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Table of Contents

Original Articles

Case Report

Erratum

Original Article

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Can integrative, complementary alternative medicine, and integrative and functional nutrition practices have a place in nutrition management?

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ABSTRACT

Objectives: This study aims to evaluate the attitudes of dietitians and dietitian candidates about integrative complementary and alternative medicine and integrative and functional nutrition.

Methods: This descriptive research was conducted with a self-reported online survey on dietitians and candidates (n = 390). Various questions were asked to evaluate the approach to functional medicine and nutrition, including the terms integrative and functional medicine nutrition therapy radial, medical history, and treatments used to treat chronic disease. The Attitude Towards Holistic Complementary and Alternative Medicine Scale evaluated participants' attitudes toward integrative complementary and alternative medicine.

Results: The majority of the participants know the terms functional medicine (95.4%) and integrative and functional nutrition (85.4%). The attitudes of dietitians towards complementary and alternative medicine were significantly more optimistic when compared to dietitian candidates (38.3±0.53 versus 34.5 ± 0.67, $p = 0.002$). When the application of the integrative and functional medicine nutrition therapy radial was examined, it was found that the majority of them always consider lifestyle (84.1%), allergens/intolerance (84.1%), negative thoughts and beliefs (80.0%), and system signs and symptoms (71.3%). Dietitians question digestive system health (94.9%), sleep and physical activity (94.4%), stress (93.4%), medication and supplement use (93.9%), and mood variability (86.9%) when taking the individual's anamnesis. The supplements that dietitians found beneficial were probiotic-prebiotic (91.4%), multivitamin-mineral (84.8%), and herbal (75.8%). Dietitian-approved diets were elimination diet (85.4%), FODMAP (80.8%), autoimmune protocol diet (72.2%), GAPS diet (70.7%), and ketogenic diet (69.2%), respectively.

Conclusion: It has been found that dietitians have positive attitudes toward integrative, complementary medicine, and functional nutrition.

Keywords: Integrative complementary alternative medicine, integrative and functional nutrition, functional nutrition practices, dietary approaches, dietitian

It is stated that chronic diseases are closely related to nutrition and lifestyle behaviors, and it is known that insufficient and unbalanced nutrition is associated with the development and prognosis of various diseases.1 Unhealthy eating habits are at the root of many chronic non-communicable diseases. The integrative and functional nutrition approach emphasizes that some precautions should be taken before

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disease reactions occur.[1,2] The integrative and functional approach to nutrition considers the interaction between genetic predispositions, microbiome, environmental factors, and lifestyle. It is recognized that this interaction leads to fundamental clinical imbalances and dysfunctions in physiological systems and the microbial ecosystem and may have a significant role in developing chronic diseases.[2,3] Evidence related to nutritional deficiencies, unhealthy eating behaviors, and chronic diseases highlights the importance of nutritional therapy management.[2,3] It is believed that along with focusing on the symptoms of the disease, adopting dietary interventions and approaches, which will positively affect health, will support being healthy by ensuring positive lifestyle development.

To standardize integrative and functional nutrition practices, medical nutrition therapy radial has been created to be used by health professionals for application in clinics.[2,4] Integrative and functional medical nutrition therapy radial was developed in 2011, updated in 2018, and is used by functional medicine dietitians registered with International Functional Medicine (IFM) to make individual evaluations and define integrative nutrition practices. Integrative and functional medical nutrition therapy focuses on five main areas: lifestyle, system signs and symptoms, biomarkers, metabolic pathways and networks, and core imbalances. It is interested in DNA helices and genetic variations that cause the development of radial disease, as well as pathogens, allergens, and environmental toxins.[2,4]

Integrative and functional medicine blends traditional medical care and complementary approaches by incorporating (mind-body) practices such as herbal supplements, yoga, chiropractic/osteopathic manipulation, and meditation.[3] Integrative medicine accepts the theory that the state of being healthy is more than the absence of disease. Functional and holistic approaches evaluate the individual as a whole. In particular, it is an approach that emphasizes the consideration of the individual as a whole through the evaluation of the body, mind, spirit, and the patient's support community as a complement to standard diagnostic evaluations.[5,6] This approach style adheres to a philosophy in which the individual has a role in the long-term goal of optimal health and healing.[6] In a study in which the orientation of dietitians to integrative medicine was examined, it was found that the vast majority of dietitians are still at the stage of adoption, awareness, and learning.[6] Whereas integrative complementary and alternative medicine and integrative and functional nutrition issues are up-to-date in our country, there is no study evaluating the perspectives of dietitians and dietitian candidates on this issue. In addition, there is no information about the usage of integrative and functional medical nutrition therapy radial in the clinic. Besides, there is no data about the use of integrative and functional medical nutrition therapy radial in the clinic. This study was planned due to the lack of research evaluating the approach to integrative and functional nutrition and its use in the clinic. The study aims to evaluate the attitudes of dietitians and dietitian candidates about integrative complementary and alternative medicine and integrative and functional nutrition and their perspectives on using functional nutrition practices in application.

METHODS

Sample Selection of the Research

This observational and descriptive research was conducted with an online questionnaire on volunteer dietitians and candidates (n = 390) aged between 18 and 64. The research population consists of dietitians who work as dietitians in universities, hospitals, or private clinics in different provinces in Türkiye and hold teaching positions in higher education institutions, as well as dietitian candidates who continue to study in the nutrition and dietetics departments of universities. The number of the study sample was calculated by the known sampling method. Since item scores are sequential variables and do not have a normal distribution, power analysis was performed in the Statistica 12 package program. According to the power analysis result (R = .08, R0 = .05, power = 80, α = .05), it has been decided that the data from 374 people is sufficient. The study was conducted with 198 dietitians and 192 dietitian candidates, with 390 participants. In order to be included in the study, it is necessary to be a volunteer dietitian and dietitian candidate (student) between the ages of 18-64 and to complete the data collection forms. Ethical approval of the study was obtained by decision No. 416 of the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University dated 15.04.2021. The participants were informed about the study in detail and were included in the study by obtaining the consent of those who volunteered to participate. All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Data Collection and Evaluation

The data were collected using an online survey technique based on self-reporting. The data collection process was conducted by sharing the online survey link (Google Forms) via social media and WhatsApp application groups of nutrition and dietetics students/dietitians. While collecting the data, the Google form's required questions feature was activated, and the survey could be approved and sent only after all the questions were answered.

Evaluation of functional medicine/approaches and clinical applications for integrative and functional nutrition

For the purpose of evaluating functional medicine and integrative and functional nutrition approaches, various questions were asked consisting of the level of knowledge of functional and integrative medicine terms, the elements used when taking the individual's medical history (digestive system health, sleep, physical activity, stress, medication/supplement use, mood variability, sex life, environmental toxin exposure, Etc.) and the treatments used to treat chronic disease (use of supplementation, ketogenic diet, GAPS, elimination diet, autoimmune protocol diet, Etc.). In preparing survey questions, the works of Goodman *et al*. (2018) and Augustine *et al*. (2016) were used.[3,7]

Evaluation of the level of knowledge and application status for integrative and functional medicine nutrition therapy radial

Integrative and functional medicine nutrition therapy radial has been developed as a conceptual framework to help integrative and functional medical nutrition therapy methods in practice. This radial was updated in 2018 by Kathie Swift, Diana Noland, and Elizabeth Redmond and is used by functional medicine dietitians in integrative nutrition practices to perform personal evaluations.[2] Survey questions related to this study were prepared according to the integrative and functional medicine nutrition therapy radial and the application situations, approaches, and application status of the participants were questioned.[2] This radial contains subcomponents such as lifestyle, nutrition, system signs/symptoms, physical signs/symptoms, metabolic pathways and networks, biomarkers, pathogens, allergens, intolerances, negative thoughts, and beliefs.[2]

Evaluation of the approach towards integrative complementary and alternative medicine

The attitudes of the participants towards integrative complementary and alternative medicine were examined by the Attitude Towards Holistic Complementary and Alternative Medicine Scale that was developed in 2003 by Hyland *et al*. and whose reliability and Turkish validity were approved by Erci in 2007.[8,9] This scale aims to evaluate the knowledge level of health professionals about complementary medicine, the role of healing methods used in alternative treatment, spiritual beliefs and intuitions in the effectiveness of treatment. The scale consists of 11 items in total and is scored according to the 6-point Likert type (1 = I definitely agree, 6 = I definitely disagree). A minimum score of 11 and a maximum score of 66 can be obtained from the scale. Low scores indicate a positive attitude towards integrative complementary and alternative medicine.[7,9]

Statistical analysis of the data

The analyses were performed in the SPSS 23.0 package program. Descriptive statistics of the study were evaluated by number, percentage, mean, and standard deviation. In statistical comparisons, bilateral comparisons were examined by the Student-t test or Wilcoxon, Mann Whitney-U tests according to parametric distribution conditions. Multiple comparisons were also examined according to the parametric distribution by ANOVA or Kruskal Wallis.

RESULTS

Approaches of dietitians and dietitian candidates to functional medicine and integrative and functional nutrition are given in Table 1. The majority of the participants stated that they knew the terms functional medicine (95.4%) and integrative and functional nutrition (85.4%). It has been observed that dietitians have significantly more knowledge of functional medicine and integrative and functional nutrition terms than dietitians. (99.5% vs. 91.1%, $p = 0.000$; 93.4% vs.77.1%, $p = 0.000$, respectively).

The components that dietitians and dietitian candidates have questioned and will question when receiving the individual's medical history are given in Table 2. Dietitians often question the components of digestive system health (94.9%), sleep and physical activity (94.4%), stress (93.4%), medication and supplement use (93.9%), and mood variability (86.9%) when taking a medical history. Dietitian candidates expressed that they would question environmental

Table 1. Approaches of dietitians and dietitian candidates to functional medicine, and integrative and functional nutrition

Approaches to functional medicine, integrative and functional nutrition		Dietitian (n = 198)		Dietitian candidate (n = 192)		Total (n = 390)		*P* value
		n	%	n	%	n	%	
Functional medicine term knowledge	Yes	197	99.5	175	91.1	372	95.4	**0.000***
	No	1	0.5	17	8.9	18	4.6	
Integrative & functional nutrition term knowledge	Yes	185	93.4	148	77.1	333	85.4	**0.000***
	No	13	6.6	44	22.9	57	14.6	
The effectiveness of integrative & functional nutrition and medicine techniques in chronic diseases	Yes	158	79.8	139	72.4	297	76.2	0.217
	No	1	0.5	2	1.0	3	0.8	
	Indecisive	39	19.7	51	26.6	90	23.0	
Integrative & functional nutrition education	Yes	72	36.4	22	11.5	94	24.1	**0.000*** 0.318
	No	126	63.6	170	88.5	296	75.9	
Integrative & functional medicine nutrition therapy radial consensus level	Yes	85	42.9	88	45.8	173	44.4	0.524
	No	17	8.6	11	5.7	28	7.2	
	Indecisive	96	48.5	93	48.5	189	48.4	

toxin exposure, social support/relationships, sexual life, and bristol stool scale more when receiving a medical history than dietitians (71.4% vs. 48.5%, p = 0.000; 81.8% vs. 72.7%, p = 0.033; 40.1% vs.23.2%, p = 0.000; 83.3% vs. 68.2%, p = 0,000, respectively).

The attitudes of dietitians and dietitian candidates towards various dietary approaches are given in Table 3. The diets that dietitians consider applicable are elimination diet (85.4%), Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP) diet (80.8%), autoimmune protocol diet (72.2%), Gut and Psychology Syndrome (GAPS) diet (70.7%), ketogenic diet (69.2%), histamine intolerance diet (68.7%), low carbohydrate diet (65.2%) and mitochondrial nutrition (52.5%), respectively. When the applicability of detox therapies and aromatherapy is examined, dietitians prefer to apply them at a higher rate compared to dietitian candidates (40.9% vs. 36.5%, p = 0.021; 66.7% vs. 48.4%, p = 0.000, respectively).

The attitudes of dietitians and dietitian candidates towards various supplementation and therapy methods are given in Table 4. The supplements that dietitians find applicable are probiotic-prebiotic use (91.4%), multivitamin-mineral (84.8%), herbal supplement (75.8%), and fatty acids supplement (73.7%), respectively. The use of mind-body therapies, detox therapies, and aromatherapy (41.9% vs.30.2%, p = 0.000; 40.9% vs. 36.5% p = 0.021; 66.7% vs. 48.4%, p = 0.000, respectively) is accepted at a higher level by dietitians.

The participants' attitudes towards using the integrative functional medical nutrition therapy radial when evaluating the nutritional status of the individuals are given in Table 5. The majority of the participants always intend to use lifestyle (84.1%), allergens and intolerances (84.1%), negative thoughts and beliefs (80.0%), system signs and symptoms (71.3%), and pathogens (59.5%) from the radial components of integrative and functional medical nutrition therapy when evaluating the nutritional status of individuals.

The usefulness ranking of integrative and functional medicine nutrition therapy radial components by dietitians and dietitian candidates is shown in Figure 1. Dietitians evaluated lifestyle (55.1%), systemic signs and symptoms (47.0%), core imbalances (35.4%), and metabolic pathways/networks (33.9%) as the first two components of integrative and functional medical nutrition therapy radial components when ranking usefulness.

The participants' attitudes towards integrative complementary and alternative medicine are given in

Table 2. Components that dietitians and dietician candidates question while taking anamnesis

Components of anamnesis		Dietitian (n = 198)		Dietitian candidate (n = 192)		Total (n = 390)		*P* value
		n	%	n	%	n	%	
Sleep	No	11	5.6	12	6.3	23	5.9	0.771
	Yes	187	94.4	180	93.8	367	94.1	
Stress	No	13	6.6	11	5.7	24	6.2	0.731
	Yes	185	93.4	181	94.3	366	93.8	
Environmental toxin exposure	No	102	51.5	55	28.6	157	40.3	**0.000***
	Yes	96	48.5	137	71.4	233	59.7	
Spirituality	No	111	56.1	74	38.5	185	47.4	**0.001***
	Yes	87	43.9	118	61.5	205	52.6	
Social support/relationships	No	54	27.3	35	18.2	89	22.8	**0.033***
	Yes	144	72.7	157	81.8	301	77.2	
Mood variability	No	26	13.1	19	9.9	45	11.5	0.317
	Yes	172	86.9	173	90.1	345	88.5	
Physical activity	No	11	5.6	11	5.7	22	5.6	0.941
	Yes	187	94.4	181	94.3	368	94.4	
Culture & traditions	No	42	21.2	27	14.1	69	17.7	0.064
	Yes	156	78.8	165	85.9	321	82.3	
Sunbathing	No	90	45.5	64	33.3	154	39.5	**0.014***
	Yes	108	54.5	128	66.7	236	60.5	
Sexual life	No	152	76.8	115	59.9	267	68.5	**0.000***
	Yes	46	23.2	77	40.1	123	31.5	
Medication & supplement use	No	12	6.1	14	7.3	26	6.7	0.626
	Yes	186	93.9	178	92.7	364	93.3	
Digestive system health	No	10	5.1	12	6.3	22	5.6	0.608
	Yes	188	94.9	180	93.8	368	94.4	
Bristol stool scale (stool physiology)	No	63	31.8	32	16.7	95	24.4	**0.000***
	Yes	135	68.2	160	83.3	295	75.6	

Table 6. The attitudes of dietitians towards integrative complementary and alternative medicine are significantly more optimistic when compared to dietitian candidates (38.3 ± 0.53 versus 34.5 ± 0.67, $p = 0.002$).

DISCUSSION

With the developing technology and various approaches, health has become a subject that includes integrative practices together with modern medicine.[10] Traditional medicine, which is one of these practices, is the use of information to be obtained in the treatment of diseases based on beliefs that society has passed from generation to generation, values, and other elements of the culture.[11] It is often preferred by an extensive range of people due to its variety of applications and the fact that it has been used since old times.[10] Integrative and functional medical nutrition therapy, on the other hand, is used to describe the practice of medical nutrition therapy, which includes both integrative and functional medicine principles and traditional nutrition practices.[4] Integrative medicine accepts the theory that health is dynamic and is more than just the presence or absence of disease.[5] Functional medicine, however, is an approach that focuses on the progression of a patient's symptoms and considers the patient's history, physiological condition, genetics, lifestyle, and environmental interaction network, which contributes to his physical and mental functional state.[12] With the idea that disease symptoms may be caused by organ functional impairment, functional medicine directs the detection and prevention of diseases by focusing on symptoms.[13] Health workers and patients have started to adopt various methods for the treatment of chronic diseases. Integrative medicine and functional nutrition practitioners interpret the patient's genetic and biochemical structure by assessing the patient's

Table 3. Attitudes of dietitians and dietitian candidates towards various dietary approaches

Dietary approaches		Dietitian (n = 198)		Dietitian candidate (n = 192)		Total (n = 390)		*P* value
		n	%	n	%	n	%	
Elimination diet	Unsuitable	16	8.1	9	4.7	25	6.4	**0.000***
	Suitable	169	85.4	131	68.2	300	76.9	
	Indecisive	13	6.5	52	27.1	65	16.6	
Low carbohydrate diet	Unsuitable	61	30.8	70	36.5	131	33.6	0.250
	Suitable	129	65.2	96	50.0	225	57.7	
	Indecisive	8	4.0	26	13.5	34	8.7	
Low FODMAP diet	Unsuitable	22	11.1	24	12.5	46	11.8	**0.000***
	Suitable	160	80.8	96	50.0	256	65.6	
	Indecisive	16	8.1	72	37.5	88	22.6	
GAPS diet	Unsuitable	34	17.2	20	10.4	54	13.8	**0.000***
	Suitable	140	70.7	91	47.4	231	59.2	
	Indecisive	24	12.1	81	42.2	105	26.9	
Ketogenic diet	Unsuitable	54	27.3	42	21.9	96	24.6	**0.000***
	Suitable	137	69.2	116	60.4	253	64.9	
	Indecisive	7	3.5	34	17.8	41	10.5	
Autoimmune protocol diet	Unsuitable	17	8.6	11	5.7	28	7.2	**0.000***
	Suitable	143	72.2	101	52.6	244	62.6	
	Indecisive	38	19.2	80	41.6	118	30.2	
Mitochondrial nutrition	Unsuitable	40	20.2	19	9.9	59	15.1	**0.000***
	Suitable	104	52.5	64	33.3	168	43.1	
	Indecisive	54	27.2	109	56.8	163	41.8	
Histamine intolerance diet	Unsuitable	19	9.6	13	6.8	32	8.2	**0.000***
	Suitable	136	68.7	88	45.8	224	57.4	
	Indecisive	43	21.7	91	47.4	134	34.4	

health history for treatment effectiveness. In addition, the view that the imbalance of the patient's biological, psychological, social, and environmental conditions can affect the disease's development may have led to the practice of integrative and functional nutrition.[14] In the study conducted by Jong *et al*. on doctors (n = 276); 52.0% of the participants reported that they had heard of integrative medicine before, 44.0% considered integrative medicine as a new approach to health care to be very important, and 40.0% had an unbiased opinion about integrative medicine.[15] In this study, a large majority of the participants declared that they knew the terms functional medicine (95.4%) and integrative and functional nutrition (85.4%). It has been observed that dietitians have more knowledge of the terms related to functional medicine, integrative, and functional nutrition and have received more education than dietitian candidates about it. Dietitians may also be doing more research on these areas in order to be able to answer questions from their patients about functional and integrative medicine while they are actively working in the field. According to Flaherty *et al*., in their studies conducted with medical students (n = 308), they concluded that physicians with integrative medicine knowledge provide better services and physicians should inform patients about the usage of herbal methods.[16]

Integrative and functional medical nutrition therapy focuses on assisting dietitians in providing individualized nutritional care by addressing five areas that define a vital assessment in integrative and functional nutrition. Kohut *et al*. (2014) reported that in their study (n = 103) in which they evaluated the attitude of dietitians towards integrative and functional medical nutrition therapy radial, 47.0% of dietitians reported using radial in their professional practices, 39.8% reported using lifestyle area for evaluation, 36.8% reported using system signs and symptoms, 20.3% reported that they always use biomarkers and core imbalances. It has been reported that the usage of radial is more as the working time in the profession increases.[4] In this study, dietitians also evaluated lifestyle (55.1%), system signs and symptoms (47.0%), core imbalances (35.4%) from radial components of

Table 4. Attitudes of dietitians and dietician candidates towards various therapy methods and supplementation

Therapy methods & supplementation		Dietitian (n = 198)		Dietitian candidate (n = 192)		Total (n = 390)		*P* value
		n	%	n	%	n	%	
Use of multivitamin-mineral	Unsuitable	12	6.1	17	8.9	29	7.4	0.125
	Suitable	168	84.8	147	76.6	315	80.8	
	Indecisive	18	9.1	28	14.5	46	11.8	
Use of probiotic-prebiotic	Unsuitable	6	3.0	13	6.7	19	4.9	0.582
	Suitable	181	91.4	156	81.3	337	86.4	
	Indecisive	11	5.6	23	12.0	34	8.7	
Use of fatty acids	Unsuitable	24	12.1	18	9.4	42	10.8	**0.024***
	Suitable	146	73.7	124	64.6	270	69.2	
	Indecisive	28	14.1	50	26.0	78	20.0	
Use of amino acids	Unsuitable	38	19.2	24	12.5	62	15.9	**0.001***
	Suitable	132	66.7	111	57.8	243	62.3	
	Indecisive	28	14.1	57	29.7	85	21.8	
Use of herbal supplements	Unsuitable	34	17.2	12	6.3	46	11.8	**0.000***
	Suitable	150	75.8	137	71.4	287	73.6	
	Indecisive	14	7.0	43.0	22.3	57	14.6	
Use of digestive enzymes and stomach acid (betaine-HCl)	Unsuitable	55	27.8	24	12.5	79	20.3	**0.000***
	Suitable	103	52.0	79	41.1	182	46.7	
	Indecisive	40	20.2	89	46.4	129	33.0	
Functional foods	Unsuitable	7	3.5	11	5.7	18	4.6	0.877
	Suitable	176	88.9	156	81.3	332	85.1	
	Indecisive	15	7.6	25	13.0	40	10.3	
Mind-body therapy	Unsuitable	43	21.7	21	10.9	64	16.4	**0.000***
	Suitable	83	41.9	58	30.2	141	36.2	
	Indecisive	72	36.4	113	58.8	185	47.4	
Detox therapies	Unsuitable	84	42.4	66	34.4	150	38.5	**0.021***
	Suitable	81	40.9	70	36.5	151	38.7	
	Indecisive	33	16.7	56	29.1	99	22.8	
Aromatherapy	Unsuitable	27	13.6	25	13.0	52	13.3	**0.000***
	Suitable	132	66.7	93	48.4	225	57.7	
	Indecisive	39	19.7	74	38.6	113	29.0	
Breathing techniques therapy	Unsuitable	174	87.9	182	94.8	356	91.3	**0.016***
	Suitable	24	12.1	10	5.2	34	8.7	
Meditation/yoga	Unsuitable	175	88.4	177	92.2	352	90.3	0.205
	Suitable	23	11.6	15	7.8	38	9.7	

integrative and functional medical nutrition therapy as essential components in the usefulness ranking, and they always intend to use lifestyle (84.1%), allergens and intolerances (84.1%), negative thoughts and beliefs (80.0%) and system signs/symptoms (71.3%) among radial components when evaluating the nutritional status of individuals. The positive attitudes of dietitians towards integrative and functional nutrition practices, which are innovative approaches, may steer the nutrition strategies to be applied in the future. Nevertheless, conducting more comprehensive detailed research in this area may encourage clinicians to be more effective in managing the disease with holistic assessment opportunities by addressing the imbalance of functional impairments and social/environmental conditions of biological, physiological, and psychological factors that may be disease factors.

Complementary medicine treatment practices usually contain acupuncture, physiotherapy, ayurveda, yoga, nutritional supplements, and nutrition practices. [17] Detoxification programs, herbal and homeopathic supplements, different dietary approaches (Mediterra-

Table 5. Approaches of dietitians and dietitian candidates to use integrative and functional medicine nutrition therapy radial while evaluating nutritional status

Integrative functional medicine nutrition therapy radial		Dietitian (n = 198)		Dietitian candidate (n =192)		Total (n = 390)		*P* value
		n	%	n	%	n	%	
Lifestyle	Never	2	1.0	1	0.5	3	0.8	0.970
	Sometimes	20	10.1	29	15.1	49	12.6	
	Every time	175	88.4	153	79.7	328	84.1	
	No idea	1	0.5	9	4.7	10	2.5	
System signs and symptoms	Never	2	1.0	2	1.0	4	1.0	0.103
	Sometimes	45	22.7	37	19.3	82	21.0	
	Every time	144	72.7	134	69.8	278	71.3	
	No idea	7	3.6	19	9.9	26	6.7	
Biomarkers	Never	9	4.5	5	2.6	14	3.6	0.086
	Sometimes	74	37.4	60	31.3	134	34.4	
	Every time	93	47.0	96	50.0	189	48.5	
	No idea	22	11.1	31	16.1	53	13.5	
Metabolic pathways/network	Never	4	2.0	3	1.6	7	1.8	0.252
	Sometimes	57	28.8	56	29.2	113	29.0	
	Every time	104	52.5	90	46.9	194	49.7	
	No idea	33	16.7	43	22.3	76	19.5	
Core imbalances	Never	10	5.1	4	2.1	14	3.6	0.496
	Sometimes	73	36.9	54	28.1	127	32.6	
	Every time	86	43.4	95	49.5	181	46.4	
	No idea	29	14.6	39	20.3	68	17.4	
Pathogens	Never	7	3.5	6	3.1	13	3.3	0.065
	Sometimes	57	28.8	58	30.2	115	29.5	
	Every time	121	61.1	111	57.8	232	59.5	
	No idea	13	6.6	17	8.9	30	7.7	
Negative thoughts and beliefs	Never	1	0.5	4	2.1	5	1.3	0.811
	Sometimes	31	15.7	30	15.6	61	15.6	
	Every time	164	82.8	148	77.1	312	80.0	
	No idea	2	1.0	10	5.2	12	3.1	
Allergens/ intolerance	Never	2	1.0	1	0.5	3	0.7	0.820
	Sometimes	20	10.1	29	15.1	49	12.6	
	Every time	175	88.4	153	79.7	328	84.1	
	No idea	1	0.5	9	4.7	10	2.6	

nean diet, DASH, Intervention for Neurodegenerative Delay Diet), and nutritional supplements are used in nutrition applications.[18] Integrative, complementary, and functional medicine draws particular attention to healthy eating habits, which are the basis of healthy lifestyle behaviors. It especially recommends reducing refined carbohydrates and increasing the intake of vegetables, fruits, and various functional nutrients rich in pulp and antioxidants.[18] The GAPS diet protocol, specially designed to heal the human body from the root, starting from the digestive system, has been used for twenty years to cure mental and physical diseases. It is recommended that health practitioners and researchers use the GAPS nutrition protocol in their practices in order to prevent intestinal dysbiosis, which is shown to be the cause of mental and physical diseases.[19] In this research, the main diets that dietitians consider applicable are the elimination diet (85.4%), low FODMAP diet (80.8%), autoimmune protocol diet (72.2%), and GAPS diet (70.7%), and the supplements they find applicable are probiotic-prebiotic (91.4%), multivitamin-mineral (84.8%) and plant-based supplements (75.8%). Although there is an opinion that the low FODMAP diet, which aims

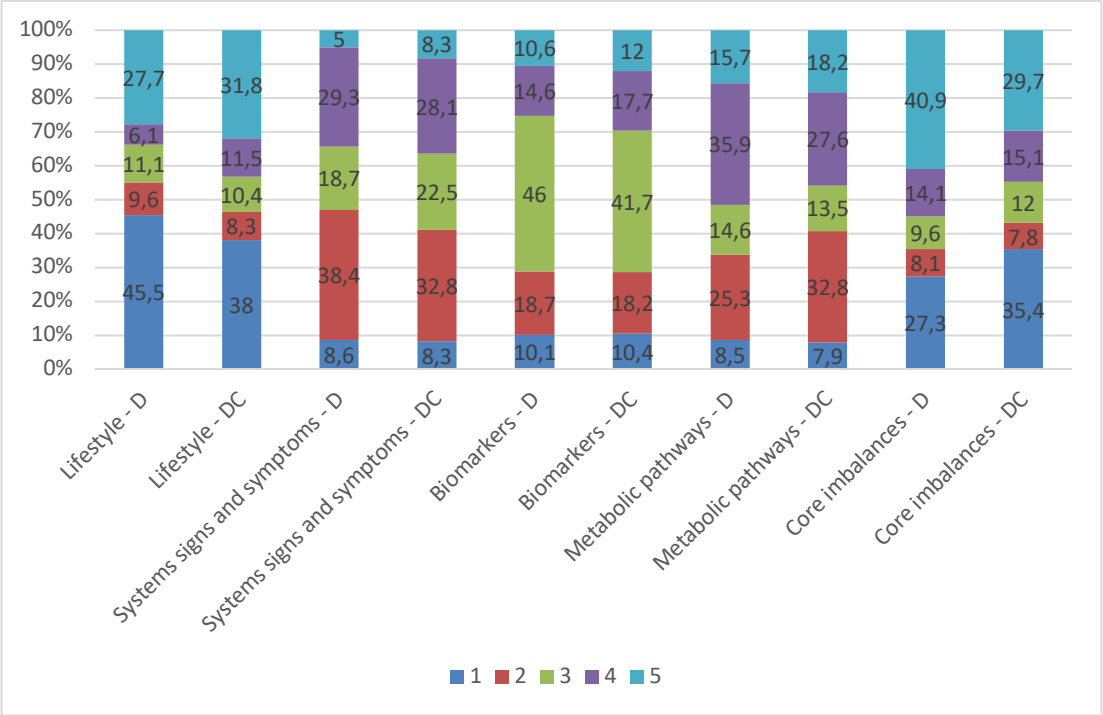

Figure 1. Ranking the usefulness of the radial components of integrative and functional medicine nutrition therapy. The numbers in the chart are ordered from the most useful to the least useful (from 1 to 5). It is given as an abbreviation "D: Dietitian, DC: Dietitian Candidate"

to find a balance between symptomatic improvements without potential negative effects on dietary restriction, can become applicable in primary care therapy, the clinical use of this diet is still limited.[20,21] Similarly, the application of elimination diets in the clinic is not very common, and the training of health professionals on the application of elimination diets is another phenomenon that guides future applications.[22] Despite the available data, such current dietary approaches are still considered very new and necessary applications for development and improvement. It will be useful to clarify dietary approaches with developments related to different areas such as pathophysiological aspects, clinical indications, and application strategies.[21] In the management of current disease-specific dietary approaches, this relationship needs to be examined in detail to develop applicable models in the clinic.[22] The dietitian who will be an integrative, complementary, and functional nutrition practitioner must be trained and competent in the use of functional nutrients as well as other integrative treatment methods. It is essential to make the necessary improvements in this area, since the lack of knowledge, experience, financial support, and management support are the main obstacles to implementing complementary medicine activities. In order to improve the skills of healthcare providers to guide patients in the use of complementary medicine, these issues should be addressed in

Table 6. Attitudes of participants towards integrative complementary and alternative medicine

General characteristics		Attitude towards Holistic Complementary and Alternative Medicine Scale (Mean ± SD)	*P* value
Current situation	Dietitian	38.3 ± 0.53	**0.002***
	Dietitian Candidate	34.5 ± 0.67	
Professional Year	< 1	34.5 ± 0.65	**0.001***
	1-5	37.4 ± 0.50	
	6-10	37.2 ± 0.50	
	> 10	38.7 ± 0.49	

future research.[17] Although more evidence is needed, it is thought that the inclusion of omics, which has emerged as an innovative holistic scope to provide a more comprehensive view of the molecular and physiological phenomena underlying diseases, in medical treatment, may be useful not only for disease risk prediction or early diagnosis but also to guide disease prognosis and develop specialized dietary therapies.[23]

In today's world, integrative complementary and alternative medicine is a new model formed by the integration of traditional Chinese medicine with classical medicine. There is increasing interest and increasing evidence that the integration of classical medicine with traditional, complementary, and alternative medicine can be helpful in the prevention and treatment of infectious and chronic diseases related to behavior and lifestyle.[24,25] The growing popularity of integrative medicine, which considers that true healing requires nourishment of the mind and soul in addition to a healthy body, is based on its effort to improve patient care and reduce pain. This approach to health care involves the patient's mind, spirituality and sense of community in the healing process. [26] The National Center for Complementary Integrative Health divides complementary and integrative approaches into three categories: mind and body practices (massage therapy, meditation, yoga, acupuncture, chiropractic/ osteopathic manipulation, hypnotherapy, TaiChi, qigong, healing touch, and relaxation exercises); natural products (herbal remedies, botanicals, vitamins, minerals, probiotics, and other nutritional supplements); other complementary approaches (indigenous healing practices, Chinese medicine, Ayurvedic medicine, homeopathy, and naturopathy).[18] A large majority (88.0%) of the World Health Organization member states (170 countries) have officially adopted integrative complementary and alternative medicine by developing policies, laws, regulations, and programs.[27,28] The use of integrative complementary and alternative medicine practices varies significantly across Western countries, ranging from 0.3% to 86% in European countries.[24] In a study examining the attitudes of health care providers and health managers working in oncology (n = 159), 68.4% of the participants stated that their organizations practice complementary medicine in oncology or anticipate applying it, while about 86.8% of the participants declared that complementary medicine is an essential complement for oncological treatment.[17] With the increasing interest in integrative complementary and alternative medicine practices in Turkey, new regulations have started to be made, thus paving the way for applications to be carried out by clinicians who have received the necessary training in health institutions.[29] It is emphasized that health professionals do not have sufficient knowledge about these practices, and health professionals are expected to have knowledge about integrative, complementary, and alternative medicine practices, understand their benefits and possible risks, and exhibit a positive attitude towards the practices.[29] There is not enough data in the literature on the attitudes of health workers.[29] When focusing on integrative medicine studies, in a study (n = 794) in which the attitudes of health professionals were examined, the Holistic Complementary and Alternative Health Questionnaire score of participants was found to be 28.7 ± 5.62.[29] A study conducted with Turkish physicians (n = 103) found that the average Holistic Complementary and Alternative Health Questionnaire score of participants was 34.9 ± 4.65, and their attitudes towards holistic complementary and alternative medicine were moderately positive.[30] Similarly, in this study, dietitians' attitudes towards integrative complementary and alternative medicine were moderately positive (38.3 ± 0.53 points). Displaying a positive attitude towards integrative complementary and alternative medicine may increase the number of clinicians being/ to be trained in this field in health institutions and may encourage clinicians to be more effective in disease management with holistic evaluation opportunities. Since there is no standardized national system for the certification of practitioners, most health professionals should be committed to pursuing the personal development of integrative medical knowledge and skills.[6]

Limitations

This study has several limitations. The relatively limited number of samples may be a limitation. It is not possible to make precise inferences because it was based on the statements of the participants, and the evaluation of dietitians' use of these approaches in the clinic was not made observationally. Studies with a larger sample size and involving all health clinicians are needed.

CONCLUSION

It has been found that dietitians and dietitian candidates have positive attitudes towards integrative and functional medicine. The majority of the participants consider using integrative and functional medicine

nutrition therapy radial components. It is thought that this positive attitude may guide clinical practices.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of İstanbul Medipol University İstanbul, Turkey. (Decision number: 416, date: 15.04.2021).

Authors' Contribution

Study Conception: HB, FT; Study Design: HB, FT; Supervision; HB; Funding: FT; Materials: FT; Data Collection and/or Processing: FT, HB; Analysis and/or Data Interpretation: HB; Literature Review: HB; Critical Review: HB, FT; Manuscript preparing: HB.

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Factors associated with COVID-19 mortality in elderly patients in intensive care unit

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ABSTRACT

Objectives: Mortality rates in patients with COVID-19 infection admitted to the intensive care unit are influenced by various factors. In this study, we aimed to investigate the mortality rate and factors affecting mortality in patients admitted to the intensive care unit due to COVID-19 infection who had not been vaccinated.

Methods: Our study was conducted retrospectively by scanning patients admitted to the intensive care unit of Izmir Bozyaka Education and Research Hospital of Health Sciences University from the beginning of 2020 to the end of 2022. Patients who were admitted to the intensive care unit were 65 years of age and older with COVID-19 infection. The patients' presenting complaints, degree of lung involvement, laboratory findings, and comorbidities were compared between patients who survived and those who passed away.

Results: A total of 166 patients were evaluated in our study. Of these, 48 patients were discharged, while 118 patients experienced an excitus. The median age (IQR) for discharged patients was 71.5 (8), and for patients who experienced an excitus, it was 78 (15), which was found to be statistically significant ($p < 0.001$). The most common presenting complaint in all patients was high fever. Patients with two or more comorbidities were more common in the excitus group ($p <0.001$). Severe involvement on initial computed tomography was observed in 28 patients in the excitus group, while no severe involvement was seen in the discharged group ($p < 0.001$).

Conclusion: Our study found that advanced age, extensive lung involvement at admission, the presence of two or more comorbidities, and the presence of dyspnea at admission were associated with increased mortality in elderly patients.

Keywords: Covid-19, Elderly patients, Mortality

COVID-19 is a SARS-CoV-2 virus infection that rapidly spread across China and subsequently affected the entire world after emerging in Wuhan at the end of 2019.[1-3] The World Health Organization declared a pandemic worldwide in 2020.

Among the symptoms of the disease are non-specific flu-like symptoms such as fever, dry cough, fatigue, headache, and dyspnea. However, symptoms and disease course can vary significantly among individuals. Many infected individuals show no symptoms, while some patients present with severe symptoms and require hospitalization.

COVID-19 infection in susceptible individuals can lead to severe respiratory failure, sepsis, coagulation disorders, acidosis, and ultimately death. Mortality rates are higher in individuals with underlying con-

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ditions such as diabetes mellitus, hypertension, renal failure, and heart disease. The severity of the disease and mortality rate are higher in elderly patients. In older patients, the course of the disease worsens, and mortality significantly increases.[4-6] One study found that advanced age is the most critical risk factor for the prognosis of the disease.[7]

One of the leading causes of death in Covid-19 is respiratory failure. Elderly patients are more sensitive to this condition because the function of many organs decreases to varying degrees with age. Additionally, it is known that the virus is more easily transmitted in elderly patients, and the inflammatory response can be dysregulated. For all these reasons, Covid-19 infection has a more severe and fatal course in the elderly population.[8]

In this study, we aimed to investigate the factors affecting mortality in patients aged 65 and over admitted to the intensive care unit due to Covid-19 infection.

METHODS

Our study was conducted retrospectively by scanning the hospital information system program of the University of Health Sciences İzmir Bozyaka Training and Research Hospital from the beginning of 2020 to the end of 2022. Patients admitted to the intensive care unit and 65 years of age and older, with confirmed COVID-19 infection through real-time polymerase chain reaction (RT-PCR) from nasal swab samples, were included.

In our study, patients under the age of 65, those vaccinated against COVID-19, patients with any malignancy, those who underwent surgical procedures for any reason during hospitalization, those with acute cerebrovascular events, and patients diagnosed with bacterial infections during admission were excluded.

Demographic data of the patients, their comorbidities, medications they were taking, reasons for hospital admission, the onset time of symptoms, findings, and extent of lung involvement in tomography, as well as hemoglobin levels, white blood cell counts, neutrophil and lymphocyte counts, C-reactive protein, procalcitonin, albumin, alanine aminotransferase, aspartate aminotransferase, d-dimer, and fibrinogen levels during admission were recorded.

Computed tomography findings of the patients were obtained from the hospital record system, based on interpretations by expert radiologists. According to the radiologist's interpretation, they were classified as mild, moderate, or severe radiological involvement. Patients without a computed tomography interpretation were excluded from the study.

At the end of hospitalization, patients were divided into two groups based on their discharge status: those with excitus and those without. A statistical comparison was performed between the two groups to identify factors potentially affecting morbidity and mortality.

Treatment Goals and Monitoring

All patients received oxygen support to maintain oxygen saturation (SpO2) levels at 94% or above. In cases where the target could not be achieved with oxygen support, the high-flow nasal cannula was provided, followed by non-invasive ventilation if necessary. Patients who did not respond to all non-invasive respiratory support systems were intubated and placed on invasive mechanical ventilation support. For patients with a PaO2/FiO2 ratio below 150, if there were no contraindications, they were positioned in the prone position for a minimum of 16 hours daily.

All patients received low-molecular-weight heparin and 0.5 mg/kg methylprednisolone treatment. In intubated patients, propofol and opioid (fentanyl or remifentanil) infusions were administered for sedation purposes. Favipiravir was administered to all patients as an antiviral agent. Additionally, patients who developed macrophage activation syndrome received pulse steroids and/or tocilizumab therapy.

Ethical approval

The study was approved by our hospital's local Clinical Research Ethics Committee (2022/38). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Statistical analysis

SPSS (Statistical Package for Social Sciences) version 21 (IBM) was used for statistical analysis. The compliance of the data to normal distribution was determined by the Shapiro-Wilk test. Normally distributed quantitative data were given as mean and standard deviation. Non-normally distributed data were given as a median and interquartile range. Categorical data were given as numbers and/or percentages. Differences in mean or median values were calculated using the Student's t-test (for normally distributed data) or Mann-Whitney U-test (for non-normally distributed data). Categorical data were evaluated using the Chi-

Squaretest. The significance level was taken as $p < 0.05$.

RESULTS

A total of 198 patients were evaluated in our study. 32 patients were excluded from the study for various reasons (23 patients had been vaccinated, four patients underwent surgical operations during their hospitalization, and five patients had life-threatening malignancies), leaving 166 patients for evaluation. Out of these, 48 patients were discharged, while 118 patients experienced an excitus. The median age (IQR) for discharged patients was 71.5 (8), and for patients who experienced an excitus, it was 78 (15), which was found to be statistically significant ($p < 0.001$). Of the patients, 82 were female, and 84 were male (Table 1). The most common presenting complaint in all patients was high fever. The most common comorbidity in both groups was hypertension. Patients with two or more comorbidities were more common in the excitus group ($p < 0.001$). Severe involvement on initial computed tomography was observed in 28 patients in the excitus group, while no severe involvement was seen in the discharged group ($p < 0.001$). During hospitalization, dyspnea was observed in 7 patients in the discharged group and 50 patients in the excitus group, which was statistically significant ($p < 0.001$). The two groups had no significant differences in other findings during hospitalization. The highest ferritin level, lowest fibrinogen level, and highest d-dimer level detected during hospitalization were statistically significant between the two groups (Table 2).

Table 1. Demographic properties, symptoms and radiologic findings

	Survive (n = 48)	Excitus (n = 118)	*p* value
Age[1]	71,5 (8)	78 (15)	< 0,001
Gender, n (%)			
Male	28 (58,3%)	56 (47,5%)	
Female	20 (41,6%)	62 (52,5%)	
Concomitant disease, n (%)			0,989
Type-2 Diabetes	11 (22,9%)	24 (20,3%)	
Hypertension	14 (29,1%)	32 (27,1%)	
Chronic renal disease	1 (2,08%)	3 (2,5%)	
Coronary arter disease	6 (12,5%)	8 (6,7%)	
COPD/Asthma	4 (8,3%)	6 (5%)	
Neurolojik disease	2 (4,1%)	4 (3,3%)	
Symptoms at admission, n (%)			0,789
Fever	28 (58,3%)	67 (56,7%)	0,954
Caught	26 (54,1%)	56 (47,5%)	0,433
Nasal congesion	7 (14,5%)	17 (14,4%)	0,977
Dispnea	7 (14,5%)	50 (42,3%)	< 0,001
Fatigue	8 (16,6%)	73 (61,8%)	0,176
Diarrhea	4 (8,3%)	9 (7,6%)	0,878
Stomach ache	8 (16,6%)	13 (11%)	0,321
Sore throat	23 (47,9%)	41 (34,7%)	0,114
Radiological findings[2], n (%)			< 0,001
No finding	14 (20,1%)	14 (11,8%)	
Mild	32 (66,6%)	36 (30,5%)	
Moderate	2 (4,1%)	40 (33,8%)	
Severe	-	28 (23,7%)	
Concomitant disease, n (%)			< 0,001
1 Concomitant disease	34 (70,8%)	46 (38,9%)	
2 or more Concomitant disease	10 (20,8%)	66 (55,9%)	

[1]median (interquartile range)
[2]lung involvement in computerized tomography
COPD: Chronic obstructive pulmonary disease

Table 2. Laboratory findings

	Survive	Excitus	*p* value
Heamoglobin[1] (g/dL)	9,6 (2)	13,6 (4,4)	0,898
Neutrophil count[1] (x10^9/L)	7030 (5783)	8120 (6810)	0,061
Lymphosit count[1] (x10^9/L)	560 (673)	610 (520)	0,930
C-reaktive protein[1,2] (mg/L)	82 (114)	89 (145)	0,248
C-reaktive protein[1,4] (mg/L)	130 (147)	155 (137)	0,129
Procalsitonine[1,2] (ng/mL)	0,32 (1)	0,5 (0,98)	0,133
D-dimer[1,4] (ng/mL)	930 (1361)	1964 (2780)	< 0 ,001
Fibrinogen[1,3] (mg/dL)	330 (157)	250 (188)	< 0,001
AST[1,2] (U/L)	33 (17)	30 (40)	0,004
ALT[1,2] (U/L)	16 (4)	23 (35)	0,308
Creatinine[1,2] (mg/dL)	0,95 (0,7)	1,2 (0,93)	0,011
Urea[1,2] (mg/dL)	87 (57)	83 (73,9)	0,029
Ferritin[1,4] (ng/mL)	606 (993)	977 (954)	0,001

[1]median (interquartile range)
[2] irst day
[3]lowest value during follow-up
[4]highest value during follow-up
ALT: Alanin aminotransferaz, AST: Aspartat aminotransferaz

DISCUSSION

In our study, we found that advanced age, the presence of two or more comorbidities, extensive lung involvement on computerized tomography, and the presence of dyspnea during hospitalization were factors associated with increased mortality in elderly patients with COVID-19. Furthermore, in the follow-up of patients, we observed higher ferritin and D-dimer levels and lower fibrinogen levels in the group with excitus patients.

In our study, the mortality rate in patients aged 65 and older was found to be 71%. This rate was similar to the mortality rate reported in previous studies on elderly patients admitted to the intensive care unit due to COVID-19 infection. In a study conducted by Xu and colleagues on critically ill patients aged 65 and older, a mortality rate of 73.2% was reported.[9] In comparison, Alshukry and colleagues found a mortality rate of 68% in COVID-19 patients aged 60 and older in a study involving 86 patients admitted to the intensive care unit. 10 Several similar studies have consistently reported higher mortality rates in the elderly compared to the younger population.[7,11-13]

Dyspnea was one of the most common symptoms in patients who had excitus, and this finding is not surprising. Dyspnea is often considered a sign of a more severe illness. The presence of dyspnea can be seen as an indication that the already limited lung reserve in elderly patients has deteriorated further. In a study conducted by Wang and colleagues, it was found that dyspnea was more common in patients admitted to the intensive care unit in adults.[14] In a study by Leung and colleagues conducted in China, it was observed that the prevalence of dyspnea and hemoptysis was higher in excitus patients, interpreted as an indicator of severe pneumonia.[15]

In our study, we found a higher prevalence of high D-dimer and low fibrinogen levels in the group with excitus patients. Elevated D-dimer levels and low fibrinogen levels are considered well-known features of COVID-19 infection and indicators of hypercoagulability and microvascular/macrovascular thromboembolic events. Many microembolic events go undiagnosed, but they can dramatically alter the severity and course of the disease. Thromboembolic events have been shown in many clinical studies to be among the poor prognostic markers of the disease in COVID-19 patients admitted to the intensive care unit with severe illness. Thromboembolic events are associated with hypercoagulability, damage to the vascular endothelial wall, and increased proinflammatory cytokines. Additionally, the virus is reported to cause direct damage by binding to type 2 pneumocytes and ACE-2 receptors in pulmonary vascular endothelium.[16-20]

In our study, patients with two or more comorbidities had a higher mortality rate, which is not surprising and can even be seen as an expected result. Comorbidities in patients can make things more complex during COVID-19 infection. While COVID-19 can aggravate comorbidities, conversely, comorbidities

often influence the immune response to COVID-19. In a study conducted by Zhou and colleagues in 2020, mortality was significantly higher in patients with hypertension, diabetes mellitus, and heart disease compared to non-excitus patients.[21]

In a study related to cases of ARDS in patients admitted to the intensive care unit due to COVID-19, mortality rates as high as 77-84% have been reported. [22] Our study also found a similar mortality rate in elderly patients with COVID-19 infection and those admitted to the intensive care unit. Studies focusing on ARDS without COVID-19 have reported much lower mortality rates in similar age groups. However, we could not make such a direct comparison due to the absence of relevant data.

One of the observations in our study is the lower frequency of high fever compared to younger individuals. Approximately 50% of the patients included in our study did not exhibit high fever. This condition is already known and attributed to the lower baseline body temperature of elderly individuals.[23-25] Additionally, dysregulated inflammatory responses in the elderly, especially those with comorbidities, may contribute to this condition. Therefore, the absence of high fever may not be a reliable diagnostic criterion in elderly patients.

CONCLUSION

Our study found that advanced age, extensive lung involvement at admission, the presence of two or more comorbidities, and the presence of dyspnea at admission were associated with increased mortality in elderly patients. Given that mortality due to COVID-19 is higher in the elderly compared to other age groups, we emphasize the importance of initiating treatment as soon as possible and utilizing support systems in these patients. Furthermore, we believe routine vaccination programs are even more crucial for the elderly.

Conflict of Interest

In this article, all authors have stated that they have no conflict of interest.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Izmir Bozyaka Training and Research Hospital, İzmir, Turkey. (Decision number: 2022/38, date: 23.02.2022).

Authors' Contribution

Study Conception: HÖ, İD; Study Design: HÖ; Supervision: HÖ, İD; Materials: HÖ; Data Collection and/or Processing: İD; Statistical Analysis and/or Data Interpretation: HÖ, İD; Literature Review: HÖ; Manuscript Preparation: HÖ and Critical Review: İD.

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The effects of working conditions on work life in Familial Mediterranean Fever (FMF) patients

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ABSTRACT

Objectives: Familial Mediterranean Fever (FMF) is a common autoinflammatory disease, especially in Mediterranean populations. FMF typically occurs with fever and serositis attacks and can negatively affect the individual's life. In our study, we aimed to investigate the effects of working conditions and the disease course on the work life of FMF patients.

Methods: The adult patients with pathogenic or likely pathogenic mutations in the MEFV gene who applied to our medical genetic outpatient clinic of the Faculty of Medicine, Çanakkale Onsekiz Mart University between 01.01.2010 and 01.08.2020 were included in our study. We created a questionnaire of 34 questions, which included sociodemographic data, information about the FMF course of the patients, and the effects of work conditions and FMF on the work life of these patients. The questionnaire link, created over Google Drive, was sent to the patient's current mobile phone numbers via text message, and the answers received until 31.12.2020 were evaluated.

Results: A total of 154 survey responses were obtained, and 113 were eligible for our study. Twenty-four of 104 (23.1%) participants who have worked in any job so far stated that they have changed or quit their jobs because of increased or worsening FMF attacks. Of 72 participants who have been working actively for the last year, 4 (5.6%) of them we are reported that they have a health problem in the workplace due to FMF disease. The statistically significant relationships were found between the FMF-induced changing or quitting job and the attack number in the last year regardless of attack severity, work-related adverse psychological effects, the mode of transportation to work, and the physical conditions in the working environment.

Conclusion: We suggest that the regulation of work environments, considering the factors that trigger attacks in FMF patients, will contribute to the increase in quality of life and work performance in these patients.

Keywords: Familial Mediterranean Fever, FMF, Job, Work, Working Conditions.

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease characterized by recurrent episodes of fever and inflammation.[1] Although it is primarily seen in Mediterranean populations, there are many reports of FMF patients all over the world. However, the highest disease prevalence is in Turks 1 / 400-1000, and Turkey is the country where there is probably the highest number of FMF patients in the world.[1,2] The disease diagnosis is based on clinical findings, and molecular genetic

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analysis of the MEFV gene is vital in confirming the diagnosis.[3,4] Although FMF is an autosomal recessive inherited disease, mutations that present autosomal dominant inheritance patterns have been reported in the literature.[5,6]

Although FMF attacks are generally characterized by fever, abdominal pain, and joint pain due to arthritis, symptoms such as pleuritis, pericarditis, erysipelas-like erythema, and meningitis can be observed. In addition, the most critical complication of FMF is amyloidosis, which can lead to renal failure and may appear as the first and only finding in asymptomatic individuals.[3] FMF attacks can be triggered by many environmental, psychological, or physiological factors (stress, menstruation, cold, Etc.).[7]

In today's society, business life has an essential place in the lives of individuals. In the developing world, employees have to adapt to these changes as business environments change in the face of economic, political, and technological developments.[8] To the best of our knowledge, there is no study in the literature on the effects of working conditions on FMF attacks and the work life of these individuals. Our study aimed to investigate how working conditions affect the work life of individuals diagnosed with FMF.

METHODS

The adult individuals (≥ 18 years old) who applied to the Canakkale Onsekiz Mart University (COMU) Faculty of Medicine (FoM) Genetic Diseases Diagnosis and Treatment Center (GDDTC) with a (pre-)diagnosis of FMF between 01.01.2010 and 01.08.2020 and detected pathogenic or likely pathogenic mutations in the MEFV gene are included in our study. Although there are conflicting interpretations regarding its clinical significance, individuals carrying the E148Q mutation, common in FMF patients in our country, were also included in the study.[9]

The mobile phone numbers of the patients eligible for our study were obtained from the records of our COMU-FoM GDDTC or the hospital information system, MIA-MED, of the COMU-Health Practice and Research Hospital. A questionnaire form with 34 questions was created over Google Drive, and the link was sent to the patients via text message to their mobile phone number. The participants who started to fill out the questionnaire by clicking on the link were asked first of all whether they gave their consent for the study, and only those who approved were allowed to continue the survey.

Survey responses from the participants until 31.12.2020 were evaluated. The survey responses obtained through the Google Drive link were uploaded to the IBM SPSS Statistics 25 program, and appropriate parametric and non-parametric statistical evaluations (Independent T-test, Mann-Whitney Test, Kruskal Wallis Test, Chi-square test) were made after the normality tests. The questionnaires of individuals who do not consent to participate, repeatedly answered questionnaires by the same individual, questionnaires of individuals under the age of 18, and questionnaires of individuals whose mutation and disease informa-

Table 1. MEFV mutation profiles of the participants

Mutation	n (%)	Mutation	n (%)
M694V / -	33 (29.2%)	M694V / R761H	1 (0.9%)
E148Q / -	20 (17.7%)	M680I / V726A	1 (0.9%)
M680I / -	12 (10.6%)	M680I / E148Q	1 (0.9%)
M694V / M694V	5 (4.4%)	M680I / M680I	1 (0.9%)
K695R / -	5 (4.4%)	V726A / P369S	1 (0.9%)
M694V / M680I	4 (3.5%)	V726A / V726A	1 (0.9%)
M694V / V726A	4 (3.5%)	E148Q / E148Q	1 (0.9%)
P369S / R408Q	4 (3.5%)	E148Q / L110P	1 (0.9%)
M694V / E148Q	3 (2.7%)	P369S / P369S	1 (0.9%)
V726A / -	3 (2.7%)	R761H / E148Q	1 (0.9%)
R761H / -	2 (1.8%)	F479L / Q405R	1 (0.9%)
P369S / -	2 (1.8%)	P369S / R408Q /E148Q	1 (0.9%)
M694I / -	2 (1.8%)	M680I / F479L / E167D	1 (0.9%)
A744S / -	1 (0.9%)		

-:Wild type allele

tion cannot be accessed because their names are not included in our text message list are excluded from the study. In the repeatedly filled questionnaires belonging to the same individual, the responses of the participant's most recent questionnaire were considered, and other answers were excluded from the study.

Our study was approved by the Canakkale Onsekiz Mart University Faculty of Medicine Ethics Committee.

RESULTS

A total of 154 survey responses were obtained through the Google Drive link. Two participants did not approve to participate in the survey. A total of 39 survey responses that were repeatedly filled by the same individual, belonging to individuals under the age of 18 and belonging to individuals whose mutation and disease information could not be reached because their names were not included in our text message list were also excluded from the study. The questionnaire data eligible for our study from 113 patients were evaluated. The MEFV gene mutations of these patients analyzed with different techniques (next-generation sequencing, fragment analysis, Sanger sequencing, real-time PCR, pyrosequencing, and strip test) are shown in Table 1.

Seventy-three patients (64.6%) were female and 40 (35.4%) were male. Participants' ages ranged from 20 to 63, with a mean of 36.93 and a median of 36. 76 (67.3%) of the patients were married, 29 (25.7%) were single, and 8 (7.1%) were divorced. Seventy of the participants (61.9%) had at least one child. Twenty-two (31.4%) of those with children had a paid caregiver or a family member (such as a mother and mother-in-law) for their children to help. While 7 (6.2%) of the patients lived alone, 77 (68.1%) lived at home with at least two people.

38 (52%) of the female participants and 17 (42.5%) of the male participants had been followed up with a diagnosis of FMF for more than five years (Fig. 1).

92.03% (n: 104) of the participants have worked in any job until today (Table 2). 69.2% (n: 72) of these people have been working actively for the last year, and 4 (5.6%) of these individuals had health problems, such as accidents, injury, mutilation,Etc., in the workplace due to FMF disease. Three of these four participants suffered the loss of workforce (getting the day off from work, rest cure, Etc.) for this reason, and one of them required hospitalization during this time.

23.1% (n: 24) of the participants who have worked in any job so far reported that they have changed or quit their jobs due to increased or worsening attacks. When the participants who changed or quit their jobs due to FMF were examined in detail, 50% of them had not been working actively for the last year, 45.8% of these individuals stated that they had more than

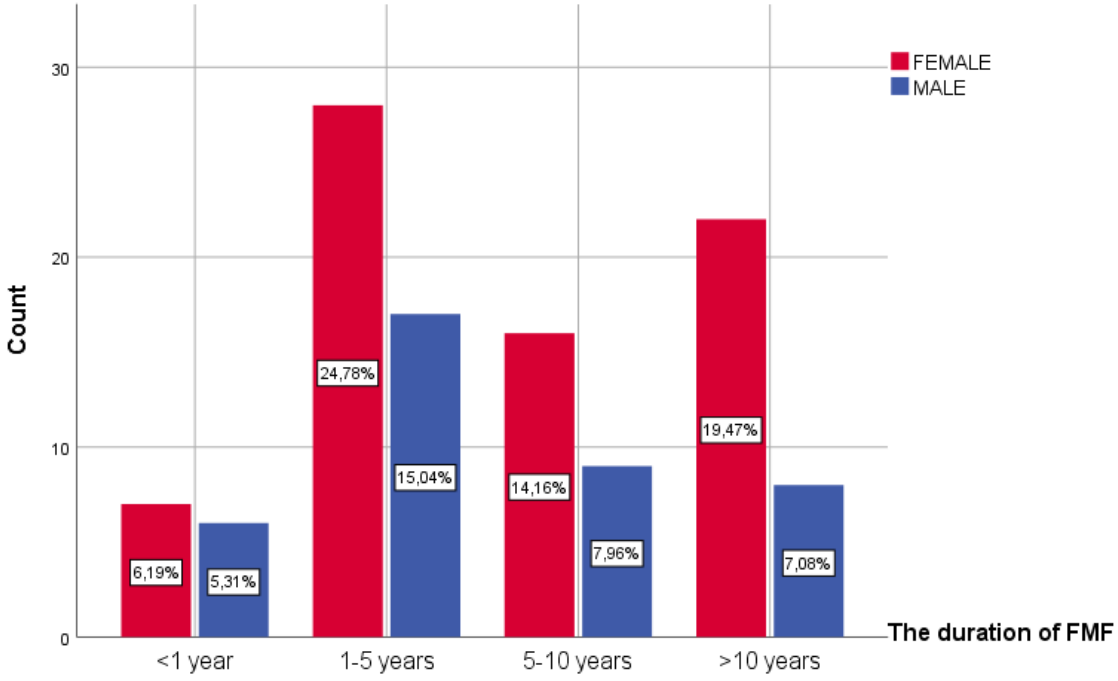

Fig. 1. The distribution of participants' FMF durations by gender

Table 2. The occupations of the participants who have worked in any job until today. Red-bolds (n: 4) present the individuals who had a health problem such as accident, injury, mutilation, Etc. in the workplace due to FMF disease.

OCCUPATION	COUNT (n)	%	OCCUPATION	COUNT (n)	%
Teacher	**1**+11	11,5%	Employee	2	1,9%
Public/Officer	7	6,7%	Accountant	2	1,9%
Academician	4	3,8%	Engineer	2	1,9%
Nurse	4	3,8%	Student	2	1,9%
Biologist	3	2,9%	**Secretary**	**1**+1	1,9%
Doctor	3	2,9%	Chef	1	1,0%
Sales and marketing	3	2,9%	Lawyer	1	1,0%
Technician	3	2,9%	**Barber**	**1**	1,0%
Administrative assistant	**1**+2	2,9%	Office staff	1	1,0%
Banker	2	1,9%	Esthetician/Beauty Specialist	1	1,0%
Physical worker	2	1,9%	Security guard	1	1,0%
Retired	2	1,9%	Shipper	1	1,0%
Artisan	2	1,9%	Paramedic	1	1,0%
Waiter	2	1,9%	Sociologist	1	1,0%
Food technician	2	1,9%	Tailor	1	1,0%
Graphic designer	2	1,9%	Other	28	26,9%
TOTAL				**104**	100%

five attacks in the last year, and 95.5% of them stated that the severity of their attacks was 3 points or more. This rate was 81.8% among the individuals without FMF-C/QJ.

When the attack severity of those who had at least one attack in the last year was evaluated, in 87.5% of these, the attack severity (between 1-5 points) was stated as 3 points and above. However, there was no statistically significant relationship between the attack severity and FMF-C/QJ. ($p > 0.05$).

41 (36.3%) of the participants reported that they had no attacks in the last year, while 17 (15.0%) had more than ten attacks. FMF-C/QJ ratio was found to be higher for those who had at least one attack in the last year compared to those who had no attack, and this result was statistically significant ($p < 0.05$).

While 39% (n:16) of the patients who had no attack in the last 1 year have received active colchicine treatment, this rate was 88.2% (n:15) of those who had more than 10 attacks. FMF-C/QJ ratios were higher in those who received active colchicine treatment than those who did not; this result was statistically significant ($p <0.05$).

No significant relationship was found between those carrying heterozygous MEFV gene mutations and those with homozygous or compound heterozygous mutations regarding FMF-induced changing or quitting jobs (FMF-C/QJ). This was similar between the groups carrying and not carrying the M694V allele ($p > 0.05$).

38.9% (n:28) of the participants who have been actively working for the last year have been working in this business for more than ten years. However, there was no statistically significant relationship between the duration of the current job and FMF-C/QJ ($p> 0.05$).

While the majority of the participants (68.1%) who have worked actively for the last year reported that they have worked an average of 40-60 hours per week, 8.3% (n: 6) stated that they have worked more than 80 hours per week. However, there was no statistically significant relationship between working time per week and FMF-C/QJ ($p > 0.05$)(Fig.2).

31.9% of the participants who have actively worked for the last year reported that they were working in shifts or on duty. In 37.5%, their jobs negatively affected their night sleep. 41.7% of them had to work at home in order to finish their work on time. However, no statistically significant relationship was found between these conditions (working in shifts or on duty, night sleep negatively affected due to job, working at home for the extra) and FMF-C/QJ ($p > 0.05$) (Fig. 2).

While 35% of those who go to work on foot or by bike reported that they had experienced FMF-C/QJ, this rate was 9.6% for those who go to work by any means of transport like car, bus, Etc., and this differ-

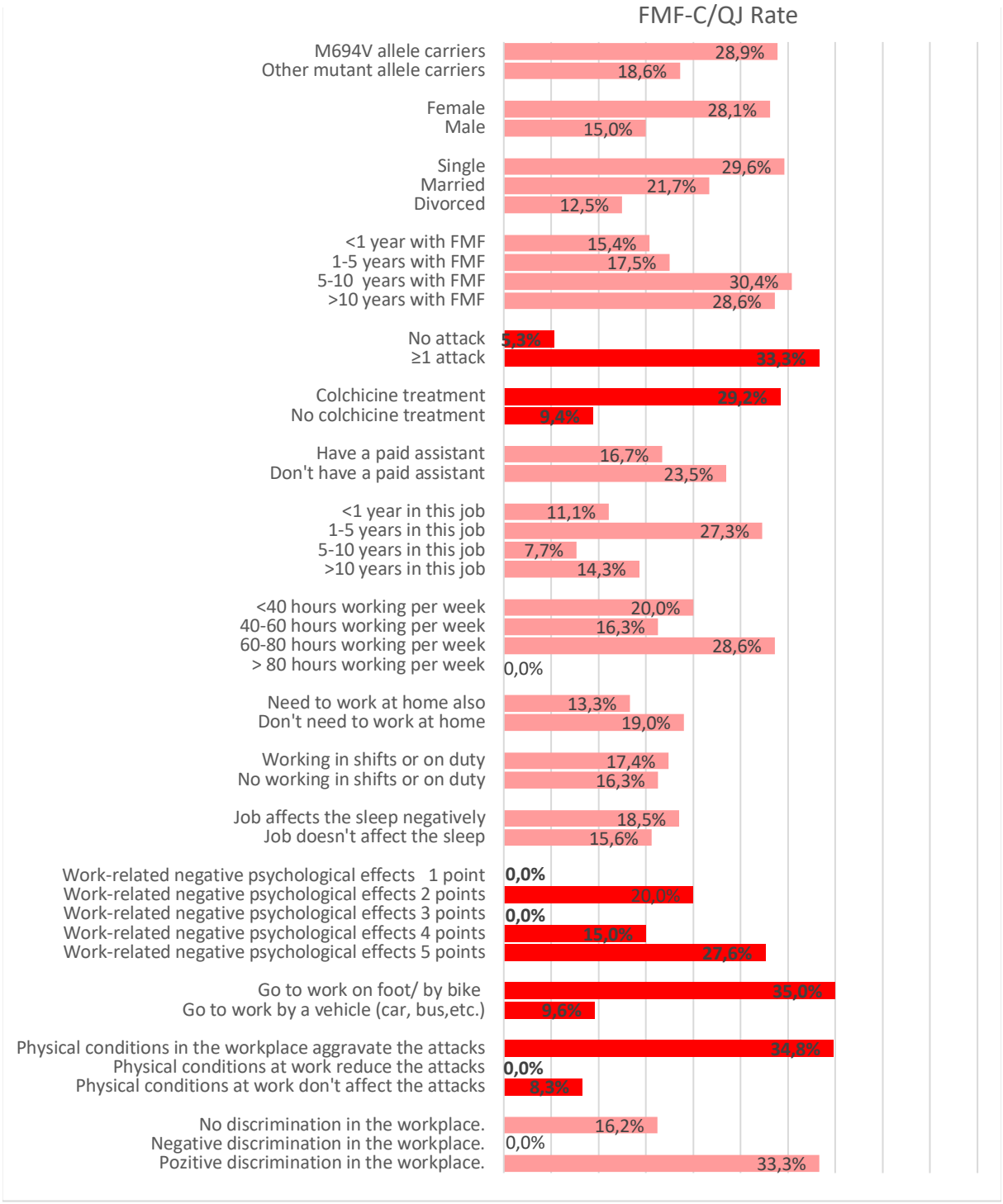

Fig. 2. The FMF-C/OJ rates of the participants in terms of some variables in the current study (The variables with dark red columns were found to the statistically significant with FMF-C/OJ)

ence is statistically significant ($p < 0.05$).

Age was found to be an essential factor in our study, and this was statistically significant for both FMF-related accidents, injury, mutilation, Etc., in the workplace and FMF-C/QJ condition ($p < 0.05$).

90.3% of the participants who worked actively for the last year stated the adverse psychological effects such as stress, workload, and extreme fatigue as 3 points and above, and a statistically significant relationship was found between the adverse psychological effects and FMF-C/QJ ($p < 0.05$) ((Table 3).

31.9% of the participants who have worked actively reported that physical conditions in their work environment (table, chair, cold, wind, Etc.) increased the frequency of FMF attacks or exacerbated their attacks. While 34.8% of these individuals changed or

Table 3. **The distribution of the work-related variables and the number of attacks according to the business sectors of the participants who have been actively working for the last year.**

Business sector		The number of attacks in the last year		Weekly working time		Working shifts or on duty		Negatively affected night sleep due to job		Adverse psychological effects such as work-related stress, workload, and extreme fatigue		The effect of physical conditions in working environment on FMF attack frequency		FMF-induced changing or quitting a job (FMF-C/QI)		
		No attack	At least one attack	Less than 40 hours	More than 40 hours	Yes	No	Yes	No	< 3 points	≥ 3 points	Aggravate the attacks	Reduce or not affect the attacks	Yes	No	Total
Health	Count	4	6	1	9	5	5	5	5	1	9	2	8	1	9	10
	%	40%	60%	10%	90%	50%	50%	50%	50%	10%	90%	20%	80%	10%	90%	100%
Education	Count	8	6	8	6	1	13	2	12	2	12	8	6	3	11	14
	%	57,15	42,90%	57,10%	42,90%	7,10%	92,90%	14,3	85,7	14,3	85,7	57,10%	42,90%	21,40%	78,60%	100%
Agriculture / Farming	Count	0	1	0	1	0	1	0	1	0	1	0	1	0	1	1
	%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	100%
Defense / Security Industry	Count	1	3	0	4	2	2	2	2	1	3	0	4	0	4	4
	%	25%	75%	0%	100%	50%	50%	50%	50%	25%	75%	0%	100%	0%	100%	100%
Trade / Craftsman	Count	6	7	0	13	3	10	7	6	1	12	5	8	2	11	13
	%	46,20%	53,80%	0%	100%	23,10%	76,90%	53,80%	46,20%	7,70%	92,30%	38,50%	61,50%	15,40%	84,60%	100%
Banking	Count	1	0	0	1	1	0	1	0	0	1	0	1	0	1	1
	%	100%	0%	0%	100%	100%	0%	100%	0%	0%	100%	0%	100%	0%	100%	100%
Food Industry	Count	3	1	0	4	2	2	0	4	1	3	1	3	2	2	4
	%	75%	25%	0%	100%	50%	50%	0%	100%	25%	75%	25%	75%	50%	50%	100%
Clothing/Women's Industry	Count	0	1	0	1	0	1	0	1	0	1	1	0	0	1	1
	%	0%	100%	0%	100%	0%	100%	0%	100%	0%	100%	100%	0%	0%	100%	100%
Other	Count	5	19	1	23	9	15	10	14	1	23	5	19	4	20	29
	%	20,80%	79,20%	4,20%	95,80%	37,50%	62,50%	41,70%	58,30%	4,20%	95,80%	20,80%	79,20%	16,70%	83,30%	100%
TOTAL	Count	28	44	10	62	23	49	27	45	7	65	23	49	12	60	72
	%	38,90%	61,10%	13,90%	86,10%	31,90%	68,10%	37,50%	62,50%	9,70%	90,30%	31,90%	68,10%	16,70%	83,30%	100%

quit their jobs due to FMF, this rate was 0% and 8.3%, respectively, for those who stated that the physical conditions reduced or did not affect the frequency and severity of their attacks. A statistically significant relationship was found between physical conditions in the working environment and FMF-C/QJ ($p < 0.05$).

Among the participants who have actively worked, none (0.0%) of those who experienced negative discrimination in the distribution of work due to FMF disease, 33.3% of those who experienced positive discrimination, and 16.2% of those who were not exposed to any discrimination reported that they experienced FMF-C/QJ. However, these differences were not statistically significant ($p > 0.05$).

DISCUSSION

To the best of our knowledge, our study is the first in the literature on the effects of working conditions and the FMF course of the patients on their work life. Four of the 72 participants reported that they have had a health problem in their workplace due to FMF disease. In addition, 23.1% (n:24/104) of the patients stated that they have changed or quited from their jobs because of FMF.

The mutations in the MEFV gene, with ten exons located on the short arm of chromosome 16, play an essential role in the development of FMF. The detection of biallelic pathogenic mutations in the MEFV gene confirms the diagnosis, and identification of the mutations contributes to different FMF phenotype diagnoses.[3,10] A total of 385 current sequence variants in the MEFV gene were reported in the INFEVERS database, and 61 of them (15.8%) were evaluated as "Pathogenic" or "Likely pathogenic".[11] All pathogenic or likely pathogenic mutations in the MEFV gene do not constitute the same clinical phenotype in FMF patients. The significant clinical findings of FMF are observed higher in those who carry one or more M694V or M680I mutant alleles, while fewer clinical symptoms have been reported in those carrying E148Q or V726A mutant alleles.[12] In addition, it has been reported that up to 25% of individuals with a clinical diagnosis of FMF may be heterozygous pathogenic mutation carriers, and FMF findings can be observed in heterozygous carriers even with the mild variants (such as V726A P369S) than the mutations that cause severe phenotype (such as M694V).[13,14]

Our study found no statistically significant difference between individuals with heterozygous MEFV mutations and with homozygous or compound heterozygous mutations in terms of FMF-C/QJ. However, in our study, different molecular techniques were used to detect mutations in the MEFV gene in the patients, and in most of these techniques, the target exons or mutations were screened, not the whole gene. Since our study was designed retrospectively, it is not known whether the heterozygous pathogenic mutation carriers also had a different pathogenic mutation(s) on the MEFV gene regions that were not screened or whether the two different mutations detected in the same patient were on the same or different alleles. Nevertheless, the most common M694V mutation in FMF patients in our country.[9] is screened even in targeted exon or mutation screening methods of the MEFV gene. However, in our study, no statistically significant difference was found between those carrying the M694V allele and not in terms of FMF-C/QJ.

It is still unknown why FMF progresses with attacks. However, it has been shown that attacks can be triggered by many factors, such as physical or emotional stress, menstruation, physical trauma, exposure to colds, infections, high-fat consumption, starvation, insomnia, and fatigue.[15-18] Factors such as job change and job interviews can be considered among the emotional stress factors .[18] In the study by Gidron *et al*., the relationship between psychosocial factors and the incidence of FMF attacks has been reported in children.[19] In another study by Kishida *et al*., 49.4% of 372 FMF patients reported that there were some triggers for FMF attacks. Among these, psychological stress and tiredness were the most frequently reported factors regardless of gender.[7] It has also been reported that depression and anxiety are more common in FMF patients compared to healthy individuals.[20,21] It is suggested that the dose of colchicine can be increased temporarily in such periods, significantly since physical and emotional stress can trigger FMF attacks (15).

In our study, a statistically significant relationship was found between work-related adverse psychological effects and FMF-C/QJ. At the same time, it was found that having an attack was significantly associated with FMF-C/QJ regardless of the severity of the attack.

In contrast to the study by Küçükşahin *et al*.[21], in which poor sleep quality in FMF patients was associated with the number of attacks in the last three months, fatigue, and inflammatory marker levels during attacks, in our study, no significant relationship was found between FMF-C/QJ and working on duty or shift, working time per week or sleep disturbance

caused by job.

One of the factors that trigger FMF attacks is exposure to cold. In a study with the medical records of 2774 children diagnosed with FMF, possible triggering factors for FMF attacks were reported in 14.9% of the patients, and the cold factor was reported as a triggering factor in 77.2% of these patients.[22] Similarly, in another study, the most common triggering factors for serositis were reported as exposure to cold (59.3%), emotional stress (49.8%), tiredness (40.0%), and menstruation (33.7% in women). In comparison, those triggers for attacks with musculoskeletal symptoms were reported as long-lasting standing (78.8%), long-duration travel (64.1%) and tiredness (47.8%) (17). In a study by Cebicci *et al*., emotional stress was reported as the most common triggering factor for abdominal pain in FMF patients in two different provinces. Physical activities that were longer than 30 minutes and caused excessive sweating, such as jogging, brisk walking for an extended period of time, climbing stairs with a heavy load, heavy household chores, and fast-paced dancing, were reported as the second trigger factor.[18] In the study by Alaylı *et al*., they reported that children with FMF not only display lower functional capacity and muscle strength but also manifest lower physical and psychosocial functioning in comparison with healthy children.[23]

In our study, a statistically significant relationship was found between the way of transportation used to work and FMF-C/QJ. Those who go to work on foot or by bike were found to have higher FMF-C/QJ rates than those who use transport vehicles to work. However, there was no significant relationship between the duration of transport and FMF-C/QJ. Karadağ *et al*. reported that standing for a long time can trigger attacks with musculoskeletal pain.[17] In another study, it has been reported that the presence of painful symptoms in the lower extremities after prolonged standing and sitting periods in FMF patients during the absence of attacks may be due to an inflammatory activity.[24] In a study in which a wearable device obtained weekly attack information of FMF patients, it was reported that FMF attacks negatively affected the daily physical life of the patient, and all attacks decreased physical activities by 33% to 84% regardless of the attack duration.[25] Our study suggests that not the duration of transport to work but the mode of transportation may affect work life by triggering FMF attacks due to exposure to physical activity or environmental factors such as cold.

In our study, it was observed that physical conditions at work (table, chair, cold, wind, Etc.) were also associated with FMF-C/QJ. This shows the importance of possible triggering factors in FMF patients' work environments.

The effects of triggers may also vary according to the MEFV gene mutations that are detected in the individual. In the study by Avagyan *et al*., a statistically significant relationship was reported between emotional stress and three primary pathogenic MEFV mutations: M694V, M680I, V726A, and their homozygous genotypes.[22] In another study, it was reported that the M694V allele was associated with starvation, the E148Q allele with high food intake, and the V726A allele with long-duration travel.[17] However, when the data in our study were analyzed, no significant relationship was found between the two groups that carried the M694V allele or not in terms of the mode of transport to work, affected by physical conditions at work, and the severity of work-related adverse psychological effects. This result was similarly statistically insignificant when patients were grouped as M694V heterozygous, M680I heterozygous, M694V / M680I homozygous or compound heterozygous, and those carrying other mutant alleles.

Although this is the first study in the literature investigating the effect of work conditions and the disease on the work-life of FMF patients, it has some limitations. The most important of these is the low number of participants. Moreover, our questionnaire was filled out individually, not by professionals. While creating the questions, in order to prevent bias due to the length and the boredom of the questionnaire, the questions about the working conditions were asked by generalization. For this reason, no evaluation could be made of the different work conditions that caused FMF-related work problems.

CONCLUSION

In the regions where there is a high number of patients with FMF, such as Turkey, we propose that the regulation of working conditions of these patients will positively affect the work performance and the quality of life of these patients. However, more comprehensive studies are needed on this subject.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Çanakkale 18 March University, Çanakkale, Turkey. (Decision number: 2020-12, date: 23.09.2020).

Authors' Contribution

Study Conception: SK, ISA; Study Design: SK, BA, ISA; Supervision; SK, BA, ISA, BFU; Funding: SK, ISA; Materials: SK, BA, ISA, BFU; Data Collection and/or Processing: SK, ISA; Analysis and/or Data Interpretation: SK, BA, ISA, BFU; Literature Review: SK, BA, ISA, BFU; Critical Review: SK, BA, ISA; Manuscript preparing: SK, BA, ISA.

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Evaluation of radiologically determined small bowel wall thickness by double-balloon enteroscopy

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ABSTRACT

Objectives: Double balloon enteroscopy (DBE) is an endoscopic method used for the evaluation of small bowel segments. Its advantage over other small bowel evaluation methods is that it allows treatment in addition to the detection of lesions. In this study, we evaluated the results of patients with small bowel abnormalities, especially wall thickness, on radiologic imaging who underwent double-balloon enteroscopy.

Methods: The data of patients who were found to have wall thickness and stenosis in the small intestine on radiological imaging and who underwent DBE between January 2007 and December 2018 at Ankara City Training and Research Hospital were retrospectively analyzed. Patients with inadequate endoscopic images or medical records were excluded from this study.

Results: The study included 112 patients. Of the patients, 69 (61.6%) were male and 43 (38.4%) were female. The mean age of the population was 45.59 ± 17 years. Abdominal pain was the main presenting symptom. The procedure was performed anterograde (oral) in 79 patients, retrograde (anal) in 25 patients, and both approaches in 8 patients. Various complications developed after 20 procedures, and no mortality was observed. Radiologically, small bowel wall thickness was most commonly detected on computed tomography, and the majority of the lesions detected were in the jejunum (63.9%). In 48 DBE procedures, no lesion was detected in the small intestine. The ulcer was the most common lesion detected during DBE (25.6%), and the majority were detected in the ileum. Crohn's disease was the most common pathology detected in the samples. Malignancy was the second most common pathology, and jejunal lymphoma was the most common malignancy.

Conclusion: DBE should be used more frequently in clinical practice to evaluate radiologically detected small bowel lesions because of the possibility of biopsy and its high diagnostic accuracy.

Keywords: enteroscopy, double-balloon, small bowel wall thickness

Double-balloon enteroscopy (DBE) is an endoscopic technique used to evaluate small bowel segments that cannot be reached by conventional endoscopy and colonoscopy. DBE using a push and pull technique was designed by Hironori Yamamoto in 2001 to facilitate small bowel evaluation because it is difficult to insert an enteroscope deeply with the push technique.[1] In the following years, in addition to the evaluation of small bowel lesions, it has also been used to investigate the etiology of conditions such as iron deficiency anemia, gastrointestinal bleeding, and chronic diarrhea, the cause of which cannot be found by endoscopy and colonoscopy.

In a 2016 study conducted in China and covering 729 procedures, it was reported to be a useful diagnostic and therapeutic tool in the investigation of small

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bowel diseases, and it is recommended to be used as the first step in the diagnosis and treatment of suspected small bowel diseases if performed by experienced endoscopists.[2] In a similar study conducted in our country, DBE was evaluated as a useful method for the diagnosis of small bowel diseases.3 In a study by Sun *et al*.4 evaluating small bowel obstructions, it was evaluated as an appropriate diagnostic tool to determine the cause of incomplete obstructions in patients without a history of abdominal surgery.

This study aims to share our experience with the retrospective performance, efficacy, and safety of double-balloon enteroscopy in patients with small bowel anomalies on radiologic imaging.

METHODS

This is a retrospective study conducted in a tertiary care center. Medical records of double-balloon enteroscopy (DBE) procedures performed between January 2007 and December 2018 at the Gastroenterology Clinic of Ankara City Training and Research Hospital were obtained. Age, gender, symptoms, radiological findings, enteroscopy findings, pathological diagnoses, localization of lesions, and complications were analyzed. The type of approach used during DBE, locations, types of lesions, complications, and pathologic diagnosis were confirmed by reviewing endoscopy examinations and medical records. Patients who could not continue the procedure due to inadequate bowel cleansing, looping, or device malfunction were excluded.

Double balloon enteroscopy (DBE) was performed by experienced endoscopists (Fujinon Inc., EN-450T5)-an anesthesiologist for all DBE procedures administered conscious sedation. No bowel preparation was performed before the procedure in the oral approach. It was given as standard colonoscopy preparation before the anal approach. Whether the procedure would be performed anally or orally was decided based on clinical and radiologic findings.

Lesions were categorized according to their location (duodenum, jejunum, and ileum). Complications were defined as minor and major adverse events occurring during and after the procedure, including postoperative abdominal pain, asymptomatic hyperamylasemia, hypoxia, arrhythmia, intestinal perforation, postoperative bleeding, procedure-related death, and pancreatitis.

The SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the data. The suitability of univariate data for a normal distribution was evaluated with the Shapiro-Wilk test. Quantitative variables are shown as mean ± SD (standard deviation) and median range (maximum-minimum), and categorical variables are shown as n (%).

This study has complied with the ethical guidelines of the 1975 Helsinki Declaration, which was then modified in 2008. The study was approved by the Ankara City Hospital Scientific Research Assessment and Ethics Committee (Date: 11.11.2020, Approval No. E1/1212/2020).

RESULTS

The study analyzed 120 DBE procedures performed in 112 patients. Of the patients, 69 (61.6%) were male and 43 (38.4%) were female. The mean age of the population was 45.59 ± 17 years. Abdom-

Table 1. Characteristics of the study population

Age (Mean ± SD)	45.59 ± 17
Gender	**n (%)**
Female	43 (38.4)
Male	69 (61.6)
Symptoms	
Abdominal pain	83 (74.1)
Weight loss	26 (23.2)
Vomiting	19 (17)
Diarrhea	14 (12.5)
Black stool	3 (2.7)
Bloody stools	2 (1.8)
Fatigue	2 (1.8)
Approach	
Anterograde	79 (70.6)
Retrograde	25 (22.3)
Both	8 (7.1)
Abdominal Surgery	
Yes	7 (6.25)
No	105 (93.75)
Biopsy	
Yes	75 (62.5)
No	45 (37.5)
Complication	
Yes	20 (16.7)
Asymptomatic hyperamylasemia	*16 (13.3)*
Acute Pancreatitis	*2 (1.7)*
Abdominal pain	*1 (0.8)*
Hypoxemia	*1 (0.8)*
No	100 (83.3)

Table 2. Radiological findings and localization

	Localization			
Radiological findings*	*Duodenum*	*Jejunum*	*İleum*	**Total, n (%)**
Wall thickness on CT	3	69	34	106 (86.9)
Mass on CT	2	4	2	8 (6.6)
Stenosis on radiograph	0	3	1	4 (3.3)
Stenosis on Abdominal US	0	1	1	2 (1.6)
Involvement on PET-CT	1	1	0	2 (1.6)
Total, n (%)	6 (4.9)	78 (63.9)	38 (31.2)	122 (100)

*In some patients, more than one localization

inal pain was the main presenting symptom (74.1%), and 22 patients had more than one symptom. Bloody stools and fatigue were the least common presenting symptoms (1.8%). The procedure was performed anterograde (oral) in 79 patients, retrograde (anal) in 25 patients, and both approaches in 8 patients. There was a history of abdominal surgery in seven patients. Biopsies were taken from lesions seen during 75 procedures. Various complications developed after 20 procedures (16.7%), most commonly asymptomatic hyperamylasemia. Except for acute pancreatitis after two procedures (1.7%), no severe complications such as bleeding, perforation, and mortality occurred (Table 1).

Radiologically, small bowel wall thickness was most commonly detected on computed tomography (86.9%), and in some patients, radiological anomalies were detected in more than one localization. The majority of the lesions detected were in the jejunum (63.9%). In four patients, small bowel segmental stenosis was found on radiography and in 2 patients on abdominal US. In two patients, PET-CT for metastasis showed uptake in small bowel segments (Table 2).

In 48 DBE procedures (40%), the small intestines were normal. Abnormal findings were detected in 72 procedures (60%). In some patients, more than one pathology was found during the procedure. An ulcer was the most common lesion (25.6%), and the majority were detected in the ileum. Edematous mucosa was the second most common pathology and was primarily observed in the jejunum. Tumoral formation was detected in 12 (10.3%) of the procedures, most commonly in the jejunum. In addition to small bowel lesions, two polyps and one diverticulum were detected in the colon (Table 3). Endoscopically, fibrotic stenosis was found in 6 patients and inflammatory stenosis

Table 3. Double balloon enteroscopy (DBE) findings and localization

	Localization				
DBE findings	*Duodenum*	*Jejunum*	*Ileum*	*Colon*	**Total, n (%)**
Tumor	2	9	1	0	12 (10.3)
Polyp	0	5	2	2	9 (7.7)
Angiodysplasia	0	2	0	0	2 (1.7)
Ulcer	2	11	17	0	30 (25.6)
Fibrotic stenosis	0	2	4	0	6 (5.1)
Inflammatory stenosis	0	6	4	0	10 (8.5)
Brid	0	2	0	0	2 (1.7)
Dilated segment	0	10	0	0	10 (8.5)
External compression	0	0	1	0	1 (0.9)
Nodular appearance	2	4	0	0	6 (5.1)
Edematous Mucosa	1	12	6	0	19 (16.3)
Diverticulum	0	0	0	1	1 (0.9)
Xanthoma	0	2	0	0	2 (1.7)
Scalloped appearance	2	3	0	0	5 (4.3)
Pearlescent lesion	1	1	0	0	2 (1.7)
Total, n (%)	10 (8.5)	69 (59)	35 (29.9)	3 (2.6)	117 (100)

Table 4. Pathology results of samples taken from the stenoses

Diagnosis	*Fibrotic stenosis*	*Inflammatory stenosis*	Total, n
Crohn's disease	3	6	9
Celiac disease	0	1	1
Lymphoma	0	1	1
Ulcerative ileitis	2	0	2
Vasculitis	1	0	1
Non-diagnostic	0	2	2
Total, n (%)	6	10	16

in 10 patients. Biopsy results were compatible with Crohn's disease in 9 patients and non-diagnostic in 2 patients. Other pathology results are shown in Table 4.

In 52 of 112 patients (46.4%), the DBE procedure yielded diagnostic results. Crohn's disease was the most common pathology detected in the samples (38.5%), and more than half were found in the ileum. Malignancy was the second most common pathology (26.9%), and jejunal lymphoma was the most common malignancy (9.6%) (Table 5).

A total of 104 DBE procedures (67 antegrade, 23 retrograde, seven both) were performed in 97 patients with small bowel wall thickness on radiologic imaging, and 35 patients (38 procedures) had no endoscopic abnormality. The final diagnosis was made in 43 of 62 patients with endoscopic abnormalities. Crohn's disease was the most common pathologic diagnosis, followed by celiac disease and lymphoma. Biopsy results were non-diagnostic in 19 patients (Table 6).

DISCUSSION

Double balloon enteroscopy has been the preferred endoscopic method for the evaluation of the small intestine in tertiary care centers since its introduction in 2001. It has advantages over non-invasive examinations (such as video capsule endoscopy and magnetic resonance enterography) that allow evaluation of the small intestine, such as taking biopsies from detected lesions and performing endoscopic treatments. In the literature review, studies evaluating small bowel stenosis and tumors with DBE were found.[5,6] Although there are studies evaluating small bowel wall thickness with computed tomography[7-9], there are no studies evaluating it with DBE. In this study, radiologically detected small bowel anomalies, especially wall thickness, were evaluated by double enteroscopy.

In this study, a total of 120 examinations were performed on 112 patients, and small bowel lesions were

Table 5. Pathological diagnoses and localizations

	Localization			
Diagnosis	*Duodenum*	*Jejunum*	*İleum*	**Total, n (%)**
Adenocarcinoma	1	2	0	3 (5.8)
Lymphoma	0	5	0	5 (9.6)
Gastrointestinal stromal tumor	0	3	1	4 (7.7)
Metastasis	1	1	0	2 (3.8)
Neurofibroma	0	1	1	2 (3.8)
Intestinal lymphangiectasia	0	4	0	4 (7.7)
Crohn's disease	0	9	11	20 (38.5)
Celiac disease	3	3	0	6 (11.5)
Eosinophilic enteritis	0	0	1	1 (1.9)
Ulcerative ileitis	0	0	3	3 (5.8)
Vasculitis	0	1	0	1 (1.9)
Infective enteritis	0	0	1	1 (1.9)
Total, n (%)	5 (9.6)	29 (55.8)	18 (34.6)	52 (100)

Table 6. Pathologic diagnoses of patients with wall thickness detected on CT

	Localization		
Diagnosis	**Radiological**	**DBE**	**Total, n (%)**
Adenocarcinoma	Jejunum	Jejunum	2 (4.7)
Lymphoma	Jejunum	Jejunum	5 (11.6)
Gastrointestinal stromal tumor	Jejunum	Jejunum	1 (2.3)
Metastasis	Duodenum-Jejunum	Duodenum-Jejunum	2 (4.7)
Neurofibroma	Jejunum	Jejunum	1 (2.3)
Intestinal lymphangiectasia	Jejunum	Jejunum	3 (7)
Crohn's disease			17 (39.5)
	İleumx10	İleumx10	
	Jejunumx6	Jejunumx6	
	Duodenumx1	Duodenumx1	
Celiac disease			6 (14)
	Jejunumx5	Jejunumx3	
	Duodenum-Jejunumx1	Duodenum-Jejunumx3	
Eosinophilic enteritis	İleum	İleum	1 (2.7)
Ulcerative ileitis	İleum	İleum	3 (7)
Vasculitis	Jejunum	Jejunum	1 (2.7)
Infective enteritis	İleum	İleum	1 (2.7)
Total, n (%)			43 (100)

detected in 72 procedures. The lesion detection rate was 60%. Gurudu reported the diagnostic rate of double-balloon enteroscopy for small bowel disease to be 82.4% to 86.8%, which is higher than our rate. The majority of our study population was male; the mean age was 45.59 years, and our findings were compatible with the data in similar studies.[11] In studies evaluating the data of double-balloon enteroscopy of the small intestine, abdominal pain was the most common symptom after gastrointestinal bleeding symptoms.[12] Although our study was performed in a specific patient population, the most common presenting symptom of our patients was abdominal pain.

The complication rate is high (16.7%). The possible reason for this is that transient conditions such as asymptomatic hyperamylasemia, abdominal pain, and hypoxia, which are not considered complications in the literature, were considered minor complications in our study. Acute pancreatitis, hemorrhage, perforation, and mortality were defined as significant complications similar to the literature.[13] Although acute pancreatitis (1.7) was observed in only two patients in our study, it was proportionally higher than the rates reported in other studies.[13] Other significant complications were not observed.

The most common abnormality found radiologically in the small intestine was wall thickness (86.9%), and the majority was observed in the jejunum. No endoscopic abnormality was detected in 48 double-balloon enteroscopy procedures (40%) performed according to imaging findings. Inflammatory findings such as ulcers and edematous mucosa were the most common endoscopic findings, similar to previous studies.[12,14] Biopsy results obtained during the procedures revealed Crohn's disease, most commonly followed by malignancy. The majority of malignancies were in the jejunum. The most common small bowel malignancy is adenocarcinoma.[15] The most common malignancy we found in this study was lymphoma, and adenocarcinoma was the third most common malignancy. Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms and usually arise in the stomach or small intestine.[16] GISTs were the second most common malignancy in this study.

Small bowel strictures are a rare condition. However, they are challenging to diagnose, characterize, and treat. Identifying the cause of the stricture is crucial in directing appropriate treatment. Previous studies have identified Crohn's disease as the most common cause of small bowel stricture.[17] In this study, Crohn's disease was the most common underlying cause in patients with endoscopic stenosis.

Small bowel wall thickening is a common but nonspecific finding on abdominal computed tomography (CT) performed for gastrointestinal symptoms.[9] Malignant and benign etiologies can cause intestinal wall

thickness. In a study where all bowel segments were evaluated in a small number of patients, adenocarcinoma was found to be the most common etiological cause.[18] In a different study conducted with more patients and evaluating small intestine wall thickness, inflammatory causes, especially Crohn's disease, were determined to be the most common etiology.[9] In our study, double balloon enteroscopy was normal in 35 of 97 patients with small bowel wall thickness on computed tomography. Sixty-two patients had an abnormal endoscopy, and 43 of them had a final diagnosis. Crohn's disease was the most common cause of wall thickness. Malignancies were the second most common cause, and lymphoma was the most common malignancy.

Celiac disease is an autoimmune disorder that damages segments of the small intestine.[19] It can cause wall thickening. In a study in which the MRI findings of 31 patients were evaluated, bowel wall thickness was detected in 5 patients (16.1%).20 In our study, we detected celiac disease in 6 patients (6.1%) with wall thickness on CT. Eosinophilic enteritis and vasculitis were found to be less common causes of wall thickening.

The most important limitation of the study is that it was retrospective. Another limitation is that the duration of the procedure and the depth of the examination need to be specified. Nevertheless, our results are valuable because they include a specific patient population with small bowel abnormalities on radiologic imaging.

CONCLUSION

In our study, Crohn's disease and malignancies were the most common causes of small bowel wall thickness. Another important finding was that the majority of endoscopically found strictures were secondary to Crohn's disease. Therefore, patients with small bowel abnormalities on radiologic imaging should be carefully evaluated, and an enteroscopic examination should be performed. In this patient population, double balloon enteroscopy may be the procedure of choice with low significant complication rates.

Conflict of Interest

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Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Ankara City Hospital, Ankara, Turkey. (Decision number: E1/1212/2020, date: 11.11.2020).

Authors' Contribution

Study Conception: BY; Study Design: BY; Supervision; MAK; Funding: BY, MY; Materials: BY, MY, MAK, VK; Data Collection and/or Processing: BY, MY, MAK, VK; Analysis and/or Data Interpretation: BY, MY, MAK, VK; Literature Review: BY, MY, MAK, VK; Critical Review: MAK; Manuscript preparing: BY, MY, MAK, VK.

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Case Reports

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An overlooked cause of hepatitis and thrombocytopenia with clinico-biochemical discrepancy: A case of infectious mononucleosis

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ABSTRACT

Objectives: A 22-year-old male was admitted to the outpatient clinic with fatigue, fever, and a sore throat. High transaminase levels, moderate thrombocytopenia, and elevated acute phase reactants were detected ten times. Ultrasound imaging revealed hepatosplenomegaly and a peripheral blood smear showed Downey cells. Epstein-Barr virus (EBV) infection was considered the definite diagnosis, and EBV serology was performed. His mild clinic improved to normal within days, but the patient's clinical progression and laboratory findings were incompatible. Laboratory results were on the extreme side, while the clinic was mildly deteriorating. EBV viral capsid antigen IgM was high, supporting the initial diagnosis. Biochemical normalization followed clinical improvement many days later. Clinicians should know that EBV infection may be mild, while laboratory results illustrate extreme findings.

Keywords: Epstein Barr virus, aminotransferase, thrombocytopenia, hepatomegaly, splenomegaly

Epstein-Barr (EBV) is a herpes virus that spreads through close contact between susceptible individuals and asymptomatic EBV carriers. While most cases are subclinical, symptomatic patients may have fever, lymphadenopathy, and tonsillopharyngitis, which are included in the classic triad. There may also be atypical cases presenting with ascites, arthritis, and severe abdominal pain.[1] Nearly 95% of adults worldwide are infected with EBV.[2] Hepatitis is a common feature of EBV infection, with 80-90% of cases demonstrating a mild to moderate and temporary rise of liver enzymes. Severe hepatocellular liver injury is rare.

Nevertheless, half of the fatal infectious mononucleosis cases have been reported as the result of liver failure.[3] An alteration in white blood cells is the most prominent hematological feature in primary EBV infection, giving the disease its name (infectious mononucleosis). Additional hematological disturbances, including mild thrombocytopenia, are less pronounced, although usually encountered.[4]

CASE PRESENTATION

A 22-year-old male was referred to our tertiary care general internal medicine clinic from a primary care center, where he was admitted with a sore throat and fever due to a low platelet count (88.000 cells/μL). He states that his fever and sore throat have subsid-

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Table 1. Results of the initial laboratory and imaging studies

Parameter	Results	Reference Range
Hemoglobin (g/dL)	15,7	13,5-18
Leukocyte (x10^3/µL)	9.61	4.5 – 11
Platelet (x10^3/µL)	94	150 – 400
Lymphocyte (x10^3/µL)	4.76	1 – 4
Monocyte (x10^3/µL)	1.74	0 – 1
CRP (mg/L)	42.2	0 – 5
Sedimentation Rate (mm/hour)	12	0 – 20
Ferritin (µg/L)	1273	21 – 274
Total Bilirubin (mg/dL)	1.00	0.3 – 1.2
Direct Bilirubin (mg/dL)	0.54	0 – 0.5
AST (U/L)	127	0.3 – 1.2
ALT (U/L)	182	0 – 0.5
ALP (U/L)	293	50 – 116
GGT (U/L)	518	< 55
Abdomen US	The liver measured 175 mm, the spleen measured 155 mm, and other findings were normal.	

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GGT: Gamma-glutamyltransferase, US:ultrasonogrophrapy

ed, but now he reports left-side, left upper quadrant pain that worsens with breathing. He reports no prior diseases. He is a regular smoker and reported binge drinking four days ago. His physical examination was unrevealing and showed typical vital signs. On physical examination, no lymph nodes other than a normal-sized, unremarkable lymph node in the suboccipital region were palpated. The respiratory examination was unrevealing. On abdominal examination, there were no palpable liver, spleen, or mass, and palpation was unremarkable. Basic laboratory tests, viral hepatitis markers, peripheral blood smear, chest radiography, and upper abdominal ultrasonography (US) were ordered. The results revealed elevated white blood cells predominately in lymphocytes and monocytes, moderate thrombocytopenia, elevated acute phase re-

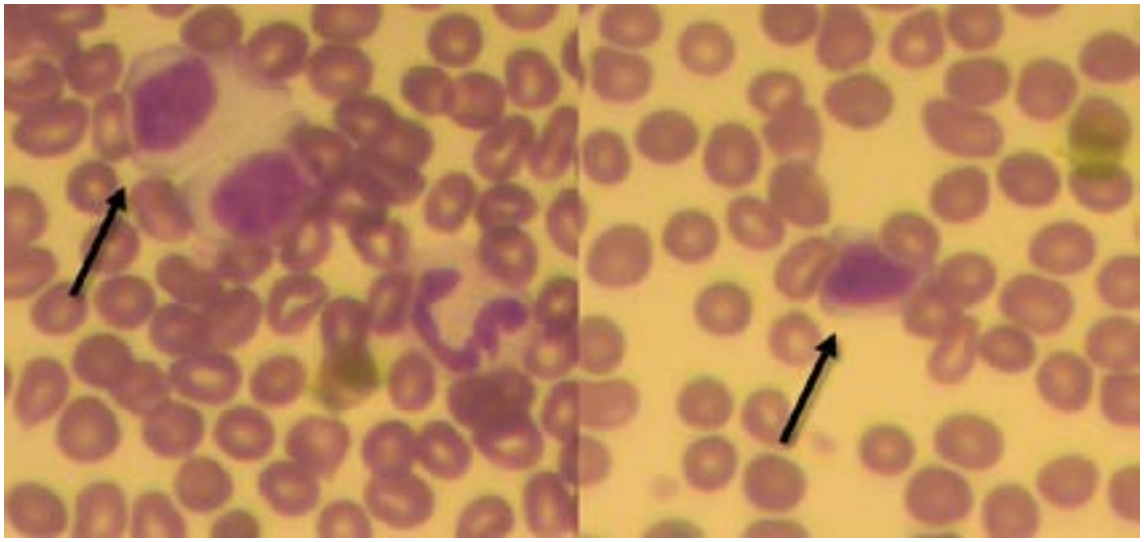

Fig. 1. Reactive lymphocytes (Downey cells) in peripheral blood smear (x400)

Table 2. Results of the control laboratory studies at day 3

Parameter	Results	Reference Range
Hemoglobin (g/dL)	15,4	13,5-18
Leukocyte (x10^3/µL)	15.7	4.5 – 11
Platelet (x10^3/µL)	126	150 – 400
Lymphocyte (x10^3/µL)	11.4	1 – 4
Monocyte (x10^3/µL)	1.41	0 – 1
CRP (mg/L)	28,1	0 – 5
Total Bilirubin (mg/dL)	1,20	0.3 – 1.2
Direct Bilirubin (mg/dL)	0,84	0 – 0.5
AST (U/L)	267	0.3 – 1.2
ALT (U/L)	413	0 – 0.5
ALP (U/L)	435	50 – 116
GGT (U/L)	714	< 55

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GGT: Gamma-glutamyltransferase

actants, and 2-3 times higher elevations of transaminases and cholestatic enzymes. Initial laboratory and radiology results were presented in Table 1 in detail. Multiple reactive lymphocytes (i.e., Downey cells) were observed in the peripheral smear, as illustrated in figure 1. Abdominal US demonstrated splenomegaly and hepatomegaly. The patient's clinical, imaging, blood smear, and laboratory results were consistent with EBV infection; hence, EBV serology was requested, and he was discharged with a follow-up plan. He returned for a follow-up visit three days later with no clinical signs or complaints. Control laboratory tests revealed even more severe lymphocytosis and an up to 10-fold increase in liver transaminases. Control laboratory results were presented in Table 2 in detail. He was assured and sent home with a follow-up plan. A few days later, EBV viral capsid antigen immunoglobulin M (VCA) IgM-2.2 S/CO was detected, and the patient's diagnosis of infectious mononucleosis was confirmed. The patient was advised to take bed rest and avoid taking hepatotoxic drugs, especially alcohol, and NSAIDs, as much as possible. The patient was monitored with close outpatient clinic follow-up. Later in the follow-up, his hematological and liver biochemistry levels returned to normal with no clinical or biochemical abnormalities. Informed consent was obtained from the patient before manuscript submission.

DISCUSSION

We report a case study on a young and healthy male patient with mild upper respiratory infection symptoms. However, the patient also displayed moderate to severe hematological and biochemical abnormalities. Based on the observed discrepancy between clinical manifestations and test findings, the patient under consideration is deemed worthy of reporting.

Epstein-Barr virus (EBV) patients may exhibit clinical manifestations such as splenomegaly, lymphadenopathy, headache, tiredness, fever, and sore throat. Patients can experience symptoms for an extended period, with exhaustion being the most frequently reported persistent symptom. It was noted that around 25% of the patients had physical examination findings such as cervical lymphadenopathy and pharyngitis six months after the first infection.[5]

Given the observation of lymphocytosis and atypical lymphocytes in blood tests, liver function tests may exhibit aberrant elevations. A study conducted by Nahum Méndez-Sánchez *et al*. aimed to elucidate the hepatic symptoms and problems related to Epstein-Barr virus (EBV) infection. The researchers documented a cohort of patients who had liver manifestations concerning EBV infection. Hepatic abnormalities, characterized by increased levels of transaminases and/or bilirubin, were observed in over 77% of the patient population.

In the aforementioned study, the hematological tests revealed that a significant proportion, precisely over 44%, of the patients exhibited concurrent manifestations of one or more symptoms. The study identified cytopenia affecting two distinct cell lines, with leukopenia (defined as a white blood cell count below 4,000 cells/µL) and thrombocytopenia (characterized by a platelet count below 150,000 platelets/µL) being the prevailing hematological abnormalities. However,

our patient exhibited heightened leukocytosis despite the presence of thrombocytopenia.[6]

Ferritin is a positive acute phase reactant, and it has been shown to correlate with disease severity.[7] Recently published case reports also illustrated similar levels of hyperferritinemia due to EBV. Similarly, their case also exhibited hepatitis to the same extent.[8]

Serological assays are the most efficacious diagnostic tools. The heterophile antibody assays detect immunoglobulin M (IgM) antibodies specific to the Epstein-Barr virus (EBV). Although the heterophile antibody test was not available at our clinic and hence was not requested, it is worth noting that this test holds value as an initial diagnostic tool due to its cost-effectiveness, prompt results, and moderate sensitivity ranging from 63% to 84% and high specificity ranging from 84% to 100%. One potential drawback is that heterophile antibodies can be activated by other disease processes, leading to a positive result unrelated to acute Epstein-Barr virus (EBV) infection. Additionally, these antibodies may persist for a duration exceeding one year, further contributing to potential false positive outcomes.[9]

The management of infectious mononucleosis typically involves supportive measures, which are comparable to the approach taken in the treatment of other viral diseases. It is recommended that clinicians guide patients regarding the importance of prioritizing sufficient periods of rest, maintaining proper hydration, and adhering to a well-balanced nutritional regimen. Acetaminophen and nonsteroidal anti-inflammatory medications (NSAIDs) are efficacious in the treatment of pain and malaise when used as required.[10]

In conclusion, EBV infection should be considered in the differential diagnosis of patients presenting with severe hypertransaminasemia, moderate to severe thrombocytopenia, and hyperferritinemia exceeding 1000 µg/L, especially when clinical and laboratory findings do not significantly overlap.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: ATG; Study Design: ATG; Supervision; ATG; Materials: ED; Data Collection and/or Processing: ATG; Analysis and/or Data Interpretation: ATG; Literature Review: ED; Critical Review: ATG; Manuscript preparing: ATG, ED.

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Smoking cessation in a 39-year-old woman: A case report

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ABSTRACT

Objectives: Smoking is a prevalent habit associated with numerous health risks, including various cancers, cardiovascular diseases, respiratory disorders, and diabetes.

Methods: According to the Lifestyle Medicine outcomes of second-grade medical students' curriculum, this case report describes the smoking cessation journey of a 39-year-old woman who has been smoking since she was 17.

Results: The participant's motivation to quit smoking stemmed from factors such as rising cigarette prices, concerns about the health of her family members, and fear of developing various smoking-related diseases. Despite several attempts to quit smoking in the past, she struggled to maintain abstinence for longer durations. This report highlights the challenges faced by the participant, including the experience of weight gain during previous quit attempts and the lack of professional support. The role of social and environmental factors, such as her husband's smoking habits and her child's exposure to secondhand smoke, is also discussed.

Conclusion: Professional assistance, behavioral interventions, and strategies targeting triggers associated with alcohol and coffee consumption may contribute to successful smoking cessation. A holistic approach and patient-family centeredness could be critical factors in achieving the LSM process for quitting tobacco usage.

Keywords: case report, tobacco usage, family medicine, lifestyle medicine

Smoking is a prevalent habit associated with numerous health risks, including various cancers, cardiovascular diseases, respiratory disorders, and diabetes.[1] Smoking cessation is crucial for improving overall health outcomes and reducing the burden of smoking-related diseases.[2] This case report presents the journey of a 39-year-old woman seeking to quit smoking due to personal and health-related concerns.

CASE PRESENTATION

The survey participant is a 39-year-old woman with a university degree. She started smoking at 17, influenced by peer pressure and a desire to fit in with her friends who smoked. Currently, she consumes approximately 180 packs of cigarettes per year, amounting to 10 cigarettes per day. Her preference is filtered cigarettes, and she does not use other tobacco products such as electronic cigarettes, cigars, or hookahs. While her cigarette consumption was higher in her youth, it has decreased over the years.

Motivation to Quit

The participant has expressed a strong desire to quit smoking for several reasons. Firstly, the increase in cigarette prices has become a financial burden. Sec-

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ondly, she is concerned about her family's health, especially her husband and child, and acknowledges the dangers of secondhand smoke exposure. Thirdly, the participant fears developing various smoking-related diseases, especially after being diagnosed with the onset of asthma.[3,4] Lastly, her family history of diabetes and chronic asthma further motivates her to quit smoking.[2,4]

Quit Attempts and Challenges:

The participant has made multiple attempts to quit smoking in the past. However, she struggled to maintain abstinence for extended periods. The lack of professional support during her quit attempts may have contributed to the relapses.[2,5] Additionally, she experienced weight gain during previous quit attempts, primarily due to increased appetite, which further demotivated her.

Social and Environmental Factors

The participant's husband smokes, creating a challenging environment for smoking cessation. Moreover, her child is exposed to secondhand smoke at home, posing additional health risks.[1] The participant's limited time at work allows her to smoke only one cigarette, reducing her overall smoking frequency during work hours.[5]

Triggers and Associations

The participant mentioned that her desire to smoke increases when consuming alcohol and coffee. These associations indicate the need for tailored strategies to address cravings during specific situations.36

What is the most challenging for my patient?

The patient said that she felt her most incredible difficulty when she was diagnosed with the onset of asthma. Because the doctor said that she needed to take some medications and use an asthma inhaler.[4] Due to this disease, she has difficulty breathing, leading to a short, wheezing breathing behavior. Also, continuing to smoke destroys her respiratory system and reduces her quality of life.

Another challenge was related to the excess weight that she gained during the periods when she quit smoking. Excessive weight gain in a short time affected her psychology negatively. Therefore, she showed signs of depression and anxiety.[3]

Finally, she had terrible psychological and physical experiences in the first month of quitting smoking. For example, she describes herself as highly irritable and nervous at the time. She had sleep problems and had a hard time concentrating on her work. She felt uncomfortable and wanted to smoke constantly to eliminate this situation.

What actions make sense to prevent the individual from smoking?

Nicotine replacement therapy may be used to prevent smoking. This therapy contains prescription nicotine in a nasal spray or inhaler, nicotine patches, gum, and lozenges (you can buy them without a prescription). Staying away from triggers for a while can also help. For instance, going to places where intense cigarette consumption should be avoided.[6]

Exercise can be done, and a regular fitness routine can be established.[2] These actions keep your mind busy and make you forget your urge to smoke. People who smoke can do activities that will help them relax, such as deep breathing, muscle relaxation, yoga, massage, or calming music. They can also take up a hobby to keep them busy. For example, these acts are gardening, knitting, handmade staff, and sewing.[5,6]

Finally, they can get professional help. There are many institutions and organizations with the theme of quitting smoking. They can ask the experienced people here to help them. They can also get exceptional support from psychologists about this situation.

CONCLUSION

This case report emphasizes the importance of smoking cessation for the well-being of individuals and their families. The participant's motivation to quit smoking, her concerns about financial implications, secondhand smoke exposure to her child, and the fear of developing smoking-related diseases highlight the need for effective interventions and support systems. Professional assistance, behavioral interventions, and strategies targeting triggers associated with alcohol and coffee consumption may contribute to successful smoking cessation. By quitting smoking, the participant aims to reduce her risk of developing diseases such as diabetes and chronic asthma, considering her family history.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: GÇ; Study Design: GÇ, OG;

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Since the name of the author Mehmet Fuat Gürkan, who contributed to the study, was forgotten to be added to the article by mistake, the name of the author in question was added to the article upon the corresponding author's written request.

Retrospective analysis of cases with tuberculous meningitis: single center experience

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ABSTRACT

Objectives: A total of 172 patients were retrospectively investigated who were admitted to the Pediatric Department of Dicle University School of Medicine with the diagnosis of tuberculous meningitis. Demographic data, clinical, laboratory and radiological findings and responses to treatment were analyzed. Of all patients 124 (72.1%) were under 5 years of age and 109 were males. The most common symptoms on admission were fever (%71), vomiting (60%), convulsion (38%), and headache (31%). Forty-seven (23.8%) patients had positive family history of tuberculosis. Tuberculin skin test positivity was seen in 19.6% and 20.1% had positive BCG scar. Of all patients 32 (18.6%) were in stage I, 82 (47.7%) were in stage II and 58 (33.7%) were in stage III on admission. Chest X-Ray showed pathological findings in 60.9% of all patients. Hydrocephalus was detected in 149 patients on cranial tomography. Ventriculo-peritoneal shunt was performed in 79 patients with hydrocephalus. Totally, 24 deaths were detected from all patient records.

Since the diagnosis of tuberculous meningitis is difficult and the disease has a high morbidity and mortality rate, the importance of preventive measures in the control of the disease has been emphasized in this study

Keywords: children, tuberculosis, meningitis

Tuberculosis (TB), one of the oldest diseases in history, continues to be one of the most common infectious diseases in the world and constitutes an important health problem especially in developing countries, including our country. Today, more than 40% of the world's population is infected with tuberculosis bacillus, and 1-3 million new tuberculosis cases are reported each year in children younger than 15 years of age. It has been reported that the majority of these cases are located in developing countries with poor living conditions. [1] In our country, the prevalence of infection was found to be 25% (11,578,000 people), and the prevalence of the disease was 0.36% per thousand, which was last done in 1982. In addition, as seen in this study, the prevalence of tuberculosis is high in our region (0.74%), and as a result, tuberculous meningitis (TBM) is frequently encountered. [2]

Although the definitive diagnosis of tuberculous meningitis is made by direct smear from CSF(Cerebrospinal fluid) or the demonstration of Mycobacterium tuberculosis (M. Tbc) by culture, the diagnosis can still be made by clinical, demographic, radiological, and contact anamnesis since it takes time and is rarely positive.

Tuberculous meningitis occurs in 0.3% of children with untreated primary infection.[3] It is an infection with high morbidity and mortality in childhood. Tuberculous meningitis is the most common form of central nervous system tuberculosis.[4] Tuberculous

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meningitis is very rare in children younger than four months because the pathological process is completed in such a short time. It is most common in children between the ages of 6 months and 4 years (first five years). At this age, it usually develops within the first 2-6 months of primary infection.[4-6]

In current study, clinical, laboratory, radiological findings and responses to treatment of 172 patients with tuberculous meningitis who were followed up in our clinic were evaluated retrospectively, and the results were evaluated in the light of today's literature.

METHODS

In this study, 172 patients were hospitalized and treated with the diagnosis of tuberculous meningitis in the Infectious Diseases Clinic of the Department of Pediatrics of the Dicle University, and then followed up in the control outpatient clinic were included.

The study was done retrospectively. General information from the follow-up cards of the patients; age, gender, residence address, application complaints, BCG (Bacillus Calmette-Guerin vaccine), PPD (Pürified Protein Derivative Test), which period they applied, family histories, PA lung grammar, cranial CT (Computed Tomography) and MRI (Manyetik rezonans) results, CSF results, blood biochemistry (ALT, AST, urea, creatinine) were recorded and the existing results were evaluated.

Diagnosis of tuberculous meningitis was based on the history, physical examination, laboratory findings, microbiological and biochemical examination findings of Cerebrospinal fluid (CSF), and radiological findings. Among these, the appearance of ARB (Acid resistant bacilli) in the "Ehrlich-ZiehlNeelsen (EZN)" staining of CSF and/or the production of Mycobacterium tuberculosis in Löwenstein-Jensen medium; Findings of more than 10 cells per mm^3 with signs of subacute meningitis (signs of meningeal irritation lasting longer than four days), biochemical features of CSF (high protein, low sugar, and chloride); M. tuberculosis growth in another anatomical region or detection of ARB in a direct stained preparation were considered as the main determinants for the diagnosis of the disease.[7]

In all patients diagnosed with TB, standard 4 antituberculous therapy (2 months INH + RIF + PZA + SM or EMB, 10 months INH + RIF) and additional methylprednisone (1-2 mg/kg/day) for the first 4-6 weeks or dexamethasone (0.5-1 mg/kg/day) and if necessary, acetazolamide (40 mg/kg/day) treatment was administered.

Descriptive statistics for continuous variables were expressed as mean, standard deviation, minimum and maximum values, while categorical variables were expressed as numbers and percentages. Chi-square test was used to determine the relationship between groups and categorical variables, and Student-t test was used to compare group means of continuous vari-

Table 1. General information about the patients

Age(years)	n	Percent
< 5 years old	124	72.1
> 5 years old	48	27.9
Gender		
Male	109	63.4
Female	63	36.6
BCG		
Positive	30	20.1
Negative	119	79.9
PPD		
Negative	115	80.4
Positive	28	19.6
Family history		
Negative	47	23.3
Positive	125	72.7

BCG: Bacillus Calmette-Guerin vaccine, PPD: Purified Protein Derivative Test

ables. Statistical significance level was accepted as $p < 0.05$ by using the "SPSS for Windows" statistical package program in the calculations.

RESULTS

172 patients who were clinically diagnosed with tuberculous meningitis were included in the study. The mean age of the patients was 59.7 ± 45.6 months (4 months-15 years). The mean age of 124 (72.1%) patients was 5 years or less, and 48 (27.9%) patients were older than 5 years (Table 1). Of the patients, 63 (36.6%) were female and 109 (63.4%) were male. The male/female ratio was found to be 1.74 (Table 1).

Patients applied mostly in June (22.1%). (Fig. 1)

In the records of the patients, 149 patients have BCG scars. Of these, 119 (79.9%) had negative BCG and 30 had positive BCG (Table 1). One-hundred and forty-three of our patients had PPD results. PPD test results were negative in 115 (80.4%) of 143 patients, and positive in 28 (19.6%) patients. (Table 1)

While there was family history in 125 (72.7%) of our patients included in the study, there was no family history in the 47 (27.3%) patients (Table 1). BCG positivity was found to be %18.3 in those with a positive family history. When the clinical period of the patients was examined at the time of hospitalization; it was seen that 32 (18.6%) of the patients came in stage I, 82 (47.7%) in stage II, 58 (33.7%) in stage III.

Fever was among the most common symptoms in 122 (71%) of our patients at the time of admission to the clinic. (Table 2).

Pathological chest X-ray findings were found in 56 (60.9%) of 92 patients whose chest X-ray findings were recorded. Of these, 27 (15.7%) parenchymal infiltration, 15 (8.7%) miliary appearance, 9 (5.2%) hilar LAP, [3 (1.7%) unilateral, 6 (3.5%) bilateral LAP], 2 (1.2%) atelectasis, 1 (0.6%) pleural effusion, 1 (0.6%) empyema, 1 (0.6%) LAP + consolidation. 36 (39.1%) chest X-ray of the patient was normal.

Pathological cranial CT imaging results were found in 157 of 172 patients. The most common complication was hydrocephalus, and 79 (45.9%) of these patients underwent ventriculoperitoneal shunt operation (Table 3).

CSF glucose levels were below 10 mg/dL in 15 (8.7%) of the patients, between 11-40 mg/dL in 99 (57.6%), and between 41-80 in 51 (29.7%) patients. Seven (4.1%) were found to be over 80. CSF glucose was below 10 mg/dL in five patients, CSF glucose was between 11-40 mg/dL in 11 patients, and CSF glucose was between 41-80 mg/dL in 8 patients.

When the CSF protein was biochemically examined, it was found that 44 (32.9%) of the patients were between 0-50 mg/dL, 19 (14.1%) of them were between 51-100 mg/dL, 53 (39.6%) of them were between 101-200 mg/dL, 13 (9.7%) were between 201-500 mg/dL and 5 (3.7%) of them were over 500 mg/dL.

Lymphocyte dominance was observed in 143 (83.1%) of the admitted patients, while PNL was dominant in CSF in 29 (16.9%). When the number of cells in the CSF was examined, 7 (4%) of the patients were between 0-10/mm^3, 55 (32%) of them were between 11-100/mm3, and 84 (48.8%) of them were between 101-500/mm^3. and in 26 (15.2%) of them were found to be above 500/mm^3. The presence of M.Tuberculosis was demonstrated in CSF by PCR (Polymerase Chain Reaction) in 3 patients.

The white blood cell (WBC) count of the patients whose hemogram results were examined was < 4000/

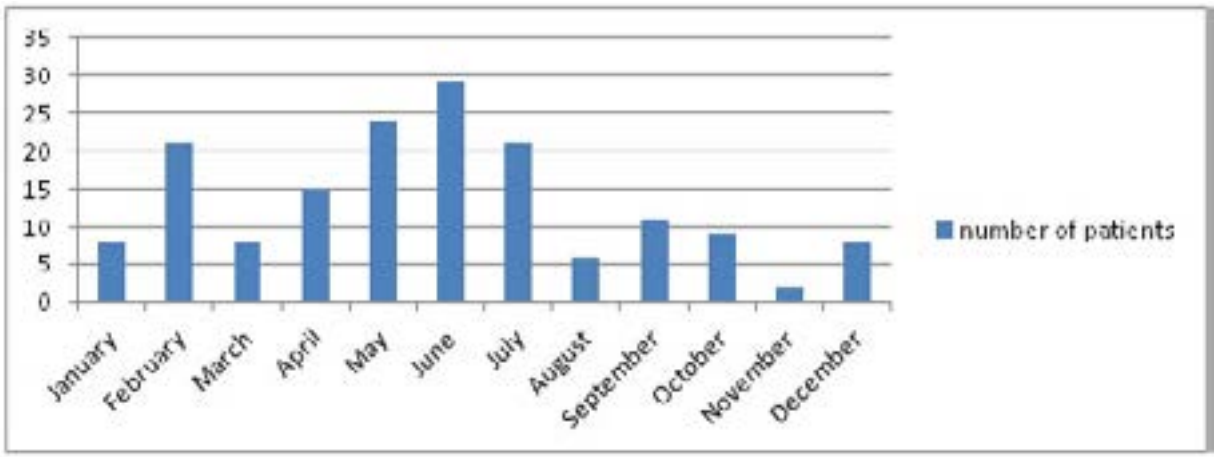

Fig. 1. Distribution of the number of patients according to the seasons

Table 2. Symptoms of the patients at the time of first admission

Symptoms	n	%
Fever	122	71
Vomiting	104	60
Epilepsy	66	38
Headache	54	31
Diarrhea	28	16
Confusion	24	14
Cough	16	9
Neurological deficit	14	8
Nausea	13	8
Abdominal pain	13	8
Dyspnea	9	6
Anorexia	5	3
Weakening	4	2
Sweating	3	2
Weakness	3	2
Not sucking	2	1
Abdominal swelling	1	1

mm3 in 3 (1.7%) and between 4000-10000/mm3 in 66 (38.4%) and > 10000/mm^3 in 103 patients. WBC mean of the patients was found as 14100/mm^3. As a result, the majority of the patients presented with leukocytosis.

When the mean AST, ALT, urea, and creatinine values of the patients whose biochemistry results were examined, it was seen that they applied with mild AST elevation. The number of patients with AST values above normal was 75. ALT, urea, and creatinine values were found to be normal.

Hydrocephalus was detected in 172 patients 149 of them who were examined retrospectively, and shunt operation was performed in 79 (45.9%) of these patients.

Toxicity was detected in 12 (7%) of the 172 patients examined. Drug toxicity was accepted as a more than a 3-fold increase in AST, ALT levels, increase in bilirubin levels, jaundice, nausea, and vomiting. medications were discontinued. In these patients, re-treatment was continued after the AST and ALT levels of the drugs returned to normal. Of 172 patients, 24

Table 3. Cranial CT results of the patients

CT findings	n	%
Hydrocephalus	149	94.9
Meningeal/parenchymal involvement	49	31.2
Subdural effusion	16	10.2
Cerebral atrophy	12	7.6
Tuberculoma	12	7.6
Cerebral infarction/embolism	11	7.0
Brain edema	7	4.5
Hematoma	3	1.9
Ischemia	2	1.3
Normal	12	7.6

(%14) died. On average, the hospital stay of the patients was 23.5 ± 14.5 days.

Of the cases that resulted in death, 19 (79.1%) were within the first 5 years of age, and 5 (20.9%) were above 5 years of age. Of the deceased patients, 3 (12.5%) were in stage I, 12 (50%) were in stage II, and 9 (37.5%) were in stage III.

DISCUSSION

Tuberculous meningitis, which is the most serious complication of tuberculosis in childhood and the most common cause of death from tuberculosis, is most common in children aged 6 months to 4 years, accounting for approximately 10% of tuberculosis cases. In our study, the ages of our patients were found to be between 4 months and 15 years. The mean age of 124 (72.1%) patients was 5 years or less, and 48 (27.9%) patients were older than 5 years (Table 1). Of the 172 cases in our study, 63 (36.6%) were female and 109 (63.4%) were male. The male/female ratio was found to be 1.74 (Table 1). The mean age of our patients was 59.7 ± 45.6 months.

Recent studies on the BCG vaccine show that the protective effect of the BCG vaccine is 50% against pulmonary tuberculosis in children and adults, and 50-80% against tuberculous meningitis and other disseminated tuberculosis types.[6, 8-11] It is widely believed that the main effect of the vaccine prevents the development of life-threatening forms such as miliary and central nervous system tuberculosis. A dose between 0-3 months in endemic populations as the age of vaccination is a second dose to be given at the beginning of school. Considering the results of our patients' vaccination with BCG vaccine, the low vaccination rate of 20.1% shows the importance of maintaining BCG vaccination for our region in preventing disease with serious morbidity and mortality, such as tuberculosis and, more importantly, tuberculous meningitis, one of the disseminated forms of tuberculosis. It can be thought that this low vaccination rate is due to social, cultural, and traditional reasons, lack of education, the inadequacy of health services, the problem of access to services, effectiveness of vaccination, inadequacy of basic and preventive health services.

In various studies, the rate of having a person with tuberculosis in the family or in the immediate environment was found to be 30-80%. The recent diagnosis of tuberculosis in 47 (27.3%) of our patients from family members or close relatives is consistent with previous studies. Despite these family histories, it was observed that most of our patients did not have family screening. Therefore, it was concluded that the deficiencies in the reporting of the disease with such serious consequences and in family screening should be reviewed. Screening the family members of adults with active tuberculosis and administering antibiotic prophylaxis to children under 5 years of age and other PPD positive individuals are of vital importance in preventing the spread of the disease.[6, 12]

PPD test maintains its importance in diagnosing tuberculosis. it has been reported in various sources that 50% of patients with tuberculous meningitis may have a positive PPD test.[6, 10, 11, 13] It may be negative in miliary spread, immunosuppression, viral infections, especially in infants and young children. In some cases, it may be positive after starting tuberculosis treatment. In tuberculous meningitis, both PPD and pulmonary findings may be negative. In our study, 115 (80.4%) of our patients had negative PPD results and 28 (19.6%) had positive PPD results. In their study consisting of 214 patients, Yaramış *et al*. found PPD positive in 64 (30%) patients.14 Nguyen *et al*. stated that PPD may be negative at a rate of 50-70% in patients.15 In previous studies, the tuberculin test performed with 100 U PPD in patients with tuberculous meningitis was found to be 20% negative.16 The PPD solution applied in our study was 5 U tuberculin test solution. In recent studies, the tuberculin test performed with 10-100 U PPD has been shown to be 75% positive.17

TB meningitis is the most serious form of tuberculosis, usually fatal if left untreated. Symptoms are similar to other forms of meningitis, with an onset that lasts days or weeks. It is clear that early diagnosis and treatment have a significant impact on mortality and morbidity. atypical onset; It may also be in the form of bronchopneumonia, findings suggestive of intracranial mass, GIS symptoms, typhoid or epilepsy. Therefore, the possibility of TBM should be considered in patients presenting with these tables. In their study consisting of 497 male and 360 female cases, Girgis *et al*. reported fever in 90% of the cases, headache in 63%, vomiting in 49%, and lethargy in 32%.18 In their study consisting of 214 cases, Yaramış *et al* found fever in 91%, vomiting in 87%, altered consciousness in 63%, seizures in 62%, and headache in 58%.14

Studies have reported that patients present with nonspecific symptoms such as restlessness, weakness, fever, fatigue, and headache.[19-21] Fever was the most common in 71% of the patients, vomiting in 60%, convulsions in 38%, headache in 31%, diarrhea in

16%, confusion in 14%, cough in 69%, cough in 8%. Neurological deficit, nausea and abdominal pain were the most common symptoms. When compared with the literature data, symptoms were found to be similar.

Diagnosis of tuberculous meningitis is still a problem, although the disease may start acutely in 50% of infants, it can be subacute in children and adults. History and laboratory tests are often nonspecific and rarely pathognomonic. Therefore, radiological imaging, especially cranial imaging, is of great importance in the early diagnosis and treatment of tuberculous meningitis, which has serious morbidity and mortality consequences.

In patients with suspected tuberculous meningitis, showing hydrocephalus, infarction, tuberculoma, edema, ventricular dilatation, involvement of the meninges and especially the basilar region, which may vary according to the degree of cranial CT disease, is important for diagnosis. Hydrocephalus is the most common complication seen in tuberculous meningitis and occurs in the acute period with obstruction of the basal systems and is usually of the communicative type.4 It is reported that the most frequently reported data in cranial CT is hydrocephalus, and it constitutes a greater majority in children than in adults.

In our study, cranial CT results of 157 patients were evaluated retrospectively, 149 (94.9%) of patients had hydrocephalus, 49 (31.2%) had meningeal/parenchymal involvement. and 12 (7.6%) patients had normal results. Hydrocephalus was the most common complication.

Doer *et al*. In their study of 31 tuberculous meningitis patients aged between 3 months and 15 years, had at least one cranial imaging performed in all of the patients. They found abnormalities in 26 (87%) of the patients. They detected hydrocephalus in 17 (57%) patients, meningeal involvement in 12 (40%) patients, tuberculoma in 8 (27%) patients, cerebral infarction in 3 (10%) patients, and multiple abnormal findings in some patients. They found normal imaging in four patients. [22]

In tuberculous meningitis, cranial tomography is useful in monitoring the disease, early diagnosis and treatment of complications, and determining the prognosis as well as in the diagnosis 23. It has been shown that there is a relationship between the symptoms of the disease in terms of onset, prognosis, and sequelae. [20]

Tuberculous meningitis usually has an insidious and chronic onset, so diagnosis can be difficult, mostly in stage II. or III. diagnosis is made. When examining the period in which the 172 cases included in the study came; it is seen that 32 (18.6%) of the patients came to stage I, 82 (47.7%) to stage II, 58 (33.7%) to stage III. Girgis *et al*. reported that 4% of patients were in stage I, 34% were in stage II, and 62% were in stage III. [18]

Chest radiography findings were recorded in 92 of 172 patients included in the study. Pathological chest radiography findings were found in 56 (60.9%) of 92 patients. Of these, 27 (15.7%) parenchymal infiltration, 15 (8.7%) miliary appearance, 9 (5.2%) hilar LAP (3 (17%) unilateral, 6 There were bilateral (3.5%) bilateral LAP), 2 (12%) atelectasis, 1 (0.6%) pleural effusion, and 1 (0.6%) LAP + consolidation. Chest X-ray of 36 (39.1%) patients was normal. Girgis *et al*. showed that lung grammar was normal in 169 (40%) of 423 cases. In the same study, perihilar nodular infiltration in the lung grammar of 125 (29.5%) patients, lower lobe infiltration in 50 (11.8%), upper lobe infiltration in 40 (9.4%) and 9 (2%) patients. They determined that there is miliary involvement.18

It was determined that 51% of the patients resided in city centers and 49% resided in districts or villages. In their study, Yaramış *et al*. showed that 14% of the patients came from the city centers, 34% from the districts, and 52% from the villages.14 CSF of our cases was evaluated in terms of protein, glucose, and white blood cell. The presence of M Tuberculosis was demonstrated by PCR in the CSF of 3 patients. CSF glucose levels were below 10 mg/dL in 15 (8.7%) patients, between 11-40 mg/dL in 99 (57.6%), 41-80 mg/dL in 51 (29.7%) patients. 7 (4.1%) were found to be above 80 mg/dL. When the CSF protein of the patients was biochemically examined, it was between 0-50 mg/dL in 44 (32.9%) patients, between 51-100 mg/dL in 19 (14.1%) and 101-200 in 53 (39.6%) patients. It was found to be between mg/dl, 201-500 mg/dL in 13 (9.7%) and over 500 mg/dL in 5 (3.7%) patients.

Lymphocyte dominance was observed in 143 (83.1%) patients, while PNL dominance was observed in CSF in 29 (6.9%). The number of cells in CSF of these patients was between 0-10/mm3 in 7 (4%) patients, between 11-100/mm3 in 55 (32%) and 101-500/mm3 in 84 (48.8%) patients and 500/mm3 and above were found to in the 26 (15.2%) patients.

Girgis *et al*. investigated CSF glucose, protein amount, and leukocyte count in cases with tuberculous meningitis. In their study, they found the average CSF glucose 22 ± 15 mg/dL, CSF protein 220 ± 20 mg/dL, and CSF leukocyte count 437 ± 347/mm3. [18]

In their study, Yaramış *et al*. found CSF glucose

below 10 mg/dL in 12% of the cases, between 10-40 mg/dL in 71% and between 40-80 mg/dL in 17%. They found CSF protein below 100 mg/dL in 23% of the patients, between 100-200 mg/dL in 62% and over 200 mg/dL in 15%.14 In the same study, the CSF leukocyte count was below 500 /mm^3 in 85% of the cases and over 500/mm^3 in 15%. And they stated that 83% of the leukocytes seen in CSF are lymphocytes and 17% are fragmented. In the CSF examination, which is the most important laboratory test, it has been reported that the leukocyte count varies between 500/mm^3 (compartmental lymphocyte dominance in the early period, lymphocyte dominance in the early period), the glucose level is low in the early period or is always low in the normal late period, and the protein level is usually high. [24] The mean white blood cell count was found to be 13.325/mm^3. Girgis et al found the mean peripheral white blood cell count of cases with tuberculous meningitis to be 11.600/mm^3. When compared with the literature data, it was seen that the patients with tuberculous meningitis who had similar leukocyte counts presented with mild leukocytosis. [19] While other laboratory results (urea, creatine, and transaminase elevation) were found to be high in approximately 20% of patients by Girgis colleagues, they were found to be high only in 10 patients who were evaluated as toxicity by Yaramış et al. [14,18]

CONCLUSION

TBM should be detected in the early period and their contagious feature should be eliminated, and uninfected people should be vaccinated. People with a high risk of infection should be protected from the disease by giving preventive antituberculosis drugs, and society and families should be educated and sensitized about the disease.

Authors' Contribution

Study Conception: YDY,; Study Design: YDY,; Supervision: YDY,; Materials: YDY,; Data Collection and/or Processing: YDY,; Funding: EY,; Statistical Analysis and/or Data Interpretation: YDY,; Literature Review: YDY,; Manuscript Preparation: YDY and Critical Review: YDY.

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