. *J Clin Med*. 2022; 11(22):6726 (doi: 10.3390/jcm11226726).
22. James C, Ranson JM, Everson R, Llewellyn DJ. Performance of machine learning algorithms for predicting progression to dementia in memory clinic patients. *JAMA netw open*. 2021;4(12):e2136553 (doi: 10.1001/jamanetworkopen.2021.36553).
23. Khaleghzadeh-Ahangar H, Talebi A, Mohseni-Moghaddam P. Thyroid disorders and development of cognitive impairment: A review study. Neuroendocrinology. 2022;112(9):835-44 (doi: 10.1159/000521650).
24. Bernal J. Thyroid hormone regulated genes in cerebral cortex development. J Endocrinol. 2017;232(2):R83-97 (doi: 10.1530/JOE-16-0424).
25. Jossin Y. Reelin functions, mechanisms of action and signaling pathways during brain development and maturation. Biomolecules. 2020;10(6):964 (doi: 10.3390/biom10060964).
26. Madhusudhan U, M K, Singaravelu V, Ganji V, John N, Gaur A. brain-derived neurotrophic factor-mediated cognitive impairment in hypothyroidism. Cureus. 2022;14(4):e23722 (doi: 10.7759/cureus.23722).
27. Yuan L, Tian Y, Zhang F, et al. Decision-making in patients with hyperthyroidism: A neuropsychological study. PLoS One. 2015;10(6):e0129773 (doi: 10.1371/journal.pone.0129773).

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):269-283 // 10.5505/amj.2023.45077

DO HEALTHCARE REFORMS AFFECT HEALTH STATUS? TÜRKİYE PRACTICE

Hasan Bağcı[1]

[1] Freelance Researcher, Health Management, Ankara, Türkiye

Correspondence:
Hasan Bağcı (e-mail: hasanbagci@gmail.com)

Submitted: 11.09.2023 // Accepted: 25.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: The aim of this study is to determine the impact of per capita health expenditure, the number of physicians, and the Health Transformation Program (HTP) implemented in Türkiye since 2003 on infant mortality.

Materials and Methods: In this study, while the infant mortality rate per 1,000 live births (IM) was used as the dependent variable, the per capita health expenditure in US dollars according to purchasing power parity (HEX), the number of physicians per 1,000 population (PHY), and the HTP were used as independent variables. The Autoregressive Distributed Lag (ARDL) bounds testing approach was used in this study. Data covering the years of Türkiye from 1975 to 2018 were obtained from the OECD health statistics database for HEX and PHY, and from the World Bank database for IM.

Results: According to the short and long term results of ARDL limit test, it was observed that the independent variables HEX, PHY and HTP reduced IM in the short term. However, it was found that the short-term results of independent variables HEX ($p=0.157$), PHY ($p=0.390$), and HTP ($p=0.420$) on IM were not statistically significant. According to the ARDL bounds test, the independent variables HEX, PHY, and HTP reduce IM in the long run. The long-term results of independent variables HEX ($p=0.007$), PHY ($p=0.004$) and HTP ($p=0.012$) on IM are statistically significant.

Conclusion: The independent variables HEX, PHY and HTP were shown to reduce IM in the long term ($p<0.05$). It is recommended to monitor these identified effects and to develop public health policies accordingly.

Keywords: Autoregressive distributed lag, ARDL, health expenditure, number of physicians, health transformation program, HTP, infant mortality rate.

ANKARA MEDICAL JOURNAL

Introduction

Since the 1990s, Türkiye has been implementing health reforms, and radical changes have been made in many related areas, from service delivery to financing and from workforce to information systems. A key turning point in these reform initiatives was the implementation of the Health Transformation Program (HTP), which began in 2003. HTP first evaluated the current situation of the Turkish health system and identified access to health services, qualified health personnel, service quality, financial protection, efficiency, management and organization, coordination, supervision, research, and development components as the key priorities.

While developing policy within the framework of HTP, the priority was the human-centered approach along with the concepts of access, quality, equity, and efficiency. Here are the basic principles used in policy development: sustainability, continuous quality improvement, participation, reconciliation, volunteerism, competitiveness in service, decentralization, and separation of powers.

HTP essentially aimed to bring the entire population under the health security umbrella, separate service provision and financing, and strengthen decentralization. For this purpose, automatization of hospital management, refocusing on preventive services and cost-effective primary care delivery, developing a more effective referral system and better management of human resources have been defined. The general purpose of the program is to increase management, effectiveness, user and supplier satisfaction and to ensure the long-term financial sustainability of the healthcare system in Türkiye.

The health transformation policy cycle in Türkiye comprises small cycles of change, and each major policy cycle needs to be accompanied by a subsequent cycle due to changing needs, expectations, resources and context.[1] The HTP consists of 8 primary parts, each explaining the program's objectives in detail.[2]

The planner and controller is the Ministry of Health: Instead of being directly involved in service provision with HTP, it has a planning and supervisory position by the principle of decentralization and has transferred the task of providing services to the Türkiye Public Health Institution and Türkiye Public Hospitals Institution, which are affiliated institutions. However, these institutions were later closed and became general directorates under the Ministry of Health. As a result of the provincial restructuring, the provincial public health directorates responsible for providing primary health care services were closed, and the general secretariats responsible for providing second and third-level health services were closed. These duties were transferred to the provincial health directorates.

Bringing everyone together under a single umbrella general health insurance: With the transfer of SSK health facilities to the Ministry of Health in February 2005, social security institutions withdrew from service provision. Ministry of Health and SSI hospitals have been combined under one roof. Thus, the Social Security Institution (SSI) focused on public health insurance and health financing issues, thus ensuring the complete separation of service-providing and financing institutions.

Another critical step in the health reform was taken in May 2006. The "Social Security Institution (SSI) Law No. 5502" provided the legal framework to combine the three existing social security systems (SSK, BAĞ-KUR and Retired Fund) under the SSI. In the Social Insurance and General Health Insurance Law No. 5510, health services offered to citizens at different standards were brought to a common standard, a compulsory universal health insurance system covering the whole society was established, and the scope and financing of health services for all citizens were unified. Both laws came into force in October 2008, after the Constitutional Court concluded their legal objections.[3]

Widespread, Accessible and Friendly Health Service System: The pilot implementation of family medicine in primary care services in Türkiye started in 2005, and its dissemination was completed in 2010. However, in most countries that practice family medicine, the average population per family physician is around 1,200; in Türkiye, this number is over 3,000. The low number of family doctors and the high population per family doctor did not make it possible to establish a compulsory referral system.[4]

The practice of family medicine, which has an essential place within the HTP, and the prioritization of preventive health services have resulted in positive developments in measurable indicators of maternal and infant health. Infant mortality per thousand live births and maternal mortality per hundred thousand live births are essential indicators of the general health status of a society. IM in Türkiye, which was 109 per thousand live births in 1975, dropped to 27‰ in 2002, the beginning of the HTP, [5] and dropped to 9.1‰ in 2021.[6] In 2020, IM in The Organisation for Economic Co-operation and Development (OECD) countries was 3.7, and in the European Union (EU) it was 3.2.[6] In Türkiye, the maternal mortality ratio, which was 64 per hundred thousand live births in 2002, decreased to 13.1 in 2021. In 2020, the maternal mortality ratio was 9.8 per hundred thousand live births in OECD countries and 5.0 in the EU-22.[6]

Figure 1 shows a significant acceleration in the decrease in infant mortality. It decreased at a Compound Annual Growth Rate (CAGR) of 5% from 1975 to 2002, while it decreased at a CAGR of 6.5% from 2003 to 2018, when the SDP began. However, despite these impressive developments, Türkiye ranked 79th among 244 countries in the IM ranking 2018.

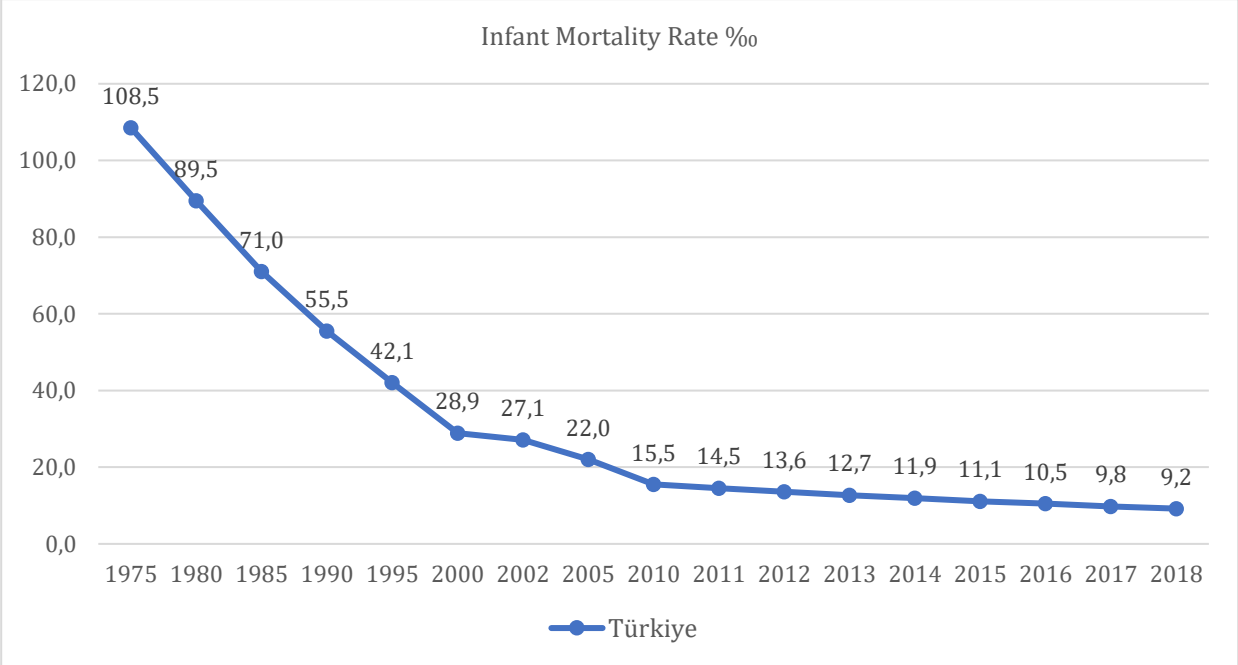


Figure 1. Infant mortality rate per thousand live births 1975-2018

While the number of applications to a physician per capita in Türkiye was 9.8 in 2019, it decreased by 26.5% to 7.2 (Ministry of Health, 2021). While 35.7% of applications to physicians in 2019 were made to institutions providing primary healthcare services, 64.3% were provided to secondary and tertiary healthcare institutions

Health Workforce that Is Knowledgeable, Competent, and Highly Motivated: According to the data from 2002 in Türkiye, there were approximately 93,586 doctors on duty, and the number of doctors per 1000 people was 1.34. There were 183,569 physicians across all sectors in Türkiye in 2021. Among these physicians, 51% were specialists, and 59% of all physicians worked in the ministry of health. Regarding PHY, Türkiye ranked last among OECD countries with 2.17 physicians, indicating a lower physician-to-population ratio than other OECD nations. PHY for 2020 is 3.93 in the OECD and 3.6 in the EU.[6]

Due to the limitations in the number of physicians, high figures have been reached in the number of outpatient clinic examinations per physician. Among OECD countries, Türkiye ranks second after South Korea, with the highest number of patients cared for per doctor. While the OECD average is 2,230 patient examinations per physician per year, physicians in Türkiye examine an average of 5,033 patients per year. The most critical problem in the Turkish healthcare system is healthcare personnel, both in quality and quantity.[7]

Institutions for science and education that support the system: The training of healthcare personnel is no longer seen as a one-time event that ends with graduation. On the contrary, education is defined as a lifelong

process that requires constant updating and in which professional values are regularly increased. Continuing professional development is gradually becoming a vital component of healthcare professional training.

Qualitative and Ethical Standards for Effective and Qualified Health Services: The Turkish Health Services Quality and Accreditation Institute (TÜSKA) was established in 2015 to carry out accreditation activities in health services.

Institutional Structure in the Management of Rational Medicine and Equipment: As a result of the studies, a reference pricing system was introduced, which takes into account the prices of the product in various comparison countries in order to determine a limit for the market entry price or reimbursement price of the product in the drug pricing system.[8] The burden of pharmaceutical expenditures on both the public and citizens has been greatly eased. These regulations played an important role in expanding access to medicine.

Access to Effective Information at Decision-Making Process: Health Information System: E-Health Applications include the web-based presentation of health services as a whole in an electronic environment, the processes of storing data, carrying out diagnosis and treatments, and evaluating the results. E-health applications in Türkiye, whose technological infrastructure has become stronger, are now more advanced than many countries worldwide.

When compared to other countries, Türkiye's health expenditure as a percentage of gross domestic product (GDP) is quite low at 4.9%, as opposed to the OECD average current health expenditure of 9.6% in 2021.[7] In Türkiye, the proportion of out-of-pocket health expenditure within the total health expenditure has shown a decrease over the years. It was 25% in 2002, but by 2021, it had decreased to 15.9% of the total health expenditure.[9] Although the rate of catastrophic health expenditure (defined as health expenditures exceeding 40% of a household's income after basic needs are met) in households decreased from 0.81% in 2002 to 0.14% in 2012, it increased again to 0.43% in 2019. The incidence of impoverishment due to HEX (the situation where a non-poor household becomes impoverished after spending on healthcare services) decreased from 0.43% in 2002 to 0.06% in 2019.[9] It has been observed that as individuals' out-of-pocket health expenditure decreased, the rate of catastrophic health expenditures also decreased. Consequently, satisfaction with healthcare services increased. This indicates that in Türkiye, the public financing model resulting from inclusive healthcare policies has a low capacity for generating poverty.[10]

In the research conducted on the population who are satisfied with the availability of quality health services in the region in which they live, the rate of satisfaction with health services on average in OECD countries is 71%. Türkiye's satisfaction rate with health services, which was 39.5% in 2003, is now close to the OECD average. Among OECD countries, Türkiye has the highest level of satisfaction with health services in terms of the resources spent on health services.

In recent years, Türkiye has faced several new significant challenges: First, demand patterns have shifted due to increased expectations and usage. Second, there has been a shift in behavior due to greater competition and a perceived fall in the standing of healthcare staff. Third, there is an increasing need to promote healthy lifestyles in chronic illness patients, as obesity and inactivity are prevalent and are anticipated to be the most severe health issues to be addressed in the near future.[1]

Literature Review

In many studies, results similar to this study showed a relationship between infant mortality and the number of physicians and health expenditure.

In many studies, results similar to this study showed a relationship between infant mortality and the number of physicians and health expenditure. Owusu 2021 found that increased health expenditure is associated with decreased infant mortality rates across different income countries.[11] Russo 2019 found that an increase of one primary care physician per 10,000 population in Brazil was associated with 7.08 fewer infant deaths per 10,000 live births.[12] Dhrifi 2018 found that health expenditure positively reduces child mortality rates in upper-middle-income and high-income countries.[13] Shi 2004 found that primary care physician supply was negatively associated with infant mortality in the US states.[14]

Subramaniam (2018) found that education, female education, income, and access to healthcare were significant determinants of IM in Malaysia, Thailand, Indonesia, and the Philippines. [15] Barenberg 2017 finds that increased public health expenditure in Indian states is associated with a reduced infant mortality rate.[16] Rhee 2012 suggests that the health system itself affects the infant mortality rate in the long run, while life expectancy at birth is immediately affected by health-related facilities.[17] However, Akinlo 2019 finds that government health expenditure positively affects under-five and infant mortality rates in sub-Saharan African countries, possibly due to corruption and fungibility issues.[18] David (2018) examined the relationship between IM and public health expenditure in Nigeria from 1980 to 2016 using the ARDL method. He concluded that this indicates the presence of a significant cointegrating (long-run) relationship between IM and government health expenditure.[19]

Ifa and Guetat, in their research, examined the short- and long-term relationship between neonatal mortality rate, economic growth, energy consumption, female literacy, and air pollution in India in 1970-2021, using the ARDL approach and VECM method.[20]

Overall, these papers suggest that increasing the number of physicians and health expenditures can help decrease infant mortality rates. This study investigated the impact of HEX, PHY, and HTP on IM.

Materials and Methods

In this study, the ARDL bounds testing approach was employed. The data covering Türkiye's years from 1975 to 2018 were obtained from the OECD Health Statistics Database for HEX and PHY and the World Bank database for IM. In this study, the ARDL bounds testing approach was employed. The data covering Türkiye's years from 1975 to 2018 were obtained from the OECD Health Statistics Database for HEX and PHY and from the World Bank database for IM.[5,7]

In the study, the natural logarithms (LOG) of variables other than the HTP were taken to obtain the logarithms of infant mortality rate (LOGIM), logarithms of healthcare expenditure (LOGHEX), and logarithms of physicians per 1,000 People (LOGPHY) variables.

The ARDL bounds testing is a time-series analysis used to determine independent variables' short-term and long-term effects on the dependent variable.

In this boundary test developed by Pesaran, Shin, and Smith (2001), after checking the stationarity of variables, the analysis proceeds to ARDL. It is a prerequisite in the ARDL bounds testing approach that a variable used must either be stationary at levels (I(0)) or become stationary at the first difference (I(1)). Therefore, in this study, the Augmented Dickey-Fuller (ADF) unit root test was used to test the stationarity of variables.[21]

As observed, in the ARDL bounds test, stationary variables at different orders can be used in the same analysis, which is a significant advantage of the ARDL bounds testing approach.[22]

In addition, another significant advantage of the ARDL bounds testing approach is that it allows for analyses with fewer observations than required by other time-series analyses.[23]

In the ARDL bounds testing approach, a boundary test based on the F-statistic is conducted to determine whether a long-term relationship exists among variables. The null hypothesis (H0) of this test is formulated as there is no long-term relationship among the variables, and in cases where H0 is rejected, the alternative hypothesis (H1) is accepted. As observed, when H1 is accepted, it implies a long-term relationship, i.e., co-integration, among the variables.

Once a long-term relationship is established in ARDL, short-term results are obtained using the Error Correction Model (ECM). In ECM, the lagged version of error correction terms (ECT (-1)) is included in the analysis.

For the Error Correction Model (ECM) to be considered statistically significant and valid, the coefficient of ECT (-1) should be statistically significant and negative, and its absolute value should typically fall within the range of 0 to 1. This condition indicates that the error correction term is effectively contributing to the adjustment process in the short term.[20]

In this study, after obtaining the results of the ARDL bounds test, the model's potential issues with autocorrelation (serial correlation) and heteroscedasticity were examined using the Breusch-Godfrey Serial Correlation LM and Breusch-Pagan-Godfrey tests. Additionally, the study investigated whether there was a model specification error using the Ramsey Reset test and assessed the normal distribution fit of the model using the Jarque-Bera test. When the null hypotheses of these tests were accepted, it was concluded that there were no issues with autocorrelation, changing variances, or model specification errors, and the model exhibited a normal distribution. Furthermore, the stability of the model was tested using CUSUM and CUSUM of Square tests.

Prior to the ARDL bounds test, the optimal lag length required for this test was determined using the Vector Autoregressive (VAR) model. Accordingly, the lag length that was most preferred among the Akaike information criterion (AIC), Schwarz information criterion (SC), and Hannan-Quinn information criterion (HQ) in the VAR model was selected as the lag length for the ARDL bounds test.

All analyses in this study were conducted at a 95% confidence level, and the Eviews 10 software package was used.

Results

Firstly, descriptive statistics for the study variables were obtained within the scope of the study. According to the results, IM takes values from 9.20 to 108.70, with a mean of 45.97±30.48. HEX has values of 37.80 to 1,223.56, with an average of 424.92±376.22. Finally, PHY takes values within the range of 0.54 to 1.88, with a mean of 1.16±0.44 (Table 1).

Table 1. Descriptive Statistics

	IM	HEX	PHY
Mean	45.97	424.92	1.16
Maximum	108.70	1,223.56	1.88
Minimum	9.20	37.80	0.54
Standard Deviation	30.48	376.22	0.44
Observations	44	44	44

ADF Unit Root test results are presented in Table 2. According to the results, the LOGIM, LOGHEX, and LOGPHY variables used in the study are non-stationary at levels but become stationary at first differences. Based on these findings, it can be concluded that the variables used in the study are suitable for the ARDL bounds test.

Table 2. ADF Unit Root Test Results

Variables	*t* statistic, At Level (I(0))			*t* statistic, At First Difference (I(1))		
	Intercept	Trend and Intercept	None	Intercept	Trend and Intercept	None
LOGIM	0.333	-2.907	-1.711	-2.991*	-3.601*	-2.001*
LOGHEX	-0.974	-2.351	4.167	-8.251**	-8.417**	-0.282
LOGPHY	-1.461	-0.333	-0.378	-4.096*	-3.767*	-2.279*

* and ** indicate the acceptance of the alternative hypothesis at 95% and 99% confidence levels, respectively.

According to the results of the VAR model, among the evaluation criteria, the Final Prediction Error (FPE), Akaike Information Criterion (AIC), Schwarz Information Criterion (SC), and Hannan-Quinn Information Criterion (HQ), the lag length of 1 is the most preferred. Therefore, a maximum lag length of 1 was chosen for the ARDL bounds test.

Based on the F-statistic results of the ARDL bounds testing approach, the F-test value (2376.34) is greater than the critical values of I0 (2.79) and I1 (3.67) at the 5% significance level. This indicates a long-term relationship among the variables in the study. The ARDL bounds test results are presented in Table 3. As seen in Table 3, the study's independent variables explain 99% of the variation in the dependent variable (R2=0.99). The model established in the study is significant (F=464226.5). The model in the study does not experience model specification errors, multicollinearity issues, and heteroskedasticity issues, as indicated by the results of the Ramsey Reset (p=0.801), Breusch-Godfrey Serial Correlation LM (p=0.187), and Breusch-Pagan-Godfrey tests (p=0.406). Furthermore, it is understood from the Jarque-Bera test results (p=0.139) that the model in the study follows a normal distribution.

The short-term and long-term results of the ARDL bounds test are presented in Table 4. According to the results, the independent variables HEX, PHY, and HTP in the short term reduce IM. The short-term results of the independent variables HEX (p=0.157), PHY (p=0.390), and HTP (p=0.420) on IM were not found to be statistically significant.

Table 3. ARDL Bounds Testing Results

Dependent Variable: LOGIM				
Model selection method: Akaike info criterion (AIC)				
Selected Model: ARDL (1, 0, 0, 0)				
Variable	**Coefficient**	**Standard Error**	**t-Statistic**	***p*-value**
LOGIM (-1)	0.977	0.005	207.543	0.001**
LOGHEX	-0.012	0.004	-2.739	0.009
LOGPHY	-0.032	0.010	-3.068	0.004*
HTP	-0.005	0.002	-2.288	0.028*
C	0.097	0.034	2.889	0.006*
R-squared (R^2)	0.999	Durbin-Watson stat		1.657
Adjusted R^2	0.999	Ramsey Reset Test p-value		0.801
Standard Error of regression	0.003	Breusch-Godfrey Serial Correlation LM Test		0.187
Log-likelihood	184.194	Jarque-Berra Test p value		0.139
F-statistic	464226.5	Breusch-Pagan-Godfrey Test p value		0.406
Prob (F-statistic)	0.000			

* and * *indicate the acceptance of the alternative hypothesis at 95% and 99% confidence levels, respectively.

According to the results, the independent variables HEX, PHY, and HTP in the long term reduce IM. The long-term results of the independent variables HEX (p=0.007), PHY (p=0.004), and HTP (p=0.012) on IM are statistically significant.

In the ECM, the lagged version of the error terms ranges from -1 to 0 and is statistically significant (p=0.001). The coefficient of ECM(-1) being approximately -0.02 suggests that deviations from the long-term level of IM decrease by approximately 2% each year (p=0.001).

Table 4. ECM and Long Run Results

Dependent Variable: LOGIM **Selected Model: ARDL (1, 0, 0, 0)**				
Short Run Coefficients				
Variable	**Coefficient**	**Standard Error**	**t-Statistic**	***p*-value**
D (LOGHEX)	-0.007	0.005	-1.446	0.157
D (LOGPHY)	-0.021	0.024	-0.870	0.390
D (HTP)	-0.003	0.004	-0.816	0.420
ECM (-1)	-0.024	0.000	-61.655	0.001**
Long Run Coefficients				
Variable	**Coefficient**	**Standard Error**	**t-Statistic**	***p*-value**
LOGHEX	-0.506	0.178	-2.838	0.007*
LOGPHY	-1.377	0.442	-3.117	0.004*
HTP	-0.240	0.091	-2.630	0.012*
C	4.185	0.960	4.358	0.001**

* and * *indicate the acceptance of the alternative hypothesis at 95% and 99% confidence levels, respectively.

CUSUM and CUSUM of Squares tests were used to test the stability of the study's model (Figure 1). When examining the results of these tests, although there is some deviation according to the CUSUM test, the model of the study is considered stable according to the CUSUM of Squares Test.

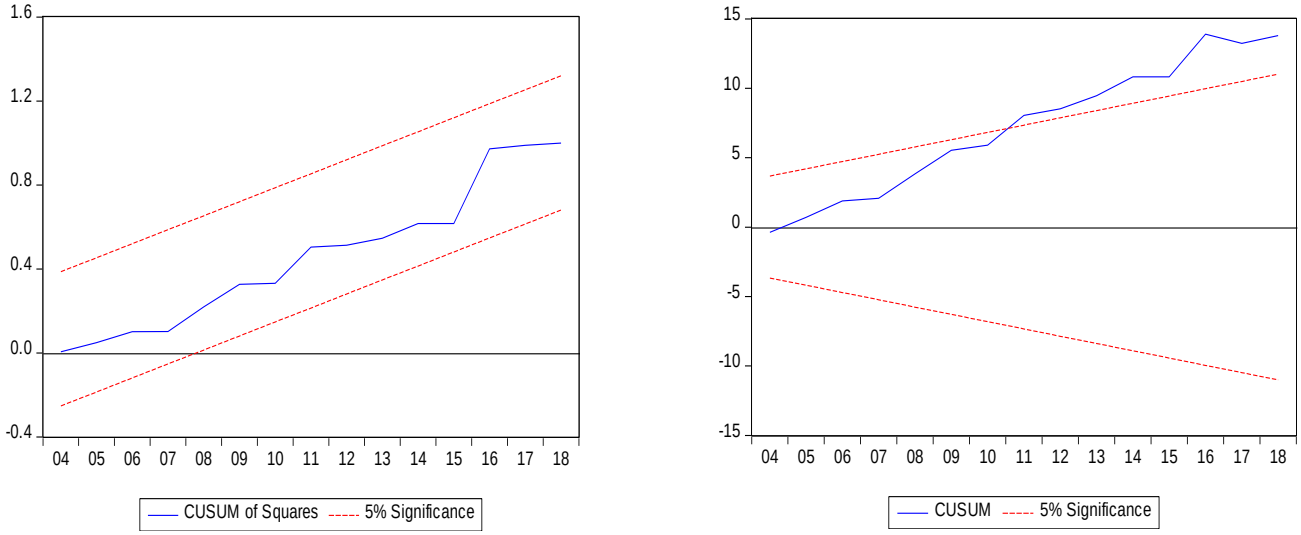


Figure 2. CUSUM and CUSUM of Squares Results

Discussion

In 2003, a system-wide, comprehensive health reform in Türkiye, the HTP, was brought to the agenda.

This rapid decrease in infant deaths and strengthening of the health care system during the HTP implementation process can be explained by outcomes such as increased access to health services as a result of the reform's expansion of newborn care specialists and facilities, health personnel providing more widespread birth services, and family physicians working in primary health services covering the entire country.

Health expenditure is critical to health systems' ability to maintain and increase human welfare; without funding, trained and competent health professionals would not be employed, medical equipment would not be available, and health promotion or illness prevention would not occur. Health spending shows the population's entire consumption of health goods and services across countries. Investing in the healthcare system results in healthier lives, produces jobs, improves political and social stability, and helps economic growth and productivity.

Increasing health expenditure is used to increase the quality and accessibility of health services by providing and developing health facilities and improving the efficiency of the health system, Additionally, expenditures on essential health services such as vaccination, infectious diseases, and preventive health services affect the reduction of diseases and infant mortality rates.

According to the short and long-term results of the ARDL limit test, it was observed that the independent variables HEX, PHY, and HTP reduced IM in the short term. However, it was found that the short-term results of the independent variables HEX (p=0.157), PHY (p=0.390), and HTP (p=0.420) on IM were not statistically significant.

According to the ARDL bounds test, the independent variables HEX, PHY, and HTP in the long term reduce IM. The long-term results of the independent variables HEX (p=0.007), PHY (p=0.004), and HTP (p=0.012) on IM are statistically significant.

According to this study, there is a strong correlation between per capita health spending and infant mortality. As health spending per capita increased, baby mortality decreased in the long run. Both HEX and PHY reduced the infant mortality rate in the long term. These results are consistent with Anwar et al.[24], Ullah et al. [25], Rahman et al.[26], Lu et al.[27], and many others.

This study, which reveals to what extent and in what direction changes in health expenditures and the number of doctors in countries will affect infant mortality, showed similarities with previous studies. Rana et al.(2018),[28] and Kara 2020 also support the relationship between health expenditure and infant mortality rates, finding a long-term relationship and causality between health expenditure and infant mortality rates.[29]

According to the study by O'Hara et al., if GDP increases by 10%, the infant mortality rate is expected to decrease by 10%.[30] These results are consistent with the expectation that government expenditure on health is likely to increase and improve medical facilities and make these accessible to all, reducing child and infant mortalities.

It is suggested that the HTP application process is progressing positively for patients and should be actively continued by turning into continuous improvement. It is recommended to monitor these identified effects and develop health policies accordingly.

Although the HTP effectively solved many health problems when envisaged twenty years ago, today, paving the way for big-data studies with health data will contribute to the development of the health field.

Considering that the most important problem in the Turkish healthcare system is qualified healthcare personnel, the number of healthcare professionals should be increased.

Developing health information systems, especially remote ones, will further increase society's/individuals' access to health services and timely and effective prenatal and postnatal care and baby-child follow-ups.

It is suggested that private health expenditures should also be considered in new studies, where there is a decrease in private health expenditures and an increase in total health expenditures per capita.

Public health expenditure could investigate the effects of incidences of environmental degradation on health status, particularly infant mortality. In addition to new research, decision-makers should review their health expenditures to curb CO2 emissions effectively, promoting a healthy environment.

Ethical Considerations: This study is within the scope of studies that do not require ethics committee approval according to the TR Index ethical principles flowchart. Publicly available data were used in the study.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Akdağ R. Lessons from health transformation in Türkiye: leadership and challenges. Health Systems & Reform. 2015;1(1):3-8.
2. Ministry of Health. Health Trasformation Program 2003, Ankara.
3. Sparkes SP, Bump JB, Reich MR. Political strategies for health reform in Türkiye: extending veto point theory. Health Systems & Reform. 2015;1(4):263-75.
4. Hone T, Gurol-Urganci I, Millett C, Başara B, Akdağ R, Atun R. Effect of primary health care reforms in Türkiye on health service utilization and user satisfaction. Health policy and planning. 2017;32(1):57-67.
5. World Bank. Mortality rate, infant (per 1,000 live births) in Türkiye. https://data.worldbank.org/indicator/SP.DYN.IMRT.IN?locations=TR.2021. (Accessed: 23.09.2023).
6. Cumhurbaşkanlığı 2022 Yıllık Programının Onaylanması Hakkında Karar 4633. https://www.resmigazete.gov.tr/eskiler/2022/10/20221025M1-1.pdf. (Accessed: 23.09.2023).
7. OECD. OECD Health Data 2023. https://data.oecd.org/searchresults/?q=health2023. (Accessed: 23.09.2023).
8. Nguyen TA, Knight R, Roughead EE, Brooks G, Mant A. Policy options for pharmaceutical pricing and purchasing: issues for low-and middle-income countries. Health Policy and Planning. 2015;30(2):267-80.
9. Ministry of Health. Sağlık Bakanlığı. Sağlık İstatistikleri Yıllığı 2021. https://dosyasb.saglik.gov.tr/Eklenti/45317,siy2021-ingilizcepdf.pdf?02022. (Accessed: 23.09.2023).
10. Atasever M, Karaca Z, Sanisoğlu SY, Alkan A, BAĞCI H. Türkiye'de katastrofik sağlık harcamaları ve sağlık hizmetlerinden memnuniyet oranı ile ilişkisi. Ankara Medical Journal. 2018;18(1):22-30.
11. Owusu PA, Sarkodie SA, Pedersen PA. Relationship between mortality and health care expenditure: Sustainable assessment of health care system. Plos one. 2021;16(2):e0247413.
12. Russo LX, Scott A, Sivey P, Dias J. Primary care physicians and infant mortality: evidence from Brazil. PLoS One. 2019;14(5):e0217614.
13. Dhrifi A. Healthcare expenditures, economic growth and infant mortality: evidence from developed and developing countries. CEPAL Rev No 125, August 2018. 2019;69.
14. Shi L, Macinko J, Starfield B, et al. Primary care, infant mortality, and low birth weight in the states of the USA. Journal of Epidemiology & Community Health. 2004;58(5):374-80.
15. Subramaniam T, Loganathan N, Yerushalmi E, Devadason ES, Majid M. Determinants of infant mortality in older ASEAN economies. Social Indicators Research. 2018;136:397-415.
16. Barenberg AJ, Basu D, Soylu C. The effect of public health expenditure on infant mortality: evidence from a panel of Indian states, 1983–1984 to 2011–2012. The Journal of Development Studies. 2017;53(10):1765-84.

17. Rhee H-J. Effects of health care expenditure on the infant mortality rate and life expectancy at birth in Korea. International Journal of Contents. 2012;8(3):52-6.
18. Akinlo AE, Sulola AO. Health care expenditure and infant mortality in sub-Saharan Africa. Journal of Policy Modeling. 2019;41(1):168-78.
19. David J. Infant mortality and public health expenditure in Nigeria: Empirical explanation of the nexus. Timisoara Journal of Economics and Business (TJE&B). 2018;11(2):149-64.
20. Ifa A, Guetat I. Save Infant's Live or Save Economic Growth? An Analysis by ARDL Approach: Case of India. Energy Exploration & Exploitation. 2023;41(2):766-84.
21. Pesaran MH, Shin Y, Smith RJ. Bounds testing approaches to the analysis of level relationships. Journal of applied econometrics. 2001;16(3):289-326.
22. Khandelwal V. Impact of energy consumption, GDP & Fiscal deficit on public health expenditure in India: An ARDL bounds testing approach. Energy Procedia. 2015;75:2658-64.
23. Tang TC. Japanese aggregate import demand function: reassessment from the 'bounds' testing approach. Japan and the World Economy. 2003;15(4):419-36.
24. Anwar A, Hyder S, Mohamed Nor N, Younis M. Government health expenditures and health outcome nexus: a study on OECD countries. Frontiers in Public Health. 2023;11:1123759.
25. Ullah I, Ullah A, Ali S, et al. Public health expenditures and health outcomes in Pakistan: evidence from quantile autoregressive distributed lag model. Risk Management and Healthcare Policy. 2021:3893-909.
26. Rahman MM, Khanam R, Rahman M. Health care expenditure and health outcome nexus: new evidence from the SAARC-ASEAN region. Globalization and health. 2018;14(1):1-11.
27. Lu Z, Bandara JS, Paramati SR. Impact of sanitation, safe drinking water and health expenditure on infant mortality rate in developing economies. Australian Economic Papers. 2020;59(1):13-33.
28. Rana RH, Alam K, Gow J. Health expenditure, child and maternal mortality nexus: a comparative global analysis. BMC international health and human rights. 2018;18:1-15.
29. Kara F, Ersin İ. The effects of health expenditures to decrease infant mortality rates in OECD countries. Multidimensional perspectives and global analysis of universal health coverage: IGI Global; 2020:357-83.
30. O'Hare B, Makuta I, Chiwaula L, Bar-Zeev N. Income and child mortality in developing countries: a systematic review and meta-analysis. Journal of the Royal Society of Medicine. 2013;106(10):408-14.

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):284-294 // 10.5505/amj.2023.03604

THE EFFECTS OF VDR GENE POLYMORPHISMS AND LIFESTYLE FEATURES ON VITAMIN D LEVELS OF POST MENOPAUSAL WOMEN

Meryem Çakır[1], Esra Meltem Koç[1], Mustafa Soyöz[2], Hatice İlayhan Karahan Çöven[2], Serpil Aydogmus[3], Kaan Sozmen[4]

[1] Department of Family Medicine, Izmir Katip Celebi University Atatürk Training and Research Hospital, Izmir, Turkey
[2] Department of Medical Biology and Genetics, Izmir Katip Celebi University, Izmir, Turkey
[3]Department of Gynecology and Obstetrics, Izmir Katip Celebi University Atatürk Training and Research Hospital, Izmir, Turkey
[4]Department of Public Health, Izmir Katip Celebi University, Izmir, Turkey

Correspondence:
Meryem Çakır (e-mail: obgndrmeryem@hotmail.com)

Submitted: 12.07.2023 // Accepted: 27.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: Vitamin D deficiency is a common situation for women who are in menopause due to various reasons. This study aims to investigate the effect of VDR gene polymorphisms and lifestyle on vitamin D levels of women in menopause.

Materials and Methods: The study was planned in a cross-sectional descriptive design. Data was collected with a sociodemographic and lifestyle habits question form, and patients' blood samples were obtained for vitamin D levels and genetic tests. The data was evaluated by using SPSS 16.0 software. The logistic regression analysis model was created using the Backward elimination method, and the P-value below 0.05 was considered statistically significant.

Results: The study was carried out on 303 menopausal women. The frequency of vitamin D deficiency in patients was 71.95%. Receiving vitamin D and Omega-3 supplements and having prolonged sleep duration were found to be protective factors from vitamin D deficiency. Of the VDR gene polymorphisms, the Bsml bb genotype was found to protect from vitamin D insufficiency, while the ApaI bb genotype increased the risk of vitamin D insufficiency.

Conclusion: Vitamin D levels may be low in people who do not have sufficient sleep time. Our study found that the APA I aa genotype increased the risk of vitamin D deficiency, while the BsmI bb genotype protected from vitamin D deficiency. More studies are needed on the effects of lifestyle habits and genetic factors on serum vitamin D levels.

Keywords: Lifestyle, menopause, polymorphism, vitamin D.

Introduction

For women who are in menopause, vitamin D deficiency is more common than the others due to reasons such as decreased amount of 7-Dehydrocholesterol in the skin, decreased renal 1-α hydroxylase activity, increased body fat mass and decreased bioavailability of vitamin D, which is a fat-soluble vitamin.[1] Vitamin D deficiency generally causes muscle weakness and muscle aches. Also, it is associated with the formation of some cancers, weak immune modulation, development of cardiovascular diseases, and impaired sexual function.[1,2]

Studies have determined that genetic variations are related to approximately 65% of vitamin D levels.[3] Many new single nucleotide polymorphisms (SNPs) have been identified for the vitamin D receptor (VDR) gene located on chromosome 12q12-14.[4] It is known that genetic variations in VDR occur in the specific regions for BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236) and FokI (rs2228570).[5] Vitamin D is an important hormone that provides calcium balance and bone mineralization in the body and acts by binding to the VDR.[6] Although VDR is mostly expressed in small intestine and osteoblasts, it is found in many human tissues.[7] FokI, BsmI, ApaI, and TaqI are the most common VDR gene polymorphisms associated with various systems such as calcium metabolism, cell proliferation and the immune system. The relation between these polymorphisms and several diseases has been reported.[5,8,9]

The basis of vitamin D production is the synthesis in the skin during exposure to sunlight.[10] Vitamin D that is taken from food sources is very limited. Therefore, it is beneficial to take it in the form of supplements.[10,11] Even though it is shown in studies that vitamin D levels can be affected by the lifestyles of people, such as exercising, smoking, and receiving multivitamins, there is not enough information in the literature about lifestyle habits that affect vitamin D levels.[12]

In this study, we aimed to investigate the effects of FokI, BsmI, ApaI, and TaqI VDR gene polymorphisms and lifestyle habits on vitamin D levels of menopausal women.

Materials and Methods

The design of the study was cross-sectional. Menopausal women between the ages of 30-70 are included in the study. The presence of menopause was determined in women who had at least one year without menstrual bleeding and had a physician-diagnosed or total abdominal hysterectomy and bilateral salpingo-oophorectomy or a history of bilateral salpingo-oophorectomy. Patients who had cancer and received vitamin D treatment within the past three months were excluded from the study. Firstly, Patients were informed about the study and informed consent was obtained. In order to collect data in the study, a data form that questioned the

sociodemographic characteristics and lifestyle habits was used, and blood samples were obtained from the patients for vitamin D levels and genetic results.

Data Collection Form

Education level (Primary school and lower, Middle school and high school or University and upper), body mass index (average (≤24.99 kg/m2), overweight (25-29.99 kg/m2) and obese (≥ 30 kg/m2)) divided into three groups; marital status (single/married) and doing sportive activity regularly (no/yes) divided into two groups. The data collection form questioned lifestyle and eating habits that may affect vitamin D levels. Information on wearing closed clothing (wearing clothing that continually covers the whole body), regular nutrition (3 meals a day at close hours), using a vitamin D preparation voluntarily beside as treatment, and using Omega-3 supplements voluntarily was coded as no/yes. Age and total sleep time in one day were coded as continuous variables. Consumption amounts (average number of days consumed in a month) of foods rich in vitamin D (milk, cheese, chicken, eggs, butter, clotted cream, cabbage, spinach, corn) were also questioned and recorded as continuous variables.

Vitamin D measurement

25-Hydroxy Vitamin (D25(OH)D3) was used to determine the vitamin D level because it had a long half-life. The active metabolite, 1.25-dihydroxy vitamin D3 (1.25(OH)2D3) levels decline only in severe deficiency and may not reflect levels in target tissues where it is generated. Accordingly, it was not used to determine the level of vitamin D. Less than 20 ng/mL D25(OH)D3 was defined as a deficiency, 20-30 ng/mL D25(OH)D3 was defined as insufficiency and higher than 30 ng/mL D25(OH)D3 was defined as sufficient. Vitamin D level was measured using the chemiluminescence microparticle immunoassay (CMIA) method in the Advia Centaur XP (Siemens, Germany) device.

Genetic study design

DNA isolation from peripheral blood was performed using the Genomic DNA Mini Kit (Invitrogen, USA). PCR amplified the obtained DNA samples. Post-PCR amplification products were run on a 1% agarose gel and visualized on a UV transilluminator. BsmI (rs1544410), TaqI (rs731236), FokI (rs2228570) and ApaI (rs7975232) VDR gene polymorphisms were detected by PCR-RFLP method. The primers required to detect BsmI polymorphism were determined based on the study of Györffy et al., TaqI, and ApaI polymorphisms were determined based on the study of Yavuz et al., and the primers required to detect FokI polymorphism were determined based on Bell et al.'s study.[13,14,15]

PCR products were discontinued according to the recommendation of the firm (Fermantas, USA), which provides restriction enzymes. The incised DNA fragments were applied electrophoresis in a 2% agarose gel and were examined under UV light. To determine the BsmI polymorphism, bands were obtained at 191 bp (base pair) for the BB genotype, 191, 115, 76 bp for the Bb genotype, and 115, 76 bp for the bb genotype. While determining TaqI polymorphism, bands were obtained at 495, 245 bp for the TT genotype, 495, 290, 245, 205 for the Tt genotype and 290, 245, 205 bp for the tt genotype. Bands were obtained at 265 bp for the FF genotype, 196, 198 bp for the Ff genotype, and 69 bp for the ff genotype to determine the FokI polymorphism. Bands in 740 bp for the AA genotype, 740,530, 210 bp for the Aa genotype and 530, 210 bp for the aa genotype were obtained to determine ApaI polymorphism. The primers required for the amplification of the VDR gene and the lengths of the amplification products are shown in Table 1.

Table 1. Primers required for amplification of VDR gene and lengths of amplification products

Name	Primer sequences	Amplification product
BsmI	5-agt gtg cag gcg att cgt ag-3	191 bp*
	5-ata ggc aga acc atc tct cag-3	
ApaI& TaqI	5-cag agc atg gac agg gag caa-3	740 bp
	5-gca act cct cat ggc tga ggt ctc-3	
FokI	5- gat gcc agc tgg ccc tgg cac tg-3	273 bp
	5- atg gaa aca cct tgc ttc ttc tcc ctc-3	

VDR: vitamin D receptor; *Bp: base pair

Statistical analysis

Statistical analysis was performed using SPSS version 16. In this study, the distribution of the data was tested with Kolmogorov-Smirnov. The statistical comparison of the mean values of two independent groups was performed using the Mann-Whitney U test. The between-group comparisons of categorical variables were performed using the Chi-square test. Independent effects of vitamin D on the different identifying factors were examined with logistic regression models. The Hosmer-Lemeshow test was used for model fit. Independent variables with a statistically significant relationship of $p \leq 0.250$ according to bivariate analysis were included in the multivariate logistic regression model with a "Backward" elimination method. A p-value lower than 0.05 was considered statistically significant.

Results

The study was carried out on 303 menopausal women. The median age (25-75p) of women participating in the study was 53 (50-57), and the frequency of vitamin D deficiency in patients was 71.95% (n = 218). In univariate analyses, those with healthy BMI and those using vitamin D and Omega-3 supplements had a higher frequency of healthy vitamin D levels (p = 0.012, p <0.001, p = 0.007, respectively) (Table 2).

Table 2. The relationship between vitamin D levels and sociodemographic characteristics

	Vitamin D Level			Statistical analysis
Sociodemographic characteristics	**Deficiency n (%) (Group I)**	**Insufficiency n (%) (Group II)**	**Normal n (%) (Group III)**	**p-value**
Body Mass Index (BMI)				
Normal (18.5-24.5)	38 (57.58)	13 (19.70)	15 (22.73)	0.012*
Overweight (25-29,9)	82 (70.69)	17 (14.66)	17 (14.66)	
Obese (30-40)	98 (80.99)	14 (11.57)	9 (7.44)	
Educational status				
Primary school and lower	149 (76.80)	23 (11.86)	22 (11.34)	0.064
Middle school and high school	47 (61.04)	14 (18.18)	16 (20.78)	
University and upper	22 (68.75)	7 (21.88)	3 (9.38)	
Regular diet				
No	62 (69.66)	13 (14.61)	14 (15.73)	0.762
Yes	156 (72.90)	31 (14.49)	27 (12.62)	
marital status				
Single	13 (56.52)	6 (26.09)	4 (17.39)	0.184
Married	205 (73.21)	38 (13.57)	37 (13.21)	
Regular sports				
No	169 (74.78)	28 (12.39)	29 (12.83)	0.129
Yes	49 (63.64)	16 (20.78)	12 (15.58)	
Take vitamin supplements				
No	202 (75.94)	39 (14.66)	25 (9.40)	<0.001*
Yes	16 (43.24)	5 (13.51)	16 (43.24)	
Take fish oil				
No	213 (72.95)	43 (14.73)	36 (12.33)	0.007*
Yes	5 (45.45)	1 (9.09)	5 (45.45)	
Wearing closed clothes				
No	100 (68.97)	24 (16.55)	21 (14.48)	0.517
Yes	118 (74.68)	20 (12.66)	20 (12.66)	
Continuous Variables	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	
Age	53 (40-71)	53.5 (43-69)	52 (40-67)	0.059
Sleep time	7 (1-10)	7 (3-10)	7 (4-10)	0.110
Milk consumption (days per month)	10 (0-30)	10 (0-30)	10 (1-30)	0.572
Cheese consumption (days a month)	30 (0-30)	30 (0-30)	30 (2-30)	0.374
Fish consumption (days a month)	4 (0-30)	4 (0-20)	4 (0-15)	0.807
Chicken consumption (days a month)	4 (0-15)	4 (0-8)	4 (0-15)	0.302
Egg consumption (days a month)	30 (0-30)	22.5 (0-30)	30 (0-30)	0.240
Butter consumption (days a month)	8 (0-30)	10 (0-30)	15 (0-30)	0.423
Clotted cream consumption (day in a month)	0 (0-30)	0 (0-30)	0 (0-4)	0.108
Corn oil consumption (day in a month)	0 (0-30)	0 (0-4)	0 (0-20)	0.102

*p value < 0.05 (row percentages have been showed.)

Considering the relationship between VDR gene polymorphisms and vitamin D levels, women with ApaI aa genotype were found to have a lower frequency of normal vitamin D levels (p = 0.029). In univariate analyses, no statistically significant difference was found between other VDR gene polymorphisms and vitamin D levels (p> 0.05) (Table 3).

Table 3. The relationship between vitamin D level and VDR gene polymorphism

	Vitamin D Level			Statistical analysis
VDR gene polymorphism	**Deficiency n (%) (Group I)**	**Insufficiency n (%) (Group II)**	**Normal n (%) (Group III)**	**p value**
Bsml				
BB	33 (78.57)	6 (14.29)	3 (7.14)	0.602
Bb	119 (73.01)	22 (13.50)	22 (13.50)	
bb	66 (67.35)	16 (16.33)	16 (16.33)	
B allele	185 (74.90)	34 (13.77)	28 (11.34)	0.159
b allele	251 (69.92)	54 (15.04)	54 (15.04)	
Taq				
TT	89 (67.94)	23 (17.56)	19 (14.50)	0.346
Tt	101 (77.10)	13 (9.92)	17 (12.98)	
tt	28 (68.29)	8 (19.51)	5 (12.20)	
T allele	279 (70.99)	59 (15.01)	55 (13.99)	0.471
t allele	157 (73.71)	29 (13.62)	27 (12.68)	
Fok1				
FF	138 (73.40)	28 (14.89)	22 (11.70)	0.657
Ff	72 (69.90)	15 (14.56)	16 (15.53)	
ff	8 (66.67)	1 (8.33)	3 (25)	
F allele	348 (72.65)	71 (14.82)	60 (12.53)	0.286
f allele	88 (69.29)	17 (13.39)	22 (17.32)	
Apa				
AA	80 (72.07)	13 (11.71)	18 (16.22)	0.029*
Aa	96 (70.59)	18 (13.24)	22 (16.18)	
aa	42 (75)	13 (23.21)	1 (1.79)	
A allele	256 (71.51)	44 (12.29)	58 (16.20)	0.180
a allele	180 (72.58)	44 (17.74)	24 (9.68)	

VDR: vitamin D receptor; *p value < 0.05

According to the logistic regression analysis based on vitamin D levels, receiving vitamin D and omega-3 supplements and prolonged sleep duration were protective factors for vitamin D deficiency (respectively; p <0.001, p = 0.020, p = 0.014). Of the VDR gene polymorphisms, the BsmI bb genotype was found to protect from vitamin D insufficiency, while the ApaI aa genotype increased the risk of vitamin D insufficiency (respectively; p = 0.013, p = 0.015) (Table 4).

Table 4. Logistic Regression Analysis on Normal Vitamin D Level

Determining factors	Odds ratio (Univariate)			Odds ratio (Multivariate)		
	β	%95 CI	p-value	β	%95 CI	p-value
Age	0.938	0.884-0.995	0.033	0.962	0.896-1.033	0.289
Education Status						
middle	2.051	1.011-4.159	0.047	0.832	0.303-2.288	0.722
high	0.809	0.227-2.877	0.743	0.267	0.048-1.480	0.131
Be married	0.723	0.233-2.244	0.575	0.495	0.102-2.396	0.382
Body mass index						
25-29,9	0.584	0.270-1.264	0.172	0.825	0.309-2.206	0.702
30-40	0.273	0.112-0.665	0.004	0.327	0.104-1.031	0.056
Regular sports	1.254	0.605-2.599	0.543	0.674	0.257-1.765	0.421
Take vitamin supplements	7.345	3.401-15.860	0<0.001	8.564	3.388-21.646	<0.001*
Take fish oil	5.926	1.720-20.417	0.005	5.947	1.330-26.599	0.020*
Sleep time	1.171	0.951-1.441	0.136	1.406	1.071-1.845	0.014*
Clotted cream consumption	0.878	0.712-1.082	0.222	0.787	0.568-1.092	0.151
Egg consumption	1.025	0.992-1.059	0.141	1.016	0.974-1.058	0.467
Corn oil consumption	0.969	0.860-1.091	0.599	0.959	0.837-1.097	0.540
Bsml						
Bb	2.028	0.577-7.132	0.270	3.301	0.684-15.931	0.137
bb	2.537	0.698-9.221	0.158	8.376	1.560-44.969	0.013*
Taq						
Tt	0.879	0.435-1.778	0.720	0.953	0.331-2.746	0.929
tt	0.819	0.285-2.350	0.710	1.587	0.303-8.314	0.585
Fok1						
Ff	1.388	0.693-2.778	0.355	1.221	0.519-2.972	0.648
ff	2.515	0.633-10.000	0.190	1.991	0.308-12.884	0.470
Apa						
Aa	0.997	0.505-1.969	0.993	0.873	0.377-2.018	0.750
aa	0.094	0.012-0.723	0.023	0.067	0.007-0.597	0.015*

β = regression coefficient, *p value < 0.05

Discussion

The study aimed to investigate the effects of lifestyle habits and VDR gene polymorphisms on vitamin D levels in menopausal women. At the end of the study, we found that receiving vitamin D supplements, Omega-3 supplements, and increased sleep duration prevented the risk of vitamin D deficiency. We concluded that the BsmI bb genotype, one of the VDR gene polymorphisms, protects from vitamin D deficiency, while the ApaI aa genotype increases the risk of vitamin D deficiency.

Our study found that taking vitamin D and Omega-3 supplements are protective factors against Vitamin D deficiency. The systemic review and meta-analysis by Alhabeeb et al. stated a significant increase in serum vitamin D levels, especially after eight weeks of omega-3 supplementation usage.[16] A randomized controlled trial by Laing et al. concluded that omega-3 and vitamin D supplements increased serum vitamin D levels.[17] Vitamin D is first hydroxylated to 25-hydroxyvitamin D and then transformed into the active form 1,25-Dihydroxy Vitamin D with the help/activation of the renal 1a-Hydroxylase enzyme. It is thought that Omega-3 fatty acid increases serum vitamin D levels by increasing external 1α-hydroxylase activity or by suppressing the 24-hydroxylase enzyme that catabolizes 1,25-Dihydroxy Vitamin D.[18] It is known that vitamin D has effects on various systems such as the cardiovascular system, hematopoietic system, and urogenital system besides its effects on bone mineral and calcium metabolism.[2,3] Therefore, serum vitamin D levels might be more critical than expected. Patients could be advised to take vitamin D and Omega-3 supplements to increase vitamin D levels.

In our study, we found that every 1-hour additional time to patients' sleep duration is protective against the risk of vitamin D deficiency. Liu et al. also concluded that sufficient sleep duration increases the levels of vitamin D.[19] Studies have also reported a positive relationship between increased sleep quality and high serum vitamin D levels.[20] The literature data are insufficient to explain sleep and serum vitamin D levels. The positive effect of vitamin D on melatonin, known as the sleep hormone, or the presence of VDR in the hypothalamus region where sleep is regulated, may be responsible for the relationship between sleep duration and quality and serum vitamin D level. More studies are needed to explain the direction and mechanism of action between vitamin D level and sleep duration and quality.[20,21] More studies are needed to explain the direction and mechanism of action between vitamin D level and sleep duration and quality.

As a result of our study found that ApaI aa genotype increases the risk of vitamin D deficiency, and the BsmI bb genotype is protective against vitamin D deficiency. When we look at the literature, it was concluded that the BsmI bb genotype protects against vitamin D deficiency in the studies of Divanoglou et al., similar to our study.[22] Likewise, the studies of Sinharay et al. in India also support the conclusion that the BsmI bb genotype protects against vitamin D deficiency.[23] Although they found lower vitamin D levels in women with bb genotype in their

study by Ahmad et al., They did not find a statistically significant difference between BB and Bb genotypes.[24] Also, we found that FokI and TaqI gene polymorphisms did not affect serum vitamin D levels. However, Ma et al. have found that vitamin D levels may change depending on FokI and TaqI VDR polymorphisms.[25]

When we look at the studies conducted in Turkey, there was no significant difference between BsmI, ApaI, TaqI and FokI polymorphisms and serum vitamin D levels in the studies of Albas et al. and Korucu et al.[26,27] In the study of Elkama et al., serum vitamin D level was found to be higher in patients with FokI ff, BsmI Bb, TaqI Tt and ApaI AA genotypes.[28] Our study concluded that people with the Apa AA genotype had higher serum vitamin D than those with the aa genotype. These differences between genetic polymorphisms and vitamin D levels may exist due to ethnic and geographic reasons, lifestyle differences, or laboratory differences between studies. Based on the current literature data, it is impossible to explain the relationship between VDR gene polymorphisms and vitamin D levels.

One of the study's limitations may be due to/caused by the patients selected only from a tertiary healthcare institution. Similar studies need to be done in other health institutions. Another limitation of the study is that the patient's responses to the questions about their lifestyle habits are based on self-report and not standardizing the vitamin D and Omega 3 supplements they use.

In conclusion, vitamin D and Omega 3 supplements can protect patients from vitamin D deficiency. It could be recommended for all patients to use supplement preparations in a certain way by measuring vitamin D levels periodically to protect patients from hypervitaminosis. It should be kept in mind that vitamin D levels may be low in people who do not have enough sleep duration. Our study found that the ApaI aa genotype increases the risk of vitamin D deficiency, while the BsmI bb genotype was protective against vitamin D deficiency. Considering that vitamin D deficiency may cause serious effects, therefore more studies are essential on this subject.

Ethical Considerations: The ethical approval of this study was received with decision no.295 (date 20.12.2017) from the Izmir Katip Çelebi University Faculty of Medicine Ethics Committee.

Conflict of Interest: Izmir Katip Celebi University Scientific Research Projects Unit covered the financial fees required for the study. The authors declare no conflict of interest.

References

1. Marino R, Misra M. Extra-Skeletal Effects of Vitamin D. Nutrients. 2019;11(7):1460.
2. Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med. 2019;380:33–44.
3. Ruiz-Ballesteros AI, Meza-Meza MR, Vizmanos-Lamotte B, et al. Association of Vitamin D Metabolism Gene Polymorphisms with Autoimmunity: Evidence in Population Genetic Studies. Int J Mol Sci. 2020;21(24):9626.
4. Jianhai T, Jian L, Long Z, et al. Vitamin D receptor gene polymorphisms and its interactions with environmental factors on renal cell carcinoma risk. Genes Environ. 2021;18;43(1):19.
5. Apaydın M, Beysel S, Eyerci N, et al. The VDR gene FokI polymorphism is associated with gestational diabetes mellitus in Turkish women. BMC Med Genet. 2019;16;20(1):82.
6. Jiang LL, Zhang C, Zhang Y, et al. Associations between polymorphisms in VDR gene and the risk of osteoporosis: a meta-analysis. Arch Physiol Biochem. 2022;128(6):1637-44.
7. Sirajudeen S, Shah I, Menhali AA. A Narrative Role of Vitamin D and Its Receptor: With Current Evidence on the Gastric Tissues. Int J Mol Sci. 2019;20(15):3832.
8. Imani D, Razi B, Khosrojerdi A, et al . Vitamin D receptor gene polymorphisms and susceptibility to urolithiasis: a meta-regression and meta-analysis. BMC Nephrol. 2020;263.
9. Shirwaikar Thomas A, Criss ZK, Shroyer NF, et al. Vitamin D Receptor Gene Single Nucleotide Polymorphisms and Association With Vitamin D Levels and Endoscopic Disease Activity in Inflammatory Bowel Disease Patients: A Pilot Study. Inflamm Bowel Dis. 2021;27(8):1263-9.
10. Polzonetti V, Pucciarelli S, Vincenzetti S, et al. Dietary Intake of Vitamin D from Dairy Products Reduces the Risk of Osteoporosis. Nutrients. 2020;12(6):1743.
11. Fraser DR. Physiological significance of vitamin D produced in skin compared with oral vitamin D. J Nutr Sci. 2022;11:e13.
12. Vieira LA, Dos Santos AA, Peluso C, et al. Influence of lifestyle characteristics and VDR polymorphisms as risk factors for intervertebral disc degeneration: a case-control study. Eur J Med Res. 2018;23(1):11.
13. Györffy B, Vásárhelyi B, Krikovszky D, et al. Gender-specific association of vitamin D receptor polymorphism combinations with type 1 diabetes mellitus. Eur J Endocrinol. 2002;147(6):803-8.
14. Gogas Yavuz D, Keskin L, Kıyıcı S, et al. Vitamin D receptor gene BsmI, FokI, ApaI, TaqI polymorphisms and bone mineral density in a group of Turkish type 1 diabetic patients. Acta Diabetol. 2011;48(4):329-36.
15. Bell NH, Morrison NA, Nguyen TV, et al. ApaI polymorphisms of the vitamin D receptor predict bone density of the lumbar spine and not racial difference in bone density in young men. J Lab Clin Med. 2001;137(2):133-40.

16. Alhabeeb H, Varkaneh HK, Tan SC, et al. The influence of omega-3 supplementation on vitamin D levels in humans: a systematic review and dose-response meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr. 2022;62(11):3116-23.
17. Brennan Laing B, Cavadino A, Ellett S, et al. Effects of an Omega-3 and Vitamin D Supplement on Fatty Acids and Vitamin D Serum Levels in Double-Blinded, Randomized, Controlled Trials in Healthy and Crohn's Disease Populations. Nutrients. 2020;12:1139.
18. Lee SM, Lee MH, Son YK, et al. Combined Treatment with Omega-3 Fatty Acid and Cholecalciferol Increases 1,25-Dihydroxyvitamin D Levels by Modulating Dysregulation of Vitamin D Metabolism in 5/6 Nephrectomy Rats. Nutrients. 2019;11(12):2903.
19. Liu X, Ke L, Ho J, et al. Sleep duration is associated with vitamin D deficiency in older women living in Macao, China: A pilot cross-sectional study. PLoS One. 2020;15(3):e0229642.
20. Abboud M. Vitamin D Supplementation and Sleep: A Systematic Review and Meta-Analysis of Intervention Studies. Nutrients. 2022;14(5):1076.
21. Gao Q, Kou T, Zhuang B, et al. The Association between Vitamin D Deficiency and Sleep Disorders: A Systematic Review and Meta-Analysis. Nutrients. 2018;10(10):1395.
22. Divanoglou N, Komninou D, Stea EA, et al. Association of Vitamin D Receptor Gene Polymorphisms with Serum Vitamin D Levels in a Greek Rural Population (Velestino Study). Lifestyle Genom. 2021;14(3):81-90.
23. Sinharay M, Roy S, Dasgupta A. Association of Serum Vitamin D Level with its Receptor Gene Polymorphism BSML in Beta Thalassemia Major Patients from East India. Kathmandu Univ Med J (KUMJ). 2018;16(64):317-22.
24. Ahmad I, Jafar T, Mahdi F, et al. Association of Vitamin D Receptor (FokI and BsmI) Gene Polymorphism with Bone Mineral Density and Their Effect on 25-Hydroxyvitamin D Level in North Indian Postmenopausal Women with Osteoporosis. Indian J Clin Biochem. 2018;33(4):429-37.
25. Ma L, Wang S, Chen H, et al. Diminished 25-OH vitamin D3 levels and vitamin D receptor variants are associated with susceptibility to type 2 diabetes with coronary artery diseases. J Clin Lab Anal. 2019;3:e23137.
26. Albas S, Koc EM, Nemli SA, et al. Vitamin D Levels and Vitamin D Receptor (VDR) Gene Polymorphisms in Inactive Hepatitis B Virus Carriers. J Coll Physicians Surg Pak. 2021;30(4):393-8.
27. Korucu B, Tukun A, Helvacı O, et al. Vitamin D receptor polymorphisms and bone health after kidney transplantation. Turk J Med Sci. 2021;51(2):802-12.
28. Elkama A, Orhan G, Karahalil B. Association of vitamin D receptor polymorphisms with vitamin D and calcium levels in Turkish multiple sclerosis patients. Neurodegener Dis Manag. 2022;12(6):323-31.

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):295-311 // 10.5505/amj.2023.90836

BIBLIOMETRIC ANALYSIS OF MEDICAL SPECIALITY DISSERTATION STUDIES IN FAMILY MEDICINE DEPARTMENTS AND CLINICS BETWEEN 2000-2020

Ayşe Karakullukçu[1], Cüneyt Ardıç[2]

[1]Konaklar Family Health Center, Ortahisar, Trabzon

[2]Recep Tayyip Erdogan University Faculty of Medicine, Department of Family Medicine, Rize

Correspondence:

Ayşe Karakullukçu (e-mail: draysesahinn@gmail.com)

Submitted: 05.07.2023 // Accepted: 14.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine

Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: This study aimed to conduct a bibliometric analysis of medical specialty dissertation studies conducted in Family Medicine departments and clinics between 2000 and 2020.

Materials and Methods: This descriptive study was conducted between 2000 and 2020 by examining 1628 dissertations in the field of family medicine specialization. In the first process, information regarding the dissertation was recorded. In the second process, the conversion of dissertations into articles was evaluated. The journal indexes, Q classification and citation numbers of the dissertations publications were determined.

Results: 1009 (61.98%) of the students were female. 977 (60.01%) of the dissertations belonged to university hospitals. The number of dissertations in which the title of advisor associate professor was 579 (35.56%). Preventive health services were the most frequently selected topic in the dissertations (8.66%). Descriptive/cross-sectional studies were the most preferred research type, with 1414 (86.85%) dissertations. Project support, laboratory, and radiological tests have decreased significantly over the years ($p<0.05$). 458 (28.13%) of the dissertations were published in any journal. Considering the databases of the publications, 92 (20.09%) were published in SCI/SCI-Expanded.

Conclusion: About a quarter of the theses have been published in any journal, and there has been a noticeable increase in publications in international indexes in recent years. Theses with research type of case-control, intervention, laboratory and radiologic test use were more likely to be published. Concordantly, it is advised to give precedence to studies situated higher on the evidence pyramid, allocate sufficient funds to finance research, and increase backing for projects.

Keywords: Family medicine, family medicine specialization education, family medicine dissertation, scientific publication.

Introduction

The clinical specialty of family practice combines clinical, biological, and behavioral sciences while providing multidimensional and uninterrupted health services to individuals, families, and society, which constitutes the first point of medical contact in the health system, dealing with all health problems regardless of age, gender or any other characteristics of the person seeking service.[1,2]

In Turkey, family medicine has been a medical discipline and specialty for over 30 years. Specialty training began in 1985 at training and research hospitals in Ankara, Istanbul, and Izmir. Nowadays, more than 250 instructors and approximately 3750 research assistants continue their education in 86 family medicine training clinics approved by the Medical Specialization Board (TUK).[3]

In order to graduate, medical specialty students are required to identify a topic related to the specialty they are studying and write a dissertation.[4] The dissertation production and writing process has many contributions to the research assistant. In addition to conducting a scientific study, it provides the opportunity to learn how to review_the literature and read articles with a critical perspective. Therefore, the dissertation preparation process should be viewed as a theoretical and practical training opportunity.[5] The process of writing a dissertation, which should be a process in which possibilities are turned into opportunities and training is received, has now begun to be seen as an obstacle and obligation only to take the specialization exam.[6]

Undoubtedly, producing an original study on the subject of interest and contributing to the literature that has never been conducted before is a challenging and demanding process for researchers. Quality scientific research requires using qualified information, avoiding plagiarism, and correctly utilizing academic language. This challenging process can be managed through a planned and balanced working approach.[7]

Several studies were identified when reviewing the literature on family medicine specialty dissertations. Yaman et al. comprehensively analyzed 140 specialty dissertations between 1981 and 2008. Similarly, Mengüllüoğlu and Ünlüoğlu conducted research involving 492 specialty dissertations from 2005 to 2015. The article by Üçer and Keten, published in 2016, investigated the publication status of 384 family medicine specialty dissertations as scientific articles.[8-10] In our study, we aimed to conduct a bibliometric analysis of medical specialty dissertation studies prepared by family medicine specialty students between 2000-2020 and present them comprehensively and up to date.

Materials and Methods

Type of Study

This descriptive study retrospectively examines the bibliometric analysis of medical specialty dissertation studies conducted in Family Medicine Departments and Clinics between 2000-2020.

Data Collection Method

Within the scope of the study, all dissertations in the field of family medicine specialization between January 1, 2000, and January 1, 2020, which were included in the thesis archive page of the National Thesis Center (https://tez.yok.gov.tr/UlusalTezMerkezi/) database of the Council of Higher Education (YÖK) were examined. Theses that had "permitted" access to dissertation content were selected, and 1630 medical specialty dissertations were included in the study. The dissertations of 2020, 2021, and 2022 were not included in the study, considering the process of dissertations becoming publications might take time. Two dissertations were excluded from the study during data analysis because one was from the Department of Forensic Medicine, and the other was from the Department of Internal Medicine. A total of 1628 theses were included in the study. After the dissertations were accessed through the YÖK National Thesis Center, information about the thesis was recorded.

The data of dissertation, number, year, name of the dissertation student; name, gender, institution, number of dissertation advisor, academic title of the dissertation advisor, subject of the dissertation, type of research, number of samples, place of the dissertation (hospital / field), number of centers where the dissertation was made (single center / multi-center), presence of questionnaire use, laboratory presence of test use, presence of radiological test use, presence of project support were recorded. In the second stage, the conversion status of the dissertation into articles was examined. In this context, the publication status of the dissertation, if it was published, the year of publication, if it was published, how long after the writing date of the dissertation it was published, the name of the publication journal, the databases in which the publication journal is included, the impact factor of the publication journal, the number of citations the publication received, the dissertation student's academic career status after the dissertation, and the dissertation student's continuation of research on the same subject as the dissertation were obtained. While investigating the publication status of the dissertation, Google (https://www.google.com/), Google Scholar (http://scholar.google.com.tr/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), TR Index TÜBİTAK ULAKBİM (https://trdizin.gov.tr/) and Dergipark (https://dergipark.org.tr/tr/) search engines were searched by entering the name and surname information of the dissertation authors and advisors, the title of the dissertation in Turkish and English and keywords.

Categorization of the Data

The institution of the dissertation student was grouped as **a** university hospital, training**,** and research hospital. If there was more than one dissertation advisor, the title of the first advisor was recorded.

The subject of the dissertation was classified according to the topics in the Family Medicine book written by Robert R. Rakel and David P. Rakel.[1] The main topics were determined as Principles of Family Medicine and Family Medicine Practices. The topics outside the book were categorized according to the International Standard for Primary Care-3 (ICPC-3) classification. Topics other than the Family Medicine book and the ICPC-3 classification were categorized as "other". In case more than one topic was examined in the dissertations, the dominant topic was considered.

When categorizing the place where the thesis was conducted, it was classified into two categories: hospital and field settings. While family health centers were considered the field, studies conducted in medical faculties were recorded as hospitals. Faculties other than medical faculties were considered as fields. When evaluating the number of centers where the dissertation was conducted, dissertations conducted in a single building or institution were considered a single center.

Evaluation of Research Types

The research type of the dissertation was grouped as descriptive-cross-sectional, case-control, cohort, intervention, methodological, qualitative, quantitative-qualitative, ecological, systematic review and meta-analysis. Due to their low number, qualitative, quantitative-qualitative, ecological, systematic review and meta-analysis research types were included in the "other" group. In dissertations where more than one type of research was used, the research type that was higher in terms of evidence value in the evidence pyramid was recorded.

Evaluation of Publication Status of Dissertations

The publication status of the dissertations was grouped as publication / non-publication. In which group of databases, the publications were indexed was examined. Indexes were categorized as SCI / SCI Expanded, international**,** and national. If a journal is included in different indexes, the index in the higher academic category is taken as the basis.

Examination of Publication Journals

The impact factor of the publication journal of the publications in SCI / SCI Expanded indexes was recorded, and the journals were classified according to the Q index. While recording the Q index data of the publication journal, it was taken into consideration that it was the same year as the publication year.

Analyzing the Citations of Publications

The citations of the publications were recorded using Web of Science (https://www.webofknowledge.com), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Google Scholar (http://scholar.google.com.tr/) websites.

Examination of the Academic Career Status of Dissertation Holders

Information on the dissertation author's academic career status after the dissertation was obtained by searching the websites of the Republic of Turkey Ministry of Health, Council of Higher Education (https://akademik.yok.gov.tr/AkademikArama/) and Google. Having an academic career was defined as working at least as an assistant professor.

Statistical analysis

The SPSS 22.0 software package was used for statistical analysis of the data obtained in the study. Descriptive statistics were given as number (n) and percentage (%) for categorical parameters and mean (mean), standard deviation (SD), median, minimum (min), and maximum (max) for numerical parameters. The chi-square test was used to analyze the percentage differences between two independent groups. A p-value <0.05 was considered significant in comparative analyses.

Results

The study included 1628 dissertations between 2000 and 2020 in the field of family medicine specialization accessed through the National Thesis Center. When the number of dissertations was distributed by year, it was observed that there was a significant increase in the number of dissertations since 2014. The highest number of dissertations was reached in 2019 (Figure 1).

ANKARA MEDICAL JOURNAL

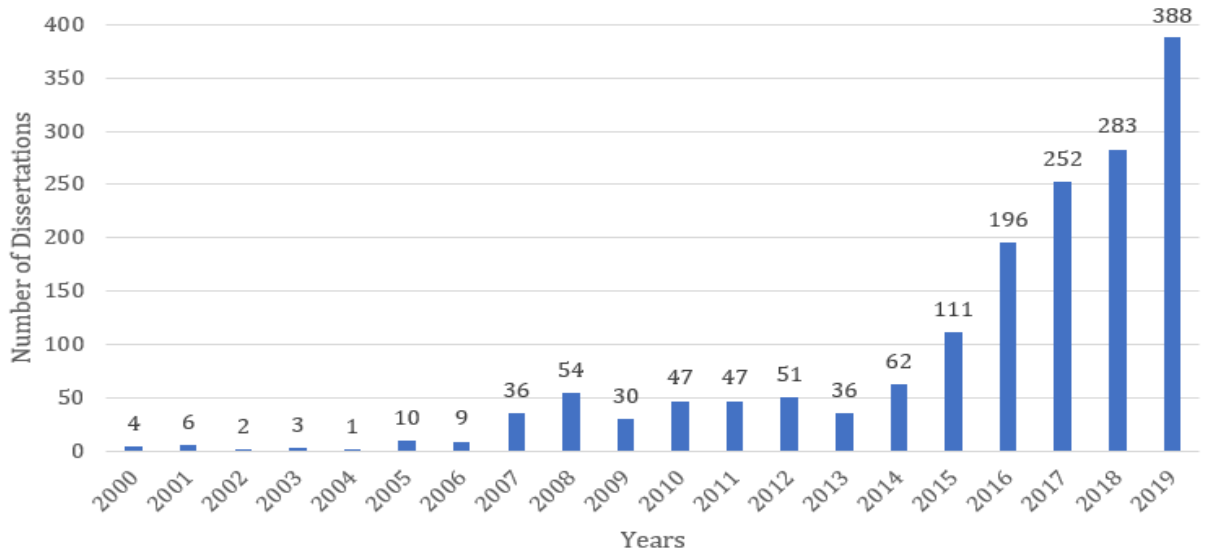


Figure 1. Distribution of the number of dissertations by years

Of the residency students, 1009 (61.98%) are women, and 977 (60.01%) dissertations belong to the university hospital. Dissertations were conducted with a supervisor at the highest rate (n=1538; 94.47%). It was determined that 579 (35.56%) were associate professors with a dissertation advisor (Table 1).

Table 1. Gender and institutional distribution of dissertation holders, number of supervisors and titles of dissertations

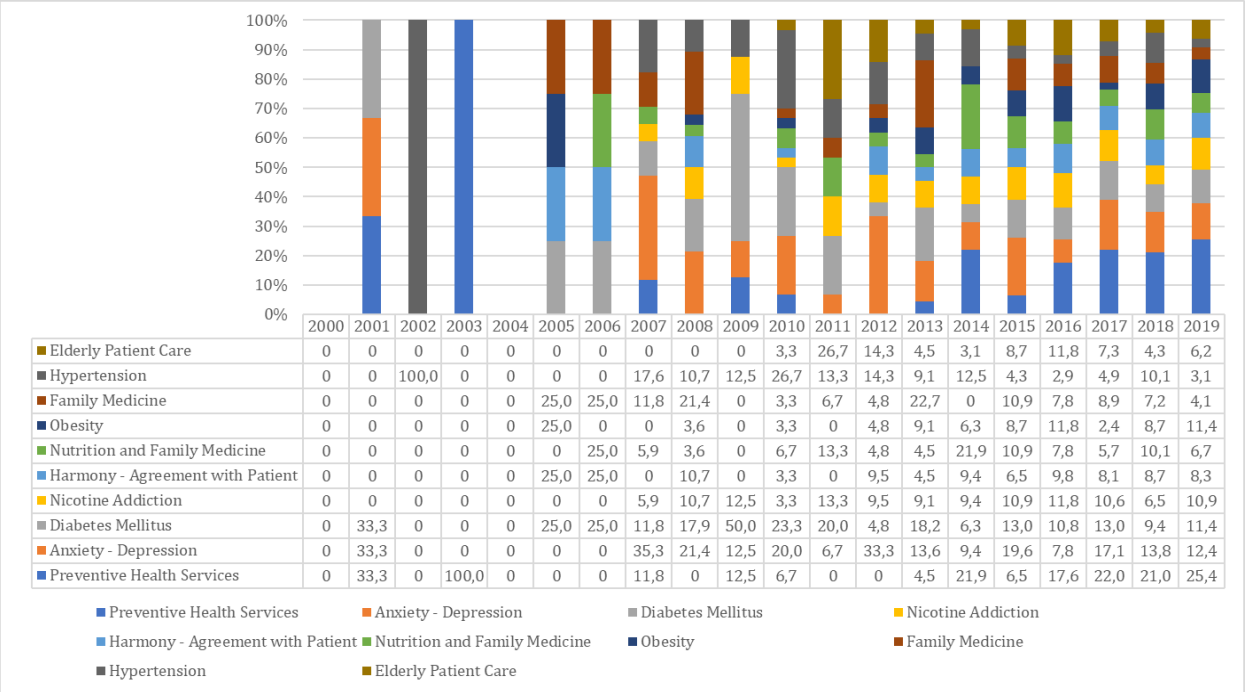
Variables	n	%
Gender		
Female	1009	61.98
Male	619	38.02
Institution		
University Hospital	977	60.01
Training and Research Hospital	651	39.9
Number of Advisors		
1	1538	94.47
2	87	5.34
3	3	0.19
Advisor Title*		
Professor	505	31.01
Associate Professor	579	35.56
Assistant Professor	353	21.68
Specialist Doctor	191	11.75

**The first advisor was considered for dissertations with more than one advisor.*

When examining the dissertations, it was observed that a majority of 1047 (64.31%) placed greater emphasis on family medicine practices. Furthermore, an analysis of the research types employed in the dissertations revealed that descriptive/cross-sectional studies were the most commonly utilized, accounting for 1414 (86.85%) of the total (Table 2).

Table 2. Distribution of dissertation topics according to titles and research types of dissertations

Topic Titles	**n**	**%**
Principles of Family Medicine	484	29.72
Family Medicine Practices	1047	64.31
ICPC-3 Coded Topics Excluded from Rakel Book	59	3.62
Other	38	2.35
Research Type		
Descriptive / Cross-Sectional Research	1414	86.85
Intervention Research	80	4.91
Case-Control	77	4.72
Methodological	26	1.59
Cohort	7	0.42
Other	24	1.51



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Elderly Patient Care	0	0	0	0	0	0	0	0	0	0	3,3	26,7	14,3	4,5	3,1	8,7	11,8	7,3	4,3	6,2
Hypertension	0	0	100,0	0	0	0	0	17,6	10,7	12,5	26,7	13,3	14,3	9,1	12,5	4,3	2,9	4,9	10,1	3,1
Family Medicine	0	0	0	0	0	25,0	25,0	11,8	21,4	0	3,3	6,7	4,8	22,7	0	10,9	7,8	8,9	7,2	4,1
Obesity	0	0	0	0	0	25,0	0	0	3,6	0	3,3	0	4,8	9,1	6,3	8,7	11,8	2,4	8,7	11,4
Nutrition and Family Medicine	0	0	0	0	0	0	25,0	5,9	3,6	0	6,7	13,3	4,8	4,5	21,9	10,9	7,8	5,7	10,1	6,7
Harmony - Agreement with Patient	0	0	0	0	0	25,0	25,0	0	10,7	0	3,3	0	9,5	4,5	9,4	6,5	9,8	8,1	8,7	8,3
Nicotine Addiction	0	0	0	0	0	0	0	5,9	10,7	12,5	3,3	13,3	9,5	9,1	9,4	10,9	11,8	10,6	6,5	10,9
Diabetes Mellitus	0	33,3	0	0	0	25,0	25,0	11,8	17,9	50,0	23,3	20,0	4,8	18,2	6,3	13,0	10,8	13,0	9,4	11,4
Anxiety - Depression	0	33,3	0	0	0	0	0	35,3	21,4	12,5	20,0	6,7	33,3	13,6	9,4	19,6	7,8	17,1	13,8	12,4
Preventive Health Services	0	33,3	0	100,0	0	0	0	11,8	0	12,5	6,7	0	0	4,5	21,9	6,5	17,6	22,0	21,0	25,4

Figure 2. Distribution of the most used subjects in dissertations by years (top 10 subjects)

The distribution of the most preferred subjects in dissertations according to years is shown in Figure 2. In recent years, preventive health services, anxiety-depression and diabetes mellitus have been particularly emphasized, whereas hypertension, care of the elderly patient and nicotine addiction have consistently found their place in the last ten years.

When the information on the materials and methods used in the dissertations was examined, we saw that most dissertations were conducted in a single center. Questionnaires were used in 1319 (81.01%) of the dissertations. Regarding the type of research, it was found in 1193 (73.28%) of the dissertations. As the years progressed, there was a statistically significant decrease ($p<0.001$) in the frequency of field studies, the use of laboratory and radiologic tests in studies and the receipt of project support, and a statistically significant increase ($p<0.001$) in the use of questionnaires and the type of research (Table 3).

Table 3. Information on materials and methods used in dissertations by years

Variables	Total	2000-2004 n (%)	2005-2009 n (%)	2010-2014 n (%)	2015-2019 n (%)	p*
Hospital / Field Study						
Hospital	1232 (75.67)	13 (81.25)[a,b]	90 (64.74)[b]	157 (64.60)[b]	972 (78.0)[a]	**<0.001**
Field	396 (24.32)	3 (18.75) [a,b]	49 (35.26)[b]	86 (35.40)[b]	258 (21.0)[a]	
Single Center / Multi-Center						
Single Center	1611 (98.95)	16 (100.00)	138 (99.28)	238 (97.94)	1219 (99.10)	0.341
Multi-Center	17 (1.05)	0 (0.00)	1 (0.72)	5 (2.06)	11 (0.90)	
Project Support Received	161 (9.88)	1 (6.25)[a,b]	24 (17.26)[b]	43 (17.69)[b]	93 (7.56)[a]	**<0.001**
Survey Usage	1319 (81.01)	10 (62.50)[a,b]	93 (66.90)[b]	184 (75.72)[b]	1032 (83.90)[a]	**<0.001**
Laboratory Usage	234 (14.37)	9 (56.3)[a]	45 (32.4)[a,b]	61 (25.1)[b]	119 (9.7)[c]	**<0.001**
Use of Radiological Testing	96 (5.89)	1 (6.25)[a,b]	15 (10.79)[b]	25 (10.28)[b]	55 (4.47)[a]	**<0.001**
Research Type Indication Status	1193 (73.28)	4 (25.00)[a,b]	41 (29.49)[b]	142 (58.43)[a]	1006 (81.78)[c]	**<0.001**

The publication status of the dissertations is shown in Figure 3. 458 (28.13%) of the dissertations were published in any journal. Reviewing the publications' databases, 92 (20.09%) were published in SCI / SCI Expanded, 190 (41.49%) in international, and 176 (38.42%) dissertations in national databases. The Q categorization of publications in SCI / SCI Expanded journals is shown in Figure 4. The average publication

period of 458 dissertations that turned into articles was 2.8±2.2 years. The latest time to become an article was found to be 17 years.

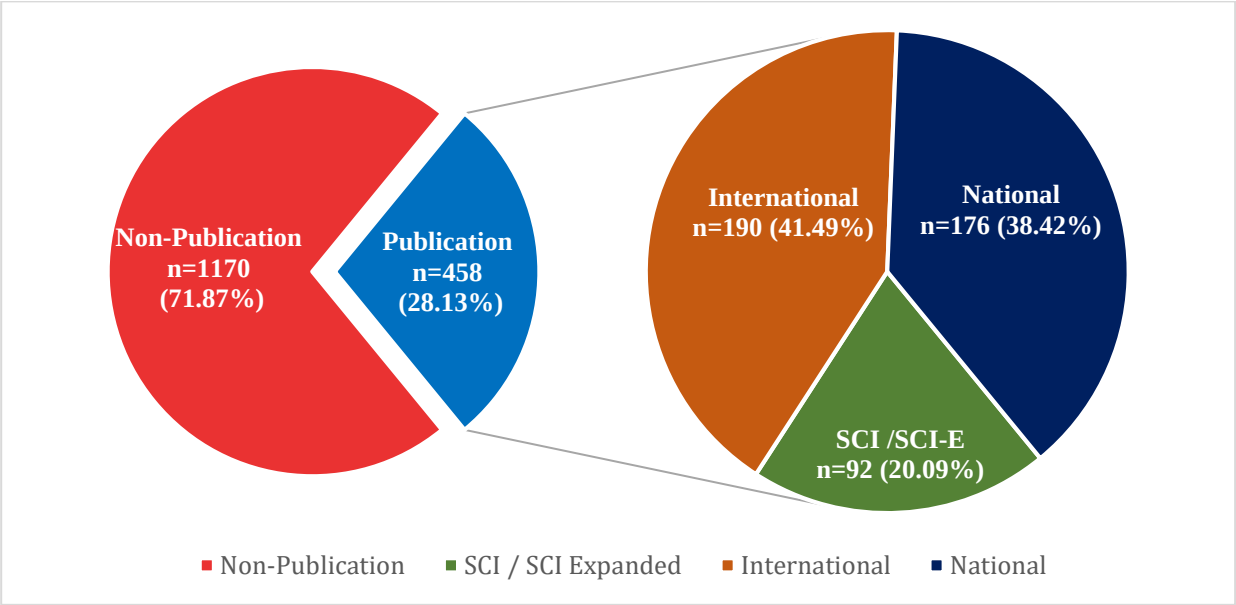


Figure 3. Publication status of dissertations

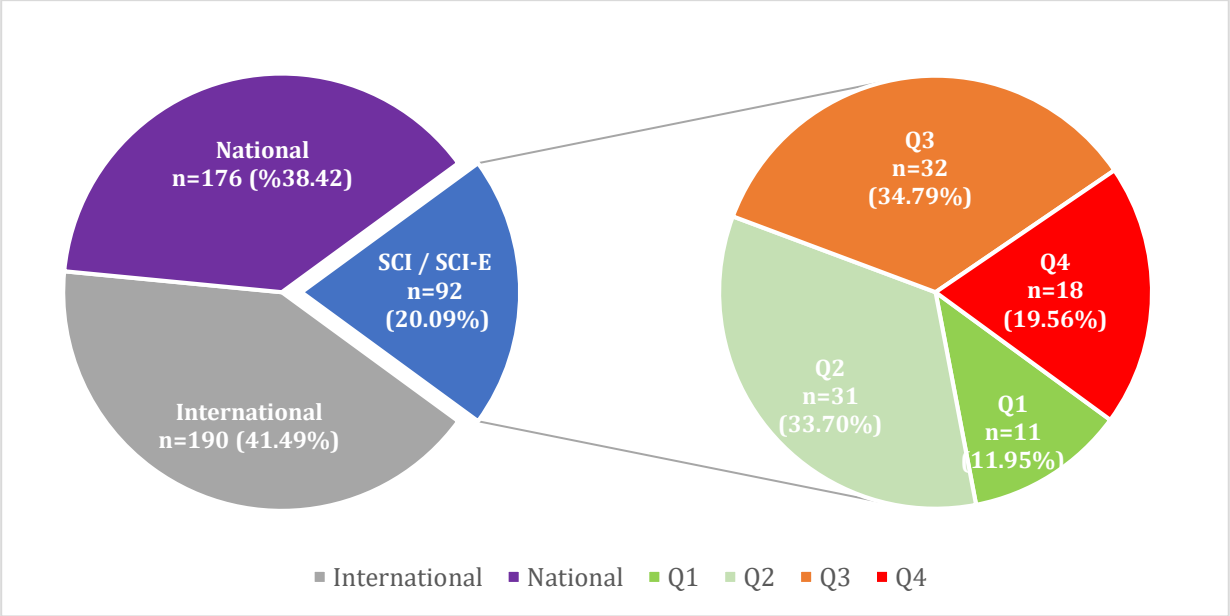


Figure 4. Indexes and Q classifications of publication journals

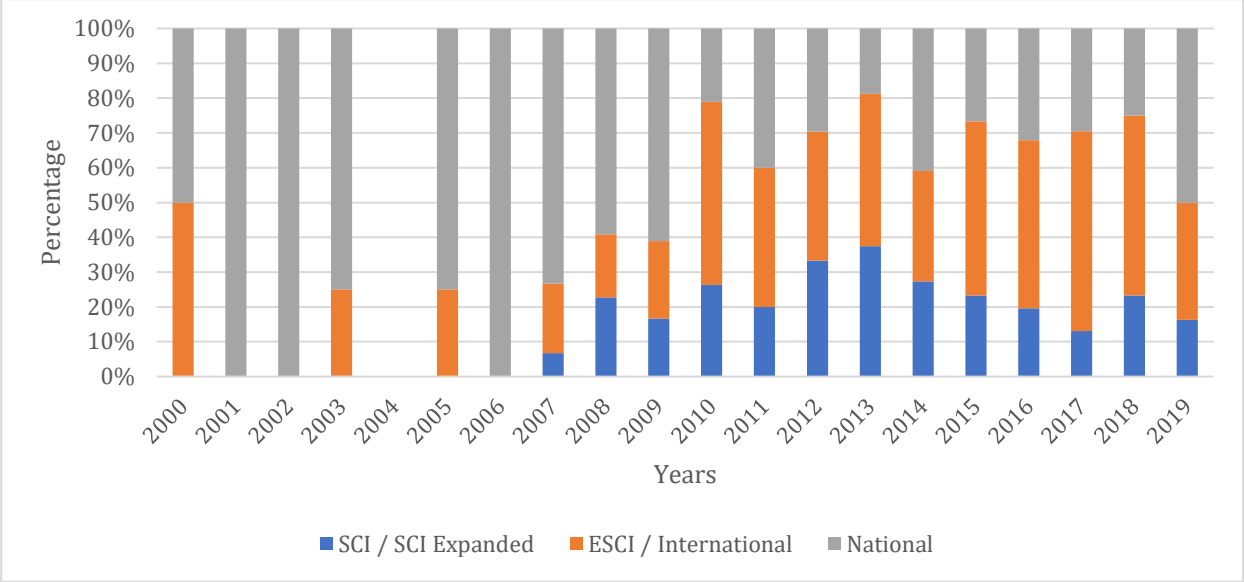


Figure 5. Journal index distribution of published dissertations

Journal index distribution of published dissertations according to years is shown in Figure 5. In recent years, there has been an increase in the percentage of publications in international journals.

The average impact factor of the publication journals was 1.5±1.3; the average number of citations was 6.0±13.2; and_the citations per year was 1.2±2.3. The post-dissertation academic career of the dissertation students and the continuation of their research on the same subject as the dissertation were examined. Of the thesis holders, 110 (6.75%) had an academic career, and 128 (7.86%) continued their research on the same subject as the dissertation.

The highest publication rate was 35.07% for dissertations with a case-control research type, 34.49% for ICPC-3 coded subjects other than Rakel's book, and 34.79% for those with anxiety and depression as the research subject. The index evaluation of the publication journals according to the research type of the dissertations, the topic of the research and the subject of the research is shown in Table 4.

The publication status of the dissertations according to the information regarding the materials and methods used in the dissertations is shown in Table 5. A statistically significant higher publication rate was found in dissertations that used laboratory and radiologic tests than in dissertations that did not ($p<0.001$; $p=0.019$, respectively).

Table 4. Evaluation of the Distribution of Dissertations According to the Type of Research, Topic of the Research and Subject of the Research with the Publication Status of the Dissertations

	Index			
	SCI / SCI-Expanded n (%)	**International n (%)**	**National n (%)**	**Non-Publication n (%)**
Research Type				
Descriptive / Cross-Sectional Research	71 (17.92)	164 (41.41)	161 (40.67)	1018 (71.99)
Intervention Research	8 (34.78)	8 (34.78)	7 (30.44)	57 (71.25)
Case-Control	9 (33.33)	12 (44.44)	6 (22.23)	50 (64.93)
Methodological	2 (33.33)	3 (50.0)	1 (16.67)	20 (76.92)
Cohort	-	1 (100.00)	-	6 (85.71)
Other	2 (40.00)	2 (40.00)	1 (20.00)	19 (79.16)
Research Topic				
Principles of Family Medicine	21 (15.78)	60 (45.11)	52 (39.11)	365 (73.29)
Family Medicine Practices	68 (22.83)	119 (39.93)	111 (37.24)	736 (71.17)
ICPC-3 Coded Topics Excluded from Rakel Book	1 (5.00)	9 (45.00)	10 (50.00)	38 (65.51)
Other	2 (28.57)	2 (28.57)	3 (42.86)	31 (81.57)
Research Subject (n=788)				
Preventive Health Services	4 (10.27)	14 (35.89)	21 (53.84)	102 (72.34)
Anxiety - Depression	9 (22.50)	11 (27.50)	20 (50.00)	75 (65.21)
Diabetes Mellitus	4 (13.80)	15 (51.72)	10 (34.48)	70 (70.70)
Nicotine Addiction	6 (31.59)	9 (47.36)	4 (21.05)	56 (74.66)
Harmony - Agreement with the Patient	4 (40.00)	4 (40.00)	2 (20.0)	53 (84.12)
Nutrition and Family Medicine	2 (14.29)	7 (50.00)	5 (35.71)	49 (77.77)
Obesity	6 (28.58)	11 (52.38)	4 (19.04)	40 (65.57)
Family Medicine	-	8 (47.06)	9 (52.94)	43 (71.66)
Hypertension	4 (22.22)	4 (22.22)	10 (55.56)	40 (68.96)
Elderly Patient Care	6 (33.36)	8 (44.44)	4 (22.22)	35 (66.03)

Table 5. Publication status of dissertations according to the information on materials and methods used in the dissertations

Variables	Publication Status		p*
	Yes n (%)	No n (%)	
Hospital / Field Study			
Hospital	352 (28.58)	880 (71.42)	0.487
Field	106 (26.77)	290 (73.23)	
Single Center / Multi-Center			
Single Center	456 (28.31)	1155 (71.69)	0.177
Multi-Center	2 (11.77)	15 (88.23)	
Project Support Received			
Yes	48 (29.82)	113 (70.18)	0.617
No	410 (27.98)	1057 (72.05)	
Questionnaire Usage			
Yes	360 (27.30)	959 (72.70)	0.120
No	98 (31.72)	211 (68.28)	
Laboratory Usage			
Yes	93 (39.75)	141 (60.25)	**<0.001**
No	365 (26.19)	1029 (73.81)	
Use of Radiological Testing			
Yes	37 (38.55)	59 (61.45)	**0.019**
No	421 (27.49)	1111 (72.51)	

**Chi-square test, (Row percentage was used.)*

When analyzing the dissertations based on the academic career of the students and whether they continued research on the same subject as their dissertation, it was found that the publication status of the dissertations was statistically significantly higher among students who had an academic career and those who continued research on the same subject ($p<0.001$) (Table 6).

Table 6. Publication status of dissertations according to dissertation students' academic career and continuation of research on the same subject as the dissertation

Variables	Publication Status		p*
	Yes n (%)	No n (%)	
Academic Career			
Yes	86 (78.18)	24 (21.82)	**<0.001**
No	372 (24.51)	1146 (75.49)	
Continuation of Research on the Same Subject as the Dissertation			
Yes	94 (73.43)	34 (26.67)	**<0.001**
No	364 (24.27)	1136 (75.73)	

**Chi-square test, (Row percentage was used.)*

Discussion

Specialization dissertations mirror the studies conducted in the health field and should have high-quality scientific research. Scientific research should be published in a peer-reviewed journal in order to reach its real value. Publishing in reputable journals with a high impact factor enables reaching a wide audience and is also the best way to evaluate quality.[11] In this way, the study's results can easily reach researchers and scientists worldwide while contributing academically and professionally to the researcher and the institution.

Bibliometric analysis of medical specialty dissertations in the field of family medicine in our country is a very important way to determine scientific field trends.

Using bibliometrics, a method used to obtain evaluation indicators of scientific literature, we analyzed 1628 dissertations in the field of family medicine from the past 20 years in our study. A gradual increase in dissertations was observed, especially after 2014. It is thought that our Ministry of Health has increased the number of family medicine quotas with the project of increasing the number of family medicine specialists, and this situation is reflected in the number of family medicine specialty dissertations.

In the study by Yaman et al. on the qualitative evaluation of specialty dissertations in the field of family medicine in Turkey, it was emphasized that most of the dissertations were related to other specialties and approximately 20% were related to the clinical practice of family medicine and principles of family medicine.[8] In the dissertations study, in which Mengüllüoğlu examined 492 specialization dissertations in the field of family medicine in Turkey in 2015, it was stated that titles such as medicine/family medicine discipline/patient-physician relationship were mentioned at a rate of 4.7%.[9] In our study, family medicine practices were the most common topic. Although the proportion of dissertations focusing on the principles of family medicine has increased over time, it is seen that there is very little emphasis on medicine and social issues in the studies, and the topics are mostly selected from topics related to family medicine practice areas. Family medicine has a clinical basis focused primarily on the medical care of the sick individual.[1] This clinical basis is also valid for family medicine residents. In addition, the fact that family medicine residents work in clinics during rotations increases their clinical observational power, which is reflected in the dissertation topics.

In our study, it was seen that 28.1% of the analyzed dissertations were published in any journal. In Kaya's study in the field of public health, it was reported that 30.3% of specialty theses were publications.[12] Akpinar Mayir et al.'s study, which evaluated the publication rates and number of citations of dissertation research conducted in gynecology and obstetrics clinics in university hospitals, reported that 39.1% of the dissertations turned into publications in total.[13] It was reported that 37.7% of dissertations in the field of psychiatry, 35.6% of

dissertations in the field of ear-nose-throat, and 32.6% in the field of forensic medicine were turned into publications.[14-16] In a study conducted by Yaman et al. in 2011, the publication rate in the field of family medicine was 10.7%, and in the study conducted by Üçer and Keten in 2016, it was reported as 11.5%.[8,10] Although it is seen that family medicine specialty dissertations have fewer publications compared to other branch dissertations, the fact that the publication rate increased to 28.2% with the examination of theses until 2020 in our study showed that the theses conducted in recent years are more valuable in terms of publication.

Regarding research types, the publication rate of case-control dissertations in our study was found to be 35.1%, whereas the rate was 28.7% in intervention studies and 28% in descriptive/cross-sectional studies. In Muştu's dissertation study analyzing publications in the family medicine field, the publication rate of studies with cohort, intervention, case-control, and experimental research methods in SCI-indexed journals was higher than descriptive and cross-sectional studies.[17] These data we obtained show us that studies at a higher level in the evidence pyramid are more valuable in publication.

When the publication status of the dissertations was examined according to the information on the equipment methods used in the theses, it was found that those who used laboratory and radiologic tests in their research had a higher publication rate. In addition, the publication rate in an SCI/SCI-Expanded indexed journal for dissertations with laboratory use was higher than those without laboratory use. It is thought that the use of laboratory and/or radiologic tests increases the scientific quality of the studies, which may contribute to the potential of the study to be published.

The difficulties of turning dissertations into articles also affect the publication time. Factors such as the writing of the dissertation article, the evaluation (positive or negative) of the article by the journal, and the resulting publication in the journal involve a significant amount of time. The average publication time of dissertations as articles varies among branches. Some examples are 2.8 years for urology and psychiatry, three years for medical ecology and hydroclimatology, 3.14 years for public health, 3.46 years for anesthesia, and 5.2 years for physiology.[12,14,18-21] In our study, the average time to turn dissertations into articles was 2.8 years, similar to most branches. This result is consistent with the literature.

Our study is the most comprehensive and up-to-date study that examines 20 years of specialty dissertations in the field of family medicine in Turkey, including 1628 dissertations. In addition to the qualitative evaluation of the dissertations, the conversion of dissertations into publications and the index and Q classification of publications were analyzed. The bibliometric analysis of the dissertations revealed the orientation of specialty theses in the discipline of family medicine. Furthermore, our study offers valuable insights to new researchers regarding under-explored topics in specialty dissertations.

Limitations

Dissertations with "permitted" access from the National Thesis Center were used in the study. The study did not include the 65 dissertations whose access was not "permitted" and those conducted in the Training and Research Hospital but not registered in the National Thesis Center.

This study used bibliometric analysis to conduct a comprehensive and up-to-date analysis of 20 years of dissertation data in Family Medicine, a critical tool for identifying trends and new research ideas in scientific studies. Dissertations have increased over the years, thus providing valuable scientific contributions, especially for primary health care services. About a quarter of the dissertations were published in a journal and the rate and process of publication of dissertations were found to be similar to other branches but higher than the studies in the literature in the field of Family Medicine. Although the discipline of Family Medicine is seen to be growing in strength, the process of the conversion of theses into articles should be further encouraged. Dissertations with a research type of case-control, intervention, laboratory and radiologic test use were published more frequently. Concordantly, it is advised to give precedence to studies situated higher on the evidence pyramid, allocate sufficient funds to finance research, and increase backing for projects.

Ethical Considerations: Ethics committee approval of the study was approved scientifically and ethically by Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee on 18.04.2022 with decision number E-40465587-050.01.04-407 and decision number 2022/95.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Rakel R. E., Rakel D. P. Aile Hekimliği [E. Saatçı (Ed.); 9th ed.]. Güneş Tıp Kitabevi. 2019;3-16.
2. The European Definition of General Practice/Family Medicine. WONCA Europe. Barcelona: WONCA Europe Office Publication; 2002:4-43.
3. Erdem Ö. Türkiye'de Aile Hekimliğinin Kısa Tarihçesi, Anabilim Dalları ve Akademisyenleri. Aile Hekimliği Literatürü ve Akademik Süreç Yönetimi: Türkiye Klinikleri. 2022;11–7.
4. Tıpta ve Diş Hekimliğinde Uzmanlık Eğitimi Yönetmeliği. [Internet]. https://www.resmigazete.gov.tr/eskiler/2022/09/20220903-2.htm. (Accessed: 03.09.2022).
5. Marušić, A., Marušić, M. Teaching Students How to Read and Write Science: A Mandatory Course on Scientific Research and Communication in Medicine. Academic Medicine. 2003;78(12),1235–9 (doi: 10.1097/00001888-200312000-00007).
6. Yılmaz, Ö., Yüksel, H. Thesis in Medical Specialty Education At a Glance: Problems and Solution Proposals. Plevra Bulteni. 2013;7(2),33–6 (doi: 10.5152/pb.2013.09).
7. Dağcı, M. Tez nasıl yazılır? Aile Hekimliği Literatürü ve Akademik Süreç Yönetimi: Türkiye Klinikleri. 2022;67–70.
8. Yaman, H., Kara, İ. H., Baltacı D., Altuğ M., Akdeniz M., Kavukçu E. Qualitative Evaluation of Theses Written in area of Family Medicine in Turkey. Konuralp Tıp Dergisi, 2011;3(3),1–6.
9. Mengüllüoğlu N. Ö., Ünlüoğlu İ. Evaluation of Family Medicine Specialty Theses Between the Years 2005-2015. Ankara Medical Journal, 2017;17(4),192–203 (doi: 10.17098/amj.364966).
10. Üçer H., Keten H. S. Aile Hekimliği Alanında Yapılan Tıpta Uzmanlık Tezleri Bilimsel Makale Olarak Yayınlanıyor Mu? Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi Dergisi. 2016;11(1),22–5.
11. Dhaliwal U., Singh N., Bhatia A. Masters Theses From a University Medical College: Publication in Indexed Scientific Journals. Indian Journal of Ophthalmology. 2010;58(2),101–4 (doi: 10.4103/0301-4738.60070).
12. Kaya E., Üçer H., Erdoğan Ö. E. Türkiye'de Halk Sağlığı Alanındaki Uzmanlık Tezlerinin Bilimsel Yayına Dönüştürülme Oranlarının Değerlendirilmesi. ESTÜDAM Halk Sağlığı Dergisi. 2020;5(3),410–7 (doi: 10.35232/ESTUDAMHSD.743925).
13. Akpinar Mayir Y., Mayir B., Erkal N., Eren Yazici L. Assessment of Publication Rates and Number of Citations of Dissertations in University Hospitals Gynecology and Obstetrics Clinics. Türkiye Klinikleri Jinekoloji Obstetrik. 2016;26(4),232–6 (doi: 10.5336/gynobstet.2016-53694).
14. Erim B. R., Petekkaya S. Türkiye'de Psikiyatri Alanında 1981-2018 Yılları Arasında Yapılmış Uzmanlık Tezlerinin Değerlendirilmesi. Türk Psikiyatri Dergisi. 2020;31(1),1–8 (doi: 10.5080/U23877).
15. Çetin B. Do the Otorhinolaryngology Specialization Theses Turn Into Publications? The Turkish Journal of Ear Nose and Throat. 2017;27(4),185–93 (doi: 10.5606/KBBIHTISAS.2017.71429).

16. Çağlayan D., Çelik C., Kaya A., Aktaş E. Ö. Evaluation of Publication Rate of Forensic Medicine Specialty Theses in Turkey. The Bulletin of Legal Medicine. 2020;25(1),1–5 (doi: 10.17986/blm.2020.v25i1.1332).
17. Muştu F. Türkiye'de Aile Hekimliği Alanında Yapılan Yayınların Kalitatif Değerlendirilmesi. Ph. D. Thesis, Çukurova University Faculty of Medicine, Department of Family Medicine, Adana; 2009;35-6.
18. Yüksel M., İpekçi T., Tunçkıran A. Publication Rates of Dissertations Written in Medical Faculties of Turkey in The Field of Urology Between The Years 2008 And 2011, And Citation Analysis: A Cross-Sectional Study. Turkish Journal of Urology. 2018;44(4),341-5 (doi: 10.5152/TUD.2017.32042).
19. Kardeş S. Publication Rate of Specialization in Medicine Theses in Medical Ecology and Hydroclimatology in Turkey: A Cross-Sectional Study. İstanbul Tıp Fakültesi Dergisi. 2019;82(1),62–8 (doi: 10.26650/iuitfd.0015).
20. Güç Z. Anesteziyoloji ve Reanimasyon Alanında 1970-2016 Yılları Arasında Üniversitelerden Yapılan Tez Çalışmalarının; Çalışma Alanları, Yayınlanma Oranları ve Kanıt Düzeylerinin Retrospektif Olarak Değerlendirilmesi. Ph. D. Thesis, Dokuz Eylül University Faculty of Medicine, Departments of Anesthesia, İzmir; 2020;47.
21. Seringeç Akkeçeci, N. Publication of Physiology Theses in Scientific Journals: Analysis of The Status From Turkey. Journal of Surgery and Medicine. 2019;3(3),235–8 (doi: 10.28982/josam.536365).

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):312-324 // 10.5505/amj.2023.92053

EVALUATION OF COMMUNICATION SKILLS OF FAMILY MEDICINE ASSISTANTS

Mehmet Murat Topaloğlu[1], Mehmet Onat Cakit[1], Ismail Arslan[1]

[1] Department of Family Medicine, University of Health Sciences, Ankara Training and Research Hospital, Ankara

Correspondence:
Mehmet Onat Cakit (e-mail: onatcakit@gmail.com)

Submitted: 14.04.2023 // Accepted: 04.08.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: This study aimed to reveal the communication skills of family medicine residents who are new to the profession and to provide formative feedback to residents in the early stages of their education.

Materials and Methods: 222 family medicine assistants studying in hospitals affiliated with the University of Health Sciences within the borders of Ankara province participated in the research online. The socio-demographic characteristics of the residents participating in the study were accepted as independent variables, and the Turkish version of the Health Professionals Communication Skills Scale (HP-CSS-TR) was considered as the dependent variable.

Results: The mean age of the participants was 22.13±2.25 years. The assistant seniority level of the participants was 1.77±1.39 years. 80.63% of the participants reported having problems with the patients and their relatives. 99.55% stated that they encountered difficult patients or their relatives. In our study, family medicine clinical assistants' communication, empathy, respect and social skills were high. Senior participants had better communication levels (p=0.011).

Conclusion: In our study, we found that family medicine residents have high communication skills, but they expressed that they have difficulties communicating with patients and wanted to receive communication training to improve their communication skills and cope with difficult patients. Giving feedback by measuring the communication skills of young assistants who are new to the profession should be included in our assistant training practice as a standard first-step assessment of the profession.

Keywords: Family Medicine, assistant, communication skills, empathy, education

Introduction

The doctor-patient relationship is one of the most important elements in patient care and directly affects patient satisfaction and treatment results. There is a growing body of evidence to suggest that effective clinical communication contributes to improved treatment outcomes. Strong communication skills are an essential component of medical school and postgraduate education.[1] Increased patient compliance and patient satisfaction through communication skills and increased quality of patient care reduce the work stress of employees.[2]

As a discipline, Family Medicine meets the health needs and expectations of the individual, family and society by establishing effective communication with a holistic and patient-centered approach.[3] Previous studies have evaluated communication mostly from a patient perspective. There are few studies evaluating communication from the physician's point of view.[4,5,6] Communication skills are not well studied for assistants new to the profession. In a study by Klein et al., first-year family medicine assistants' verbal and online communication skills were evaluated, and they emphasized the importance of feedback on communication skills at the beginning of specialty training. Participating assistants also found the assessment helpful and stated that it offers an opportunity for introspective learning and has the potential to change their practice.[1]

In a qualitative study conducted to evaluate the problems faced by primary care physicians with patients in the province of Istanbul, it was found that the most common problems encountered by physicians related to patients were violence against physicians, prescribing off-label prescriptions, out-of-hours examination requests, problems related to the examination order, unnecessary complaints by patients and communication problems. As solution suggestions, increasing the training to improve communication skills, establishing institutions to provide legal consultancy to physicians, various sanctions to prevent unnecessary complaints and some administrative recommendations were presented.[7]

Evaluating the communication skills of family medicine and primary health care physicians and trying to increase their communication skills are attracting more and more attention and are the subject of research.[1-3] This study aims to reveal the communication skills of family medicine residents new to the profession and provide formative feedback to residents in the early stages of their education.

Materials and Methods

Our study is observational and descriptive. There are approximately 513 family medicine residents in Ankara. In the calculation made by taking the confidence interval of 95% and the margin of error of 5%, the sample size was calculated as at least 220 people when the population was 513. Between June 2021 and August 2021, 222

family medicine assistants studying at the Health Sciences University Hospitals within the borders of Ankara province participated in the online study. Those who started residency less than three months after the working period were excluded from the study. Participants' consent to participate in the study was obtained online.

The gender, age, marital status and seniority of the assistants were recorded. Whether they had any problems with the patients and their relatives was questioned. It was recorded whether they received communication training and drama training. It was questioned whether they found the communication training they received was sufficient or not. It was determined whether they encountered difficult patients and their relatives and whether they wanted to receive communication training to cope with this patient group. The socio-demographic characteristics of the assistants participating in the study were considered independent variables, and the Turkish version of the Health Professionals Communication Skills Scale (HP-CSS-TR) was considered dependent variables.

HP-CSS-TR consists of four factors: 1) Empathy, 2) Informative Communication, 3) Respect, and 4) Social Skills. The resulting scale consists of 18 items divided into four dimensions, including empathy (five items), informative communication (six items), respect (three items) and social skill (four items). The participants were assessed on how often each item applies to themselves by using a six-point Likert-type scale from 1 to 6 (1 = almost never, 2 = once in a while, 3 = sometimes, 4 = normally, 5 = very often, 6 = many times). Empathy includes items 2, 4, 6, 11 and 12, and the score ranges between 5 and 30; informative communication includes items 5, 8, 9, 14, 17 and 18, and the score ranges between 6 and 36; respect includes items 1, 3 and 15, and the score ranges between 3 and 18; social skill includes items 7, 10, 13 and 16, and the score ranges between 4 and 24. Higher scores reflect better communication skills of health professionals. It was determined that HP-CSS-TR is a valid and reliable instrument for evaluating the communication skills of healthcare professionals.[8]

Descriptive statistics were presented with frequency, percentage, mean and standard deviation values. Normality was assessed by skewness and kurtosis. All values were normally distributed. The t-test and analysis of variance (ANOVA) test were applied to examine the measurements according to the study groups. Sidak post-hoc test was conducted to evaluate the measurements that differed as a result of ANOVA. The Chi-square analysis was used to examine the relationships between categorical variables according to groups. Correlation analyses were applied to determine the relationship among the dimensions. Multiple linear regression analysis was performed to examine the relationship between the research sub-dimensions and the general level of the scale. In the study, p-values less than 0.05 were considered statistically significant. Statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) 25.00 package program.

Results

Demographic Features

Two hundred twenty-two family medicine residents were included in our study. The mean age of the participants was 22.13±2.25 years. The professional seniority level of the participants was 1.77±1.39 years. Demographic characteristics are shown in Table 1.

80.63% of the participants reported having problems with the patients and their relatives. It was observed that 6.31% of the participants received certified communication training, while 25.68% received communication training but did not have certificates. It was determined that 71.83% of the participants considered the communication training they received sufficient. Communication-related features are shown in Table 1.

Table 1. Demographic data and communication-related characteristics of the participants

		n	%
Gender	Female	140	63.06
	Male	82	36.94
Marital Status	Single	99	44.59
	Married	123	55.41
Assistant Seniority	1. Term	63	28.38
	2. Term	83	37.39
	3. Term	76	34.23
Do you have problems with patients and relatives?	Yes	179	80.63
	No	43	19.37
Have you received communication training?	Yes Certified	14	6.31
	Yes Uncertified	57	25.68
	No	151	68.01
Do you think the training you received was adequate?	Yes	51	71.83
	No	20	28.17
Would you like to receive communication training?	Yes	157	70.72
	No	65	29.28
Have you had drama training before?	Yes	22	9.91
	No	200	90.09
Do you encounter difficult patients and/or relatives?	Yes	221	99.55
	No	1	0.45
Would you like to receive training on communication with difficult patients and their relatives?	Yes	182	81.98
	No	40	18.02

The participants' scores for the sub-dimensions of the communication in health scale are given in Table 2. In general, it can be stated that the communication scores of the group are at a high level.

Table 2. Investigation of Dimension Scores

Dimension	Mean±SD
Empathy	23.20±3.68
Informative Communication	25.08±3.04
Respect	14.62±2.39
Social Skills	15.68±2.22

Examination of Scale Dimensions According to the Characteristics of the Participants

Regarding the hospitals of the participants, the empathy levels of the residents working at Ankara Training and Research Hospital (TRH) were higher (p=0.032), while the communication levels of the residents working at the Dışkapı and Keçiören TRH were found to be higher (p=0.024).

It was observed that residents who had problems with patients and their relatives had higher levels of empathy and informative communication (p=0.011, p=0.010, respectively). It was determined that the participants who thought their education was sufficient had higher levels of empathy and informative communication (p=0.013, p=0.008, respectively). The comparison of empathy and informative communication dimensions according to the characteristics of the participants is given in Table 3.

Participants' respect and social skill levels were found to be similar regarding gender (p=0.248, p=0.324, respectively), marital status (p=0.320, p=0.052, respectively), and assistant seniority (p= 0.221, p=0.328, respectively). It was observed that the social skill levels of the residents who had problems with the patients and their relatives were higher (p=0.033). It can be stated that residents who received certified training had higher levels of social skills (p=0.028). It was observed that residents who stated that the communication training received was adequate had higher levels of social skills (p=0.032). Participants who received drama training had higher levels of respect and social skills (p=0.009, p=0.007, respectively). The distribution of the dimensions of respect and social skills according to the characteristics of the participants is given in Table 4.

There was a significant positive correlation between the participants' empathy levels and their communication and respect levels (r=0.76, r=0.78, p=0.01, respectively) (Table 4).

In general, it was seen that the sub-dimensions were positively correlated among themselves. Multiple Linear Regression analysis was conducted to see how communication level was related to the sub-dimensions. It was seen that the explanation percentage of the model was 85% (R2=0.851). Regression analysis showed that empathy, communication and social skill levels were significantly associated with the general patient communication level (p=0.012, p=0.014, p=0.017, respectively). According to the regression model, empathy

is the most important independent variable on the general communication level (β=0.561). It was observed that the respect sub-dimension did not significantly affect the general patient communication level (Table 5).

Table 3. Investigation of Empathy and Informative Communication Dimensions According to Participants' Characteristics

		Empathy	p	Informative Communication	p
		Mean±SD		Mean±SD	
Gender	Female	24.00±4.50	0.132	25.26±3.11	0.193
	Male	23.25±3.23		24.76±2.9	
Marital Status	Single	23.22±4.05	0.405	25±2.86	0.328
	Married	23.23±4.12		25.14±3.19	
Assistant Seniority	1. Term	24.00±3.32	0.206	25.17±2.89	0.079
	2. Term	23.52±4.22		24.67±3.1	
	3. Term	23.26±4.41		25.43±3.07	
Hospital	Ankara ETH	24.50±4.00	0.032*	24.95±3.06	0.024*
	Ankara City Hospital	23.40±3.05		24.94±3.2	
	Dışkapı ETH	23.00±3.90		25.54±2.88	
	Gülhane ETH	23.60±4.20		24.68±2.81	
	Keçiören ETH	23.80±4.05		25.86±3.39	
Do You Have Problems with Patients and Relatives?	Yes	23.55±4.20	0.011*	25.36±3.01	0.010*
	No	22.25±4.50		23.91±2.95	
Have you received communication training?	Yes Certified	24.55±2.13	0.053	25.64±2.68	0.089
	Yes Uncertified	23.30±3.10		25.44±2.91	
	No	23.10±4.40		24.89±3.11	
Do you think the training you received was adequate?	Yes	24.10±3.90	0.013*	26.68±2.85	0.008*
	No	23.00±3.10		24.85±2.63	
Would you like to receive communication training?	Yes	23.70±4.20	0.233	24.99±3.10	0.077
	No	23.80±3.80		25.28±2.9	
Have you had drama training before?	Yes	23.40±3.00	0.423	24.77±2.91	0.234
	No	23.30±4.50		25.11±3.06	
Would you like to receive training on communication with difficult patients and their relatives?	Yes	23.25±4.11	0.282	25.2±3.04	0.084
	No	23.10±4.23		24.53±3.01	

Table 4. Investigation of Respect and Social Skills Dimensions According to Participants' Characteristics

		Respect	p	Social Skills	p
		Mean±SD		Mean±SD	
Gender	Female	14.72±2.47	0.248	15.81±2.14	0.324
	Male	14.44±2.26		15.45±2.33	
Marital Status	Single	14.69±2,3	0.320	15.34±1.89	0.052
	Married	14.56±2.47		15.95±2.42	
Assistant Seniority	1. Term	14.90±2.20	0.221	15.65±1.91	0.328
	2. Term	14.42±2.40		15.85±2.16	
	3. Term	14.59±2.53		15.97±2.46	
Hospital	Ankara TRH	15.90±2.28	0.001*	15.43±2.01	0.001*
	Ankara City Hospital	14.10±2.43		15.44±1.99	
	Dışkapı TRH	14.23±2.52		16.12±2.46	
	Gülhane TRH	14.18±2.51		15.55±2.17	
	Keçiören TRH	14.71±2.33		17.07±3.00	
Do You Have Problems with Patients and Relatives?	Yes	14.72±2.33	0.258	15.85±2.28	0.033*
	No	14.19±2.60		14.25±1.79	
Have you received communication training?	Yes Certified	14.71±2.13	0.291	16.93±2.2	0.028*
	Yes Uncertified	14.81±2.22		15.32±2.16	
	No	14.54±2.49		15.42±2.2	
Do you think the training you received was adequate?	Yes	14.78±2.3	0.193	16.65±2.01	0.032*
	No	14.9±2.26		15.85±2.28	
Would you like to receive communication training?	Yes	14.69±2.39	0.164	15.62±2.19	0.351
	No	14.43±2.4		15.83±2.30	
Have you had drama training before?	Yes	15.91±2.11	0.009*	15.91±1.62	0.007*
	No	14.59±2.42		14.71±2.27	
Would you like to receive training on communication with difficult patients and their relatives?	Yes	14.72±2.31	0.333	15.77±2.26	0.375
	No	14.15±2.73		15.28±1.97	

Table 5: Multiple Linear Regression analysis results

Dependent Variables	**Independent Variables (X)**			**F_{Model}**	**R^2**
	Empathy	**Informative Communication**	**Social Skills**		
	(β)	**(β)**	**(β)**		
General Communication Level (Y)	0.561	0.340	0.234	1332.45	0.851
	t=36.29	t=22.41	t=17.35	(p=0.011)	
	p=0.012	p=0.014	p=0.017		

The group was divided into clusters according to the general patient communication scores. As a result of the clustering analysis applied in this context, it was seen that the group gathered under two clusters. The first of these groups was n=112, 51.45% (21.57±1.36) with high scores and n=110, 49.55% (17.67±1.43) with moderate scores. The characteristics of the participants according to the general patient communication level are shown in Table 6.

Table 6. Identification of clusters belonging to the general communication level

Group	n	%	Mean±SD
High	112	51.45	21.57±1.36
Moderate	110	49.55	17.67±1.43

It was seen that the participants who had problems with patients and their relatives received certified communication training, found the communication training sufficient, and wanted to receive communication training about difficult patients and their relatives were in the group with a higher level of communication (p=0.001 for all). Participants with medium and high communication levels had a similar rate of wanting to receive communication in health (p=0.092). It was observed that the communication levels of the residents were similarly high and moderate according to their drama education status (p=0.394). Senior participants had better communication levels (p=0.039) (Table 7).

Table 7. Characteristics of participants according to general level of communication

Characteristics of participants		General Level Of Communication				p
		High		Moderate		
		n	%	n	%	
Gender	Female	75	53.57	65	46.43	0.001*
	Male	37	45.12	45	54.88	
Marital Status	Single	51	51.5	48	48.49	0.258
	Married	61	49.59	62	50.41	
Assistant Seniority	1. Term	33	52.38	30	47.62	0.039*
	2. Term	38	45.78	45	54.22	
	3. Term	41	53.95	35	46.05	
Hospital	Ankara TRH	41	47.67	45	52.33	0.031*
	Ankara City Hospital	25	50.00	25	50.00	
	Dışkapı TRH	23	56.09	18	43.91	
	Gülhane TRH	15	48.39	16	51.61	
	Keçiören TRH	8	57.14	6	42.86	
Do You Have Problems with Patients and Relatives?	Yes	97	54.19	82	45.81	0.001*
	No	15	34.88	28	65.12	
Have you received communication training?	Yes, Certified	9	64.29	5	35.71	0.001*
	Yes, Not Certified	32	56.14	25	43.86	
	No	71	47.02	80	53.98	
Do you think the training you received was adequate?	Yes	27	67.50	13	32.50	0.001*
	No	20	50.00	20	50.00	
Would you like to receive communication training?	Yes	76	48.41	81	51.59	0.092
	No	36	55.38	29	44.62	
Have you had drama training before?	Yes	11	50.00	11	50.00	0.394
	No	101	50.50	99	49.50	
Would you like to receive training on communication with difficult patients and their relatives?	Yes	95	52.19	87	47.81	0.026*
	No	17	42.50	23	57.50	

Discussion

In our study, informative communication, empathy, respect and social skills of family medicine clinical assistants were high. In general, it was observed that the dimensions were positively correlated with each other at moderate and high levels. It was observed that the levels of empathy, communication, respect and social skills were in interaction with each other. The level of empathy was the most important factor affecting patient communication. Participants who received certified communication training were likelier to be in the group with a high communication level. Participants who had problems with patients and their relatives were in the group with a higher level of communication. Participants who received drama training had higher levels of respect and social skills. Assistants who received certified training had higher levels of social skills. There was a positive correlation between age, assistant seniority, and communication and social skill levels.

Very few studies evaluate the communication skills of resident physicians who have just started their profession and specialization from the physicians' perspective. In a study by Klein et al., first-year family medicine residents' verbal and online communication skills were evaluated, and their communication skills were measured as quite good. Making new assistants aware of their expectations and basic skills at the beginning of their training, providing feedback with specific suggestions in a non-threatening environment, and the potential of the provided feedback to cause behavioral changes are considered quite beneficial.[1]

A study conducted in Antalya reported that 92% of medical students encountered difficult patients.[9] The encounter with difficult patients, which starts during the student period, increases even more during the residency period and is definitely encountered in medical life.

On the basis of communication between women and men, gender roles, not biological sex, make a difference. Despite this, many studies have shown that there is no significant difference in communication skills between genders.[10] Similarly, in our study group, it was determined that there was no communication difference between the genders. The fact that there is very little gender discrimination in the practice of medicine and that society's perspective is generally not sexist may be why there is no difference between the genders in terms of communication and empathy among those who practice medicine.

Many studies have shown that empathy increases the satisfaction level of patients.[11-13] The fact that the employees show individual attention to the patients through empathy has positive effects on the psychology of the patients.[14] In our results, it was seen that the most important factor affecting the patient communication level was the level of empathy. Participants who received certified communication training were likelier to be in the group with a high communication level. It was observed that the empathy and communication levels of the participants who thought that their education was sufficient were higher. From this point of view, we

emphasize the importance of informative communication education and empathy in the communication of healthcare professionals, and we think that empathy should be emphasized as a key factor in communication.

It is known that the inability to establish correct communication between people causes conflicts to arise.[5] In our study, when the communication level of the participants who had problems with the patients and their relatives was examined, it was found that their communication level was higher than expected. It made us think that only physician communication is not sufficient in today's conditions and may not be able to prevent quarrels.

Surprisingly, the social skill levels of residents with problems with patients and their relatives are significantly higher. It is stated that physicians with high social skills use conflict management styles of compromise and cooperation more, and when physicians prefer cooperation conflict management style in conflicts, cases of violence can be reduced. However, when they prefer avoidance and competition conflict management styles, the incidence of violence cases may even increase.[15] As it is known, patient-physician communication is at least a two-way communication between two people. No matter how good a party's communication skills are, it becomes ineffective if the other party has poor communication skills.[16] For this reason, the extremely conciliatory attitude of the assistant group with high social skills may sometimes be misunderstood in society and trigger violence. Therefore, we think that standard communication training should be adapted according to the characteristics of the society served. In fact, an empathetic approach to the physician is also necessary. Just as communication is not one-sided, one-sided empathy cannot provide healthy communication.[4]

In a study by Hakverdi et al. in which the relationship between the communication skills of family physicians and their approach to patients was evaluated, it was suggested that although physicians' current communication skills are high, practical training in human resources, human psychology, body language, communication difficulties, and practical and healthy communication techniques should be emphasized in training programs, starting before graduation.[6] Drama education includes training such as role models, disease simulation, standardized patient scenarios, and intervention in times of crisis. In our study, there was no difference in communication and empathy skills between the group that received drama education and the group that did not. Nonetheless, the literature has determined that training with role models, standardized patients, simulated patients and real patients increases communication skills.[17,18] However, the educational content of the drama education group receiving this training in our research group was not evaluated in quality and quantity. That is one of the limitations of our study.

In conclusion, we found that family medicine residents have high communication skills, but they expressed that they had difficulties communicating with patients and that they want to receive communication training to increase their communication skills and cope with difficult patients. Measuring the communication skills of

young assistants who are new to the profession and giving feedback to them should be included in our resident training practice as a standard first-step assessment.

Acknowledgment: We would like to thank Dr. Onur Mendi, who published Cross-cultural Adaptation, Reliability, and Validity of the Turkish Version of the Health Professionals Communication Skills Scale, for his deontological approach and kind attention.

Ethical Considerations: Local ethics committee approval was obtained from Health Sciences University, Ankara Training and Research Hospital Clinical Research Ethics Committee with decision number 720/2021 on 29.07.2021.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Klein D, Nagji A. Assessment of communication skills in family medicine. Can Fam Physician. 2015;61(9):e412–6.
2. Ranjan P, Kumari A, Chakrawarty A. How can doctors improve their communication skills? J Clin Diagnostic Res. 2015;9(3):1–4.
3. Çiftetepe Öztürk D, Dağdeviren H. Hekimlik Pratiğinde Etkili İletişimin Yeri. Eurasian Journal of Family Medicine. 2018; 7(2): 41 - 6.
4. Zorlu D , Cingi CC. Hekimlerin sosyal iletişim becerileri. Pam Tıp Derg. 2021;14(1): 191-200.
5. Dökmen Ü. İletişim Çatışmaları ve Empati, 38. Baskı, Sistem Yayıncılık, 2008, s.19, İstanbul.
6. Hakverdi ÖA. Aile hekimlerinin iletişim becerileriyle hastaya yaklaşımları arasındaki ilişkinin değerlendirilmesi. Türk Aile Hek Derg. 2022;26(1):17-24.
7. Doğan E, Hıdıroğlu S, Karavuş M. Birinci basamak hekimlerinin hastalarla ilgili karşılaştıkları sorunların değerlendirilmesine yönelik niteliksel bir araştırma. Jour Turk Fam Phy 2017; 08 (1): 02-10.
8. Mendi O, Yildirim N, Mendi B. Cross-cultural Adaptation, Reliability, and Validity of the Turkish Version of the Health Professionals Communication Skills Scale. Asian Nurs Res (Korean Soc Nurs Sci). 2020 Dec;14(5):312-9.
9. Acar G, Buldukoğlu K. Student Difficulties Communicating with Patients and Their Perceptions of the Characteristics of Difficult Patients. Journal of Psychiatric Nursing 2016;7(1):7–12
10. Görmüş A, Aydın S, Ergin G. İşletme Bölümü Öğrencilerinin İletişim Becerilerinin Cinsiyet Rolleri Bağlamında İncelenmesi. Afyon Kocatepe Üniversitesi Sosyal Bilimler Dergisi. 2013;15(1):109-28.
11. Beydoğan G. Ş. Kalyoncuoğlu, S. Fizik tedavi ve rehabilitasyon hizmeti alan hastaların kalite algılarının memnuniyetleri üzerindeki etkisi: Kırşehir ilinde bir araştırma. 2nd International Congress On Political, Economic And Social Studies, 2017,19-22.
12. Derksen F, Bensing J, Lagro-Janssen A. Effectiveness of empathy in general practice: a systematic review. Br J Gen Pract. 2013 Jan;63(606):e76-84.
13. Mercer SW, Neumann M, Wirtz M, Fitzpatrick B, Vojt G. General practitioner empathy, patient enablement, and patient-reported outcomes in primary care in an area of high socio-economic deprivation in Scotland--a pilot prospective study using structural equation modeling. Patient Educ Couns. 2008 Nov;73(2):240-5.
14. Tigli A. Fizyoterapistlerde Empati Becerisinin Mutluluk ve Tükenmişlik Düzeyi ile İlişkisi . OPUS International Journal of Society Researches 2019;14(20):1011-24.

15. Kağan G. Sağlık kurumlarında şiddet vakalarını engelleme yönünde çatışma yönetimi tarzları, öz liderlik ve iletişim becerilerinin rolü: hekimler üzerine bir araştırma [Ph.D. Thesis]. Kocaeli Üniversitesi Sosyal Bilimler Enstitüsü İşletme Anabilim Dalı, 2021.
16. Friedlander ML, Kangos KA, Maestro KJ. Introducing an observational rating system for studying concordance in patient–physician relationships, The Counseling Psychologist 2019;47(5):796–819.
17. Şenol Y, Özdoğan M, Oktay C, Yılmaz TT, Bozcuk H. Hasta-Hekim İletişimi-İletişim Becerileri Eğitimi ve Eğiticilerin Rol Modelliği. Tıp Eğt Dünyası 2011;(31):38–44.
18. Joyner B, Young L. Teaching medical students using role play: twelve tips for successful role plays. Med Teach 2006;28(3):225-9.

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):325-335 // 10.5505/amj.2023.99083

EVALUATION OF THE RELATIONSHIP BETWEEN FRAILTY, POLYPHARMACY, AND DEPRESSION IN PEOPLE 65 YEARS OF AGE AND OLDER

Irem Erdoğan[1], Ozge Tuncer[2]

[1]Kuluncak Mehmet Ali Sekerci District Integrated State Hospital, Malatya, Turkey

[2]Department Of Family Medicine, University of Health Sciences İzmir Bozyaka Education and Research Hospital, Turkey

Correspondence:

Özge Tuncer (e-mail: dr.ozgeucman@gmail.com)

Submitted: 03.05.2023 // Accepted: 26.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine

Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: This study aims to determine the level of frailty in patients aged 65 and over who apply to the family medicine clinic to evaluate the relationship between polypharmacy, depression, and socio-demographic characteristics with frailty.

Materials and Methods: This is a single-center, cross-sectional, descriptive survey. One hundred forty-four participants aged 65 and over who applied to the family medicine clinic at Training and Research Hospital in Izmir were included. The Yesavage Geriatric Depression Scale (GDS)-Short Form was used to measure participants' depression levels, and the Edmonton Frail Scale (EFS) was used to determine the level of frailty. The data obtained were analyzed using IBM SPSS 21.0, and a statistical significance value of $p < 0.05$ was accepted.

Results: The group with the highest percentage of participants was under 75 years old, constituting 65.32% of the total group. According to the GDS score average, a significant relationship was found between depression and gender, education level, monthly income, and falls. According to the EFS-TR score average, a significant relationship was found between frailty and age, gender, education level, marital status, monthly income, lifestyle, number of medications used, number of emergency hospital admissions, and falls. A moderate positive correlation was found between GDS and EFS.

Conclusion: The study found that many socio-demographic characteristics affect depression and frailty. It was observed that frailty increases as depression and polypharmacy increase, but there was no significant relationship between polypharmacy and depression. These results are important for better support and protection of elderly individuals in health and social care.

Keywords: Frailty, depression, polypharmacy.

Introduction

With the decrease in the birth rate and the improvement in living standards around the world, the extension of human life is provided, and the elderly population is gradually increasing.[1] The ongoing expansion in the elderly population over time emphasizes the importance of health among elderly individuals. The elderly population accounted for 9% of the world's population in 2019, and it is estimated to increase up to 16%; in other words, one out of every six people will be elderly in 2050.[2]

Aging is a universal process in all living organisms and manifests as progressive functional loss and impairment, resulting in a reduction in all functions.[3] The World Health Organization (WHO) defines old age as a "decrease in the ability of adaptation to environmental factors." Normal aging is a process characterized by social and psychological changes as well as anatomic alterations without disease by advancing age over time. Pathological aging involves all pathological events that interact with the normal aging process.[4] Although the aging process can show individual variations, it should not be assessed according to age alone. An elderly individual can be termed as healthy, frail or terminal based on functional capacity.

Frailty is defined as "reduction in physiological reserves together with weakness due to many factors including physiological changes by advancing age, genetic predisposition, nutritional status and comorbid disease".[5] The frailty is important since recovery from diseases is prolonged, and it is more likely to recover with a sequel following disease in frail individuals. If frailty is recognized early, the likelihood of sequels and deaths can be decreased.[6]

Aging comes with many chronic diseases, resulting in a number of drugs used in the elderly individual. Multiple drug use is also termed polypharmacy. Although there is no clear definition of polypharmacy, it can be defined as "simultaneous use of many drugs generally for multiple indications".[7] Polypharmacy is also defined as "concurrent use of 2 or more drugs for at least 240 days", "concurrent use of 4 or more drugs" according to National Service Framework (NSF) or "concurrent use of 5 or more drugs".[8-10] Polypharmacy can lead inappropriate drug use, drug-drug interaction, drug-patient interaction, adverse effects, higher costs, fall, weight loss, impaired cognitive functions, hospitalization, increased dwelling in the nursing home and death which are highly important for health of elder individuals.[11] Physiological changes, such as forgetfulness or challenges in perception, may appear by aging; psychological alterations can also develop. The strength and prestige, relationship with relatives, social life, reputation and expectations of elderly individuals are decreased, and the individual becomes helpless. During old age, individuals experience depression for several reasons, including loss of relatives and decreased ability to adapt to technology and social life. Depression is a significant factor regarding quality of life and can lead to impairment in general health status and premature death if left untreated.[12]

The frailty of the elderly in terms of health is affected by many factors. Comprehensive geriatric assessment should be performed for early diagnosis and treatment of frailty, and depression and polypharmacy should be questioned during the elderly examination. Our study aimed to determine measures of frailty and assess the link between frailty and polypharmacy, depression and socio-demographic characteristics in patients aged ≥ 65 years who presented to our outpatient clinic of family medicine.

Materials and Methods

This study was designed as a single-center, cross-sectional, descriptive survey. In determining the study sample, the frailty rate was determined as 10% in studies conducted in Turkey, using the sample calculation for an unknown population with a confidence level of 95 % and a margin of error of 0.05; at least 136 individuals were calculated. Between May 2020 and July 2020, face-to-face interviews were conducted with 144 participants who were 65 years and older and met the inclusion criteria of the study and who applied to the family medicine clinic. After providing information about the study to the participants reached during the research process, those who were capable of answering the questions and willing to participate were included. The Socio-demographic data form, Yesavage Geriatric Depression Scale (GDS)-Short Form, and Edmonton Frailty Scale (EFS) were used to be filled out by individuals who applied to the clinic. Patients who use five or more medications are defined as having polypharmacy. The Turkish validity and reliability of the Edmonton Frailty Scale were conducted by Aygor et al. in 2018.[1] The GDS short form consists of 15 questions, and the Turkish validity and reliability of the scale were conducted by Ertan et al. in 1996.[13]

Descriptive statistics are summarized as frequency, percent, mean and standard deviation. The statistical analyses were performed using IBM SPSS version 21.0 (Statistical Package for the Social Sciences). Mann Whitney U test was used for comparisons between two groups, while the Kruskal-Wallis test was used for comparisons among three or more groups. Pearson's Chi-square test was used to analyze differences in qualitative variables between groups when appropriate. Spearman rho correlation test was used to define the strength and direction of linear correlations between quantitative variables. A p-value>0.05 was considered statistically significant in all analyses.

Results

As shown in Table 1, individuals aged<75 years comprised 94 (65.32%) of the study population as being the largest group among participants. Of the study population, 87 (60.41%) were women; 101 (70.11%) were married; 24 (16.72%) were illiterate; and almost one-half had primary school graduation. Of the participants, income was greater than expense; 44 (30.61%) and 26 (18.13%) lived alone. There was a comorbid disease in 135 (93.82%) of participants, including hypertension in 95 (70.38%), cardiovascular disease in 56 (41.5%),

hyperlipidemia in 22 (16.29%), and cerebrovascular disease. 137 (95.12%) of participants were using drugs. Of these, 117 (81.31%) were using regularly, and 56 (38.93%) were using five or more drugs.

Table 1. Distribution of participants according to socio-demographic characteristics (n=144)

Demographic characteristics		**n**	**%**
Gender	Female	87	60.41
	Male	57	39.59
Age	<75	94	65.32
	75- 84	39	27.11
	≥85	11	7.57
Marital status	Married	101	70.11
	Single	4	2.74
	Divorced	3	2.11
	Widow	36	25.04
Education level	Illiterate	24	16.72
	Primary school	68	47.23
	Secondary school	13	9.01
	High school	13	9.02
	University	26	18.02
Income	Income less than expenses	44	30.61
	Income equal to expenses	78	54.23
	Income more than expenses	22	15.26
Residence	Alone	26	18.13
	With partner	94	65.32
	With relatives	24	16.65
Comorbid disease	Yes	135	93.82
	No	9	6.18
Hypertension	No	40	29.62
	Yes	95	70.38
Hyperlipidemia	No	113	83.71
	Yes	22	16.29
Chronic lung disease	No	120	88.86
	Yes	15	11.14
CVD*	No	79	58.51
	Yes	56	41.49
CVD**	No	122	90.41
	Yes	13	9.59
Thyroid disorder	No	120	88.87
	Yes	15	11.13
Osteoporosis	No	120	88.88
	Yes	15	11.12
Depression	No	122	90.44
	Yes	13	9.56
Total			100.0

*CVD: Cardiovascular Disease, **CVD: Cerebrovascular Disease

The socio-demographic characteristics were compared by the Yesavage Geriatric Depression Scale. A significant correlation was detected between age, education level, monthly income and fall (Table 2 and Table 3). The female patients, those who were illiterate, those having income less than the expense and those with a history of 2 or fewer falls were found to be more depressive.

There was no significant difference in mean Yesavage GDS Score according to age group, marital status, lifestyle, number of drugs used and number of emergency department visits.

Table 4 and Table 5 compare socio-demographic characteristics with the Edmonton Frail scale. It was found that there was a significant relationship between age, gender, marital status, education level, monthly income, lifestyle, number of drugs used, number of emergency department visits and falls. Based on these results, female patients, those aged ≥ 85 years, those who were illiterate, widows, those having monthly income less than the expense, those living with relatives, those using five or more drugs, those with a history of more than two falls and those presented to the emergency department more than twice were found to be more frail.

Table 6 shows a moderate, positive correlation between the Yesavage Geriatric Depression Scale and Edmonton Frail Scale according to Spearman's rho correlation test.

Table 2. Results of Yesavage Geriatric Depression Scale according to socio-demographic characteristics

Yesavage Geriatric Depression Scale		**n**	**Median**	**t**	**df**	**p**
Age	<75	94	5.00	1.891	2	0.388
	75- 84	39	6.00			
	≥85	11	4.00			
Education	Illiterate	24	9.00	30.375	4	**<0.001***
	Primary school	68	6.00			
	Secondary school	13	7.00			
	High school	13	3.00			
	University	26	3.00			
Marital status	Married	101	5.00	5.976	3	0.113
	Single	4	3.00			
	Divorced	3	8.00			
	Widow	36	7.50			
Income	Income less than expenses	44	8.50	24.502	2	**<0.001***
	Income equal to expenses	78	6.00			
	Income more than expenses	22	2.00			
Residence	Alone	26	6.50	3.301	2	0.192
	With partner	94	4.50			
	With relatives	24	7.00			
Number of emergency visits	No	86	4.00	4.284	2	0.117
	≤2	39	6.00			
	>2	19	8.00			
Number of falls	No	72	4.00	6.100	2	**0.047***
	≤2	44	8.00			
	>2	28	6.00			

* p<0.05 was considered as statistically significant (Kruskall Wallis test)

Table 3. Results of Yesavage Geriatric Depression Scale according to socio-demographic characteristics

Yesavage Geriatric Depression Scale		N	Median	Z	p
Gender	Female Male	87 57	7.00 4.00	2.92	**0.003***
Number of medication	<5 ≥5	88 56	5.50 6.00	0.86	0.391

* p<0.05 was considered as statistically significant (Mann Whitney U test)

Table 4. Results of Edmonton Frail Scale according to socio-demographic characteristics

Edmonton Frail Scale		N	Median	Z	p
Gender	Female Male	87 57	7.00 4.00	3.11	**0.002***
Number of medication	<5 ≥5	88 56	5.00 7.00	2.76	**0.006***

* p<0.05 was considered as statistically significant (Mann Whitney U test)

Table 5. Results of Edmonton Frail Scale according to socio-demographic characteristics

Edmonton Frail Scale		N	Median	t	Df	p
Age	<75 75- 84 ≥85	94 39 11	5.00 8.00 8.00	20.610	2	**<0.001***
Education	Illiterate Primary school Secondary school High school University	24 68 13 13 26	10.00 7.00 4.00 6.00 3.50	44.469	4	**<0.001***
Marital status	Married Single Divorced Widow	101 4 3 36	6.00 2.50 6.00 8.50	12.316	3	**<0.006***
Income	Income less than expenses Income equal to expenses Income more than expenses	44 78 22	8.00 5.50 2.50	22.924	2	**<0.001***
Residence	Alone With partner With relatives	26 94 24	5.00 6.00 8.50	8.549	2	**0.014***
Number of emergency visits	No ≤2 >2	86 39 19	5.00 8.00 10.00	23.678	2	**<0.001***
Number of falls	No ≤2 >2	72 44 28	5.00 7.00 8.00	16.007	2	**<0.001***

* p<0.05 was considered as statistically significant (Kruskall Wallis test)

Table 6. Correlation test for Yesavage Geriatric Depression Scale and Edmonton Frail Scale

			Yesavage Geriatric Depression Scale	**Edmonton Frail Scale**
Spearman's Rho	Yesavage Geriatric Depression Scale	Correlation Coefficient Sig. (2-tailed) n	1.000 144	**0.677**** 0.001 144
	Edmonton Frail Scale	Correlation Coefficient Sig. (2-tailed) n	**0.677**** 0.001 144	1.000 144

* p<0.05 was considered as statistically significant
**Spearman's rho correlation test

Discussion

The birth rate is decreasing worldwide, and the elderly population is consistently expanding with a decrease in the younger population. Although the community's aging showed variation regarding time and process, it is observed in almost all countries, and it is thought that this issue will become an important problem in emerging countries.[14] If social and health-related problems accompanying aging are recognized early, they can be prevented or delayed. Thus, problems in this age group should be addressed using a public health approach. In this study, we evaluated the effects of socio-demographic characteristics, depression and polypharmacy on frailty in elderly individuals.

In our study, frailty increased with increasing age. In a study using EFS, Fabricio-Wehbe found that frailty levels varied across age groups, with increased frailty with advancing age.[15] In a study using EFS, Ching Chang et al. found that there was no statistical correlation between age groups and frailty total score.[16] This may be due to the difference in age distribution between studies. In a study of 1013 participants aged ≥ 74 years, Masel et al. found a correlation between frailty and economic challenges [17]. On the other hand, no significant correlation was found between education level and frailty.[1] It may be due to the higher education level among the study population in a study by Aygor et al.

Although many factors are involved in the etiology of falls, frailty also leads to falls. In a study by Morley, it was found that fall incidence was increased by increasing frailty.[18] In our study, it was found that the patients with a history of more than two falls were frailer.

In the geriatric age group, the number of comorbid diseases increases with age, which in turn increases the number of medications used. In our study, it was observed that individuals using five or more medications were more fragile. In the literature, it has been shown in several studies that there is a statistically significant relationship between polypharmacy and frailty.[16,19-22] The FRAILTURK study (2015) found that women are frailer than men.[23] In a study by Fabricio-Wehbe et al., it was found that there was a significant correlation between female gender and frailty.[15] Our study also found that women were frailer than men, in agreement with the literature. Although it has been observed that women are frailer than men in most studies, the underlying cause hasn't been fully elucidated. This may be due to the role of women in society as well as biological and social causes.

In addition to physiological alteration induced by aging, social and psychological changes also affect the individual's social life, communication and prestige. The individual becomes helpless. The loss of relatives and the challenges of adapting to technology lead to isolation, psychological distress and depression.[12] Feeling unhappy within the prior two weeks is a condition that warrants further evaluations for depression.[24] In a study on subjects aged ≥ 65 years, Yalinkilic et al. observed that the mean frailty score as rated by EFS was higher in subjects feeling unhappy within the prior two weeks.[25] In our study, a moderate, positive correlation was detected between Yesavage GDS and Edmonton Frail Scale in Spearman's rho correlation test, indicating increased frailty by increasing severity of depression. Our results are in agreement with the literature.

Among socio-demographic characteristics, education level and income are highly effective on the quality of life of an individual. In our study, the participants with lower income and those who were illiterate were found to be more depressive. In a study on elderly individuals in nursing homes by Gümüş et al. (2007), it was observed that low-income level led to increased hopelessness level[26] while in the study by Balci et al., it was found that low-income increased depression.[27] The household problems as well as social and environmental factors resulting from low income, lead to being more depressive. In a study using the Yesavage Geriatric Depression Scale by Discigil et al., it was found that female gender and the presence of 2 or more chronic diseases were risk factors for depression, while age, education status and social security status did not affect risk for depression.[28] Although many studies showed that depression is more commonly seen among women when compared to men, the social role, coping abilities and biological causes may have caused such findings. In our study, those who were illiterate were found to be more depressive; this may be due to higher rates of investigation and reading, ability to cope with stress and more willingness to cope with depression among elderly individuals with higher education levels.

In our study, no significant relationship was found between polypharmacy and depression.[29,30] However, in some other studies, it has been determined that individuals using multiple medications and having a higher

number of chronic illnesses are at risk for depression. It is believed that the different categorizations of multiple medication use and the scales used in these may account for these divergent results.

This study has some limitations. The study randomly assigned 144 patients aged ≥ 65 years who presented to the family medicine outpatient clinic of Bozyaka Training and Research Hospital; thus, the study population may not be representative of the geriatric population in Turkey. Secondly, the study's cross-sectional design resulted in a heterogeneous study population regarding socio-demographic characteristics; thus, results cannot be generalized.

In conclusion, it has been found that women, older adults, and individuals who are economically challenged are more fragile. Additionally, a statistically significant relationship exists between polypharmacy, depression, and frailty. These findings emphasize the importance of a preventive healthcare approach for the elderly.

Ethical Considerations: Ethical approval was obtained from the Clinical Research Ethics Committee of Education and Research Hospital in İzmir (decision no:17) on May 12, 2020.

Conflict of Interest: The authors declare no conflict of interest.

Funding: The authors received no financial support for this article's research, authorship and/or publication.

References

1. Aygor H, Fadıloglu C, Sahin S, Aykar F, Akcicel F. Validation of the Edmonton Frail Scale İn To Elderly Turkish Population. Archives of Gerontology and Geriatrics. 2018; 76:133-7.
2. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2019: Highlights (ST/ESA/SER.A/423). New York: United Nations.
3. Lopez PM, Fernandez-Ballesteros R, Zamarron MD, Lopez SR. Anthropometric, body composition and health determinants of active ageing: a gender approach. J BiosocSci. 2011;43(5):597-610.
4. Akgun S, Erdal R. The Concept of Aging and Approach to the Elderly. Holy YG Eds. Basic Geriatrics, Günes Medical Bookstores. Ankara; 2007:73-86.
5. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and aetiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006;54(6):991-1001.
6. Kayhan Kocak O, Sahin S, Akcicek F. Fragility Handbook.5 rd ed. Izmir; 2017:15-30.
7. Wyles H, Rehman HU. Inappropriate polypharmacy in the elderly. Eur J InternMed. 2005; 16:311-3.
8. Veehof L, Stewart R, Haaijer-Ruskamp F, et al. The development of polypharmacy. A longitudinal study. FamPract. 2000; 17:261-7.
9. Medicines and older people: implementing medicines-related aspects of the NSF for older people. http://www.gov.uk/nsf/ olderpeople/htm.
10. Linjakumpu T, Hartikainen S, Klaukka T, et al. The use of medications and polypharmacy are increasing among the elderly. J ClinEpidemiol. 2002; 55:809-17.
11. Yesil Y, Cankurtaran M, Kuyumcu ME. Polypharmacy. Clinical Progress. 2012; 25:18-23.
12. Sahin M, Yalcın M. Comparison of depression frequency between elderly individuals living in nursing homes and their own homes. Turkish Journal of Geriatrics.2003;6(1):10-3.
13. Ertan T, Istanbul University Cerrahpasa Faculty of Medicine, Department of Psychiatry, Investigation of Validity and Reliability of the Geriatric Depression Scale and the Self-Evaluation Depression Scale in the Turkish Population Aged 60 and Over. Istanbul, 1996.
14. UN. (2010). World Population Aging 2009. New York: United Nations.
15. Fabrício-Wehbe SCC, Schiaveto FV, Vendrusculo TRP, Haas VJ, Dantas RAS, Rodrigues RAP. Cross-Cultural Adaptation and Validity of the Edmonton Frail Scale in a Brazilian Elderly Sample, RevLatinoam Enfermagem.2009;17(6):1043-9.
16. Chang C, Chan D-C, Kuo K-N, Hsiung CA, Chen CY. Prevalence and Correlates of Geriatric Frailty in a Northern Taiwan Community, J FormosMed Assoc.2011;110(4):247–57.

17. Masel MC, Graham JE, Reistetter TE, Markides KS, Ottenbacher KJ. Frailty and health-related quality of life in older Mexican Americans, Health and Quality of Life Outcomes 2009;7(70): 2-7.
18. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle-aged African Americans. J Nutr Health Aging. 2012;16(7):601-8.
19. Hilmer SN, Perera V, Mitchell S, Murnion BP. Research The Assessment of Frailty in Older People in Acute Care Departments of Aged Care and Clinical Pharmacology.2009;28(4):182-8.
20. Herr M, Robine J-M, Pinot J, et al. Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people. Pharmaco epidemiol Drug Saf. 2015; 24:637-46.
21. Yuki A, Otsuka R, Tange C, et al. Polypharmacy is associated with frailty in Japanese community-dwelling older adults. Geriatr Gerontol Int. 2018; 18:1497-500.
22. Arslan M, Keskin Arslan E, Koc E.M, Sozmen M.K, Kaplan Y.C. Association Between Frailty and Medication Use and Polypharmacy in Individuals Aged 65 Years and Older. Med Bull Haseki. 2020; 58:33-41.
23. Akin S, Mazicioglu MM, Mucuk S et al. The prevalence of frailty and related factors in community-dwelling Turkish elderly according to modified Fried Frailty Index and FRAIL scales. Aging ClinExpRes. 2015;27(5):703-9.
24. Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002;136(10):765–76.
25. Yalınkılıc M, Kılıcaslan K, Uysal H, Bilgin S, Enc N. Identification of Frailty Status in Elderly Individuals with Heart Failure. Turk J CardiovascNurs. 2020;11(25):51–9.
26. Gumus Babacan A, Ozgur G, Yıldırım S. The levels of hopelessness and affecting factors in elderly individuals living in nursing homes. Ege University Nursing School Journal 2007;23(2):105-16.
27. Balcı E, Senol V, Elmalı F, Esel E, Elmalı F. The relationship between depression and malnutrition status of individuals aged 65 years and older. Turkish Journal of Public Health.2012;10(1):37-43.
28. Discigil G, Gemalmaz A, Basak O, Gurel FS, Tekin N. Depression in geriatric age group in primary care. Turkish Journal of Geriatrics. 2005;8(3):129-33.
29. Varma GS, Oguzhanoglu NK, Amuk T, Atesci F. Depression Frequency and Associated Risk Factors in Elderly Residents of Nursing Homes. Clinical Psychiatry. 2008; 11:25-32.
30. Karahan FS, Hamarta E. Polypharmacy in Geriatric Cases. Aegean J Med Sci. 2019; 1:08-13.

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):336-343 // 10.5505/amj.2023.47887

AN ANALYSIS OF THE DISTRIBUTION OF PATIENT DIAGNOSES BASED ON ICD CODES IN TURKEY BETWEEN 2016 AND 2022: A DESCRIPTIVE STUDY

Mustafa Mahir Ülgü[1], Şuayip Birinci[2]

[1]Ministry of Health, General Directorate of Health Information Systems

[2]Ministry of Health, Deputy Minister

Correspondence:

Mustafa Mahir Ülgü (e-mail: mahir.ulgu@saglik.gov.tr)

Submitted: 02.08.2023// Accepted: 25.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine

Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: It is very important for the individual to get to the hospital correctly and on time. This study aims to evaluate hospital admissions and diagnoses nationwide and guide policies to improve patient admissions.

Materials and Methods: All data on outpatient and inpatient treatment applications between 01.01.2016 and 31.12.2022 were examined retrospectively by examining the data of the national registry system. The diagnoses entered at each visit on these dates were classified according to ICD-10 and divided into 21 categories. Data related to specialty, hospital level and seasonal information of diagnoses were evaluated.

Results: During the study period, 6,662,007,644 diagnoses were entered in hospital visits. While it was seen that the number of diagnoses entered increased gradually from 2016 to 2019, it was noted that there was a decrease in 2020 due to the COVID-19 pandemic. The three most common diagnoses were musculoskeletal system diseases, circulatory system diseases, and diseases due to infectious causes. Infectious, eye, and gastrointestinal diseases were found to vary seasonally in the frequency of diagnosis.

Conclusion: Evaluating seasonal and hospital-level patient applications is essential in establishing effective health policies. Raising awareness of patients and increasing the number of health personnel is necessary to use health services effectively.

Keywords: Diagnosis, nationwide, ICD-10 code, health policy.

Introduction

The most fundamental health needs include individuals reaching the hospital as quickly as possible and accessing the correct specialties. That is crucial for the benefit of the individual and the proper functioning of health services in society. The main obstacle to achieving this goal is the inability to properly care for patients due to a shortage of healthcare workers and the unnecessary burden on the healthcare system of people with insufficient knowledge. In order to solve this problem, the healthcare system needs to be organized, and everyone needs to be educated. When diagnosing patients, universally accepted ICD-10 codes are used.[1] These codes not only enable a common language to be used in providing health services but also participate in forming health policies by identifying missing areas. It is necessary to evaluate the diagnoses of individuals during seasonal diagnostic changes or special situations such as a pandemic.[2] In forming these policies, it will be important to determine the distributions within the emergency department and basic medical specialties, including internal medicine, pediatrics, general surgery, and obstetrics and gynecology. In the literature, there are various studies where the diagnoses of patients applying to the emergency department are evaluated on a large scale.[3-5] These studies show that some patients applying to the emergency department have non-specific diagnoses that do not require emergency intervention and can be managed at the primary level. For example, some studies understood that a significant portion of dermatological complaints, which constitute 3-9% of emergency applications, were not urgent.[6,7] This situation leads to the obstruction of the operation of the health system and results in the victimization of really urgent individuals. Not only for normal times, there is a need for alternative ways to prevent such misuse in extraordinary situations like a pandemic. This study aims to compare the temporal changes in the diagnoses received nationwide by specialties and hospital levels during hospital applications. In this way, it is aimed to create health policies that will better direct individuals applying to the hospital.

Materials and Methods

In the Republic of Türkiye, all individuals' health-related data are recorded with a system called E-nabız.[8] It is possible to obtain disease, medication, mortality, allergies, examination information for each visit, as well as demographic data of patients from the e-Nabız system, which has been actively used since 2014. The study period was taken between 01.01.2016 and 31.12.2022, and all data related to outpatient and inpatient hospital visits during these dates were retrospectively examined. The diagnoses entered during each visit during these dates were classified according to ICD-10. The ICD-10 codes received during hospital visits were also grouped into 21 upper diagnoses, which the Ministry of Health established based on organ and etiology. Patients' diagnoses in 2020 and 2021, the pandemic period, were compared with other years. As shown in some

dermatological and infectious diseases before, seasonal frequency changes were examined nationwide and reviewed seasonally for all diseases.

Results

Between determined dates, a total of 6,662,007,644 diagnoses were entered in hospital visits. The number of diagnoses entered gradually increased during the 2016 – 2019 period, and a decrease occurred in 2020, with a 30.1% decrease in the number of diagnoses taken compared to the previous year. The number of diagnoses in 2019 was reached again in 2022 (Figure 1). The top 10 diagnoses entered according to the ICD-10 codes were as follows: musculoskeletal system diseases (n=2), circulatory system diseases (n=1), illnesses due to infectious causes (n=2), situations due to symptoms and abnormal laboratory findings (n=3), gastrointestinal diseases (n=1) and eye diseases (n=1). When examined as an upper group, 17.14% of all diagnoses were respiratory system diseases, 12.55% were digestive system diseases, and 11.81% were musculoskeletal system diseases. In terms of the years, this order was followed by respiratory system diseases, musculoskeletal system, and digestive system diseases in 2020 and 2021. The most common ten diagnoses were given in Table 1 in terms of years and specialties in Table 2. When examined seasonally, musculoskeletal system diseases and primary hypertension were in the first two places, while acute upper respiratory tract infections were in the third place in the winter and fall periods, and gastroesophageal reflux disease was in the third place in the summer. It was observed that the number of visits and the incidence of eye (from 4.74% to 4.93%) and dermatological (from 3.99% to 4.68%) diseases increased in the summer season.

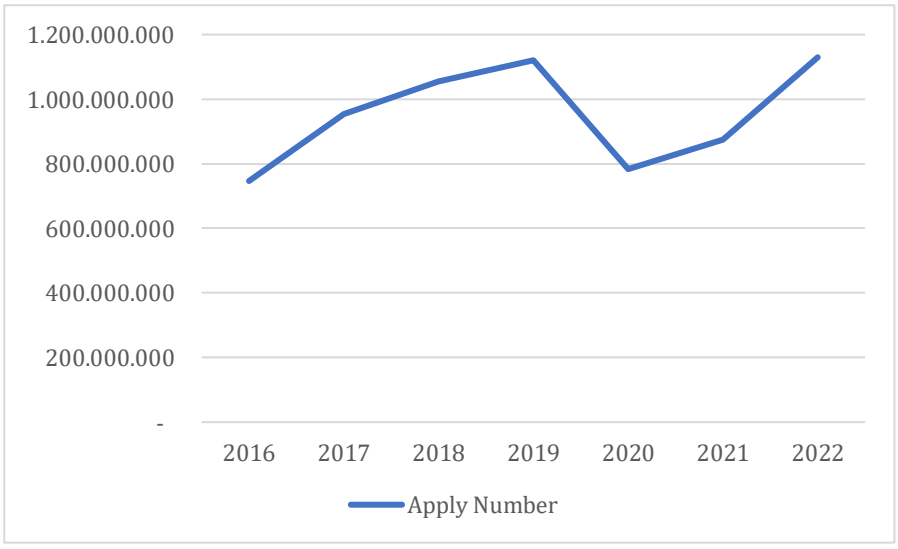


Figure 1. Number of admissions in terms of years

Table 1. The most common 10 diagnosis in terms of years

Diagnosis	2016 (%)	2017 (%)	2018 (%)	2019 (%)	2020 (%)	2021 (%)	2022 (%)
Respiratory Disease	19.17	17.22	17.40	17.47	15.68	15.03	17.79
Gastrointestinal Disease	13.26	13.03	12.63	12.39	12.04	12.42	12.20
Musculoskeletal Disease	11.57	11.56	11.47	11.39	12.26	12.75	11.88
Symptoms, Abnormal Laboratory Findings	9.84	10.43	10.51	10.39	10.78	11.79	10.88
Circulatory Disease	8.21	8.29	8.26	8.33	7.92	6.25	7.31
Endocrine Disease	6.54	6.98	7.49	8.56	8.40	8.60	9.43
Genitourinary Disease	5.79	6	5.90	5.81	6.24	6.41	5.64
Eye Disease	4.74	4.96	4.94	4.81	4.60	4.96	4.68
Skin Disease	4.20	4.24	4.19	4.19	4.58	4.64	4.18
Mental and Behavioral Disease	3.30	3.24	3.18	2.94	2.76	2.23	2.29

Table 2. Frequency of diagnosis in terms of specialties

Diagnosis	Primary care (%)	Emergency Medicine (%)	Internal Medicine (%)	Pediatrics (%)	General Surgery (%)	Obstetrics and Gynecology * (%)
Respiratory Disease	20.28	28.33	11.05	43.46	1.23	0.27
Gastrointestinal Disease	12.62	6.83	14.23	6.30	31.50	1.40
Musculoskeletal Disease	12,91	14.71	8.72	0.94	6.73	0.49
Symptoms, abnormal lab findings	5.83	24.96	11.15	14.99	15.44	9.56
Circulatory Disease	11.99	3,04	11.45	0.28	6.22	0.67
Endocrine Disease	11.07	0.92	27.67	8.67	8.58	4.21
Genitourinary Disease	3.81	4.02	4.23	3.58	15.05	48.30
Eye Disease	1.82	1.10	0.21	0.99	0.12	0.00
Skin Disease	5.48	1.76	1.01	4.05	8.58	0.59
Mental and Behavioral Disease	3.03	0.91	0.86	0.56	0.29	0.04
Other	11.16	13.42	9.42	16.18	6.26	12.4

* The second most common diagnosis was pregnancy, accounting for 22.07% of all diagnoses; the fourth most common diagnosis was blood and blood-producing organs, accounting for 7.06% of all diagnoses.

Discussion

In this comprehensive study examining all the data across the country, it is seen that the most common diagnoses are musculoskeletal system diseases, infectious causes, and circulatory system diseases, although they are susceptible to seasonal changes and influences like a pandemic.[9,10] While this cannot be known with certainty in the analysis of big data, The fact that primary care and emergency services are the same in terms of the most common diagnosis makes us believe that the problems of individuals who apply for emergency services are not typically urgent and can be resolved at the primary level. That supports the idea that individuals are not directed correctly and that the system is improperly used. As seen in some studies, the non-emergency use of the emergency department is common in many countries and is an important problem to be solved in health services.[3,4] Besides, Considering the diverse work environment in the emergency department has been shown to put pressure on the physician when entering the ICD code in the ED.[11,12] Studies are carried out to reduce the differences in diagnosis codes that occur during admission and discharge in the emergency department, among the solutions proposed to reduce the workload in the emergency, the establishment of online triage systems has become an option.[13] "Neyim var?" (https://neyimvar.gov.tr/) application, a type of online triage system also mentioned in the MHRS appointment system by the Ministry of Health, has recently started to be used for this purpose. In a comprehensive review, the accuracy of the pre-diagnosis for online triage was not as good as the doctor's, and the patient's compliance with the online recommendations was poor. On the other hand, it has been revealed that the satisfaction rate with this system is high and young and educated individuals are more willing to use it.[14] In particular, it is very important to increase the health literacy of patients applying to the hospital to receive appropriate treatment in the appropriate branch. In addition, emphasis can be placed on strengthening primary health care services to prevent hospital crowding. Entering the wrong diagnosis in outpatient clinic applications other than the emergency department is among the important problems. A study conducted in the USA revealed that about 5% of annual outpatient clinic admissions are diagnostic errors, and 12 million people are affected by this condition, half of which may face serious consequences.[15] As all these studies show, health policies should be developed to prevent these diagnostic errors in hospital admissions.

In this study, there has been observed a seasonal increase in the frequency of dermatological and eye diseases, and the prevalence of both diseases was increased in the summer period as they were in our study.[6,7,16] This is important in terms of forming and arranging health policies. It is expected that there will be an increase in the diagnosis rate of respiratory system diseases in 2020 and 2021 due to the COVID-19 pandemic, but this increase is much less compared to the total applications, and there is a decrease in the total number of diagnoses due to the decrease in total applications.[17-19] In our study, a 30.1% decrease was detected in 2020, when the COVID pandemic started, compared to the previous year, while a decrease between 20.1% and 73.2% was found in the studies looked at in this literature. That may result from the fear caused by the pandemic and

the reduced accessibility of other services due to the focus of health services on pandemic management. Once again, this shows how important it is to prepare health services for extraordinary situations such as a pandemic.

This study, while comprehensive in its approach, does present several limitations. Firstly, the data was retrospectively obtained from a single health information system, e-Nabız. As a result, this study may be subject to biases inherent in retrospective studies, and the generalizability of the findings may be limited to regions using similar health systems. Furthermore, while standardized, the ICD-10 coding system leaves room for interpretation and variability in coding practices, potentially impacting the accuracy of diagnosis classifications. Seasonal variations in diseases were analyzed; however, the specific geographic and climatic factors of different regions within the country that might influence these variations were not considered. The pandemic years of 2020 and 2021 also present unique circumstances that significantly influenced healthcare practices and patient behavior, making comparisons with these years complex. It should be remembered that ICD-10 codes do not reflect the real diagnoses of the patients, and sometimes diagnoses that will facilitate the payment of medicines are entered into the system. Lastly, this study did not evaluate the impact of various healthcare policies or educational programs that might have been implemented during the study period and could have influenced hospital visit trends and diagnosis distributions.

In conclusion, this study reveals the importance of examining the distribution of diagnoses received in hospital applications according to time, season, and specialties for the effective management of health services and the formation of health policies. It emphasizes the need to increase the awareness of individuals and increase health personnel to unnecessarily reduce the number of patients applying to the emergency department. Patients using primary care more effectively will reduce the workforce burden on hospitals, especially emergency services. Therefore, there is a need for more comprehensive and detailed studies to plan and manage health services more effectively.

Ethical Considerations: This study was conducted according to the Declaration of Helsinki and received approval from the Turkish Ministry of Health for retrospective data analysis (95741342-020/27112019).

Conflict of Interest: The authors declare no conflict of interest.

References

1. Xue QL. The frailty syndrome: definition and natural history. Clinics in geriatric medicine. 2011;27(1):1-15 (doi:10.1016/j.cger.2010.08.009).
2. Cao Y, Shan J, Gong Z, Kuang J, Gao Y. Status and Challenges of Public Health Emergency Management in China Related to COVID-19. Frontiers in public health. 2020;8:250 (doi:10.3389/fpubh.2020.00250).
3. Hooker EA, Mallow PJ, Oglesby MM. Characteristics and Trends of Emergency Department Visits in the United States (2010-2014). The Journal of emergency medicine. 2019;56(3):344-51 (doi:10.1016/j.jemermed.2018.12.025).
4. Quinn K, Herman M, Lin D, Supapol W, Worster A. Common Diagnoses and Outcomes in Elderly Patients Who Present to the Emergency Department with Non-Specific Complaints. Cjem. 2015;17(5):516-22 (doi:10.1017/cem.2015.35).
5. Wier LM, Yu H, Owens PL, Washington R. Overview of Children in the Emergency Department, 2010. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006.
6. Kilic D, Yigit O, Kilic T, Buyurgan CS, Dicle O. Epidemiologic Characteristics of Patients Admitted to Emergency Department with Dermatological Complaints; a Retrospective Cross sectional Study. Archives of academic emergency medicine. 2019;7(1):e47.
7. Rubegni P, Cevenini G, Lamberti A, et al. Dermatological conditions presenting at the Emergency Department in Siena University Hospital from 2006 to 2011. Journal of the European Academy of Dermatology and Venereology : JEADV. 2015;29(1):164-8 (doi:10.1111/jdv.12513).
8. Birinci Ş. A Digital Opportunity for Patients to Manage Their Health: Turkey National Personal Health Record System (The e-Nabız). Balkan medical journal. 2023;40(3):215-21 (doi:10.4274/balkanmedj.galenos.2023.2023-2-77).
9. Rusticucci M, Bettolli ML, de l A. Association between weather conditions and the number of patients at the emergency room in an Argentine hospital. International journal of biometeorology. 2002;46(1):42-51 (doi:10.1007/s00484-001-0113-z).
10. Vilkman S, Keistinen T, Tuuponen T, Kivelä SL. Seasonal variation in hospital admissions for chronic obstructive pulmonary disease in Finland. Arctic medical research. 1996;55(4):182-6.
11. Zavala AM, Day GE, Plummer D, Bamford-Wade AJAHR. Decision-making under pressure: medical errors in uncertain and dynamic environments. 2017;42(4):395-402.
12. Newman-Toker DEJD. A unified conceptual model for diagnostic errors: underdiagnosis, overdiagnosis, and misdiagnosis. 2014;1(1):43-8.
13. Hautz SC, Schuler L, Kämmer JE, et al. Factors predicting a change in diagnosis in patients hospitalised through the emergency room: a prospective observational study. 2016;6(5):e011585.

14. Chambers D, Cantrell AJ, Johnson M, et al. Digital and online symptom checkers and health assessment/triage services for urgent health problems: systematic review. 2019;9(8):e027743.
15. Singh H, Meyer AN, Thomas EJJBq, safety. The frequency of diagnostic errors in outpatient care: estimations from three large observational studies involving US adult populations. 2014;23(9):727-31.
16. Gorski M, Genis A, Yushvayev S, Awwad A, Lazzaro DR. Seasonal Variation in the Presentation of Infectious Keratitis. Eye & contact lens. 2016;42(5):295-7 (doi:10.1097/icl.0000000000000213).
17. Rabbone I, Tagliaferri F, Carboni E, et al. Changing Admission Patterns in Pediatric Emergency Departments during the COVID-19 Pandemic in Italy Were Due to Reductions in Inappropriate Accesses. Children (Basel, Switzerland). 2021;8(11) (doi:10.3390/children8110962).
18. Kalanj K, Marshall R, Karol K, Tiljak MK, Orešković S. The Impact of COVID-19 on Hospital Admissions in Croatia. Frontiers in public health. 2021;9:720948 (doi:10.3389/fpubh.2021.720948).
19. Henriques CO, Gouveia MC. Assessing the impact of COVID-19 on the efficiency of Portuguese state-owned enterprise hospitals. Socio-economic planning sciences. 2022;84:101387 (doi:10.1016/j.seps.2022.101387).

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):344-356 // 10.5505/amj.2023.70842

EVALUATION OF MEDICATION ADHERENCE OF INDIVIDUALS WITH CHRONIC DISEASES DURING RAMADAN

Tuğba Yılmaz[1]

[1] Department of Family Medicine, Ankara Bilkent City Hospital, Ankara, Türkiye

Correspondence:
Tuğba Yılmaz (e-mail: tugbagoktas88@hotmail.com)

Submitted: 14.08.2023 // Accepted: 07.09.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: Our study aimed to evaluate the adherence of individuals with chronic diseases who need to take regular medication during Ramadan.

Materials and Methods: A total of 152 fasting individuals over 18 years with at least one chronic disease who visited Ankara City Hospital Family Medicine Outpatient Clinic for any reason within one month between April and May 2023 during Ramadan were included. A unique structured questionnaire form and the MMS (Modified Morisky Scale-Turkish version) measuring medication adherence were used in the study.

Results: Among the participants of the study, 55.92% of the patients were female, 89.47% of the patients were married, and 61.18% were unemployed. 38.16% of the patients were elementary school graduates. The most common chronic diseases were found as hypertension at 54.95%, diabetes at 38.16%, and hypothyroidism at 17.11%. The rate of disruption in medication compliance was statistically higher among employed patients (p=0.040). It was observed that elementary school graduates were significantly more compliant in medication use than graduates with higher education levels (p=0.005; p=0.031). 67.11% of the patients stated that they "always" used their medications regularly.

Conclusion: Medication use was found to be affected by many factors in patients with chronic diseases who should take medication regularly. There was a change in the time of taking medication during Ramadan. Most of the patients were found to have high motivation and a high level of knowledge, according to the MMS. Patients' medication compliance increased with increasing age. In light of these findings, proactive assessment by primary care physicians prior to the start of Ramadan may play a pivotal role in improving medication and treatment adherence among affected patients.

Keywords: Medication compliance, chronic diseases, family medicine, Ramadan.

ANKARA MEDICAL JOURNAL

Introduction

During Ramadan, many Muslims around the world, including our country, observe daily fasting from dawn until dusk. This fasting practice entails refraining from eating and drinking during these periods. The duration of fasting varies, ranging from 10 to 18 hours, depending on the season and geographical location.[1] Some individuals who wish to fast as a religious obligation may also have chronic diseases or illnesses that necessitate regular treatment. In such cases, adjusting the timing of medication becomes imperative. While maintaining consistent medication compliance under medical supervision is crucial, healthcare professionals should ensure that such adjustments respect the individual's autonomy. Physicians should employ relevant resources to facilitate optimal treatment modifications during Ramadan.[2]

It is important for patients to have the ability to adhere to their medication regimen while fulfilling their religious obligations. The primary goal of medication management is to achieve maximum effectiveness. The patient's attitudes and behaviors significantly impact the management of medication use. Hence, assessing patients' adherence to treatment during Ramadan becomes vital. Our intended study aims to evaluate the adherence of individuals with chronic diseases to their treatment regimens during Ramadan. These patients, who opt to fast during Ramadan, often need to modify their medication schedules accordingly. Developing a tailored treatment plan specific to Ramadan is essential to safeguard patients' health status. Our study is anticipated to contribute to the successful alignment of individuals with chronic diseases with their treatment plans during Ramadan. By doing so, we will further enhance secondary and tertiary preventive healthcare services, aligning with our core competency in comprehensive patient care within the field of family medicine.[3] Furthermore, our efforts will ensure the uninterrupted continuation of patients' ongoing treatments, thus preventing the exacerbation of their medical conditions.

Materials and Methods

Our study is a cross-sectional observational study. It encompasses a sample of 152 individuals who visited Ankara City Hospital Family Medicine Outpatient Clinic for any reason during the period from April 6, 2023, to May 6, 2023. To be eligible for inclusion, participants needed to be over 18 years old, have at least one chronic disease and observe fasting during Ramadan. A unique structured questionnaire form and the MMS (Modified Morisky Scale Turkish version) were used.[4]

Data Collection Tools and Evaluation

In our study, a questionnaire form and the MMS were used to collect information about the patient's age, gender, educational status, smoking status, height, weight, monthly income, employment status, chronic

diseases, medications used, regular use of medications, disruption in medication use, getting up for Suhoor and medication use during Ramadan. This scale consists of six questions. The questions are answered as yes/no. The data collection questionnaire of our study was completed by the responsible researcher in the Family Medicine Outpatient Clinic of Ankara Bilkent City Hospital by face-to-face questionnaire administration method.

In the Modified Morisky Scale, the questions will be answered as Yes/No and in the evaluation, in questions 2 and 5, yes is 1 point, no is 0 points; in the other questions, yes is 0 points, no is 1 point. The total score obtained by the patient from the 1st, second and sixth questions gives the Morisky motivation score, while a total score of 0 or 1 indicates a low motivation level, and >1 indicates a high motivation level. The total score obtained from questions 3, 4 and 5 gives the Morisky knowledge score, whereas a total score of 0 or 1 indicates a low level of knowledge and >1 indicates a high level of knowledge.[5]

Statistical Analysis

All data were combined in a common database, and statistical analysis was performed with the SPSS 25.0 program. Descriptive statistical data were expressed as mean ± standard deviation for continuous variables, number and % for discrete data. The conformity of continuous variables to normal distribution was evaluated by examining histogram graphs and interpreting Kolmogorov Smirnov and Shapiro-Wilk tests. The independent T-test was used to determine whether there was a statistically significant relationship between the two independent groups. Correlation analysis was performed to determine whether there is a relationship between two or more variables and, if so, its strength and direction. The chi-square test was used to compare qualitative data between and within groups. Differences between groups were accepted as significant at $p<0.05$ with a reliability interval of 95%.

Results

In our study, 152 fasting individuals aged 18 years and older with at least one chronic disease visited Ankara City Hospital Family Medicine Outpatient Clinic for any reason within one month between April 6, 2023, and May 6, 2023, during Ramadan. Among the patients, 55.92% (n=85) were female, and 44.08% (n=67) were male. 89.47% (n=136) were married, and 10.53% (n=16) were single. The mean age was 57.28 ± 13.08 years (25-85 years), the mean height was 165.32 ± 9.30, and the mean weight was 78.39 ± 15.16. Body mass index was mostly overweight. 61.18% (n=93) of the patients were unemployed, and 38.82% (n=59) were working. 38.16% (n=58) were elementary school graduates, and 34.87% were university/high school graduates. The sociodemographic findings of the patients are shown in Table 1.

Table 1. Variables showing the sociodemographic characteristics of the patients

Descriptive variables (n=152)			**n**	**%**
Gender	Male		67	44.08
	Female		85	55.92
Marital status	Married		136	89.47
	Single		16	10.53
Education status	Illiterate		11	7.23
	Elementary education		58	38.16
	High School		30	19.74
	University/College		53	34.87
Employment status	Not working		93	61.18
	Working		59	38.82
Income status	Bad		9	5.92
	Middle		105	69.08
	Good		38	25.00
Cigarette	I quit		31	20.39
	None		97	63.82
	Yes		24	15.79
BMI	Normal		37	24.34
	Overweight		61	40.13
	Obese		54	35.53
Chronic disease groups (n=278)*	Cardiovascular diseases		106	69.74
	Endocrine system diseases		106	69.74
	Lung diseases		20	13.16
	Rheumatic diseases		8	5.26
	GI diseases		7	4.61
	Mental illness		6	3.95
	Neurological diseases		6	3.95
	Other		19	12.50
	The most common chronic diseases	Hypertension	82	53.95
		Diabetes Mellitus	58	38.16
		Hypothyroidism	26	17.11
		Dyslipidemia	20	13.16
		Asthma, COPD	19	12.50
		Heart failure	10	6.58

*More than one disease is marked. BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease

There was no statistical difference between gender and experiencing interruptions in medication use (p=0.913). There was no statistical difference between marital status and experiencing interruptions in medication use (p=0.183). The rate of interruption in medication use was statistically lower in those with lower educational status. The rate of interruption in medication use was statistically higher in employees (p=0.040). No significant difference was found between income status and disruption in medication use (p=0.869). Table 2 shows the comparison of patients' sociodemographic information with disruption in medication use.

It was found that the patients had been taking medication for an average of 10.74±8.14 years. Patients' attitudes towards medication use during Ramadan are shown in detail in Table 3. While 59.21% (n=90) of the participants stated that they experienced interruptions in medication use, the most common interruptions were travel 54.44% (n=49), Ramadan 23.33% (n=21), vacation 8.88% (n=8) and weekends 6.67% (n=6).

Table 2. Comparison of descriptive data with disruption in patients' medication compliance

Comparison			Disruption in medication compliance		p*
			No	Yes	
Education status	Elementary School	n	37	32	**0.005**
		%	37.38	32.32	
	High School	n	7	23	
		%	7.07	23.23	
	Elementary School	n	37	32	**0.031**
		%	30.33	26.23	
	University/College	n	18	35	
		%	14.75	28.69	
	High School	n	7	23	0.311
		%	8.43	27.71	
	University/College	n	18	35	
		%	21.69	42.17	
Employment status	Not working	n	44	49	**0.040**
		%	28.95	32.24	
	Working	n	18	41	
		%	11.84	26.97	

*Pearson Chi-Square Test

The relationship between the participants' descriptive data on medication use and disruption in medication use was examined, and no significant relationship was found (Table 4). A similar relationship was found between the diagnosis of the patients and regular medication use (p=0.668). The relationship between experiencing disruption in medication compliance and motivation and knowledge level according to the Modified Morisky Scale is shown in Table 5.

According to the Modified Morisky Scale, 69.74% (n=106) of the patients included in the study had high motivation, and 88.82% (n=135) had high knowledge (Figure 1). The correlation analysis between sociodemographic findings and Morisky Motivation and Knowledge Scores in our study is shown in Table 6.

Table 3. Patients' attitudes towards medication use during Ramadan

Parameters		n	%
How many different medicines do you take during the day?	1	**45**	**29.60**
	2	42	27.63
	3	25	16.45
	4	11	7.24
	5 and above	29	19.08
Do you take the medicines prescribed for your illness regularly?	Always	**102**	**67.11**
	Usually	40	26.32
	Occasionally	8	5.26
	Rarely	1	0.66
	Never ever	1	0.66
Do you ever forget a dose?	Never ever	38	25.00
	Rarely	**60**	**39.47**
	Occasionally	46	30.27
	Usually	8	5.26
If you forget a dose, when do you take it?	I don't forget	36	23.69
	I take it when I remember	**70**	**46.05**
	I don't take any	46	30.26
Does anyone remind you to take your medication?	Yes	37	24.34
	No	**115**	**75.66**
Do you carry your medicines with you?	Always	**101**	**66.45**
	Usually	14	9.21
	Occasionally	4	2.63
	Rarely	7	4.60
	Never ever	26	17.11
In which cases do you experience interruptions in your medication?	Never ever	**62**	**40.79**
	When I travel	49	32.23
	On weekends	6	3.95
	During Ramadan	21	13.82
	During vacation periods	8	5.26
	Other	6	3.95
Do you wake up for Suhoor?	Always	**115**	**75.66**
	Usually	9	5.92
	Occasionally	3	1.97
	Rarely	1	0.66
	Never ever	24	15.79
How does the way you take your medication change during Ramadan?	No change	23	15.13
	I take it all at Iftar	19	12.50
	I take it all at Suhoor.	24	15.79
	I divide it between Iftar and Suhoor	**84**	**55.26**
	I never use it	2	1.32

(The highest volumes are shown in bold.)

Table 4. Descriptive Data on Medication Use and Disruption in Medication Compliance

		n	Average	SD	p*
How many diseases do you have for which you take medication all the time?	No	62	1.90	1.04	0.325
	Yes	90	1.74	0.93	
How many years have you been taking medication continuously?	No	62	11.68	8.93	0.242
	Yes	90	10.10	7.54	
How many different medicines do you take during the day?	No	62	2.82	2.01	0.832
	Yes	90	2.76	1.83	

* Independent Samples T Test

Table 5. The Relationship Between Experiencing Disruption in Medication Compliance and Motivation and Knowledge Level According to the Modified Morisky Scale

Modified Morisky Scale		**Experiencing interruptions in medication use**		Total	p
		No	Yes		
Morisky motivation points	Low motivation	7 (4.61%)	39 (25.66%)	46 (30.26%)	**<0.001**
	High motivation	55 (36.18%)	51 (33.55%)	106 (69.74)	
	Total	62 (40.79%)	90 (59.21%)	152 (100.0%)	
Morisky knowledge score	Low knowledge	3 (1.97%)	14 (9.21%)	17 (11.18%)	**0.039**
	High knowledge	59 (38.82%)	76 (50.00%)	135 (88.82%)	
	Total	62 (40.79%)	90 (59.21%)	152 (100.0%)	

Table 6. Correlation of Morisky Motivation and Knowledge Score with Sociodemographic Results

		Age (years)	Total monthly income level	Motivation Score	Knowledge Score
Age (years)	Pearson Correlation	1	0.026	0.217*	0.022
	Sig. (2-tailed)		0.754	0.007	0.792
	N	152	8152	152	152
Total monthly income level	Pearson Correlation	0.026	1	0.097	0.272*
	Sig. (2-tailed)	0.754		0.236	0.001
	N	152	152	152	152
Motivation Score	Pearson Correlation	0.217*	0.097	1	0.364*
	Sig. (2-tailed)	0.007	0.236		0.000
	N	152	152	152	152
Knowledge Level Score	Pearson Correlation	0.022	0.272*	0.364*	1
	Sig. (2-tailed)	0.792	0.001	0.000	
	N	152	152	152	152

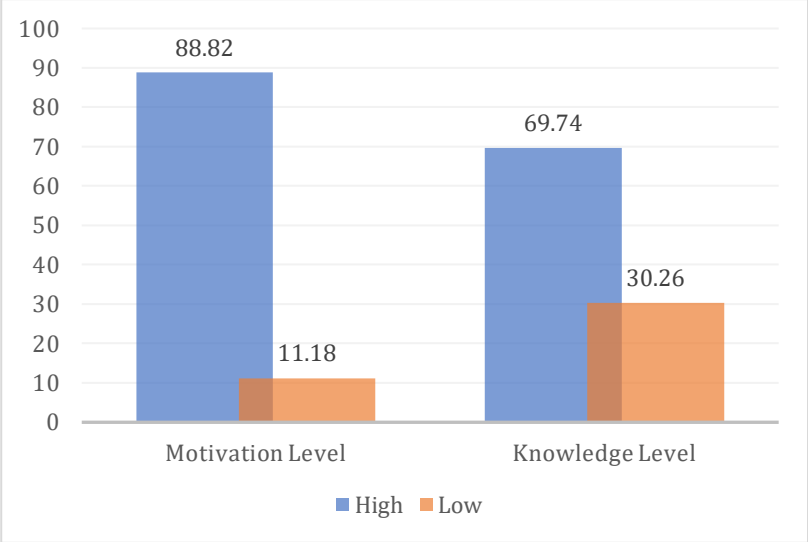


Figure 1. Patients' Motivation and Knowledge Levels According to the Modified Morisky Scale

Discussion

During Ramadan, many Muslims fast from dawn until sunset. Depending on where they live, the duration of the fast varies between 10 and 18 hours.[8] This is very important for patients with chronic diseases who need to take regular medication. Patients who want to fast may need to change their medication times under the supervision of a doctor. When this change is made, it is important that patients comply with the treatment so that the treatment is not interrupted. Patients' compliance with treatment is affected by many factors.

In our study, it was determined that there was a significant difference between the educational status of the participants and medication compliance. When the difference between the groups was examined, it was found that elementary school graduates did not experience significant disruption in medication compliance compared to both high school graduates and university/college graduates. In contrast to our study, in a thesis study, it was found that elementary school graduates had significantly lower regular medication use than both high school and university graduates.[5] In a study by Yakar et al., 54.3% of illiterate participants showed low compliance with antihypertensive treatment.[6] In a study by Demirbaş et al., the medication compliance score was higher in those with primary education and above compared to those who were only literate.[7] According to the literature, it can be said that medication compliance increases with increasing education levels. In our study, the result that medications were used more regularly in elementary school graduates compared to high school and university graduates may be attributed to the fact that the patients in our study were mostly primary

school graduates. In addition, as a result of the fact that fasting acclimatizes individuals to a certain amount of physical exercise and makes individuals more compliant in terms of medication use, it may have emerged as a positive reflection of fasting in our participant group, the majority of whom were elementary school graduates.[8]

In our study, a significant difference was found between the participants' employment status and medication use. There was no interruption in medication use, significantly more in those who were not working. Similarly, in a study by Lee et al., patients who were not working or retired used their medications more regularly.[9] According to the study by Kang et al., working patients were less compliant with their medications.[10] According to our study and the literature, employment status affects medication adherence. While non-working individuals use their medications more regularly, it can be said that the opposite situation in working individuals is due to the intense pace of working life.

Our study was conducted on patients who were fasting during Ramadan; 67.11% of the patients "always" and 26.32% "usually" took their medications regularly. In our study, 54.44% of patients who could not take their medications regularly stated that they experienced interruptions in medication use when traveling, 23.33% during Ramadan, and 8.88% during vacation periods. In a thesis study conducted during Ramadan, 71.3% of the participants were found to take their medications regularly. In this study, the regular medication use of the participants was analyzed according to their fasting status, but it was found that there was no statistically significant difference. In addition, 64.3% of the participants who were fasting stated that they used their medication regularly, while the participants experienced disruption in the use of medication during feast, Ramadan, vacation and travel, respectively.[5] When we look at our study and the thesis study, it can be said that Ramadan does not affect regular medication use very much, although many factors affecting regular medication use are seen.

In our study, 55.26% of the patients took their medications between Iftar and Suhoor, 15.79% at Suhoor and only 15.13% stated that the time of medication intake did not change. In a study conducted in Sudan, almost all of the participants took their medications at night between Iftar and Suhoor.[11] In a thesis study, 33.3% of patients took some of their medication at Iftar and some at Suhoor.[5] In a study conducted by Aydın et al., it was found that the majority of asthma patients used their inhaled medications, which should be used regularly, during iftar and Suhoor hours during Ramadan, and in the same study, it was observed that the majority of patients with Chronic Obstructive Pulmonary Disease stopped using their medications during Ramadan.[12] In another study, it was found that the common practice in the use of medication during Ramadan was to take a single dose a day or two doses between Iftar and Suhoor.[1] In a study conducted by Pehlivan et al. during Ramadan, 52.9% of the patients continued to use their medications without any change, while 73.3% did not use them at all.[13] Considering our study and the literature, it is seen that individuals with chronic diseases need to take medication regularly and fast. However, it is understood that patients change their medication times

during Ramadan. It is important for patients to change their medication times under the control of a doctor for their health. It is recommended that patients should apply to their family physician 4-6 weeks before Ramadan in order to fast properly during Ramadan.[14]

In our study, the relationship between the number of diseases, the number of medications used continuously, the duration of medication use and the disruption in medication use during Ramadan was examined, and no significant relationship was found. In a study conducted by Demirbaş et al., the relationship between the duration of the disease diagnosis, the number of medications used by the patients and the total score of the drug therapy compliance scale was examined, a significant relationship was found, and it was observed that the compliance scale score decreased with the increase in the duration of diagnosis and the number of medications used.[7] In a thesis study, it was found that there was a statistically significant difference in the regular use of medication according to the number of different medications used by the participants, and the rate of regular use of medication was higher in those who used 1-2 medications daily than in those who used five or more medications daily.[5] In the study by Jankowska-Polańska et al., it was observed that people who were prescribed monotherapy or single-tablet polytherapy used their medication more regularly than those taking more than one medication.[15] In the study by Teshome et al., people taking less than two antihypertensive drugs per day had more regular medication use than those taking two or more drugs.[16] There was a difference between our study and other studies in the literature. According to studies in the literature, patients' medication adherence decreased with increasing number of medications used. The different results in our study may have been due to the fact that our study was conducted on fasting patients during Ramadan.

In our study, 69.74% of the patients had high motivation, and 88.82% had a high knowledge level, according to the MMS. In our study, a significant correlation was found between the MMP (Morisky Motivation Point) and MKP (Morisky Knowledge Point) and the opinion of not experiencing a disruption in medication use during Ramadan. It was understood that those who experienced disruption in medication use had significantly low motivation and low knowledge scores. If the patient's motivation and knowledge level are high, they experience fewer interruptions in medication use even if the time of medication use changes during Ramadan; this may be explained by the fact that informing and motivating patients about their treatment contributes to the regular use of medications.

In our study, there was a significant weak positive correlation between age and MMP. In a study by Kara et al., it was found that the mean MMP scores tended to increase with increasing age, but the relationship was not statistically significant.[17] In a meta-analysis of international publications, 15 studies showed that medication adherence increased with age.[18] This result may be attributed to the patient's acceptance of their disease over time and regular visits to their follow-up visits. Two different studies in the literature showed that medication adherence decreased with increasing age.[19,20] In a study conducted by Yakar and colleagues, it was found that

the compliance of participants aged 65 years and older with antihypertensive treatment was statistically significantly lower than that of individuals under 65 years of age.[6] This may be related to the decrease in functional and mental capacity due to old age or the increased likelihood of diseases such as dementia and Alzheimer's disease, which may cause cognitive impairment with age.

Conclusions

In our study, medication use was found to be affected by many factors in patients with chronic diseases who should take medication regularly. It was found that there were more disruptions in medication use in people who are working. It was found that those with elementary education used their medications more regularly. It was found that patients experienced disruptions in medication use when traveling, during Ramadan and during vacation periods, respectively. It was observed that there was a change in the time of taking medication during Ramadan. Most of the patients were found to have high motivation and a high level of knowledge, according to the MMS. It was observed that medication adherence increased with increasing age.

Compliance with treatment is very important for patients with chronic diseases who need to take medication regularly. It is especially important for patients who will be traveling to visit their family physician before traveling and for patients who will be fasting during Ramadan to visit their family physician before Ramadan. Again, it is necessary for patients to be informed about the diseases they have in order to ensure compliance with treatment. Patients' acceptance of their diseases and their follow-ups will increase their motivation and contribute to more regular use of their medications. These follow-ups need to be revised in every possible change, and Ramadan is one of these periods. It is important for physicians to turn these periods into an opportunity to follow up with their patients.

Ethical Considerations: Ethics committee approval dated April 5, 2023, and numbered E1-23-3443, was obtained from the local ethics committee for research authorization.

Conflict of Interest: The author declares no conflict of interest.

References

1. Aadil N, Houti IE, Moussamih S. Drug intake during Ramadan. BMJ. 2004;329:778-82.
2. Özkaya H, Yılmaz TE. Ramazan Orucuna Hasta ve Hekim Açısından Etik Yaklaşım. In: A Özkara, M Altay, ed. Oruç ve Kanıta Dayalı Tıp. Ankara: Ankara Nobel Tıp Kitabevleri; 2020:14-18.
3. Fevzi Dikici MF, Kartal M, Alptekin S, Çubukçu M, Ayanoğlu AS, Yarış F. Concepts, Job Description and History of the Discipline in Family Medicine. Turkiye Klinikleri J Med Sci. 2007;27:412-8.
4. Vural B, Acar ÖT, Topsever P, Filiz TM. Turkish Validity and Reliability Study of Modified Morisky Scale. The Journal of Turkish Family Physician. 2012;3(4):17-20.
5. Alioğlu O. Evaluation of Treatment Compliance of Diabetes and High Blood Pressure Patients During Ramadan. Master's Thesis, T.C. Istanbul Medipol University Institute of Health Sciences, İstanbul;2021.
6. Yakar B, Demir M. Investigation of Antihypertensive Drug Therapy Compliance Rates and Affecting Factors in Patients with Chronic Renal Failure. Dicle Medical Journal / Dicle Med J. 2019;46(4):685-96.
7. Demirbas N, Kutlu R. Treatment Compliance and Self-Efficacy Levels of Adult Individuals Using Multiple Drugs. Ankara Med J. 2020;(2):269-80.
8. Attarzadeh Hosseini SR, Sardar MA, Hejazi K, Farahati S. The effect of ramadan fasting and physical activity on body composition, serum osmolarity levels and some parameters of electrolytes in females. Int J Endocrinol Metab. 2013 Spring;11(2):88-94 (doi: 10.5812/ijem.9602).
9. Lee GKY, Wang HHX, Liu KQL, Cheung Y, Morisky DE, Wong MCS. Determinants of medication adherence to antihypertensive medications among a Chinese population using morisky medication adherence scale. PLOS ONE. 2013;8(4):1-7.
10. Kang CD, Tsang PPM, Li WTL, et al. Determinants of medication adherence and blood pressure control among hypertensive patients in Hong Kong: a cross-sectional study. Int. J. Cardiol. 2015;182:250-7.
11. Ahmed AAE, Jalal M, Haleem SEAHA. Evaluation of the drugs' regimens during Ramadan, in Sudan: Patients' prospective. Medical Science. 2021;25(117):2769-77.
12. Aydin Ö, Celik GE, Onen ZP, et. al. How do patients with asthma and COPD behave during fasting? Allergol Immunopathol (Madr). 2014;42:115-9.
13. Pehlivan S, Pehlivan Y, Yağız B, et. al. Rheumatology patients' attitude regarding Ramadan and fasting. Int J Rheum Dis. 2020;23(8):1082-7.
14. Yılmaz TE, Başara E, Yılmaz T, Kasım İ, Özkara A. Approaches and awareness of family physicians on diabetes management during Ramadan. The International Journal of Clinical Practice. 2021;75(7):1-10.
15. Jankowska-Polańska B, Chudiak A, Uchmanowicz I, Dudek K, Mazur G. Selected factors affecting adherence in the pharmacological treatment of arterial hypertension. Patient Prefer. Adher. 2017;11:363-71.

16. Teshome D. F., Bekele K. B., Habitu Y. A., Gelagay A. A. (2017). Medication adherence and its associated factors among hypertensive patients attending the Debre Tabor General Hospital, northwest Ethiopia. Integr. Blood Press. Control. 2017;10:1-7.
17. Kara DD, Mert E, Uysal Y, Başhan İ. Evaluation of Medication Adherence in Adults Who Use Multiple Medications in The Context of Illness Perception, Acknowledgement and Attitude Characteristics TJFMPC. 2017;11(4):227-34.
18. Uchmanowicz B, Jankowska EA, Uchmanowicz I, Morisky DE. Self-Reported Medication Adherence Measured With Morisky Medication Adherence Scales and Its Determinants in Hypertensive Patients Aged _60 Years: A Systematic Review and Meta-Analysis. Front Pharmacol. 2019;10(168):1-11.
19. Ross S, Walker A, MacLeod MJ. Patient compliance in hypertension: Role of illness perceptions and treatment beliefs. J Hum Hypertens. 2004;18(9): 607-13.
20. Enlund H, Jokisalo E, Wallenius S, Korhonen M. Patient-perceived problems, compliance, and the outcome of hypertension treatment. Pharm World Sci. 2001;23:60-4.

ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2023;(3):357-365 // 10.5505/amj.2023.36786

THE COMPARISON OF THE LABORATORY PARAMETERS OF INACTIVATED CORONAVIRUS VACCINATED AND NON-VACCINATED COVID-19 PATIENTS APPLIED HOSPITAL

Burcu Ozdemir[1], Levent Özdemir[1], Bilge Akgunduz[2]

[1] Samsun Education And Research Hospital, Chest Diseases, Samsun, Türkiye

[2]Eskişehir City Hospital, Chest Diseases, Occupational and Occupational Diseases, Eskişehir, Türkiye

Correspondence:

Levent Özdemir (e-mail: levent2408@mynet.com)

Submitted: 28.03.2023 // Accepted: 18.08.2023

Ankara Yıldırım Beyazıt University Faculty of Medicine

Department of Family Medicine

ANKARA MEDICAL JOURNAL

Abstract

Objectives: The comparison of laboratory parameters of non-vaccinated and inactivated coronavirus-vaccinated patients who came down with COVID-19.

Materials and Methods: The study was designed as a retrospective cross-sectional study between March 2020 and April 2021. 154 patients who had no vaccination(n=77) and one-dose (n=28) or two-dose (n=49) inactivated coronavirus vaccination, demographical data's, hemogram, C-reactive protein (CRP), ferritin and D-dimer levels were evaluated.

Results: In total, 154 patients were included in the study (84 female, 54.5%). The mean age was 65.1±14.5 years. The ferritin level was 449.93±443.48 ml/ng in one-dose vaccinated patients, 297.68±340.32 ml/ng in two-dose vaccinated patients and 568.70±539.41 ml/ng in unvaccinated patients; this difference was statistically significant (p=0.008). The D-dimer level was 0.86±0.89 µg/L in one-dose vaccinated patients, 0.67±0.79 µg/L in two-dose vaccinated patients and 1.62±1.93 µg/L in unvaccinated patients; again, a statistically significant difference existed (p=0.002). The rates of hospitalization in the ward and intensive care unit (ICU) and D-dimer levels were lower in two-dose vaccinated patients than in unvaccinated patients (p=0.015). No significant difference was detected concerning hemogram and CRP level of non-vaccinated, one-dose vaccinated and two-dose vaccinated patients.

Conclusion: Even if vaccinated, individuals can get COVID-19, but disease progression is milder, and ferritin and D-dimer levels related to disease severity are higher in unvaccinated patients.

Keywords: Inactivated coronavirus vaccine, COVID-19, lymphocyte, CRP, ferritin, D-dimer.

Introduction

The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020. To prevent the spread of the COVID-19 pandemic and to control the disease, among other measures, a mass COVID-19 vaccination program has been implemented in our country and worldwide. Since the beginning of the epidemic, numerous vaccines have been formulated worldwide, including inactivated, live virus, recombinant protein, vector, DNA or RNA vaccines developed by various companies. In our country, risk groups were established on January 13, 2021, and the CoronaVac vaccine, an inactivated SARS-CoV-2 vaccine, was used for the first time.[1]

In viral diseases that affect respiratory passage, consistent correlations are reported among C-reactive protein (CRP), ferritin, erythrocyte sedimentation speed, fibrinogen, haptoglobulinemia, serum amyloid A, acute phase proteins like procalcitonin and lymphocyte, and D-dimer levels with the progression of the disease. CRP, ferritin, and d-dimer levels were increased in the serum of the organisms that were affected by the viruses that caused respiratory passage disease compared to healthy samples. Acute-phase proteins are a good marker for showing the severity of viral replication, evaluating the individual immune response to the virus, diagnosing the disease, and evaluating the response to antiviral agents. As with other viral infections, vascular damage occurs in COVID-19 disease in association with the systemic inflammatory response.[2] The severity of vascular damage and mortality in COVID-19 disease is thought to be related. D-dimer and troponin are other laboratory parameters used to predict cardiovascular damage and mortality in coronavirus disease.[3,4]

In our study, we aimed to compare the patients' hemogram, CRP, ferritin, and d-dimer levels who caught COVID-19 after having inactivated coronavirus vaccination and the patients' hemogram, CRP, ferritin, and d-dimer levels who caught COVID-19 before being vaccinated.

Materials and Methods

The study was designed as a retrospective cross-sectional study. Between March 2020 and April 2021, patients older than 18 years who were hospitalized in the ward or intensive care unit (ICU) for COVID-19 in the pre-vaccination period and patients who developed COVID-19 and who were hospitalized in the ward or ICU in the post-vaccination period (one- or two-doses) were enrolled (77 vaccinated, 77 unvaccinated). Patients who had received Biontech's mRNA vaccine were excluded.

COVID-19 patients were divided into three groups based on treatment site: outpatients, inpatients in the ward, and inpatients in the ICU.

Patients were administered CoronaVac, an inactivated viral vaccine. We divided patients according to their vaccination status into unvaccinated, one-dose vaccinated, and two-dose vaccinated patients (unvaccinated patients n=77, one-dose vaccinated patients n=28, two-dose vaccinated patients n=49).

Non-vaccinated patients: The patients were composed of the ones who caught COVID-19 before the vaccination period and were outpatients or received treatment in a ward or intensive care unit.

The patients who had one-dose CoronaVac: The patients were composed of the ones who had COVID-19 after one-dose vaccination and were outpatients or received treatment in a ward or intensive care unit.

The patients who had two-dose CoronaVac: The patients were composed of the ones who had COVID-19 after two-dose vaccination and were outpatients or received treatment in a ward or intensive care unit.

Patient demographic characteristics and laboratory data (hemogram, CRP, ferritin, D-dimer) were obtained from the hospital database. Hemogram, CRP, ferritin, and D-dimer values of patients were measured in blood drawn at the time of hospital admission.

Statistical Analysis

All analyses were performed via SPSS V22 for Windows program (SPSS Inc., Chicago, IL, USA). Frequencies and percentages of categorical variables: mean, median and standard deviation values of numerical variables were calculated. T-tests or One-way ANOVA were conducted for numerical variables showing homogeneous distribution. Categorical variables were tested with the chi-square test. A p-value of <0.05 was considered statistically significant.

Results

In total, 154 patients were included in the study (one-dose vaccinated patients: 28, two-dose vaccinated patients: 49, unvaccinated: 77), of whom 70 were male and 84 (54.54%) were female. The mean age was 65.14±14.5 years (vaccinated: 65.40±15, unvaccinated: 64.71±14.17). There was no statistical difference between vaccinated and unvaccinated patients in terms of age and gender ratio. Comorbidities were found in 127 patients. The most common comorbidities were hypertension (n=104, 67.53%), heart failure (n=42, 27.27%), asthma (n=32, 20.77%), and COPD (n=31, 20.12%), respectively. Of the exitus patients with a rate of %19.49, 56.66% (n= 17) were unvaccinated, 23.33% (n= 7) were two-dose vaccinated, and there was no statistical significance between vaccination status and mortality rate (Table 1).

Table 1. Demographic characteristics of patients with COVID-19 (n=154)

	1-dose vaccinated patients	2-dose vaccinated patients	Unvaccinated patients
Age, year (mean±SD)	68.57±8.15	63.73±17.62	64.71±14.17
Gender (n, %)			
Male	13(8.44)	22(14.28)	35(22.72)
Female	15(9.74)	27(17.53)	42(27.27)
Comorbidity (n, %)			
Hypertension	24(23.07)	32(30.76)	48(46.15)
Heart failure	15(35.71)	14(33.33)	13(30.95)
Asthma	4(12.50)	12(37.50)	16(50)
COPD	8(25.80)	9(29)	14(45.16)
Diabetes mellitus	1(4)	8(32)	16(64)
Cerebrovascular Event (CVE)	5(23.80)	10(47.61)	6(28.57)
Alzheimer's disease	1(11.11)	3(33.33)	5(55.55)
Malignancy	3(60)	1(20)	1(20)
Obesity	1(25)	2(50)	1(25)
Chronic Renal Insufficiency	3(75)	0(0)	1(25)
Disease severity (n, %)			
Outpatient	17(11.03)	0(0.00)	17(11.03)
Inpatient	22(14.28)	20(12.98)	43(27.92)
İntensive care unit	10(6.49)	8(5.19)	17(11.03)
Survival (n,%)	7(4.54)	6(3.86)	17(11.03)
Non-survival (n,%)	25(16.23)	22(14.28)	43(27.92)

When comparing laboratory parameters between one-dose vaccinated, two-dose vaccinated and unvaccinated patients, no statistical significance was found in leukocyte, neutrophil, lymphocyte, monocyte and CRP levels. Ferritin level was 449.93±443.48 ml/ng in one-dose vaccinated patients, 297.68±340.32 ml/ng in two-dose vaccinated patients and 568.70±539.41 ml/ng in unvaccinated patients and was statistically significant (p=0.008). The D-dimer level was 0.86±0.89 µg/L in one-dose vaccinated patients, 0.67±0.79 µg/L in two-dose vaccinated patients and 1.62±1.93 µg/L in the unvaccinated patients and was statistically significant (p=0.002) (Table 2).

While the rate of those with D-dimers <0.5 µg/L was 12.98% (n=20) in the unvaccinated patients, it was 20.12% (n=31) in two-dose vaccinated patients (p=0.001). The rate of those with D-dimers ≥1.0 µg/L (20.77%, n=32) was significantly higher in unvaccinated patients than in two-dose vaccinated patients (6.49%, n=10) (p=0.001) (Table 3).

In those with severe disease who were hospitalized in the ICU, ferritin and D-dimer levels were significantly higher in unvaccinated patients than in one-dose vaccinated and two-dose vaccinated patients (D-dimer

p=0.015; ferritin p=0.029). In outpatients with milder disease, D-dimers were lower in two-dose vaccinated patients than in unvaccinated patients, which was statistically significant (p=0.002) (Figure 1-2).

Table 2. Comparison of laboratory parameters in vaccinated and unvaccinated COVID-19 patients

	1-dose vaccinated patients	2-dose vaccinated patients	Unvaccinated patients	p
Leukocyte $X10^3/\mu l$	8.73±5.33	8.23±4.00	9.06±4.60	0.606
Neutrophil $X10^3/\mu l$	7.07±4.94	6.04±3.56	7.24±4.52	0.302
Lymphocyte $X10^3/\mu l$	1.01±0.53	1.46±0.90	1.20±0.83	0.051
Monocyte X103/µl	0.59±0.41	0.60±0.36	0.56±0.45	0.838
CRP mg/L	69.21±54.60	62.01±68.67	82.90±66.70	0.203
Ferritin, ml/ng	**449.93±443.48**	**297.68±340.32**	**568.70±539.41**	**0.008***
D-dimer, µg/L	**0.86±0.89**	**0.67±0.79**	**1.62±1.93**	**0.002***

CRP= C-reactive protein, p<0.05 The means of the groups were analyzed with the One-Way ANOVA test.
*A post-hoc test was performed for Ferritin and D-dimer levels. For Ferritin Mean Square=0.61, F= 1.69; for D-dimer Mean Square: 0.61, F= 1.14 was determined.

Discussion

The goal of vaccines developed against viral diseases is to completely prevent the disease, ameliorate the severity of the disease, or prevent mortality and morbidity. Studies of vaccine efficacy have shown that the efficacy of two doses of an mRNA vaccine ranges from 95 to 81%. [4,5] The host immune response to the coronavirus vaccine is highly variable, and even when vaccinated, COVID-19 can occur in the vaccinated population because the effect of the vaccine on new variants is not yet known. According to the WHO report, the success of the inactivated coronavirus vaccine used in China, Chile, Turkey, Indonesia, and Brazil varies between 84-50% in preventing symptomatic disease and between 100-85% in preventing hospitalization.[6] When the disease emerges, the effect of vaccination is not known on laboratory parameters (lymphocyte, CRP, D-dimer and ferritin). This study showed that ferritin and D-dimer levels are higher in non-vaccinated patients when compared to the severity of disease among two-dose vaccinated ones.

Vaccinations have a role as an immunomodulator in the emergence of disease by generating immune body against viruses. The roles of CRP, ferritin, erythrocyte sedimentation rate, fibrinogen, haptoglobulinemia, serum amyloid A, and acute phase proteins such as procalcitonin.[2] The APPs, which are the indicator of individual immune response in COVID-19 disease, are significant parameters in evaluating disease severity, indicating organ damage and mortality.

Although CRP level is known to be elevated in noninfectious diseases, it is also an APP that has been routinely used in clinical practice for many years to assess disease progression and response to treatment of infectious

diseases. In a meta-analysis, CRP was found to indicate disease severity but did not increase mortality.[7] A study by Liu et al. reported that COVID-19 disease progressed severely in cases with a CRP > 41.8 mg/L.[8] Yormaz et al. emphasized that 67.47% of cases with COVID-19 disease had high CRP levels.[9] It is not clear how CRP levels develop in people with the disease, even if they are vaccinated. We detected no significant difference between CRP levels considering non-vaccinated one-dose vaccinated and two-dose vaccinated in our study.

Ferritin, often used to diagnose iron-deficiency anemia, is another APPs that can increase with viral infections.[10] A retrospective study of COVID-19 mortality by Ruan et al. concluded that IL-6, ferritin, and CRP were higher in non-survivors than in survivors.[11] Moreover, ferritin level was an independent APP in COVID-19, ARDS and mortality in different studies. CRP, lymphopenia and D-dimers have been shown to have an effect on survival, but ferritin has not been shown to be related to survival.[12,13] In our study, ferritin levels were significantly lower in two-dose vaccinated patients than in one-dose vaccinated and unvaccinated patients.

D-dimer level is a good marker to indicate thrombi as well as a good APP associated with fibrin degradation, leading to activation of the fibrinolytic system and reflecting coagulation activity.[14] In a study by Yu et al. comparing D-dimer level in bacterial pneumonia and COVID-19 pneumonia, it was revealed that D-dimer level in COVID-19 disease was associated with inflammation.[15] Again, several studies have reported that high D-dimer levels increase the risk of thrombosis and mortality.[16,17] Similar to other studies, Tang et al. showed that D-dimer level in COVID-19 was associated with mortality and that prophylactic anticoagulant therapy reduced 28-day mortality by 20%.[18] There is no study examining D-dimer level and mortality in people with COVID-19 who had been previously vaccinated. In our study, the D-dimer level in unvaccinated individuals was approximately twice that in two-dose vaccinated individuals. We found that in patients hospitalized in the ICU, D-dimer levels were 4.4 times higher in unvaccinated patients than in two-dose vaccinated patients

The lower hospitalization rate in vaccinated individuals suggests that vaccinated individuals have a mild disease course, even if they had a prior disease due to COVID-19. The high hospitalization rate in the unvaccinated patients and the higher D-dimer level in this group led us to believe that the vaccine might also be effective in preventing microthrombus formation. This result should be supported by other studies, as the information in the literature is insufficient.

There are many studies showing an association between the severity of COVID-19 and lymphopenia.[19,20] Lymphopenia has been associated with severe disease requiring hospitalization. 80% of patients hospitalized for severe COVID-19 disease and 25% of patients for moderate COVID-19 disease had lymphopenia.[13] In our study, lymphocyte levels were lower in unvaccinated patients than in two-dose vaccinated patients. When comparing hospitalizations due to COVID-19 disease, indicating the severity of the disease, the lymphocyte

count was lower in unvaccinated hospitalized patients, especially in the ICU, than in two-dose vaccinated patients.

Our limitations were having a limited number of patients, evaluating the data retrospectively, and as the first practiced vaccination was inactivated coronavirus vaccination and later practiced mRNA vaccination's effect on laboratory figures could not be evaluated. The strength of our study is using inactivated SARS-CoV-2 vaccine is valuable as it reflects real-world experience.

In conclusion, even when unvaccinated patients were vaccinated and became ill, the COVID-19 disease is milder and ferritin and D-dimer levels related to disease severity are higher. Although the vaccine is not sufficient to completely prevent the disease, it may lead to a milder course, and this should be supported by further clinical studies.

Ethical Considerations: Ethics committee approval (Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee permission dated 06.05.21 and numbered 12) was obtained for this study.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Balaban GB, Tanyeri Y, Tokyay BK et al. Vaccines and Production Methods Developed Against SARS-CoV-2. JHIT 2021; 14-32
2. Perez L. Acute phase protein response to viral infection and vaccination. Arch Biochem Biophys. 2019 August 15;671: 196-202
3. Iba T, Connors JM, Levy JH. The coagulopathy, endotheliopathy, and vasculitis of COVID-19. Inflamm Res. 2020 Dec;69(12):1181-9.
4. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? Expert Rev Vaccines. 2021 Jan; 20(1): 23-44.
5. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 December 31;383(27):2603-15.
6. Strategic Advisory Group of Experts on Immunization-SAGE (WHO). Evidence Assessment:Sinovac/CoronaVac COVID-19 vaccine. Report from 29/04/2021. https://translate.google.com/website?sl=en&tl=tr&hl=tr&prev=search&u=https://cdn.who.int/media/docs/defaultsource/immunization/sage/2021/april/5_sage29apr2021_critical-evidence_sinovac.pdf (accessed May 26, 2021).
7. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020 Oct;26(10):1636-43.
8. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2020 Jun;127:104370
9. Yormaz B, Ergun D, Tulek B, et al. The evaluation of prognostic value of acute phase reactants in the COVID-19. Bratisl Lek Listy. 2020;121(9):628-33
10. Branco RG, Garcia PC. Ferritin and C-Reactive Protein as Markers of Systemic Inflammation in Sepsis. Pediatr Crit Care Med. 2017 Feb;18(2):194-6.
11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 May;46(5):846-8.
12. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020 Jul;92(7):856-62.
13. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-81
14. Sathe PM, Patwa UD. D Dimer in acute care. Int J Crit Illn Inj Sci. 2014 Jul;4(3):229-32
15. Yu B, Li X, Chen J, et al. Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. J Thromb Thrombolysis. 2020 Oct;50(3):548-57

16. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with COVID-19 pneumonia. Eur Respir J. 2020 Jul 30;56(1):2001365.
17. Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol. 2020 Aug;190(4):e192-e95
18. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020 May;18(5):1094-9.
19. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020 Jul;95(7):834-47.
20. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020 Jun;42 Suppl 1:11-8.