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Investigation of psychopathology in patients with chronic idiopathic urticaria

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ABSTRACT

Aims: Aim of this study is, to establish the frequency of axis I and axis II comorbidity and post-traumatic stress disorder (PTSD) and coping ability of patients who admitted to allergy policlinics of dermatology and respiratory diseases departments and who were diagnosed as chronic idiopathic urticaria (CIU).

Methods: Study population divided into three groups consisted of fifty patients each, chronic urticaria, contact dermatitis and control groups, respectively. All patients underwent SCID-I (structured clinical interview for DSM-IV axis-I disorders) and SCID-II (structured clinical interview for DSM-III-R personamy disorders) for determining axis I and axis II diagnosis and trauma evaluation form for traumatic life events. Patients who showed high scores in this test also underwent SCID-I PTSD module. Coping scale (COPE) was applied in order to evaluate patients' coping ability for problems which he encounters.

Results: In our study, when axis I diagnosis were compared; major depression (48%) and anxiety disorder (48%) were significantly more frequent in CIU group than other two groups. When it came to comparison of axis II diagnosis, avoidant personal disorder (20%) and dependent personality disorder (16%) were significantly more frequent in CIU group than other two groups. Urticaria group also showed significantly higher frequency for PTSD (42%) than other two groups. Patients with CIU used religious (64%), denial (26%), substance abuse (40%), adoption (40%), emotional social support (32%) and abstaining (26%) maladaptive coping methods which were incoherent, significantly more than other two groups.

Conclusion: Probability of mental disorders is high among patients with CIU. It is important to consider existence of PTSD and coping methods for life events. Studies enrolling larger patient groups are needed for detailed investigation of cause-and-effect relationship.

Keywords: Chronic idiopathic urticaria, mental disease, comorbidity

INTRODUCTION

Chronic idiopathic urticaria (CIU) is a multifactorial disease that is closely related to emotional factors and causes skin itching, redness and blisters.[1] Association with psychological factors with chronic urticaria puts this disease in the group of psychosomatic diseases. In this group, psychological factors dominate both in the formation of the disease and in the occurrence of attacks.[2,3] The relationship between skin and mental state has been a known fact since the 12th century, although it has not been fully named. As mentioned among the public, "breaking out in hives due to boredom", "getting gray hair due to sadness", "getting acne due to boredom" show that people are aware of a relationship between mental states and some skin diseases, even though they do not know exactly what psychosomatization is or how it happens.[4] In recent years, scientific studies have mentioned approaches that concern more than one discipline, including spiritual, neurological, hormonal and immune system sciences, along with new explanations about the relationship between mental state and skin.[5]

After the 1960s, studies on the importance of psychological factors gained momentum, and it was shown that Axis I diagnoses such as anxiety and depression and personality structure affect the course of chronic urticaria.[1,6-9] Studies examining psychiatric comorbidities and personality traits in urticaria and other dermatological diseases are becoming widespread.[10-12] Patients with CIU transform their traumatic experiences into psychological symptoms, and this increases the likelihood of lesions occurring, although this cannot be clearly explained medically.[13-16] Although the rate at which patients with CIU encounter stressful life events is similar to that of other dermatological diseases, there are few publications in the literature examining the relationship between the disease and

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the ability of these patients to cope with stressful life events. It is very important to evaluate coping skills, as coping with a chronic disease alone will provide important information about the patient's coping strategies.[17]

Allergic contact dermatitis (CD) is a late type (type IV) allergic reaction that occurs in a person who has previously been in contact with an allergen, and 3700 chemicals have been identified that can cause allergic CD. Apparently, psychological factors have little role in the etiology of allergic CD.[18]

This study aimed to evaluate if;

- The prevalence of psychiatric comorbidity is higher in patients with CIU than in the healthy control group and the CD group.
- The prevalence of post-traumatic stress disorder (PTSD) in patients with CIU is higher than in the healthy control group and the CD group.
- The ability of patients with CIU to cope with stress is weaker than the healthy control group and the CD group.

METHODS

Ethics

This study is derived from doctorate thesis of Dr. Gözde Yontar. This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were expected to give signed informed consent. Cumhuriyet University Ethics Committee approval was received from the Scientific Researches Evaluation Board (Date: 26.04.2011, Decision No: 2011-04/18), the study conducted at Faculty of Medicine Psychiatry Polyclinic.

Patients

Patients over the age of 18 who applied to the Dermatology and Allergy Polyclinics of Cumhuriyet University Faculty of Medicine Hospital, were being followed up with a diagnosis of CIU, and agreed to participate in the study were included in the study. Informed written consent was obtained from 50 patients who agreed to participate in the study and met the study criteria before the psychiatric interview at the hospital.

Criteria for inclusion in the study:

- Participants must be over 18 years of age
- Chronic idiopathic urticaria must be diagnosed in accordance with the latest Guide (2010) issued by European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Disability Forum (EAAC1/GA2LEN/EDF)
- People who do not have malignancy, central nervous system (CNS) disease, cognitive impairment or mental retardation due to psychotic or cerebral disease
- People who were not receiving psychiatric treatment at the time of participating in the research
- People who volunteer to participate in the study

For the control group, people who were visiting the inpatient services at Cumhuriyet University Faculty of Medicine Hospital, who were over the age of 18, who were determined to have no disease through physical examination and routine examinations, who volunteered to participate in the study, and who had similar sociodemographic characteristics with the patient group were included.

Data Collection Tools

Sociodemographic Information Form: Three separate sociodemographic information forms were prepared by the researcher for CIU, CD and control groups. The information was obtained from the individuals themselves. People diagnosed with CIU should be informed about their age, gender, marital status, education level, occupation, total monthly income, family structure, how many years they have been diagnosed with CIU and the total number of attacks, whether there is a history of psychiatric diagnosis before, a history of psychiatric diagnosis in the family. Whether there was any exposure to trauma (physical, sexual abuse, accident, exposure to natural disaster, history of sudden death or fatal disease in a relative and witnessing these) were asked.

Structured clinical interview for DSM-IV axis I (SCID-I): SCID-I is a structured clinical interview scale applied by an interviewer to investigate diagnoses of Axis I disorders according to Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). It consists of six modules. DSM-IV investigates 38 of the Axis I disorders with diagnostic criteria and 10 without diagnostic criteria. The application takes approximately 25-60 minutes. It is almost always done with the patient alone. In practice, the application booklet containing the interview questions and the scoring sheet book on which the findings are recorded are used together. The diagnosis of the patient is investigated by considering 'currently' and 'lifelong'. Even if the questions provide help, they are not considered absolute truth. A 'yes' answer should be investigated to determine whether it exceeds the threshold. Additionally, desired questions can be asked. Whether the symptoms individually exceed the threshold severity and combine to meet a diagnosis is up to the interviewer's interpretation. The Turkish adaptation and reliability study of the scale developed by Özkürkçügil et al.[20] in 1997.[19] The inter-interviewer agreement rate for all diagnoses was found to be 98.1% and the Kappa coefficient was 0.86. Kappa coefficients for diagnostic categories range between 0.52–1.00 and all are statistically significant ($p<0.0001$). In this study, SCID-I was also used to make a diagnostic evaluation in terms of PTSD.

Structured clinical interview for DSM-III-R personality disorders (SCID-II): According to DSM-III-R classification, it is II. It is an individually applied clinical interview method developed by Spitzer et al.[19] to diagnose axis personality disorders. It evaluates individuals in terms of 12 personality disorders. These; avoidant personality disorder, dependent personality disorder, obsessive personality disorder, passive aggressive personality disorder, self-defeating personality disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, histrionic personality disorder, narcissistic personality disorder, borderline personality disorder, antisocial personality disorder. An adaptation and reliability study were conducted for Turkish population.[21]

Trauma Assessment Scale (TAS): It is a scale developed by DSM IV that evaluates the severity of PTSD symptoms determined according to DSM IV. Each item is a four-point scale ranging from zero (never or only once) to three (five times a week or more often).

Participants answer questions about a specific trauma experience. It determines the severity of trauma from none to severe. Its Turkish validity and reliability were determined by Işıklı.[22]

Coping Skills Assessment Scale (COPE): It is a self-report scale. The scale begins with an explanation paragraph as follows: "With the help of this scale, we aim to investigate how people react when they encounter difficult or distressing events or problems in their daily lives. There may be many ways that people cope with the problems they face. However, try to mark the options by thinking about what you do or how you behave in general when you encounter a problem. "When choosing the options, be careful to think independently of the previous ones." Sixty different situations are answered using four options. These answers:

1=I would never do such a thing; 2=I rarely do this; 3=I do this moderately; 4=I mostly do this. The scale consists of 60 questions and 15 subscales. Each subscale consists of four questions. Each of these subscales provides information about a separate coping attitude. As a result, high scores from the subscales provide the possibility of commenting on which coping attitude is used more by the person. These 15 coping attitudes or subscales are: 1. Positive reinterpretation and development, 2. Mental disengagement, 3. Focusing on the problem and revealing emotions, 4. Use of helpful social support, 5. Active coping, 6. Denial, 7. Religious coping, 8. Joking, 9. Behavioral letting go, 10- Withholding, 11. Using emotional social support, 12. Substance use, 13. Acceptance, 14. Suppressing other preoccupations, 15- Making plans.[23]

Application of Tests

For the CIU group, 50 patients who were diagnosed with CIU in the chest diseases, allergy and dermatology outpatient clinics and who met the inclusion criteria for the study were evaluated. For the patient group with CD, 50 patients who were diagnosed with CD by applying a patch test in the dermatology outpatient clinic and who met the inclusion criteria for the study were evaluated. For the control group, 50 people who were visiting the inpatient services at Cumhuriyet University Faculty of Medicine Hospital, who were determined by medical examinations to have no disease, who met the inclusion criteria for the study, and who had similar sociodemographic characteristics with the patient group, were evaluated. Written informed consent was obtained from all participants. In the first stage of the study, sociodemographic information obtained from the participants was recorded in the form prepared by the researcher. SCID-I/SCID-II was applied to detect accompanying axis I and axis two diagnoses. In the second stage, after determining the type and severity of the traumatic experience of the patients using the Post-Traumatic Stress Diagnostic Scale, the researcher applied the PTSD module in the SCID-I to those who scored high. In the final stage, COPE was administered to patients who underwent SCID-I and SCID-II. The interviews lasted an average of 1-1.5 hours.

Statistical Analysis

Parametric variables are expressed as mean ± standard deviation, and categorical variables are expressed as percentages and numbers. Parametric variables were evaluated with t-test in independent groups, and categorical variables were evaluated with Pearson chi-square test and Fisher's Exact test. A p value of 0.05 was accepted as the limit of statistical significance and all statistical operations were performed in the Statistical Package for Social Sciences (SPSS) 13.0 program.

The power analysis was conducted using the R 3.0.1. open-source program, with a confidence level of 95% (1-α), a test power of 95% (1-β), and an effect size (f) of 0.342, the minimum number of patients to be included in the study is determined to be 48 in each group, totaling 144 patients.

Data Availability Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

RESULTS

Sociodemographic Data

Fifty CIU patients, 50 CD patients and 50 people as a control group were included in the study. Of the CIU patients, 24 were women (48.0%) and 26 were men (52.0%), and the average age was 41.22 ± 13.92 years. In the control group, 24 patients were female (48.0%) and 26 were male (52%), and their average age was 43.64 ± 12.36 years. In the group with CD, 25 were women (50%) and 25 were men (50%). There was no statistically significant difference between the groups in terms of mean age and gender distribution (Table 1).

Table 1. Comparison of three groups in terms of average age and gender distribution

		Gender				f=0.75, x2=0.05, p=0.974
		Female		Male		
Groups	Age (years)	n	%	n	%	
Chronic urticaria	41.22±13.92	24	48	26	52	
Contact dermatitis	43.64±12.36	24	48	26	52	
Control group	44.20±12.34	25	50	25	50	

When groups were compared in terms of their marital status, occupational distribution, education level, socioeconomic level and social security, presence of physical illness in their medical history, psychiatric disorder in their medical history, and psychiatric disorder in their family history, the statistical difference was found to be insignificant. When the groups were compared in terms of where they lived, the difference was found to be statistically significant. It was observed that more patients with CIU lived in cities (Table 2).

Axis and II. axis diagnostics: SCID-I and SCID-II were applied to CIU, CD and control groups to determine the first axis and second axis diagnoses. Chronic idiopathic urticaria, CD and the control group were compared in terms of axis one diagnoses (Table 3). Of the group diagnosed with CIU, 24 (48%) were diagnosed with major depression, and when the three groups were compared in terms of major depression, a significant difference in favor of CIU. Of the group diagnosed with CIU, 24 (48%) were diagnosed with anxiety disorder, and when the three groups were compared in terms of anxiety disorder, significant difference in favor of CIU was found. In the group with CIU, 18 (36%) had any two of the axis I diagnoses. Of the patients with anxiety disorders, 18 (75%) had panic disorder, 2 (8.3%) had obsessive compulsive disorder, 3 (12.5%) had social phobia, and 1 (4.1%) had specific phobia. There was 1 person (5.5%) diagnosed with major depression and obsessive-compulsive disorder, 1 person (5.5%) with obsessive-compulsive disorder and social phobia, and 1 person (5.5%) with major depression and social phobia. It was found that 18 people (36%) had only one of the first axis diagnoses. Of these 18 people, 7 (38.8%) had only major depression, 9 people (50%) had only panic disorder, 1 person had only social phobia (5.5%) and 1 person had only specific phobia (5.5%).

Table 2. Comparison of sociodemographic characteristics of groups

Parameter		Groups							
		Chronic urticaria		Contact dermatitis		Control group		Total	
		n	%	n	%	n	%	n	%
Marital status	Single	8	16	9	18	9	18	26	17.3
	Married	40	80	40	80	39	78	119	79.3
	Divorced	2	4	1	2	2	4	5	3.3
	Total	50	100	50	100	50	100	150	100
	x^2=0.49, p=0.974, p>0.05								
Occupation	Unemployed	3	6	4	8	1	2	8	5.3
	Student	4	8	3	6	3	6	10	6.7
	Official	6	12	13	26	6	12	25	16.7
	Worker	1	2	1	2	6	12	8	5.3
	Self-employment	5	10	4	8	7	14	16	10.7
	Retired	10	20	7	14	5	10	22	14.7
	House-wife	21	42	18	36	22	44	61	40.7
	Total	50	100	50	100	50	100	150	100
	x^2=15.14, p=0.974, p>0.05								
Educational degree	Illiterate	1	2	4	8	3	6	8	5.3
	Elementary	18	36	12	24	17	34	47	31.3
	Juniorhigh	15	30	10	20	4	8	29	19.3
	Highschool	10	20	14	28	14	28	38	25.3
	University	6	12	10	20	12	24	28	18.7
	Total	50	100	50	100	50	100	150	100
	x^2=12.18, p=0.143, p>0.05								
Settlement	Village	0	0	3	6	3	6	6	4
	Town	4	8	6	12	13	26	23	15.3
	City	46	92	41	82	34	68	121	80.7
	Total	50	100	50	100	50	100	150	100
	x^2=10.62, p=0.031, p<0.05								
Socioeconomial status	Low income	1	2	2	4	4	8	7	4.7
	Average	46	92	43	86	40	80	129	86
	High income	3	6	5	10	6	12	14	9.3
	Total	50	100	50	100	50	100	150	100
	x^2=3.41, p=0.490, p>0.05								
Social security insurance	None	1	2	1	2	2	4	4	2.7
	Present	49	98	49	98	48	96	146	97.3
	Total	50	100	50	100	50	100	150	100
	x^2=0.51, p=0.490, p>0.05								
History of organic disease	Negative	33	66	35	70	42	84	110	73.3
	Positive	17	34	15	30	8	16	40	26.7
	Total	50	100	50	100	50	100	150	100
	x^2=4.56, p=0.110, p>0.05								
History of psychiatric disease	Negative	47	94	47	94	48	96	142	94.7
	Positive	3	6	3	6	2	4	8	5.3
	Total	50	100	50	100	50	100	150	100
	x^2=0.26, p=0.876, p>0.05								
Family history of psychiatric disease	Negative	45	90	47	94	43	86	135	90
	Positive	5	10	3	6	7	14	15	10
	Total	50	100	50	100	50	100	150	100
	x^2=1.77, p=0.411, p>0.05								

Chronic idiopathic urticaria, CD and the control group were compared in terms of second axis diagnoses. In CIU group, 10 people (20%) were diagnosed with avoidant personality disorder and when the three groups were compared in terms of avoidant personality disorder, the statistical difference in favor of CIU was found to be significant. In addition, 8

Table 3. Comparison of three groups according to I. and II. axis diagnoses

Diagnoses	Chronic urticaria		Contact dermatitis		Control group		X^2	p
	n	%	n	%	n	%		
Axis I diagnoses								
Major depression	24	48	8	16	11	22	14.14	<0.001
Anxiety disorder	24	48	4	8	4	8	31.78	<0.001
Axis II diagnoses								
Obsessive-compulsive personality disorder	5	10	2	4	1	2	3.433	0.180
Avoidant personality disorder	10	20	1	2	2	4	12.296	0.002
Dependent personality disorder	8	16	1	2	2	4	8.437	0.015
Antisocial personality disorder	3	6	2	4	1	2	1.042	0.594

people (16%) were diagnosed with dependent personality disorder, and when the three groups were compared in terms of dependent personality disorder, the statistical difference was in favor of CIU (Table 3). In CIU group, no second axis diagnosis was found in 32 people (64%), only 10 people (20%) had a second axis diagnosis, and 5 people (50%) had obsessive compulsive personality disorder and 2 people (20%) had avoidant personality. disorder, and 3 people (30%) were found to have antisocial personality disorder. Lastly, 8 people (15%) had any two of the second axis diagnoses. It was determined that all of these patients had avoidant personality disorder and dependent personality disorder.

PTSD comorbidity: SCID-I was applied to CIU, CD and control groups to determine the diagnosis of PTSD. 21 (42%) of CIU group were diagnosed with PTSD. When they were compared in terms of PTSD diagnosis, the statistical difference was found to be significant in favor of the group with CIU (Table 4). When the coexistence of major depression and PTSD was investigated, it was found that 12 of 24 patients (50%) with major depression in the group with CIU were diagnosed with PTSD. When the coexistence of another anxiety disorder and PTSD was investigated, 9 of 24 anxiety disorder patients (37.5%) in the urticaria group were also diagnosed with PTSD.

Table 4. Comparison of three groups according to post-traumatic stress disorder

Group		Post-traumatic stress disorder		Total
		Negative	Positive	
Chronic urticaria	n	29	21	50
	%	58.0	42.0	100.0
Contact dermatitis	n	46	4	50
	%	92.0	8.0	100.0
Control group	n	46	4	50
	%	92.0	8.0	100.0
Total	n	121	29	150
	%	80.7	19.3	100.0

x^2=24.70, p<0.001

Coping skills: The COPE test was applied to evaluate the coping skills of the three groups. The distribution of the 15 coping skills included in this test was compared between individual groups (Table 5). More in the CIU group compared to the other two groups; 6 people (12%) who cope actively, 4 people (8%) who focus on the problem and reveal their emotions, 4 people (8%) who use useful social support, 4 people (8%) who cope with the problem by making plans, 4 people (8%) who cope with the problem by making a religious coping It was determined that there were 32 people (64%) who used it as a drug abuse method, 13 people (26%) who denied it, 14 people (28%) who used substances and 20 people (40%) who accepted it. It was determined that there were 16 people (32%) who used emotional social support and 13 people (26%) who tried to cope by holding back against the problem. The statistical difference was insignificant compared to the other groups, but both coping strategies were seen more frequently in the group with CIU. There were 5 (10%) people in the CIU group who coped with the problem by reinterpreting it positively, and although the difference was statistically insignificant, it was found to be less common than the other two groups. There were eight people (16%) each who used mental and behavioral letting go methods, and there were three people (6%) who joked, but when the three groups were compared, the statistical difference was found to be insignificant.

Table 5. Comparison of three groups according to coping skills

Coping skill type	Chronic urticaria		Contact dermatitis		Control group		x^2	p
	S	%	S	%	S	%		
Active coping	6	12	23	46	23	46	17.013	<0.001
Religion	32	62	19	38	19	38	9.054	0.011
Denial	13	26	4	8	6	12	6.881	0.032
Acceptance	20	40	7	14	10	20	9.974	0.007
Emotional social support	16	32	7	14	9	18	5.323	0.070
Planning	4	8	12	24	19	38	12.596	0.002
Holding back	13	26	7	14	10	20	2.25	0.325
Drug abuse	14	28	8	16	4	8	7.072	0.029
Use of helpful social support	4	8	24	48	21	42	21.156	<0.001
Joking	3	6	1	2	3	6	1.199	0.549
Mental letting go	8	16	6	12	8	16	0.426	0.808
Positive reinterpretting	5	10	11	22	13	26	4.446	0.108
Behavioral letting go	8	16	7	14	9	18	0.298	0.862
Focusing on problem	4	8	13	26	7	14	6.174	0.046

p<0.05 is considered significant

Among the patients diagnosed with major depression in the group with CIU, 17 (70.8%) people used religion as a coping method, 11 (45.8%) people accepted it, 9 (37.5%) people denied it, and 7 (33.3%) people used the withdrawal method. It was determined that there were 4 (16.7%) people who used substances, 6 (25%) people who were mentally indifferent, and 5 (20.8%) who were behaviorally indifferent. There were

no patients in the group diagnosed with major depression who used methods such as planning, active coping, positive reinterpretation and focusing on the problem.

Among patients diagnosed with anxiety disorder in the group with CIU, 16 (66.7%) used religion as a coping method, 6 (25%) denied it, 10 (41.7%) accepted it, and 7 (29.2%) used the withdrawal method, 9 (37.5%) people used substance abuse, 4 (16.7%) people used the mental letting go method, and 3 (12.5%) people used the behavioral letting go method. There was only one person (4.2%) who coped actively, and one person each who reinterpreted it positively, focused on the problem and found a solution, and made a plan. There were no patients in this group who used helpful social support.

DISCUSSION

In this study, it was planned to investigate whether there are differences in the SCID-I and SCID-II diagnoses, the presence of PTSD, and the patients' ability to cope with the problem in patients with CIU, by comparing them with the CD group and the control group. The probability of major depression and panic disorder in the group with CIU was statistically significantly higher than the other groups. The likelihood of avoidant personality disorder and dependent personality disorder in the group with CIU was statistically significantly higher than the other groups. The diagnosis of PTSD was statistically significantly higher in the group with CIU. The patients in the group with CIU used adaptive coping skills such as active coping, focusing on the problem and revealing emotions, use of useful social support, and planning, significantly less than the other two groups. Compared to the other two groups, the group with CIU used non-adaptive coping strategies such as acceptance, religious coping, substance use (smoking), denial, and holding back in the face of the problem. It was determined that the patients diagnosed with major depression and panic disorder in the group with CIU used adaptive methods such as active coping, focusing on the problem, positive reinterpretation, and planning significantly less than the other two groups.

Although it has been known since the 1930s that many factors such as personality traits, unconscious conflicts and psychosocial stress play a significant role in the development of urticaria, psychiatric evaluation is still performed in very few of these patients in dermatology and allergy outpatient clinics.[6] Recently, in addition to psychiatric comorbidities, the diagnosis of PTSD in patients with CIU has also been emphasized. The diagnosis of PTSD is often overlooked due to inappropriate screening during psychiatric evaluation and the reluctance of the traumatized individual to seek treatment.[24] Two publications examining this relationship have been found in the literature, and it is noteworthy that only one of them is a research article, other than a case report.[25,26]

In the study, no difference was observed between the groups in terms of sociodemographic characteristics, but when the groups were compared according to where they lived, it was noteworthy that more individuals with CIU lived in cities. The most likely explanation for this situation is that the number of patients was low due to difficulties in providing transportation from the city center, districts and villages during the winter months when individuals with chronic urticaria were included in the study.

In the study of Özkan et al.[27] in 2007, 60% of CIU patients received a psychiatric diagnosis. 40% of these are depression, 12% are anxiety disorder, 2% are bipolar disorder, and the remaining 17% are a previous psychiatric illness. In Staubach et al.'s[28] study, 25 out of 100 chronic urticaria patients were diagnosed with anxiety and 11 with depression. According to a study published in 1996, at least one third of urticaria patients have depressive symptoms.[9] In a review, it was found that somatization, anxiety and psychotic disorder were significantly higher in patients with urticaria.[12] Chronic skin conditions, which are often overlooked because they are not life-threatening, can actually cause very significant psychosocial disorders. Skin diseases, along with psychiatric symptoms, also cause significant deterioration in the quality of life. Itching in chronic urticaria negatively affects patients.[30] As a result, the most common psychopathologies we encountered in the psychiatric examination results of chronic urticaria patients in our study were anxiety disorder and depression. However, it is not surprising to see psychiatric symptoms or comorbidities in patients with chronic urticaria, which has a chronic course and can seriously impair the patient's quality of life.

The answer to the question of whether psychiatric comorbidity develops due to chronic urticaria or creates a predisposition for chronic urticaria has not been fully clarified.[31] In our study, avoidant and dependent personality disorders were detected at a higher rate in patients with CIU than in the control group and the group of CD patients. In a study, a higher rate of obsessive-compulsive personality disorder and avoidant-dependent personality disorders were found in the CIU group compared to the control group. In the same study, no significant difference was found in schizotypal, schizoid, borderline and antisocial personality disorders compared to the control group.[32] In a study which authors compared personality disorders in patients with CIU, avoidant personality disorder was detected at a significantly higher rate in cases in which an urticaria attack occurred following a certain event that caused extreme stress and anxiety.[33] In their study using the well-standardized Minnesota multiphasic personality inventory (MMPI) test, researchers divided patients with urticaria into two main categories: the group with more passive-dependent personality disorders and the group with aggressive features.[8] In our study, avoidant and dependent personality disorders were found more frequently in the group with CIU than others, which complies with literature.[29,34] The concerns of people with avoidant and dependent personality disorders about not being accepted, being criticized, and being excluded create extreme stress and anxiety in individuals. Since these people's low self-esteem and hypersensitivity to exclusion restrict their interpersonal relationships, they live away from society and stay away from social support. As a result of personality characteristics, the inability of patients to cope with a chronic illness and the negative social consequences of the disease and the scarcity of support resources may be the reasons why we detected avoidant and dependent personality disorders in CIU group at a higher rate than others.

Current and lifetime PTSD diagnosis was detected in 21 (42%) people in the group with CIU, and this rate was found to be significantly higher. However, 50% of patients with CIU and major depression are also diagnosed with PTSD. Additionally, concurrent PTSD was detected in nine (37.5%) of the patients with CIU and anxiety disorder. There are very few publications in the literature investigating the relationship between PTSD

and CIU. In one of these, the group with CIU was compared with the control group, and the PTSD rate was found to be significantly higher. In addition, significant impairment in social functioning, somatic complaints, and an increase in anxiety and depression scores were detected in these patients. The study emphasized that a more detailed investigation of the cyclical disorders in the neurology, immune system and endocrine system seen in PTSD will help us understand the formation of urticaria. It was argued that neuroticism is effective in the development of psychiatric comorbidity. It has been emphasized that the addition of major depression or anxiety disorders to the coexistence of PTSD and chronic urticaria can be explained by the negative effect of neuroticism. It has been mentioned that the development of urticaria in patients with PTSD is closely related to personality traits.[25]

In 2012, Gupta et al.[26] published five case examples evaluating the coexistence of CIU and PTSD. It is interesting that in each of these cases, the urticarial attacks occurred after life events that reminded the patients of their previous trauma. Although resistance to treatment developed, after the diagnosis of PTSD was made, pharmacotherapy was applied to the patients along with trauma-oriented psychotherapy, and they reported that they did not observe any urticaria attacks at the end of a one-year follow-up.

In PTSD, psychogenic exacerbation and increased activity of the sympathetic nervous system may trigger urticaria and angioedema. Overstimulation of the central nervous system can manifest itself as "common urticaria" that occurs during sleep. Patients describe waking up with nightmares and intense anxiety, and consult a doctor with the presence of itching and urticaria. Sometimes they talk about complaints that specifically symbolize their traumatic experiences, such as constant itching of the stab wound.[35,36] Traumatic experience and subsequent PTSD are the main source of stress for the patient. It is also known that the frequency and severity of attacks of previously diagnosed urticaria patients increase with stressful life events. Considering that PTSD may significantly affect individuals' ability to cope with stressful life events, it is not surprising that the association of urticaria and PTSD was found to be statistically significantly higher in our study than in the other two groups.

Information about the mechanism underlying the relationship between urticaria and PTSD is based on experimental observations. It is thought that the intense stress that comes with PTSD causes allergic and inflammatory skin diseases by triggering or increasing the local neuro-immuno-endocrine response in the skin.[37,38] According to this theory, if stress management can be achieved, the biological response in the skin can also be controlled. In order to control stress, individuals have been tried to reduce the inflammatory response by teaching techniques such as relaxation exercises, hypnosis and individual stress management.[39]

In the case report of a couple who developed chronic urticaria, life events that caused stress in the couple who developed chronic urticaria and ways of coping were discussed. They emphasized that, as a result of stressful living conditions, both of them had psychological strains that led to a psychiatric diagnosis as dysthymic disorder, as well as the discharge of emotions through the skin in the form of chronic urticaria. They emphasized that various problems may arise in both individuals as a result of interaction between spouses, and that the loss of boundaries within the family and the perception of themselves as extensions of each other may lead to the development of urticaria symptoms in both individuals. They mentioned that spouses can be influenced by each other and develop common coping methods or reactions such as urticaria, and that they can gradually become similar to each other in various ways in order to create harmony in their marriage, and in this way, they try to create an equal and therefore safe environment.[40]

In our study, the distribution of 15 coping skills in the coping skills scale was compared between individual groups. It was observed that the patients in the group with CIU used adaptive coping skills such as active coping with the problem, focusing on the problem and revealing emotions, use of useful social support and planning, significantly less than the other two groups. It was revealed that in the patient group with CIU, people used non-adaptive coping methods such as acceptance, religious coping, substance use (smoking), denial, and holding back in the face of the problem. It was also observed that these people had a clear tendency to use emotional and social support, but they were far from coping with the problem by reinterpreting it positively. It is noteworthy that the patients we found to be diagnosed with major depression and panic disorder in the group with CIU seek emotion-focused solutions rather than adaptive methods such as active coping, focusing on the problem, positive reinterpretation, and planning.

There are only a few publications which investigate the stress coping skills of patients with CIU. One of these is the research conducted by Chung et al.[41] in 2010. In this study, in which other allergenic diseases were taken as the control group, it was revealed that the group with CIU used emotion-oriented coping skills, not adaptation-oriented, in the face of stress. It has been observed that people's use of emotion-focused strategies triggers the emergence of psychological symptoms and causes more serious urticaria attacks. It has been emphasized that patients should reduce subjective evaluation of their situation and emotion-oriented approach in order to ensure their physical and spiritual well-being.

Coping attitudes have an important role in adapting to challenging situations. "coping" is defined as all of the cognitive, emotional and behavioral reactions of the individual to resist and resist events or factors that create stress for him/her. Therefore, there is a close relationship between coping attitudes and the degree of challenging experiences. For example; effective coping attitudes protect the person against cognitive, environmental and biological factors that cause anxiety. Coping attitudes can vary depending on a wide variety of factors such as age, gender, culture and disease, and are specific to the individual.[23] While problem-solving-oriented coping attitudes reduce psychological distress, emotionally focused approaches can increase it. However, whether coping attitudes are adaptive or not varies depending on the nature of the stressor.[23] Although emotionally focused attitudes are beneficial in responding to some stressors, they are usually accompanied by severe psychopathology and impairment in functionality.[42,43] Studies indicate that there is a relationship between emotionally focused coping attitudes and anxiety and depression levels.[43-45] The use of emotionally focused coping attitudes also poses a risk for the development of mood disorders.[46] Perceiving life events as negative creates a deficiency in coping skills. As a result, passive coping skills gain dominance while active skills are used to a lesser extent.[44] It has been stated that negative cognitive evaluations facilitate

the development of mental disorders. It can be said that differences in interpreting stressors will create a tendency to develop different coping skills. This also means that there is an individual sensitivity factor for that individual.[45]

Presence and level of social support systems is vital in coping. Social support is one of the important variables in the continuity of healthy behaviors. Low social support has been associated with lower levels of health. Quality of life is equally effective.[46] In a study where stress and CIU were evaluated together, it was found that the social support resources of these people were significantly lower than the control group.[47] The lack of social support resources may negatively affect the way these patients cope. When coping with a chronic illness is considered a major source of stress, patients' ability to cope with stressful life events may be negatively affected. It has been previously discussed that using non-adaptive coping methods poses a risk factor for psychiatric disorders. So, it can be concluded that emotion-focused coping methods in CIU patients increase the comorbidity of psychiatric disorders in the disease. The use of non-adaptive coping methods in patients with CIU may negatively affect patients' ability to cope with a disease such as PTSD, which seriously affects the quality of life and causes mental and physical symptoms, and the social consequences of the traumatic experience. As a result, it can be concluded that there is a risk that the number of attacks will increase and become more severe in PTSD patients with urticaria. It is clear that when CIU itself, stress factors, non-adaptive coping methods and the presence of psychiatric comorbidity come together, the quality of life of patients can be seriously affected. Impairment in quality of life may negatively affect patients' functionality. Since the negative impact on functionality is also a source of stress, a vicious cycle may occur, especially in patients who are resistant to treatment.

Psychiatric disorders, psychosocial stress factors, difficult life events, and traumatic experiences of urticaria patients presenting to dermatology and allergy clinics should be carefully considered. Considering that fighting a chronic disease may negatively affect patients' evaluation and insight of their situation, detailed information should be given about the disease and its negative consequences.

Limitations

Due to the use of a cross-sectional examination method in this study, a cause-effect relationship between CIU and PTSD could not be established. In order to elucidate the possible relationship between them, studies with larger sample sizes and long-term follow-up are needed. The fact that the rates of obsessive-compulsive disorder and obsessive-compulsive personality disorder were not significant in the CIU group and that the results were not compatible with the literature may be due to the insufficient number of patients for comparison. In addition, when comparing the coping skills of the patients, the fact that the personality characteristics and important life events of the CIU group were not examined in detail can be considered a limitation.

CONCLUSION

We suggest that treatment strategy should focus on detailed trauma history of patient and also support adaptive coping skills to overcome problems in cases resistant to medical treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Cumhuriyet University Ethics Committee (Date: 26.04.2011, Decision No: 2011-04/18).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Endovascular treatment for carotid stenosis developing after neck radiotherapy

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ABSTRACT

Aims: One of the causes of carotid stenosis is radiation therapy to the neck area. Cervical irradiation is frequently used in the treatment of head and neck cancers. However; the ionizing effect of radiation causes arteritis, which can lead to acceleration of fibrosis or atherosclerosis, thrombosis, stenosis, or occlusion. Carotid stenosis due to radiation is relatively rare. Accordingly, in this study, our aim was to assess the feasibility, safety and preliminary efficacy of endovascular therapy for carotid stenosis developing after neck radiotherapy.

Methods: This study was a retrospective review of a prospectively maintained database of a consecutive unselected group of symptomatic and asymptomatic patients with carotid artery stenosis developing after neck radiotherapy. Data was collected from 2017 to 2023. A total of 17 patients who developed carotid stenosis due to neck radiotherapy were included in the study. Neck irradiation was applied in 76.5% of cases due to laryngeal cancer. All statistical analysis was performed using R version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Univariate analysis was performed using c2 and Wilcoxon tests. Cumulative survival estimates were assessed using the life-table method.

Results: One patient had a technical failure due to a difficult aortic arch. Because of the degree of stenosis (40≤) was not serious in conventional angiography of 2 patients, medical follow-up was decided. 3 patients were admitted to the emergency department due to acute ischemic stroke. Endarterectomy was performed in 4 patients due to the complex structure of the aortic arch and carotid arteries for carotid artery stending. The number of patients with stenosis in the right carotid was 10, while the number of patients with stenosis in the left carotid was 7. No restenosis was observed in patients with stent placement in follow-up carotid Doppler and CT angiography performed 3 months later. Additionally, no new neurodeficit was observed in the neurological examinations 3 months later.

Conclusion: This retrospective study demonstrates that endovascular treatment for carotid stenosis developing after neck radiotherapy is safe, effective and reliable.

Keywords: Carotid stenosis, neck radiotherapy, endovascular treatment, carotid stending, stroke

INTRODUCTION

Carotid artery stenosis is one of the important causes of ischemic stroke. One of the causes of carotid stenosis is radiation therapy to the neck area. Cervical irradiation is frequently used in the treatment of head and neck cancers. However; the ionizing effect of radiation causes arteritis, which can lead to acceleration of fibrosis or atherosclerosis, thrombosis, stenosis, or occlusion (Figure 1). It also causes fibrosis in soft tissue and skin (Figure 2).[1-3]

Radiation-induced carotid artery stenosis is a major high-risk entity for carotid endarterectomy. Open surgical therapy for patients with radiation-induced lesions has been associated with higher rates of stroke, cranial nerve damage, and problems with wound healing such as necrosis, infection, and skin breakdown. Therefore, endovascular treatment is more advantageous than open surgery.[4,5] However, high rates of restenosis and reintervention have been reported in patients with radiation-induced carotid stenosis.[6,7] Carotid stenosis due to radiation is relatively rare. Accordingly, in this study, our aim was to assess the feasibility, safety and preliminary efficacy of endovascular therapy for carotid stenosis developing after neck radiotherapy.

METHODS

Study Design

This study was a retrospective review of a prospectively maintained database of a consecutive unselected group of symptomatic and asymptomatic patients with carotid artery stenosis developing after neck radiotherapy. Data was collected

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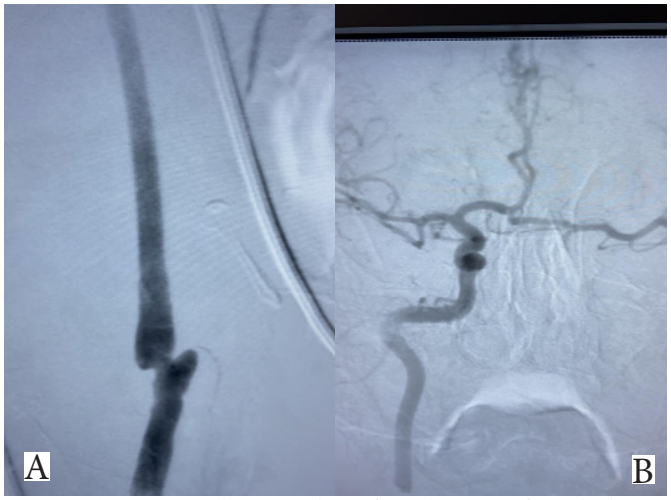

Figure 1. a) Conventional angiography performed 13 years after radiotherapy shows a decrease in carotid artery calibration and stenosis. b) Because of the same patient's left carotid is occluded, the entire anterior system filling with right carotid contrast material injection

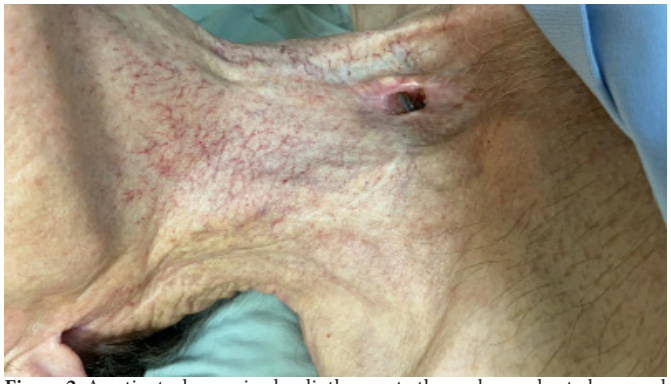

Figure 2. A patient who received radiotherapy to the neck area due to laryngeal cancer. Atrophy, scar tissue on the skin and tracheostomy are observed in the neck area

from 2017 to 2023. This study was approved by the Selçuk University Ethics Committee with a waiver of informed consent (Date: 13.12.2023, Decision No: 2024/30). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

A total of 17 patients who developed carotid stenosis due to neck radiotherapy were included in the study. Neck irradiation was applied in 76.5% of cases due to laryngeal cancer. The number of patients who received radiotherapy due to hematological and other cancers such as parotid, thyroid of the neck area was 23.5%. Consecutive patients with carotid stenosis developing after neck radiotherapy based on computed tomography angiography, magnetic resonance imaging angiography or carotid artery doppler ultrasound were included in this study. The degree of carotid artery stenosis was assessed on conventional angiography according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. The choice of CAS was made based on the individual judgment of the treating practitioner, based on clinical experience and the learning curve, as well as the patient's anatomical considerations regarding the feasibility of carotid artery stending (CAS). During the study period, 11 patients with carotid artery stenosis after neck irradiation were selected for carotid artery stending. We applied medical treatment to 2 patients while 4 patients were give to open surgery. The choice of carotid artery stending was made based on the individual judgment of the treating practitioner, based on clinical experience and the learning curve, as well as the patient's anatomical considerations regarding the feasibility of carotid artery stending and the contraindication to carotid open surgery. Modified Rankin Score (mRS) of the patients was checked at admission and at the 3-month follow-up.

Mean age was 60.7± (SD) 15.8 (range, 37-84 years), and 82.4% were men. Demographic and clinical characteristics are listed in Table 1. We did not apply general anesthesia to any patient during the procedure.

Table 1. Demographic and clinical characteristics in patients with carotid stenosis developing after neck radiotherapy

Characteristic	Value n (%)
Age, mean±SD years (range)	60.7±(SD)15.8 (range, 37-84)
Sex, number (%)	
Male	14 (82.4)
Female	3 (17.6)
Risk factors, number (%)	
Hypertension	8 (47.1)
Diabetes	4 (24.5)
Smoking	14 (82.4)
Hypercholesterolemia	3 (17.6)
Coronary disease	6 (35.3)
Patients with laryngeal cancer	13 (76.5)

SD: Standard deviation

Technique and the Device Description

All of the endovascular interventions were performed with a 6-8F sheath (short or long) via femoral, radial or brachial artery puncture. The guiding catheters (7F or 8F) were used more often than long sheaths. One or more treatment strategies were applied for the carotid stenosis (carotid stenting and/or balloon angioplasty). Protégé RX Self-expanding, Balton® Carotid self-expanding stent with delivery system RX, MER device were used for carotid stenosis. Stent models, diameters and lengths vary significantly depending on the characteristics of the carotid lesion and the operator's preferences. Digital subtraction angiography was performed to evaluate carotid stenosis. Carotid angiographic images were obtained from anterior to posterior angles, and multiple images were taken. It was also focused to improve stenosis image quality.

Statistical Analysis

All statistical analysis was performed using R version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Univariate analysis was performed using c2 and Wilcoxon tests. Cumulative survival estimates were assessed using the life-table method.

RESULTS

The smoking rate of these patients was 82.4%. Hypertension was the second most common condition with 42.1% (Table 1).

One patient had a technical failure due to a difficult aortic arch. Because of the degree of stenosis (40≤) was not serious in conventional angiography of 2 patients, medical follow-up was decided. 3 patients were admitted to the emergency department due to acute ischemic stroke. Endarterectomy was performed in 4 patients due to the complex structure of the

aortic arch and carotid arteries for carotid artery stending. We performed all angiography procedures under local anesthesia, including patients taken from the emergency department. We did not use a cerebral protection device in any of the patients in whom we performed carotid stenting. None of the patients had stent thrombosis during the procedure. Additionally, no patient developed dissection or major stroke.

The number of patients with stenosis in the right carotid was 10, while the number of patients with stenosis in the left carotid was 7. No restenosis was observed in patients with stent placement in follow-up carotid Doppler and CT angiography performed 3 months later. Additionally, no new neurodeficit was observed in the neurological examinations 3 months later. There were 3 patients taken from the emergency department to the angiography suite due to stroke. Before the procedure, mRS was between 1-3. At their 3-month follow-up, the neurological examination of 2 patients was normal. The mRS of 1 patient decreased from 3 to 1 (Table 2). Medical follow-up decision was made for 2 patients. The neurological examination of these patients 3 months later was normal. Additionally, there was no increase in the degree of stenosis in control imaging.

Table 2. The endovascular procedures and clinical characteristics in patients with carotid stenosis developing after neck radiotherapy

Treatment selection	**Value n (%)**
Medical	2 (11.8)
Stending	11 (64.7)
Open surgery	4 (23.5)
Mortality	none (0)
Use of cerebral protection device	none (0)
Anesthesia in angiography	
Local	17 (100)
General	none (0)
Side	
Right	10 (58.8)
Left	7 (41.2)
Symptomatic stenosis, mRS score, mean±SD (range)	5 (29)
mRS before treatment	0.4±0.94 (0-3)
mRS after treatment	0.06±0.25 (0-1)

mRS: Modified rankin score, SD: Standard deviation

DISCUSSION

No patient died after 3 month. Also no patient developed a major or minor stroke. This study showed that the result of endovascular treatment for carotid artery stenosis after neck irradiation can be considered satisfactory. The Stent-Protected Percutaneous Angioplasty and Carotid Endarterectomy and EVA-3S studies showed stroke and death rates of 7.7% and 9.6%, respectively.[8] Our results were better compared to this large-scale study. However, it should be emphasized that all patients in this study presented with symptomatic tight atherosclerotic stenosis, which is associated with a higher risk of embolism during endovascular treatment. In our study, only 29% of the patients were symptomatic and the stenoses were non-atherosclerotic lesions. In another multicenter study, the combined stroke and death rates were 1.5% after 1 month.[5] The results in this study were much better, similar to ours.

We could not place the stent in only one patient. The technical success rate of endovascular treatment in our study was good according to intention-to-treat analysis. Other studies had a similarly high success rate.[5,8] Endovascular treatment may sometimes not be perform due to vascular access problems, extensive aortoiliac occlusive disease or the complex anatomy of the aortic arch. In our patient, the aortic arch prevented intervention from both the arm and femoral access.

Our clinical results were satisfactory at the end of the 3th month as well as at the end of the process. In addition, no occlusion or restenosis was observed in the control Doppler and CT angiography performed at the end of the 3th month. Favre et al.[5] stated that statin use positively affects long-term results in stenting carotid stenosis that develops after radiation. Therefore, they recommended the use of statins in patients receiving neck radiotherapy. In their study, the survival rate without developing new neurological deficits was 93% at 3-year follow-up. The number of patients in whom the procedure failed or who developed restenosis during the 3-year follow-up was 27. In our study, we did not use statins in any patient who did not have atherosclerosis. But it should also be emphasized that; while they presented their 3-year results, we presented their 3-month results.

Radiotherapy applied to head and neck region damages artery walls through three mechanisms.[9] The first mechanism is that radiation causes ischemia by causing occlusion in the vasa vasorum. Thus, fibrous tissue develops instead of elastic tissue and muscular fibers layers. This process leads to focal sclerosis. The second mechanism is that fibrous tissue causes occlusion in the artery lumen. Muzaffar et al.[10] demonstrated that a significant increase in arterial wall thickness within the first year after radiotherapy. These two mechanisms are important reasons for the development of restenosis after carotid stenting. The other mechanism is the acceleration of atherosclerosis process. The time interval the flow pattern in the carotids deteriorates after radiation is variable. In our study, it ranged from 3 to 22 years. In general, this interval varies between 2 and 30 years in studies.[4,11] The neck radiotherapy does not always lead to carotid artery occlusion or stenosis. It varies depending on the type of cancer in the neck area. Carotid stenosis is more common in the laryngeal carcinoma and nasopharyngeal. It has also been associated with age, coronary artery disease and smoking. It is observed more frequently in local cancers originating from the neck region than in hematological diseases.[9] In most of our patients, the reason was radiotherapy due to laryngeal cancer. Some studies claim that radiotherapy-induced ischemia also causes atherosclerosis in the carotid artery. However; there are studies suggesting that there is no relationship between radiotherapy and atherosclerosis.[5] Stenosis due to radiotherapy is observed especially in the common carotid arteries. Stenosis due to atherosclerosis develops especially at the origin and proximal segment of the internal carotid artery. In our study, common carotid involvement was also high. The cause of death of patients with carotid stenosis due to radiotherapy after stenting was usually cancer recurrence. Stroke or heart attack were less common causes of death. It is remarkable that in our study, no one died due to cancer, cerebrovascular or heart disease at the end of the 6-month follow-up. The question of when to intervene in carotid stenosis in cancer patients who have received radiotherapy is unclear. Stent placement is recommended for stroke prevention in patients with potentially severe stenosis. But it still needs to be evaluated according to the patient. The death and ischemic-hemorrhagic stroke have been reported

in large series studies using open surgery. There were also restenosis, nerve injury, and delays in wound healing.[12] The treatment outcomes of our patients were better compared to these patients who underwent open surgery. Additionally, our results were better than the mid-term results of open surgery. Other carotid stenting studies comparing with open surgery have similar results.[5] Therefore, it seems possible to recommend carotid artery stending as the primary treatment for stenosis occurring after neck irradiation. We did not use a cerebral protection device in our study. In other studies, different amounts of cerebral protection devices were used. Cerebral protection device is used against embolism complication. We think that the risk of embolism is reduced in these patients because they do not have atherosclerosis. Therefore, there is no need to use a cerebral protection device in the treatment of radiotherapy-related stenosis.

Limitations

This study has several limitations, including the relatively small sample size, its retrospective design and the we did not have a control group of medically treated carotid stenosis occlusions.

CONCLUSION

This retrospective study demonstrates that endovascular treatment for carotid stenosis developing after neck radiotherapy is safe, effective and reliable.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Selçuk University Ethics Committee (Date: 16.01.2024, Decision No: 2024/30).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

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

Financial Disclosure

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Author Contributions

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

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Cerebral venous thrombosis with clinical, etiological and radiological findings

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ABSTRACT

Aims: Thrombosis of the cerebral veins is a disease that can be caused by many factors and puts clinicians in a difficult situation during diagnosis and treatment. Our study investigated clinical findings, etiological causes, localization of thrombosis detected by neuroimaging tests, and the treatments received by the patients with cerebral venous thrombosis who were followed up as inpatients in our clinic.

Methods: We retrospectively analyzed 44 patients between the ages of 18-80 years who were hospitalized with a diagnosis of cerebral venous thrombosis. Age, duration of admission, initial symptoms, neurological examination findings, Glasgow Coma Scale values at admission, etiological causes, topographic areas of involvement in neuroradiological examinations, and inpatient medical treatment were analyzed.

Results: Forty-four patients (26 females, 18 males) with cerebral venous thrombosis were included in our study. According to the duration of presentation, 47.7% presented in the subacute period. Headache was the most common presenting symptom, with a rate of 90.9%, while nausea and vomiting (68.2%) and papilledema (54.5%) were the other common symptoms. Multiple vein and/or sinus involvement was present in all 17 patients with seizures. The most common etiological factors were thrombophilia (54.5%), pregnancy and the postpartum period (18.8%), and oral contraceptive use (15.9%). Multiple sinus involvement was observed in 41 patients (93.2%), while three had single sinus involvement. The rate of sinus involvement was 86.4% (38 patients) in the transverse sinus, 77.3% (34 patients) in the sigmoid sinus, and 52.3% (23 patients) in the superior sagittal sinus.

Conclusion: Cerebral venous thrombosis has many etiological causes that can be overlooked due to the variety of clinical manifestations and changes in the prognosis when treated. Early treatment is essential because it can reduce the risk of death and severe disability. Our study is critical because it covers a relatively large number of cases.

Keywords: Sinus vein thrombosis, etiology, topography

INTRODUCTION

Cerebral venous thrombosis (CVT), which is caused by thrombosis of dural veins and sinuses, is a rare form of cerebrovascular disease and incidence between 14 and 20 cases per million population. Still, this fatal disease is observed more frequently in the young age group and women.[1]

While many intracranial and extracranial causes may lead to CVT, prothrombotic state, venous stasis, and direct involvement of the venous wall may be considered as the three primary mechanisms in the formation of clinical findings of the disease. Still, the cause cannot be determined in 20-25% of patients despite all investigations.[2] Depending on the location of the thrombus and the rate of thrombus formation, the spectrum and onset of clinical findings are quite variable. Increased intracranial pressure or focal brain damage is frequently responsible for the findings.[3] The disease's recognition is tricky because it may mimic many neurological diseases.

Cranial computed tomography (CT) may give a quick idea when the clinician suspects CVT, but cranial magnetic resonance imaging (MRI) and cranial MRI venography (MRV) are recommended for definitive diagnosis.[3] Treatment of CVT mainly consists of anticoagulant agents in addition to treatment of symptoms and etiological causes. Despite treatment, mortality is observed at a rate of 3-15%, especially in the acute phase of the disease.[4]

In our study, patients with CVT who were followed up in our clinic were retrospectively analyzed, and clinical findings,

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etiological factors, localization of thrombosis detected by neuroimaging examinations, and the treatments they received were examined.

METHODS

Our study analyzed patients with CVT diagnosed by MRI and/or MRV between January 2008 and December 2014. Approved by the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Date: 12.11.2015, Decision No: 212). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Age, gender, initial symptoms and findings (headache, nausea/vomiting, pupil edema, focal deficit, focal and generalized seizure, confusion, abducens nerve palsy), Glasgow Coma Scale (GCS) values at the time of initial presentation to our clinic, Topographic areas of involvement in neuroradiological examinations such as CT, CTV, MRI, MRV, conventional angiography and medical treatments used during hospitalization were retrospectively reviewed from patient files and patient information management system. The presence of focal neurological deficit (hemiparesis and/or hemihypoalgesia) and accompanying focal or generalized seizures were determined from the records. Possible etiological causes evaluated in the clinic during the treatment of the patient: hereditary thrombophilia panel (prothrombin G20210A mutation, factor V leiden mutation, protein C deficiency, protein S deficiency, antirombin III mutation, MTHFR C667T mutation, and homocysteinaemia), malignancy, surgical intervention, lumbar puncture, trauma, oral contraceptive drug use, presence of infection, pregnancy and the postpartum period, iron deficiency anemia, connective tissue disease, inflammatory bowel disease thrombocytosis, chronic renal failure were recorded. Patients were accepted as acute (<48 hours), subacute (48 hours-30 days), and chronic (>30 days) according to the duration of onset. Patients whose data could not be accessed from the hospital information system were excluded.

Statistical Analysis

Statistical analysis of the data was performed in SPSS 22.0 for the Windows package programme with 95% confidence. Chi-square and Fisher exact tests were used to compare categorical variables between groups, and independent two-sample test statistical analyses were used to compare continuous data between groups. $p<0.05$ was considered statistically significant, and $p\geq0.05$ was considered statistically insignificant.

RESULTS

Between January 2008 and December 2014, 49 patients who were hospitalized with a prediagnosis of sinus vein thrombosis in the Neurology Clinic of İzmir Katip Çelebi University Atatürk Training and Research Hospital were identified. Five of them were excluded from the study due to incomplete data. 18 of 44 patients were male, and 26 were female. The ages of the patients at the time of the event ranged between 18 and 80 years. The age distribution of the patients according to gender is shown in Figure 1.

When the onset of symptoms at presentation was analyzed, the rate of presentation in the acute period was 31.8% (<48 hours), in the subacute period 47.7% (48 hours-30 days), and in the chronic period 20.5% (>30 days).

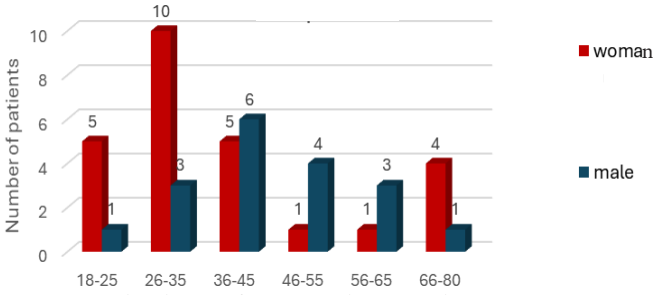

Figure 1. Age distribution of cases according to gender

The distribution of symptoms and signs detected in the patients is shown in Figure 2.

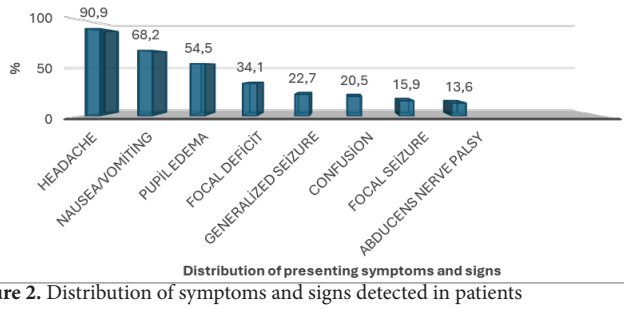

Figure 2. Distribution of symptoms and signs detected in patients

While multiple complaints and findings were found simultaneously in all patients, headache was the most common symptom in 90.9%. Isolated headache without any neurological deficit was not found in any patient. A total of 24 patients had papilledema, 3 of whom presented in the acute, 16 in the subacute, and 5 in the chronic phase. In 22 patients, papilledema was accompanied by headache, while headache was absent at presentation in 2 patients.

Focal neurological deficit (hemiparesis and/or hemihypoalgesia) was found in 34.1% (15 patients). The frequency of focal and generalized seizures in patients with focal neurological deficits is shown in Table 1.

Table 1. Frequency of focal and generalized seizures in patients with focal neurological deficit

		Focal seizure	Generalize seizure	Non-seizure	Total
Focal neurological deficit	yes	5 (11.3%)	7 (15.9%)	3 (6.8%)	15 (34.1%)
	no	2 (4.6%)	3 (6.8%)	24 (54.5%)	29 (65.9%)
Total number of patient		7 (15.9%)	10 (22.7%)	27 (61.3%)	44

The possible etiological causes found in the patients are briefly summarised in Table 2.

Table 2. Possible etiological causes detected in patients

Etiological factor	Number of patients
Hereditary thrombophilia	24 (54.5%)
Malignancy	8 (18.2%)
Surgical intervention, lumbar puncture, trauma	7 (15.9%)
Oral contraceptive drug	7 (15.9%)
Infection	4 (9.1%)
Pregnancy	4 (9.1%)
Postpartum period	4 (9.1%)
Iron deficiency anemia	3 (6.8%)
Connective tissue disease	2 (4.6%)
Inflammatory bowel disease	2 (4.6%)
Thrombocytosis	1 (2.3%)
Chronic renal failure	1 (2.3%)

While clouding of consciousness was present in 20.5% of the patients, GCS values at admission were analyzed. GCS>12 in 88.6% of the patients, GCS 9-12 in 11.4%, and GCS≤8 in no patient.

The rates of hereditary thrombophilia detected in patients are summarised in Table 3.

Table 3. Rate of hereditary thrombophilia detected in patients

Hereditary thrombophilia	Number of patients
MTHFR C667T	11 (25%)
Faktor V leiden	5 (11.4%)
Protein C deficiency	3 (6.8%)
Prothrombin G20210A	2 (4.6%)
Homocysteine	2 (4.6%)
Protein S deficiency	1 (2.3%)
Total	24

Among 11 patients with homozygous MTHFR gene mutation, 1 patient had simultaneous factor V leiden (FVL), 1 patient had homozygous protein C deficiency mutation and 1 patient had homozygous protein S deficiency mutation.

Four of twenty-six female patients (15.3%) were pregnant at presentation. It was learned that one of them was in the 1st trimester, 1 in the 2nd trimester, 2 in the 3rd trimester, and 4 patients (15.3%) presented in the postpartum period. There were seven patients who were using oral contraceptive drugs (OCS), and when the accompanying aetiological factors were examined, methylene tetrahydrofolate reductase (MTHFR) C667T gene mutation was homozygous in 2 patients and heterozygous in 2. factor V leiden mutation was detected in 1 patient.

MRI and MRV were performed together for diagnostic purposes in 38 of forty-four patients. Three patients were diagnosed with CT and MRI evaluations, and three patients were diagnosed with CT and MRI together. The number of patients with direct and indirect thrombosis on neuroimaging is shown in Figure 3.

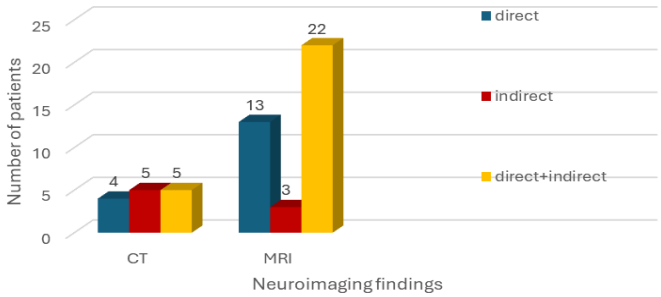

Figure 3. Number of patients with direct and indirect thrombosis detected on neuroimaging

MRI and/or MRV results of 44 patients included in the study were evaluated together, and the localization of thrombosis was defined. Multiple sinus involvement was observed in 93.2% of the patients. The topographic distribution in patients with CVT is shown in Figure 4.

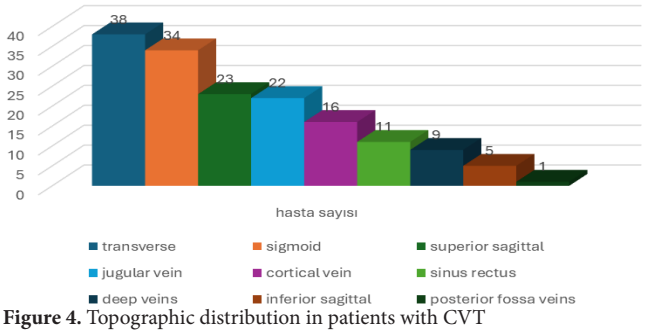

Figure 4. Topographic distribution in patients with CVT

CVT: Cerebral venous thrombosis

DISCUSSION

CVT is a complex disease to diagnose because of the variability of clinical signs and symptoms, which frequently affects young adults and children.[5] The estimated incidence is 3-4 per million population.[3] While a homogeneous distribution is observed at all ages in males, it is observed more frequently in females between the ages of 20-35 years in relation to pregnancy, puerperium, and OCS drug use.[6] In our study, the mean age was found to be 41.8±15.8 years, but the mean age of female patients was younger than that of male patients. It was thought that this may be related to gender-specific risk factors observed in women at younger ages.

In the literature, CVT is grouped as acute (2 days or less, 20-30%), subacute (2 days-1 month, 50-80%), or chronic (more than two months, 10-20%) according to the time from onset to diagnosis.[7] A study conducted in our country found that 33% of the patients presented in the acute, 40% in the subacute, and 27% in the chronic period.[8] When the duration of the presentation was analyzed in our study, it was observed that patients presented most frequently in the subacute period, followed by the acute period, and least frequently in the chronic period, similar to the literature.[8]

The mode of onset and clinical manifestations of CVT have a broad spectrum due to the diversity of collateral venous drainage, and it is known that it can mimic many neurological diseases. Headache caused by distension of pain-sensitive structures (veins and sinuses) or increased intracranial pressure is the most common symptom of CVT. Headache does not have a typical characteristic or temporal profile, is usually severe and progressive, and may mimic other primary causes of headache.[6] In two studies conducted with 624 and 1144 patients, the most common presenting symptom was headache.[9,10] Although the incidence of papilledema in sinus vein thrombosis varies between 45-86%, it has been reported to be less frequent in acute cases.[11] At the same time, papilledema was found in 24 cases; 3 of these patients presented in the acute, 16 in the subacute, and 5 in the chronic period. While focal deficit, seizure, and confusion were observed at a rate of 50-75% in the old series, they are now observed in 1/3 of the cases with early diagnosis enabled by neuroimaging methods.[12] Focal brain damage caused by venous ischemia or hemorrhage may lead to neurological signs and symptoms related to the affected area, most commonly hemiparesis and aphasia.[13] Epileptic seizures are observed with a rate of 35-40%, and literature analyses show that focal motor deficit, cortical vein thrombosis, and supratentorial parenchymal lesions are associated with the risk of early seizure development.[14,15] In a series of 100 patients with seizure accompanying thrombosis, a GCS below 8, focal damage, presence of hemorrhagic infarction, frontal lobe involvement, and superior sagittal sinus thrombosis and high D-Dimer levels were reported as risk factors for acute seizure development.[16] In our study, focal seizures were observed in 5 of 15 (34.1%) patients with focal neurological deficits, while generalized seizures were observed in 7 patients. In patients

without focal neurological deficits, 2 had focal seizures, and 3 had generalized seizures. Changes in consciousness in CVT frequently occur when deep venous structures are affected.[14] Our study found clouding of consciousness in 20.5% of the patients (9 patients), whereas cavernous sinus syndrome, recognized by painful ophthalmoparesis, chemosis, and proptosis findings, was not found.

When etiological causes are examined, the main cause cannot be found in 20-30% of patients.[2] Pregnancy, puerperium, OCS use, coagulopathies, intracranial infections, cranial tumors, penetrating head traumas, lumbar puncture, malignancy, dehydration, inflammatory bowel disease, connective tissue diseases, Behçet's disease, sarcoidosis, nephrotic syndrome, parenteral infusions, and various drugs lead to CVT.[9] In the ISCVT study, the most common cause was reported as OCS use (54.3%), followed by hypercoagulation (34.1%), pregnancy, and the postpartum period (20.1%).[9] In the VENOST study, gynecological causes were the most common cause in women and prothrombotic conditions in men, followed by infections in both sexes.[10] In our research, the most common cause in both sexes was thrombophilia (54.5%), while pregnancy and puerperium were found to be 18.8% and OCS use 15.9% in women. Compared with the literature, it is noteworthy that coagulation disorders were found at a high rate in our patients.

Pregnancy, puerperium, and OCS use are common in women, especially between the ages of 20-35 years. In the ISCVT study, pregnancy was found in 6.3% and puerperium in 13.8% of women under 50 years of age.[9] In the VENOST study, 41.7% of gynecological causes were found in our country.[10] Among 26 female patients included in our study, 4 (15.3%) were pregnant, 4 (15.3%) were in the postpartum period, and 7 (26.9%) were using OCS drugs.

In the literature, it has been reported that OCS use increased the risk of CVT from 13% to 34% in patients with hereditary thrombophilia.[17] In 7 patients with OCS use, the finding of homozygous MTHFR C667T gene mutation in 2, heterozygous in 2, and Factor V Leiden mutation in 1 (3.8%) patient is compatible with the literature.

Prothrombotic factors are among the well-defined etiological factors with a frequency of 15-35%.[18] Thrombophilic conditions including factor V Leiden mutation (FVL), protein C, protein S, antithrombin III deficiencies, factor II gene mutation, and hyperhomocysteinemia, which can be genetically demonstrated, cause a predisposition for CVT.[19] In the ISCVT study, hereditary thrombophilia was found in 22.4% of patients, and acquired thrombophilia was found in 15.7% of patients.[9]

FVL mutation is frequent in patients with CVT, and the risk increases in the presence of concomitant OCS use, pregnancy, or puerperium. In a series of 55 patients by Lüdemann et al.,[20] the presence of FVL mutation was found with a rate of 14.5%, which was significant compared with the control group. In our study, the presence of factor V Leiden mutation was found in 5 (11.4%) of 44 patients. Three of these patients were female, and 1 case had concomitant OCS use. In a study, the frequency of prothrombin G20210A mutation was reported to be 11% in patients with a diagnosis of CVT. The association of this mutation with OCS use increases the risk of CVT 10.2-fold. In patients with prothrombin G 20210 A mutation, the risk of thrombosis increased from 14.7 to 19.8 in the presence of concomitant protein C mutation.[21,22] Factor II mutation was found in 2 of our patients, one female, and one male, and there was no concomitant OCS use. Hyperhomocysteinaemia is among the causes defined in the etiology of CVT. In a case-control study published by Martinelli et al.[17] in patients with CVT, hyperhomocysteinemia was found in 33 of 121 patients and 21 of 242 healthy controls. In our study, methylene tetrahydrofolate reductase (MTHFR) C667T gene mutation was found to be homozygous in 11 patients (25%) and heterozygous in 6 patients (13.7%). In 2 patients (4.6%), homocysteine level was found to be isolated high. When compared with the literature, the reason for the lower homocysteine level in our study was thought to be inadequacies in the sampling conditions. Although protein-C, protein-S, and antithrombin III deficiency are well-known causes of venous thromboembolism, their role in CVT is unclear. Publications are reporting an association. In our study, antithrombin III deficiency was not found, protein C deficiency was found in 2 patients, and protein S deficiency was found in 1 patient.

Due to its practicality and prevalence, brain CT is used as a diagnostic method, especially in patients presenting to emergency departments with headaches. On brain CT, hyperdense appearance due to acute thrombosis in the affected sinus region, filling defects in contrast-enhanced images (delta sign), hyperdense tentorium, findings secondary to congestion in cortical veins or cerebral edema may be detected, or it may be completely normal.[23] CT shows direct findings of CVT in approximately one-third of the cases. Indirect findings are observed in 60% to 80% of cases. Small ventricles are encountered in 20% to 50% of cases. Contrast uptake in the falx and tentorium is observed in 20% of cases, and CT is normal in up to 30% of cases.[24] In our study, direct evidence of thrombosis was found in 4 (28.6%), indirect evidence in 5 (35.7%), and the presence of direct and indirect thrombosis indicators in 5 (35.7%) of 14 patients who underwent CT scans, similar to the literature.

Cranial MRI and MRV are the first choice non-invasive examinations in diagnosing CVT. Cranial MRI may show infarcts, especially hemorrhagic infarcts, which do not fit into the arterial irrigation area, and the absence of signal in venous sinuses is also diagnostic. The thrombosed sinus is best visualized on T1, T2, and FLAIR sequences and MR angiography with T2 sequence addition. Diagnosis is easy when the occlusion is complete; however, it may be difficult in partial occlusions where the flow is still present but irregular. Intraarterial angiography, previously accepted as the gold standard in the diagnosis of CVT, is currently performed only in cases in which the diagnosis cannot be confirmed by MRI and MRV.[25,26] In our study, MRI and MRV were performed together for diagnostic purposes in 38 of 44 patients. While the diagnosis of 3 patients was made by CT and MRI evaluations, the diagnosis of 3 patients was made by CT and MRV evaluation. MRI was performed in 41 cases (93.2%), and MRI revealed direct thrombosis in 13 cases (31.7%), indirect thrombosis in 3 cases (7.3%), and direct and indirect thrombosis in 22 cases (53.7%). In 3 patients (7.3%), no direct or indirect thrombosis was found, and the diagnosis was made based on the presence of thrombosis on MRV. The presence of direct and indirect thrombosis findings is similar to the literature.

In the most extensive series of 624 cases in the literature, the superior sagittal sinus (62%) was reported as the most common site of involvement. The left transverse sinus (44.7%) and the right transverse sinus (41.2%) followed, respectively.[9] In a study

conducted by Cantu et al.[27] with 113 patients, involvement was found to be 97.8%, involvement 43.4%, thrombosis of deep venous structures 21.7%, and thrombosis of cortical veins 30.4%.

MRI and/or MRV results of 44 patients included in our study were evaluated together, and the localization of thrombosis was defined. More than one sinus was observed in 41 patients (93.2%), while a single sinus was found in 3 patients. In order of frequency, transverse sinus 86.4%, sigmoid sinus 77.3%, superior sagittal sinus 52.3%, jugular vein 50%, cortical veins 36.4%, sinus rectus 25%, deep veins 20.5%, inferior sagittal sinus 11.4%, posterior fossa veins 2.3%. When compared with the literature, it is noteworthy that the transverse sinus was most commonly involved in our patients, and the superior sagittal sinus was thrombosed at a lower rate.

Treatment of CVT consists of reversal of an identifiable cause, control of seizures and intracranial hypertension, and antithrombotic therapy. Anticoagulation is the mainstay of treatment for CVT in the acute and subacute setting. Currently, most centers start treatment with subcutaneous low molecular weight heparin or intravenous heparin as soon as the diagnosis is made, even if hemorrhagic infarcts are found, and continue treatment with warfarin.[28] When the anticoagulant therapies received by the patients during follow-up in our clinic were analyzed, it was found that 56.9% started intravenous heparin and 27.3% started low molecular weight heparin. In 88% of the patients in whom heparin was initiated after the acute period, warfarin was continued in 88%, and low molecular weight heparin was continued in 12%. Among the 12 patients who received low molecular weight heparin, 66.7% of 8 patients received warfarin in the long term, and 33.3% did not. Only warfarin was given to 13.6% of the patients. In 1 case (2.3%), anticoagulant treatment was not started because of hematological contraindications.

CONCLUSION

Nowadays, with the development of new diagnostic tests, CVT recognition rates are increasing, and we have more information about the disease. Especially in the presence of an identifiable etiological cause, the mortality and morbidity of the disease can be reduced with cause-oriented treatments. It is necessary to carefully examine the coagulopathy conditions,which were especially frequently detected in our studay. Therefore, more studies on CVT are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ethics Committee of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Date: 12.11.2015, Decision No: 212).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Investigation of the effect of disease acceptance and action status of type 2 diabetes patients receiving oral antidiabetic and insulin treatment on their compliance to treatment

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ABSTRACT

Aims: This study aimed to determine the effect of disease acceptance and action status on treatment compliance in type 2 diabetes mellitus (DM) patients receiving oral antidiabetic and insulin treatment.

Methods: This study is a comparative cross-sectional study. A total of 122 patients, including 61 patients receiving oral antidiabetic treatment and 61 patients receiving insulin treatment, were included in this study. The data of the study were collected with the "Individual Introduction Form", "Acceptance and Action Diabetes Questionnaire", and "Type 2 DM Treatment Patient Compliance Scale".

Results: There is a significant and negative correlation between the total score of the acceptance and action diabetes questionnaire and the total score of the Type 2 DM Treatment Patient Compliance Scale ($r=-0.375$; $p<0.05$). The study observed that as the total score of the Acceptance and Action Diabetes Questionnaire increased, the total score of the type 2 DM Treatment Patient Compliance Scale decreased.

Conclusion: In our study, it was observed that the compliance level of type 2 DM patients using insulin or OAD was moderate, and their acceptance and action levels were above average.

Keywords: Diabetes, insulin, antidiabetic, compliance

INTRODUCTION

Diabetes mellitus (DM) is a wide-spectrum metabolic disease which affecting many organs. Medical nutrition therapy, exercise, physical activity, antihyperglycemic drugs, and insulin therapy treat diabetes.[1] The prevalence of type 2 DM has increased significantly in recent years.[2] It is important to focus on prevention, early diagnosis and initial management of macrovascular and microvascular complications of DM in adults.[3] For these reasons, patient compliance with treatment and acceptance of the disease is essential. The World Health Organization (WHO) defines medication compliance as "the degree to which a person's behavior conforms to the accepted recommendations of a health care provider".[4] Long-term adherence to pharmacotherapy in the treatment of chronic disease is considered crucial for treatment success.[5] Adherence to prescribed medication in DM is crucial to achieve metabolic control, as nonadherence to blood glucose-lowering or lipid-lowering medication is associated with higher HbA1c and cholesterol levels, respectively.[6]

People may have difficulty accepting lifestyle changes because they do not consider the disease's short- and long-term complications and may experience depression, anxiety, and similar psychiatric problems.[7,8] It is important to help individuals with DM to identify the most appropriate adaptive strategies to improve their quality of life.[9] DM has been associated with psychological problems, which in turn have been associated with poorer glycaemic control [glycosylated haemoglobin (HbA1c)].[10] Piotrkowska et al.[11] found that life satisfaction increased in patients who expressed a higher level of acceptance of their illness. Considering all these, this study aimed to determine the effect of disease acceptance and action status on treatment compliance of type 2 DM patients receiving oral antidiabetic (OAD) and insulin treatment.

METHODS

The Kastamonu University Clinical Researches Ethics Committee gave its written approval (Date: 30.01.2023,

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Decision No: 2023-KAEK) for the survey to be carried out. Data collection was authorized by the institution (dated 2 March 2023). Permissions were obtained via e-mail for the use of the scales. After informing the participants about the study, their informed consent was obtained. The Helsinki Declaration's guidelines were respected. A comparative cross-sectional study.

Study Design and Participant

The number of patients participating in the study was determined as 120 (OAD-treated=60 and insulin-treated=60) with G*Power 3.1 at 80% confidence level (significance level α=0.05), p=0.52.[13] A total of 122 patients (61 patients receiving OAD treatment and 61 patients receiving insulin treatment) were included in the study. Criteria for inclusion in the survey: agreeing to participate in the research and being a type 2 DM patient using insulin or OAD.

Data Collection

The data were collected by a face-to-face questionnaire at the Kastamonu Training and Research Hospital Diabetes Outpatient Clinic. "Individual Introduction Form," "Acceptance and Action Diabetes Questionnaire (AADQ)" and "Type 2 DM Treatment Patient Compliance Scale" were used to collect the data of the study.

Individual Introduction Form: It consisted of 11 statements, including socio-demographic characteristics and health status of diabetic patients.

Acceptance and Action Diabetes Questionnaire (AADQ): The scale was evaluated to measure the acceptance of thoughts and feelings about DM and how much they interfere with valuable actions. The Cronbach's alpha value of the scale, which consists of nine statements, is 0.836. The statements are evaluated as "1=never true" and "7=always true". All items except item 1 are reverse-scored. It is stated that as the score increases, psychopharmacology flexibility increases. The form has no cut-off score of.[14]

Type 2 DM Treatment Patient Compliance Scale: The Cronbach alpha value of this scale, which consists of 30 items and uses a 5-point Likert-type scale in scoring, is 0.77. The score range that can be obtained from the scale is between 30 and 150. Total scale scores are used in the interpretation of the scores obtained from the scale; scores in the 0-20% range (30-54) are interpreted as "good compliance to treatment," scores in the 20-80% range (55-125) as "moderate compliance to treatment" and scores in the 80-100% range (126-150) as "poor compliance to treatment." The scale consists of 7 subscales.[15]

Statistical Analysis

In the study, data were analyzed with the SPSS 21 package program. Since the data were not normally distributed, Mann-Whitney U test was used for comparisons between paired groups and Kruskall Wallis H test was used for comparisons between three or more groups. The relationship between categorical data was analyzed by Chi-square analysis. Spearman correlation analysis was used for the relationship between variables. Descriptive statistical method was used to evaluate the study data. The significance level is 0.05.

RESULTS

The socio-demographic characteristics of the patients participating in the study are shown in Table 1. It can be said that the two groups were homogeneous in terms of socio-demographic variables (Table 1). The average age of the patients and the time they were diagnosed with diabetes are in Table 2. There is no significant difference between treatment groups, age values, and duration of diabetes diagnosis (p>0.05) (Table 2).

Table 1. Socio-demographic characteristics of Type 2 DM patients using insulin and OAD treatment

		Treatment groups						Chi-square analysis	
		OAD		Insulin		Total			
Characteristics		n	%	n	%	n	%	Chi-square	p
Gender	Male	24	39.3	29	47.5	53	43.4	0.834	0.361
	Female	37	60.7	32	52.5	69	56.6		
Education status	Literate	9	14.8	9	14.8	18	14.8	0.58	0.748
	Primary school/ secondary school	44	72.1	41	67.2	85	69.7		
	High school and others	8	13.1	11	18.0	19	15.6		
Marital status	Single	8	13.1	12	19.7	20	16.4	0.538	0.463
	Married	53	86.9	49	80.3	102	83.6		
Income status	Low	11	18.0	14	23.0	25	20.5	0.201	0.654
	Middle/high	50	82.0	47	77.0	97	79.5		
Employment status	Yes	14	23.0	16	26.2	30	24.6	0.044	0.833
	No	47	77.0	45	73.8	92	75.4		
Participation in diabetes education	Yes	36	59.0	43	70.5	79	64.8	1.293	0.256
	No	25	41.0	18	29.5	43	35.2		
Regular visits to physician controls	Yes	41	67.2	47	77.0	88	72.1	1.019	0.313
	No	20	32.8	14	23.0	34	27.9		
Using medications regularly	Yes	54	88.5	57	93.4	111	91.0	0.4	0.527
	No	7	11.5	4	6.6	11	9.0		
Using alternative treatment methods	Yes	12	19.7	10	16.4	22	18.0	0.055	0.814
	No	49	80.3	51	83.6	100	82.0		

DM: Diabetes mellitus, OAD: Oral antidiabetic

Table 2. Mean age and duration of diabetes diagnosis of type 2 DM patients using insulin and OAD treatment

Characteristics	Treatment groups	Mean	Min	Max	SD	Mann-Whitney U test Mean ranks	U	p
Age	OAD	57.18	24.00	82.00	10.88	60.95		
	Insulin	57.02	20.00	78.00	13.75	62.05	1827	0.864
	Total	57.10	20.00	82.00	12.35			
Duration of diabetes diagnosis	OAD	5.90	1.00	30.00	6.75	62.30		
	Insulin	6.72	1.00	35.00	8.87	60.70	1812	0.784
	Total	6.31	1.00	35.00	7.86			

DM: Diabetes mellitus, OAD: Oral antidiabetic, Min: Minimum, Max: Maximum, SD: Standard deviation

For the OAD group, the Type 2 DM Treatment Patient Compliance Scale total score is 81.67±10.10, while the AADQ total score is 46.79±11.56. For the insulin group, the Type 2 DM Treatment Patient Compliance Scale total score is 84.75±13.56, while the AADQ total score is 47.59±10.69. In the study, there was no significant difference between the treatment groups in terms of all sub-dimensions, the AADQ, and the type 2 DM Treatment Patient Compliance Scale (p>0.05) (Table 3).

Table 3. Total scores of Type 2 DM Treatment Patient Compliance Scale and acceptance and action diabetes questionnaire according to treatment groups

Mean		Treatment groups				Mann-Whitney U test		
		Mean	Min	Max	SD	Mean ranks	U	p
Emotional difficulties in compliance	OAD	23.34	15.00	36.00	5.21	57.67	1627	0.231
	Insulin	24.48	8.00	40.00	6.05	65.33		
Physical difficulties in compliance	OAD	13.30	7.00	24.00	4.13	58.40	1671.5	0.332
	Insulin	13.82	6.00	23.00	3.97	64.60		
Changing difficulties in compliance	OAD	8.05	3.00	15.00	2.43	58.95	1705	0.421
	Insulin	8.48	3.00	15.00	2.43	64.05		
Acceptance difficulties in compliance	OAD	8.49	3.00	15.00	3.11	58.43	1673.5	0.335
	Insulin	9.08	3.00	15.00	3.14	64.57		
Awareness difficulties in compliance	OAD	7.92	4.00	14.00	2.82	61.07	1834.5	0.893
	Insulin	7.84	4.00	13.00	2.37	61.93		
Diet difficulties in compliance	OAD	11.10	3.00	15.00	2.58	59.98	1768	0.632
	Insulin	11.25	5.00	15.00	2.43	63.02		
Denial difficulties in compliance	OAD	9.48	3.00	15.00	2.95	58.87	1700	0.408
	Insulin	9.82	3.00	15.00	3.39	64.13		
Type 2 DM Treatment Patient Compliance Scale total score	OAD	81.67	57.00	103.00	10.10	55.92	1520	0.081
	Insulin	84.75	44.00	126.00	13.56	67.08		
Acceptance and Action Diabetes Questionnaire total score	OAD	46.79	15.00	59.00	11.56	60.85	1821	0.839
	Insulin	47.59	24.00	63.00	10.69	62.15		

DM: Diabetes mellitus, Min: Minimum, Max: Maximum, SD: Standard deviation, OAD: Oral antidiabetic

There is a significant and negative correlation between the total score of the AADQ and the emotional difficulties in compliance subscale score (r=-0.322; p<0.05), physical difficulties in compliance subscale score (r=-0.181; p<0. 05), changing difficulties of habits in compliance subscale score (r=-0.415; p<0.05) and acceptance difficulties in compliance subscale score (r=-0.288; p<0.05) (r=-0.322; p<0.05). As the total score of the AADQ increases, the emotional difficulties in compliance, physical difficulties in the compliance subscale score, changing difficulties of habits in the compliance subscale score, and acceptance difficulties in the compliance subscale score decrease. There was no significant relationship between the total score of the AADQ and the awareness difficulties in compliance subscale score, diet difficulties in compliance, and denial difficulties in compliance subscale score (p>0.05). There is a significant and negative correlation between the total score of the AADQ and the total score of the Type 2 DM Treatment Patient Compliance Scale (r=-0.375; p<0.05). As the total score of the AADQ increases, the total score of the Type 2 DM Treatment Patient Compliance Scale decreases (Table 4).

In the study, a significant and negative relationship was observed between the total score of the AADQ and the emotional difficulties in compliance subscale score (r=-0.303; p<0.05), changing difficulties of habits in compliance subscale score (r=-0.359; p<0.05), and acceptance difficulties in compliance subscale score (r=-0.279; p<0.05) in patients using OAD treatment. As the total score of the AADQ increases, the emotional difficulties in the compliance subscale score, changing difficulties of habits in the compliance subscale score, and acceptance difficulties in the compliance subscale score decrease. There was no significant relationship between the total score of the AADQ and the physical difficulties in the compliance subscale score, the awareness difficulties in the compliance subscale score, the diet difficulties in the compliance subscale score, and the denial difficulties in the compliance subscale score (p>0.05). There is a significant and negative correlation between the total score of the AADQ and the total score of the Type 2 DM Treatment Patient Compliance Scale (r=-0.352; p<0.05). As the total score of the AADQ increased, the total score of the Type 2 DM Treatment Patient Compliance Scale decreased (Table 5).

In the study, a significant and negative correlation was observed between the total score of the AADQ and the emotional difficulties in compliance subscale score (r=-0.341; p<0.05), changing difficulties of habits in compliance subscale score (r=-0.480; p<0.05), awareness difficulties in compliance subscale score (r=-0.262; p<0.05) and acceptance difficulties in compliance subscale score (r=-0.303; p<0.05). As the total score of the AADQ increases, the emotional difficulties in the compliance subscale score, changing difficulties of habits in the compliance subscale score, awareness difficulties in compliance, and acceptance difficulties in the compliance

Table 4. The relationship between the total scores of the Type 2 DM Treatment Patient Compliance Scale and the AADQ

		Correlation							
		Emotional difficulties in compliance	Physical difficulties in compliance	Changing difficulties of habits in compliance	Acceptance difficulties in compliance	Awareness difficulties in compliance	Diet difficulties in compliance	Denial difficulties in compliance	Type 2 DM Treatment Patient Compliance Scale total score
AADQ total score	r	-0.322**	-0.181*	-0.415**	-0.147	-0.288**	-0.074	0.055	-0.375**
	p	0.000	0.046	0.000	0.106	0.001	0.420	0.545	0.000

DM: Diabetes mellitus, AADQ: Acceptance and Action Diabetes Questionnaire

Table 5. The relationship between the total scores of the Type 2 DM Treatment Patient Compliance Scale and AADQ using oral antidiabetics

		OAD treatment							
		Correlation							
		Emotional difficulties in compliance	Physical difficulties in compliance	Changing difficulties of habits in compliance	Acceptance difficulties in compliance	Awareness difficulties in compliance	Diet difficulties in compliance	Denial difficulties in compliance	Type 2 DM Treatment Patient Compliance Scale total score
AADQ total score	r	-0.303*	-0.189	-0.359**	-0.029	-0.279*	0.070	0.074	-0.352**
	p	0.017	0.145	0.004	0.822	0.030	0.593	0.571	0.005

DM: Diabetes mellitus, AADQ: Acceptance and Action Diabetes Questionnaire

subscale score decreases. There was no significant relationship between the total score of the AADQ and the physical difficulties in the compliance subscale score, the diet difficulties in the compliance subscale score, and the denial difficulties in the compliance subscale score ($p>0.05$). There was a significant and negative correlation between the total score of the AADQ and the total score of the Type 2 DM Treatment Patient Compliance Scale ($r=-0.415$; $p<0.05$). As the total score of the AADQ increases, the total score of the Type 2 DM Treatment Patient Compliance Scale decreases (Table 6).

DISCUSSION

Identifying and resolving the factors that lead to non-compliance in patients diagnosed with DM can reduce complications, mortality, and economic burden.[16] In our study, patients with DM who use insulin and OAD have moderate compliance with treatment and good acceptance and action status. A study by Kim et al.[17] found that poorer medication adherence led to worsening health outcomes that needed to be addressed in previous studies. Therefore, this study found that as the disease acceptance and action score of DM patients using OAD therapy increased, attitudes and emotional factors, emotions, and behaviors suitable for lifestyle change compliance decreased. This may be because patients may get bored of doing the same practices over time. It was found that there are studies on different topics in the literature, and there are some similarities with our research. The survey conducted by Balkhi et al.[18] found that almost half of the patients had good adherence. In a study by Haskani et al.,[19] most participants reported nonadherence for various reasons. Eze et al.[20] found that 79.5% of the patients had poor glycemic control, and moderate medication adherence was predominant. A study conducted by Çorak et al.[21] found that 45.2% of the patients had a low level of adherence. Jiraporncharoen et al.[22] reported that symptoms at the time of diagnosis were associated with understanding and acceptance of medication intake, presence of family support, physician's perception of concern, and increased medication adherence. Our study also observed that as the total score of the AADQ increased, the emotional difficulties in adjustment subscale score, the difficulty in changing habits subscale score, and the difficulty in acceptance subscale score decreased.

Our study observed similar results in insulin replacement therapy users as in OAD users. Only differently, it was found that anger decreased as the disease acceptance and action scores of DM patients increased. This was thought to be because offense declined as the patients accepted the disease. Consoli and Formoso[23] found that only 25% of DM patients had high adherence, and 28% had low commitment. In the same study, in general, patients reported that they needed to remember the timing or dosage of their last injection an average of 2.4 times a week, and the most frequently cited reasons for this were difficulty following instructions and having too much information to manage. Chefik et al.[24] found that compliance with insulin treatment was low. It has also been determined that compliance with insulin therapy is affected by having a glucometer, regular hospital follow-up, knowledge, and positive attitude. In a survey conducted by Güleyyupoğlu et al.[25] to determine the effect of fear of finger pricking and insulin injection on adherence to treatment in individuals diagnosed with DM, it was determined that fear of self-testing in patients was effective on compliance to treatment.

In our study, it was observed that as the total score of the AADQ increased, the total score of the Type 2 DM Treatment Patient Compliance Scale decreased in patients using OAD and insulin. This was thought to be because patients got bored of doing the same practices over time. In the literature, similar to our study, Chin et al.[26] found that approximately 60.3% of the participants adhered to their medications, and increasing age was significantly associated with nonadherence to drugs. In a study conducted by Kara et al.[27] to investigate the relationship between depressive symptoms, quality of life, and treatment adherence in patients diagnosed with Type 2 DM and the type of treatment used and socio-demographic variables, patients with OAD + insulin had poorer treatment adherence, HbA1c, depression and quality of life scores. In the study conducted by In their research on family support in individuals with type 2 DM, Arı and Özdelikara[28] found the mean total score

Table 6. The relationship between the total scores of the Type 2 DM Treatment Patient Compliance Scale and the AADQ in patients using insulin

		Insulin treatment							
		Correlation							
		Emotional difficulties in compliance	Physical difficulties in compliance	Changing difficulties of habits in compliance	Acceptance difficulties in compliance	Awareness difficulties in compliance	Diet difficulties in compliance	Denial difficulties in compliance	Type 2 DM Treatment Patient Compliance Scale total score
AADQ total score	r	-0.341**	-0.141	-0.480**	-0.262*	-0.303*	-0.231	0.036	-0.415**
	p	0.007	0.278	0.000	0.041	0.018	0.073	0.783	0.001

DM: Diabetes mellitus, AADQ: Acceptance and Action Diabetes Questionnaire

of the Illness Acceptance Scale to be 24.97±5.00. The mean total score of the Type 2 DM Treatment Patient Compliance Scale was 82.77±9.19. In the study conducted by Şireci and Yılmaz Karabulutlu[29] to determine the disease acceptance status, self-efficacy levels, and affecting factors of patients with type 2 DM and to investigate the relationship between disease acceptance and self-efficacy, the disease acceptance scale score of the patients was found to be 27.82±5.70. The same study determined that some patients' descriptive and disease-related characteristics affected disease acceptance and self-efficacy. In the survey conducted by Alharbi et al.,[30] the critical analysis of 20 selected studies revealed the diversity of drug adherence levels in adults with type 2 DM. In the same survey, studies showed that older adults and women adhered to medications more than younger adults and male patients.

CONCLUSION

In our study, the treatment compliance of patients with DM using insulin and OAD was moderate. Their acceptance and action status were also good. This study observed similar results in patients with insulin treatment groups as in patients using OADs. Our research found that anger decreased over time as the acceptance and action scores of diabetic patients increased. In addition, our study observed that compliance decreased as acceptance and action rates increased in patients using oral antidiabetics and in patients using insulin. Therefore, it is essential to ensure continuous patient follow-up over time and the continuity of training. In addition to repeating this study to include different regions, it may be recommended to investigate patients' thoughts on this issue. Awareness of DM complications by patients provides excellent support in slowing and preventing the progression of the disease course and in protecting and improving the individual's health. Improving the self-care behaviors of DM patients and managing the disease are essential in preventing acute and chronic complications of DM. In conclusion, our study contributes to the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Clinical Researches Ethics Committee (Date: 30.01.2023, Decision No: 2023-KAEK).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Clinical characteristics of patients admitted to Samsun Training and Research Hospital from the Turkiye-Syria earthquake region

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ABSTRACT

Aims: After the two major earthquakes that occurred in the Turkiye-Syria region on February 6th, 2023, earthquake casualties presented to hospitals in various centers across the country. This study aimed to analyze the characteristics of the presentations made to the emergency department and outpatient clinics of our tertiary hospital from the earthquake region after the earthquake.

Methods: A total of 1534 earthquake casualties who were admitted to the Samsun Training and Research Hospital Emergency Department and outpatient clinics with the diagnosis code X-34 were included in the study. The data of the patients were scanned retrospectively through the online system and age, sex, presentation date, clinic and hospitalization status were recorded.

Results: The mean age of the patients was 24.6±25.9 (range: 0-98) years. Six hundred eighty-six (44.7%) patients were male, 441 (28.7%) were age under 18 years, and 1199 (78.2%) were admitted or brought to the emergency room or intensive care units (ICUs). A total of 210 (13.7%) patients were hospitalized after being admitted or brought to the hospital. No fatalities were recorded among the earthquake casualties who presented. A total of 730 (47.6%) patients were admitted to our hospital within the first 30 days after the earthquake. The highest presentation peak period was between days 5 and 9. The mean age in women, inpatients, patients presnting to outpatient clinics, and patients from Adana, Hatay, Kahramanmaraş and Osmaniye provinces was significantly higher than the other groups ($p<0.001$ for each). The rates of hospitalized patients were found to be significantly higher in women ($p=0.002$), patients presenting to outpatient clinics ($p<0.001$), and patients presenting within the first 30 days after the earthquake compared to other groups ($p<0.001$). The rates of patients presenting to emergency rooms or ICUs were significantly higher in men ($p=0.011$) and in those who presented within the first 7 days after the earthquake compared with the other groups ($p=0.001$).

Conclusion: The findings obtained from our study indicated that the prognosis was good for earthquake casualties who presented to our hospital, which is far from the center of a major earthquake, that the highest number of presentations was between the 5th and 9th days, the period between the earthquake and the hospital admission was a determining factor in terms of the clinic presented and hospitalization, and the proximity to the center of the earthquake did not affect the prognosis in presentations. Our findings also show that the age group is an important factor in terms of the clinic of presentation, hospitalization, the period after the earthquake, and the province from which the presentation is made.

Keywords: Earthquake, hospitalization, emergency ward, Turkiye, earthquake casualties

INTRODUCTION

Natural disasters are ecologic events that disrupt the normal order of life in a society beyond its adaptive capabilities and therefore result in the need for urgent and major foreign aid. Compared with other natural disasters such as floods, landslides, avalanches, hurricanes, volcanic eruptions, and droughts, earthquakes are much more harmful and cause the

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most deaths and disabilities both in our country and globally. Earthquakes cause serious financial losses as well as loss of life.[1-4]

On February 6th, 2023, the so-called '2023 Kahramanmaraş earthquakes' or '2023 Turkiye-Syria earthquakes' occurred 9 hours apart, with epicenters in Pazarcık and Elbistan districts of Kahramanmaraş, respectively, with 7.8 Mw (±0.1) and two earthquakes with magnitudes of 7.5 MW occurred. In Turkiye, 10 provinces with a total population of 13.5 million were directly affected by these earthquakes, and according to the 2023 Earthquake Research Commission Report of the Turkish Grand National Assembly, the total cost of the earthquakes to the Turkish economy reached 4 trillion Lira (148.8 billion dollars). As of March 30th, more than 50,000 deaths and a total of around 125,000 injuries were detected in Turkiye and 8000 in Syria.[2-4] After the earthquakes, a significant part of the cities collapsed and almost all of the people had to migrate to different provinces. The earthquakes also caused temporary disruptions in Turkiye's health system. Many hospitals and emergency response systems were damaged, and healthcare workers were forced to work long and tiring shifts. Temporary hospitals with tents were built in open areas, and many patients were transferred to hospitals in provinces outside the disaster area by roads, airlines, and sea lines.[3-6] Various problems arise in the treatment of traumatic injuries, including crush injuries and renal failure resulting from their complications, after earthquakes. To eliminate the problems that present in survivors' access to healthcare providers and services need to be planned separately outside the earthquake zone.[7]

This study aimed to analyze the characteristics of the presentations of earthquake casualties who presented to the emergency department and outpatient clinics of our tertiary hospital from the earthquake region after the Turkiye-Syria earthquake that occurred on February 6th, 2023.

METHODS

Ethics

This study was approved by the Samsun University Clinical Researches Ethics Committee (Date: 09.08.2023, Decision No: 2023/14/13) and was planned retrospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Collection and Identification of Samples

Patients who presented to our hospital until January 31st, 2024, after the Turkiye-Syria earthquake, were included in the study.

Patients who entered the Samsun Training and Research Hospital emergency department and outpatient clinics with the diagnosis code X-34 (earthquake casualty) in ICD-10 were examined in the study. Patients with duplicate entries and insufficient data were not included in the study. As a result, the data of 1534 earthquake casualties who met the study criteria were retrospectively scanned through the hospital information management system. The patients' age, sex, presentation date, clinic, hospitalization status, and the earthquake region they came from were recorded.

Statistical Analysis

The sample size in the study was calculated using power analysis with the G*Power software package (version 3.1.9.6, Franz Faul, Universitat Kiel, Germany). Effect size 0.16; Type 1 error was taken as 0.05 and test power as 0.95, and the total required sample size was determined as at least 773.

All statistical analyses in the study were performed using the SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are given as mean and standard deviation in numerical data, and distributions of nominal or ordinal variables are given as numbers and percentages. Comparisons between groups in terms of categorical variables were made using the Chi-square test. Whether continuous variables conformed to normal distribution was analyzed using the Kolmogorov-Smirnov test. Differences between two groups in terms of non-normally distributed continuous variables were analyzed using the Mann-Whitney U test, and differences between multiple groups were analyzed using the Kruskal-Wallis test. The results were evaluated within the 95% confidence interval and p-values <0.05 were considered significant. Bonferroni correction was made where necessary.

RESULTS

The mean age of the patients was 24.6±25.9 (range: 0-98) years, 686 (44.7%) patients were male, and 441 (28.7%) were aged under 18 years. One thousand one hundred ninety-nine (78.2%) were admitted or brought to the emergency department or intensive care units (ICU), and 210 (13.7%) were hospitalized after being admitted or brought to the hospital. No fatalities were reported among the earthquake casualties who presented. The provinces from where the patients mostly came were Hatay (25.9%), Kahramanmaraş (24.4%), and Malatya (17.4%). Seven hundred thirty (47.6%) patients were admitted to our hospital within the first 30 days after the earthquake. Presentation rates decreased rapidly in the months after the earthquake (Table 1) (Figure 1).

When age groups were examined, hospitalization rates in the 18-65, over 65, and 0-2-years age groups were significantly higher than other age groups (p<0.001). The rate of admission to outpatient clinics was found to be significantly higher in the 18-65 and over 65 years age groups compared with other age groups (p<0.001). The presentation rates for the 18-65 years age group within the first 7 days after the earthquake, the 0-2, 18-65, and over 65 years age groups 8-30 days after the earthquake, and the rates for child groups aged over 2 years as of 30 days after the earthquake were found to be significantly higher compared to other age groups (p<0.001). The number of patients in the 18-65 age group in patients coming from Hatay, 65 years and above in patients coming from Kahramanmaraş, 3-6 and 7-11 age groups in patients coming from Adıyaman, 12-17 age group in patients coming from Gaziantep, other age groups were significantly higher than the other groups. In patients coming from Turkiye, the rates of patients in the 12-17 age group were significantly higher than other age groups (p<0.001) (Table 2).

In women, inpatients (Figure 2), in patients presenting to outpatient clinics (Figure 3), and in patients from Adana, Hatay, Kahramanmaraş and Osmaniye provinces (Figure 4), the mean age was significantly higher than the other groups (p<0.001 for each) (Table 3).

The rates of hospitalized patients were found to be significantly higher in women (p=0.002), patients presenting to outpatient clinics (p<0.001), and patients presenting within the first 30 days after the earthquake (p<0.001) (Figure 5) compared with

Table 1. General distributions according to some variables of earthquakes

	n	%
n	1534	100.0
Sex		
Male	686	44.7
Female	848	55.3
Age (years)		
<18	441	28.7
18+	1093	71.3
Age (years)		
0-2	291	19.0
3-6	255	16.6
7-11	167	10.9
12-17	157	10.2
18-65	495	32.3
>65	169	11.0
Patient type		
Outpatient	1324	86.3
Inpatients	210	13.7
Patient's province		
Hatay	398	25.9
Kahramanmaraş	374	24.4
Malatya	267	17.4
Adıyaman	190	12.4
Gaziantep	132	8.6
Osmaniye	29	1.9
Adana	27	1.8
Şanlıurfa	19	1.2
Diyarbakır	15	1.0
Other	83	5.4
Month		
February	598	39.0
March	432	28.2
April	212	13.8
May	112	7.3
June	72	4.7
July	44	2.9
August	26	1.7
September	13	0.8
October	13	0.8
November	6	0.4
December	2	0.1
January	4	0.3
Time passed after the earthquake (days)		
1-30 days	730	47.6
>30 days	804	52.4
Time passed after the earthquake (days)		
1-7 days	195	12.7
8-30 days	535	34.9
31-60 days	364	23.7
>60 days	440	28.7
Clinic		
Emergency/ICU	1199	78.2
Clinics	335	21.8
Clinic		
Pediatric emergency room	806	52.4
Adult emergency room	314	20.4
Home care clinic	101	6.6
Obstetrics emergency room	69	4.5
Gynecology and obstetrics	50	3.3
Family medicine	42	2.7
Chemotherapy unit	38	2.5
Pediatry	27	1.8
Radiation oncology	10	0.7
ICUs	10	0.7
Other	68	4.4

ICU: Intensive care unit

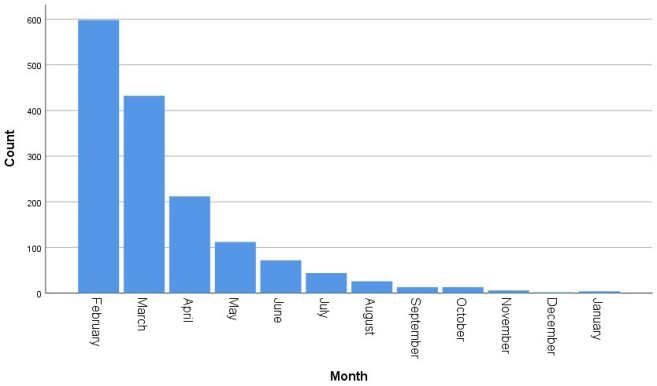

Figure 1. Distribution of patients according to the months they presented to our hospital

other groups. Hospitalization rates were similar between the provinces that patients came from (p=0.449) (Figure 6) (Table 4).

The rates of patients presenting to emergency rooms or ICUs were significantly higher in men (p=0.011) and in those who presented within the first 7 days after the earthquake (p=0.001) compared with other groups. The rates of clinic types consulted were similar between the provinces that patients came from (p=0.17) (Figure 7) (Table 5).

DISCUSSION

The traumas experienced by earthquake casualties after major earthquakes occur in a wide variety of forms and intensities. Accordingly, the presentations of earthquake casualties to hospitals and their admission characteristics vary greatly.[4-8] In this study, some characteristic features of patients who were admitted to a hospital far from the epicenter of a major earthquake after an earthquake were analyzed.

Gürü et al.[9] analyzed 124 earthquake casualties' presentations to the emergency department in hospitals in Ankara within 3 weeks after the Turkiye-Syria earthquake, and reported that 14.5% of the presentations were admitted. In our study, it was determined that 78.2% of earthquake casualties were brought to the emergency department or ICUs, and 13.7% were hospitalized after being admitted or brought to the hospital. Considering that our hospital is 700 km away from the earthquake zone, it can be assumed that those who were seriously injured in the earthquake were taken to hospitals in nearby provinces. These findings show that those with less serious conditions may have been brought to or presented to our hospital, and that the majority were treated as outpatients and discharged after presenting to the emergency department. This may indicate that the distance of the hospital to the earthquake epicenter significantly affects the patient portfolio. Other studies reported that mortality rates were high in hospitals close to the earthquake zone, but there was no mortality in hospitals in remote centers.[9-13] In our study, there was no mortality among the earthquake casualties who presented to our hospital. This situation can be explained by the fact that those in critical condition died before moving away from the earthquake zone, and those who moved away from the area had lesser injuries anyway.

Gürü et al.[9] reported that approximately half of the earthquake casualties came from Hatay to their hospital in Ankara. Cakin et al.[10] also found that half of the patients in their hospital in Antalya after the same earthquake came from Hatay. In our study, it was determined that patients mostly came from Hatay (25.9%), Kahramanmaraş (24.4%), and Malatya (17.4%). This

Table 2. Distribution of some variables according to age groups

	0-2		3-6		7-11		12-17		18-65		>65		p
	n	%	n	%	n	%	n	%	n	%	n	%	
Patient type													**<0.001**
Outpatient	250	85.9	247	96.9	166	99.4	149	94.9	369	74.5	143	84.6	
Inpatient	41	14.1	8	3.1	1	0.6	8	5.1	126	25.5	26	15.4	
Clinic													**<0.001**
Emergency/ICU	266	91.4	249	97.6	164	98.2	150	95.5	321	64.8	49	29.0	
Clinics	25	8.6	6	2.4	3	1.8	7	4.5	174	35.2	120	71.0	
Patient's province													**<0.001**
Hatay	58	19.9	51	20.0	35	21.0	38	24.2	174	35.3	42	24.9	
Kahramanmaraş	71	24.5	55	21.5	42	25.0	40	25.4	111	22.4	55	32.4	
Malatya	60	20.6	42	16.5	37	22.2	29	18.5	68	13.7	31	18.3	
Adıyaman	30	10.3	45	17.6	32	19.2	17	10.8	53	10.7	13	7.7	
Gaziantep	23	7.9	27	10.6	9	5.4	24	15.3	43	8.7	6	3.6	
Osmaniye	3	1.0	6	2.4	4	2.4	2	1.3	8	1.6	6	3.6	
Adana	9	3.1	2	0.8	0	0.0	2	1.3	10	2.0	4	2.4	
Şanlıurfa	7	2.4	2	0.8	2	1.2	0	0.0	7	1.4	1	0.6	
Diyarbakır	7	2.4	3	1.2	0	0.0	0	0.0	5	1.0	0	0.0	
Other	23	7.9	22	8.6	6	3.6	5	3.2	16	3.2	11	6.5	
Month													**<0.001**
February	109	37.4	68	26.6	38	22.8	53	33.9	252	51.0	78	46.1	
March	82	28.2	68	26.6	52	31.0	43	27.4	145	29.3	42	24.9	
April	32	11.0	34	13.3	29	17.4	29	18.5	67	13.5	21	12.4	
May	22	7.6	30	11.8	21	12.6	14	8.9	15	3.0	10	5.9	
June	25	8.6	15	5.9	11	6.6	4	2.5	7	1.4	10	5.9	
July	9	3.1	18	7.1	5	3.0	4	2.5	3	0.6	5	3.0	
August	4	1.4	9	3.5	5	3.0	2	1.3	4	0.8	2	1.2	
September	1	0.3	5	2.0	1	0.6	4	2.5	2	0.4	0	0.0	
October	3	1.0	6	2.4	3	1.8	1	0.6	0	0.0	0	0.0	
November	4	1.4	1	0.4	1	0.6	0	0.0	0	0.0	0	0.0	
December	0	0.0	0	0.0	0	0.0	2	1.3	0	0.0	0	0.0	
January	0	0.0	1	0.4	1	0.6	1	0.6	0	0.0	1	0.6	
Time passed after the earthquake (days)													**<0.001**
1-7 days	30	10.3	16	6.3	11	6.6	14	8.9	100	20.2	24	14.2	
8-30 days	116	39.9	74	29.0	35	21.0	48	30.6	194	39.2	68	40.2	
31-60 days	52	17.9	59	23.1	52	31.1	41	26.1	122	24.6	38	22.5	
>60 days	93	32.0	106	41.6	69	41.3	54	34.4	79	16.0	39	23.1	

ICU: Intensive care unit

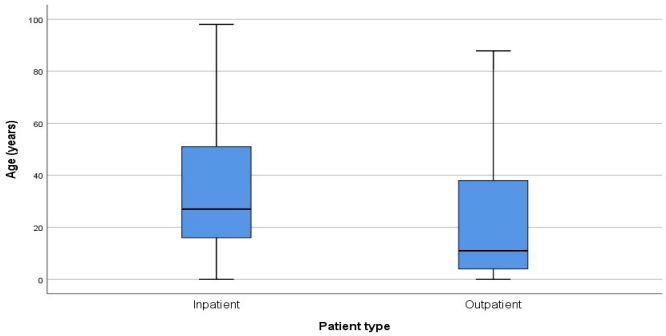

Figure 2. Box-plot graph comparing the average age of patients according to whether they received outpatient or inpatient treatment

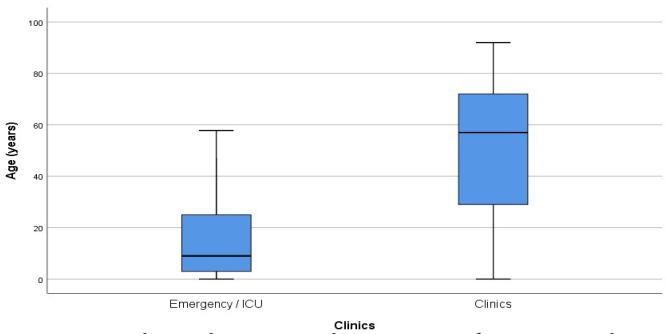

Figure 3. Box-plot graph comparing the average age of patients according to the type of clinic they presented to

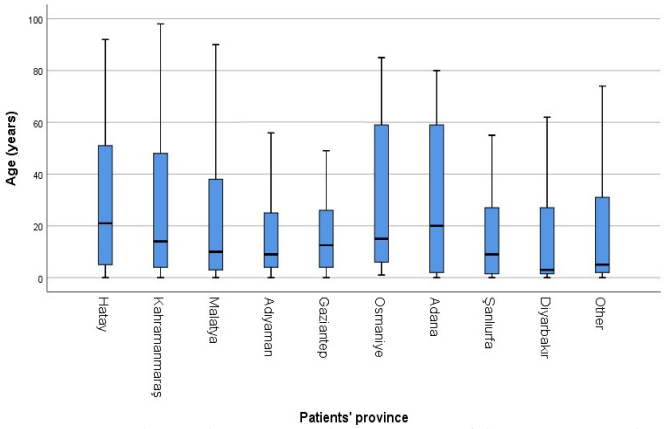

Figure 4. Box-plot graph comparing the average age of the patients according to their province of origin

finding may indicate that both the severity of earthquake exposure, clinical status, transportation facilities, and distance affect the patient distribution in provinces affected by the earthquake in very different ways.

Cagiran et al.,[11] Dursun et al.,[12] Bulut et al.,[13] and Eyler et al.[14] reported that the peak admission period to hospitals close to the earthquake was in the first 12 or 24 hours after a previous earthquake. After an earthquake in Nepal, it was reported that

Table 3. Comparison of patient ages (years) according to some variables

	Mean	SD	p
General	24.6	25.9	
Sex			**<0.001**
Male	18.2	23.3	
Female	29.8	26.8	
Patient type			**<0.001**
Outpatient	23.5	26.0	
Inpatient	31.6	24.5	
Clinic			**<0.001**
Emergency/ICU	17.2	20.0	
Clinics	51.4	27.1	
Time passed after the earthquake (days)			**<0.001**
1-7 days	31.7	25.0	
8-30 days	26.6	26.7	
31-60 days	24.8	25.0	
>60 days	18.9	25.2	
Patient's province			**<0.001**
Adana	29.0	29.6	
Adıyaman	19.9	23.4	
Diyarbakır	15.3	22.0	
Gaziantep	18.0	19.0	
Hatay	29.3	26.5	
Kahramanmaraş	26.9	27.6	
Malatya	22.3	24.9	
Osmaniye	28.7	27.5	
Şanlıurfa	17.2	20.3	
Other	21.7	29.4	

SD: Standard deviation, ICU: Intensive care unit

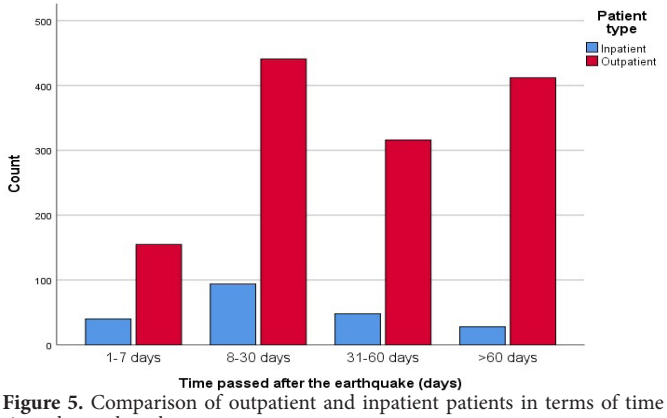

Figure 5. Comparison of outpatient and inpatient patients in terms of time since the earthquake

the peak number of admissions to hospitals not very close to the earthquake zone was on the 5th day.[15,16] Gürü et al.[9] reported that no earthquake casualties came to hospitals in Ankara in the first two days of the earthquake, and the highest peaks were on the 3rd and 4th days. Cakin et al.[10] reported that the peak of presentations to hospitals in the middle distance from the earthquake occurred between the 5th and 7th days. In our study, earthquake casualties started to arrive the day after the earthquake, increased significantly on the 3rd day, but the

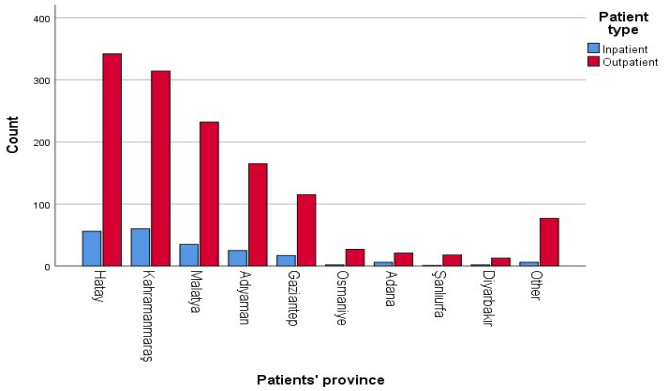

Figure 6. Comparison of the rates of patients receiving outpatient and inpatient treatment according to the provinces they come from

Table 4. Distribution of patients according to whether they received outpatient or inpatient treatment

	Outpatient		Inpatient		Total	p
	n	%	n	%	n	
Total	1324		210		1534	
Sex						**0.002**
Male	613	89.4	73	10.6	686	
Female	711	83.8	137	16.2	848	
Clinic						**<0.001**
Emergency/ICU	1121	93.5	78	6.5	1199	
Outpatient	203	60.6	132	39.4	335	
Time passed after the earthquake (days)						<0.001
1-7 days	155	79.5	40	20.5	195	
8-30 days	441	82.4	94	17.6	535	
31-60 days	316	86.8	48	13.2	364	
>60 days	412	93.6	28	6.4	440	
Patient's province						**0.449**
Hatay	342	85.9	56	14.1	398	
Kahramanmaraş	314	84.0	60	16.0	374	
Malatya	232	86.9	35	13.1	267	
Adıyaman	165	86.8	25	13.2	190	
Gaziantep	115	87.1	17	12.9	132	
Osmaniye	27	93.1	2	6.9	29	
Adana	21	77.8	6	22.2	27	
Şanlıurfa	18	94.7	1	5.3	19	
Diyarbakır	13	86.7	2	13.3	15	
Other	77	92.8	6	7.2	83	

ICU: Intensive care unit

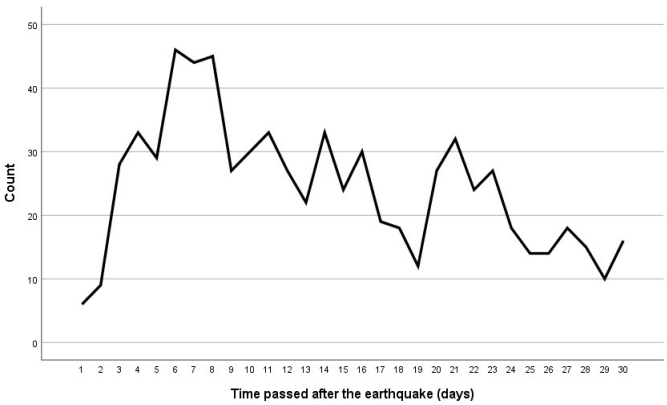

Figure 7. Line graph showing the number of earthquake casualties who presented to our hospital in the days after the earthquake

Table 5. Distribution of patients according to their admission to the emergency department or outpatient clinics

	Emergency/ICU		Clinics		Total	p
	n	%	n	%	n	
Total	1199		335		1534	
Sex						**0.011**
Male	581	84.7	105	15.3	686	
Female	618	72.9	230	27.1	848	
Time passed after the earthquake (days)						**0.001**
1-7 days	170	87.2	25	12.8	195	
8-30 days	417	77.9	118	22.1	535	
31-60 days	264	72.5	100	27.5	364	
>60 days	348	79.1	92	20.9	440	
Patient's province						**0.170**
Hatay	302	75.9	96	24.1	398	
Kahramanmaraş	286	76.5	88	23.5	374	
Malatya	225	84.3	42	15.7	267	
Adıyaman	147	77.4	43	22.6	190	
Gaziantep	110	83.3	22	16.7	132	
Osmaniye	21	72.4	8	27.6	29	
Adana	19	70.4	8	29.6	27	
Şanlıurfa	16	84.2	3	15.8	19	
Diyarbakır	12	80.0	3	20.0	15	
Other	61	73.5	22	26.5	83	

ICU: Intensive care unit

real peak period was between days 5 and 9. Afterwards, the number of presentations started to decrease slowly. The reason for these differences may be the difference in transportation facilities between hospitals from the earthquake zone. In our study, it was found that 47.6% of the patients presented to our hospital within the first 30 days after the earthquake, and the presentation rates decreased rapidly in the months after the earthquake. This finding suggests that admissions due to exposure to the earthquake were naturally high immediately after the earthquake, but in the following months, perhaps earthquake casualties presented to the hospital for reasons other than earthquake exposure. This finding also shows that in a short time after the earthquake, our hospital served an intense number of earthquake casualties despite its long distance from the affected areas.

When the age groups were examined in our study, hospitalization rates were found to be significantly higher in the 18-65, over 65, and 0-2-years age groups compared with other age groups, and the rate of admissions to outpatient clinics was found to be significantly higher in the 18-65 and over 65 years age groups compared with other age groups. It was observed that there were significant changes in the age groups of the patients who presented in the periods after the earthquake. We also found significant differences in age groups depending on the provinces the patients came from. In our study, the mean age was found to be significantly higher in women, inpatients, patients presenting to outpatient clinics, and patients from some provinces compared with other groups. All these findings show that age is an important factor in patients coming to our city from the earthquake zone and presenting to the hospital, and that very young and older patients are more likely to present to the emergency department or be hospitalized.

In our study, the rates of hospitalization in patients admitted within the first 30 days after the earthquake were found to be significantly higher than other groups. These findings show that the clinical conditions of patients arriving immediately after the earthquake are naturally more severe.

Reasons for hospitalization in internal medicine and emergency departments after natural disasters vary. Studies on this subject will be useful for designing specific intervention programs before disasters that may occur in the future and mitigating the harmful effects of earthquakes.[17] In the study, hospitalization rates were found to be similar between the provinces the patients came from. This finding shows that the clinical condition is not the main determinant between proximity to the earthquake epicenter and coming to our province far from the earthquake. This may be due to various factors such as the fact that the seriously injured were taken to provinces near the earthquake, the treatments were given in the same province in provinces that were less affected by the earthquake, the transportation facilities from each province differed in the first days of the earthquake, our province was far from the earthquake zone, and the number of presentations was not as much as in larger provinces.

Intensive care support is provided to a significant portion of those trapped under rubble after earthquakes. There are few studies in the literature examining the clinical course and intensive care needs of earthquake casualties and showing the experiences of physicians.[18,19] In our study, the rates of patients admitted to the emergency department or ICU in the first 7 days after the earthquake were found to be significantly higher than the other groups. This finding indicates that those with more serious clinical conditions consulted the emergency department.

Limitations

There are some limitations in this study. For example, because the study aims to profile earthquake casualties who were admitted to a hospital that is not close to the epicenter of a large and devastating earthquake, the findings obtained will be very different from the findings of a hospital in the earthquake zone. Accordingly, in our study, where it is normal that critical injuries and mortality are not observed, risk factors in this regard were not evaluated. However, in line with our study purpose, the fact that the number of patients for 1 year was very high at 1534 was a factor that made the analyses within the study strong.

CONCLUSION

In conclusion, the findings obtained from our study indicated that the prognosis was good for earthquake casualties who presented to our hospital, which was far from the center of a major earthquake, that the highest number of presentations was between the 5th and 9th days, the period between the earthquake and the hospital admission was a determining factor in terms of the clinic of presentation and hospitalization, and the proximity to the center of the earthquake did not affect the prognosis in presentations. Our findings also show that the age group is an important factor in terms of the clinic of presentation, hospitalization, the period after the earthquake, and the province from which the presentation is made. This study provides demographic data that will contribute to the improvement of health service delivery after future earthquakes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Samsun University Clinical Researches Ethics Committee (Date: 09.08.2023, Decision No: 2023/14/13).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Evaluation of dyspepsia symptom severity in pediatric patients: association with endoscopic and pathological findings

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ABSTRACT

Aims: There is diagnostic difficulty in distinguishing between organic and functional causes of dyspepsia, which is characterized by a variety of gastrointestinal symptoms. This study aimed to evaluate the correlation between dyspeptic complaints, clinical symptoms, endoscopic findings, and pathology results in pediatric patients.

Methods: A total of 159 children aged 8-17 years with dyspeptic complaints underwent upper gastrointestinal endoscopy (UGE). The Dyspepsia Symptom Severity Index (DSSI), comprising three parts (dysmotility-like, reflux-like, and ulcer-like symptoms) and 19 questions, was used to assess symptom severity. Endoscopic procedures were performed under general anesthesia, and biopsy samples were obtained.

Results: The study included 159 patients with a median age of 15 years (ranging from 8 to 17 years). Among them, 38 (29.1%) were male and 121 (76.9%) were female. DSSI scores were calculated for each subgroup and the total score. When assessing the relationship between chronic diseases and DSSI scores, no significant association was found (p=0.48). However, smoking showed a significant correlation with DSSI scores (p=0.01 for dysmotility-like, p=0.02 for reflux-like, and p<0.01 for ulcer-like symptoms). Gender differences were observed in DSSI scores, with girls exhibiting significantly higher median scores for dysmotility-like findings compared to boys (p=0.02). Endoscopy findings also correlated with DSSI scores, with significantly higher scores in patients with ulcers (p<0.01). Pathological findings such as esophagitis were found to have significant associations with reflux-like symptoms (p=0.04), and crypt hyperplasia was associated with ulcer-like symptoms (p=0.04) in patients with DSSI subgroup scores. However, no significant differences were found between pathology findings and dyspepsia severity, significant associations were observed between UGE findings (such as ulcers, pangastritis, erosional areas, and fragility) and ulcer-like symptoms.

Conclusion: The study found significant links between dyspepsia severity and endoscopic results, stressing the need for reliable symptom scales for pediatric patients. It also highlights smoking as a factor in dyspepsia severity in children. Further research is needed to evaluate endoscopy's effectiveness in distinguishing between organic and functional dyspepsia. The study points out the limited understanding and consensus on diagnosing and managing dyspepsia in children, calling for the development of validated symptom scales and further research into cost-effective management strategies.

Keywords: Dyspepsia, pediatric patients, symptom severity, endoscopy, pathology findings

INTRODUCTION

Dyspepsia is characterized by various interconnected symptoms such as abdominal pain, distension, postprandial fullness, early satiety, anorexia, nausea, belching, and regurgitation. However, these dyspeptic complaints are non-specific and insufficient to distinguish between organic and functional gastrointestinal causes.[1]

Currently, there is no consensus on the diagnosis and management of functional dyspepsia (FD) in children. While some scales have been developed to assess the severity of dyspeptic symptoms in adults and differentiate between functional and organic dyspepsia (OD),[2,3] the reliability and validity of these dyspepsia symptom scales are not yet fully established.[4] Moreover, there is no universally accepted dyspepsia symptom scale specifically designed for children and adolescents. The validity and reliability of the existing dyspepsia symptom scale for this age group are lower compared to adults.[5,6] Additionally, the data on the cost-effective method of using endoscopy based on the score results, which is

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commonly employed in adults, are limited for pediatric and adolescent populations.[7,8]

Early and accurate diagnosis through upper gastrointestinal system endoscopy (UGE) is crucial in order to prevent unnecessary treatments. Several studies have compared clinical findings with endoscopic findings in children who underwent UGE during childhood.[9,10] However, the number of studies comparing dyspepsia symptom scales with endoscopy findings is relatively limited. Most of these studies have focused on evaluating the reliability and utility of scales for distinguishing between organic and functional dyspepsia in children.[4]

The aim of our study is to assess the correlation between complaints and clinical symptoms in pediatric patients who presented with dyspeptic complaints at our hospital and underwent UGE, as well as the UGE findings. With the data we collected, we aim to evaluate the effectiveness of the Dyspepsia Symptom Severity Index (DSSI) scores used in this study in distinguishing functional and organic dyspepsia and the relationship between these scores and upper gastrointestinal tract problems.

METHODS

This study was produced from the thesis study conducted in 2015. Institutional approval was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study involved 159 pediatric patients aged 8-17 years who visited the Pediatric Gastroenterology outpatient clinic at the Ministry of Health Ankara Training and Research Hospital, Department of Pediatrics, for dyspeptic complaints and subsequently underwent UGE.

The patient group consisted of children who presented at the pediatric gastroenterology outpatient clinic with continuous or intermittent upper gastrointestinal system complaints persisting for at least two months, including symptoms such as epigastric pain, discomfort in the upper abdomen, burning sensation in the chest, sour taste in the mouth, halitosis, belching, nausea, and rapid satiety. Exclusion criteria for the study included a previous diagnosis of organic or systemic disease, peptic ulcer, gastroesophageal reflux (GER) disease, and *Helicobacter pylori (H. pylori)* infection; neurological disorders; elevated transaminase levels and amylase-lipase levels; positive stool test results for parasites or giardia antigen; recent antibiotic or anti-secretory drug use for dyspeptic complaints within the last month; and previous treatment for similar complaints at other medical facilities.

In addition to sociodemographic questions, all participating children and their parents were asked about cigarette and alcohol use, as well as existing diseases. The patients were also questioned regarding hoarseness, rapid weight loss, abdominal pain accompanied by fever, history of jaundice, dysphagia, hematemesis, and melena. DSSI was performed on all patients at the time of admission.

The DSSI consists of three parts: dysmotility-like symptoms, reflux-like symptoms, and ulcer-like symptoms, with a total of 19 questions (Figure). Dysmotility-like symptoms include belching, bloating, postprandial fullness, inability to finish meals, abdominal discomfort, abdominal bloating, pre-meal nausea, post-meal nausea, and morning sickness. Reflux-like symptoms include bitter water in the mouth, chest burning, and stomach burning. Ulcer-like symptoms include abdominal pain after meals, before meals, or at night. Patients were asked to rate the severity of each symptom on a scale from 0 to 4 (0=no symptoms, 1=mild, 2=moderate, 3=severe, 4=very severe). Average scores between 0 and 4 were calculated for each part (dysmotility-like, reflux-like, and ulcer-like), as well as a total mean score for DSSI by averaging the three parts.[11,12]

Dysmotility-like
1.Frequent burping or belching
2. Bloating
3.Feeling full after meals
4.Inability to finish normal-sized meals
5.Abdominal (belly) discomfort, without pain, after meals
6. Abdominal (belly) distension (feels as though you need to loosen your clothes)
7.Nausea before meals
8.Nausea after meals
9.Nausea when you wake up in the morning
10.Retching (heaving as if to vomit, with little result)
11.Vomiting

Refluxlike
12.Burping with bitter tasting fluid in throat
13. Regurgitation of bitter fluid into your mouth (reflux) during the day
14. Regurgitation (reflux) at night
15. Burning feeling in your chest (heartburn)
16.Burning feeling in your stomach

Ulcerlike
17. Abdominal (belly) ache or pain right after meals
18.Abdominal (belly) pain before meals or when hungry
19. Abdominal (belly) pain at night

Figure. Dispepsia Symptom Severity Index

The endoscopic procedures for the study participants were conducted in the operating room under general anesthesia. Biopsy samples were taken from the stomach (corpus, antrum, and pylorus), lower esophagus, and duodenum during the upper gastrointestinal endoscopy. The Pentax EPM 3500 device was used for the endoscopic examinations.

The data from the study were analyzed using the 'SPSS 15.0' statistical program. Statistical analyses included Kruskal-Wallis and Chi-Square tests. Results with p-values less than 0.05 were considered statistically significant.

RESULTS

The median age of the 159 patients included in the study was 15 years (ranging from 8 to 17 years). Among the participants, 29.1% were male (38), while 76.9% were female (121). Smoking history was reported by 22.6% (36) of the patients. Of the 36 patients who reported smoking, 39% (14) were female, and 61% (22) were male.

Upper gastrointestinal system endoscopy was performed on all patients included in the study. There were no complications related to general anesthesia. Macroscopically, erythematous gastritis was observed in 95% (151) of the patients, nodular gastritis in 21% (34), and erosive gastritis in 20% (33). Additionally, edema was present in 61% (98) of the patients, mucosal fragility in 4.4% (7), lower esophageal sphincter laxity in 6.9% (11), and z-line irregularity in 7.5% (12). Ulcer findings were observed in 13.2% (21) of the patients. In the duodenal examinations, flattening of the folds was observed in 6.9% (18) of the patients. Antral gastritis was found in 84.3% (134) of the patients included in the study, pangastritis in 10.1% (16), and alkaline reflux gastritis in 7.5% (12). Among the patients, 36.4% (58) had one or more of the following macroscopic findings: nodularity, ulcer, and erosional area.

The responses of the patients to the DSSI were calculated for each subgroup as well as the total score (Table 1).

Table 1. Data of subgroups and total values obtained by DSSI

	Mean	Median	SD	Min	Max
Dysmotility-like symptoms	0.8	0.90	0.40	0.18	1.91
Refluxlike symptoms	0.99	1.00	0.67	0	2.40
Ulcerlike symptoms	1.04	1.00	0.70	0	3.00
Total score	1.01	0.96	0.43	0.22	2.37

DSSI: Dyspepsia Symptom Severity Index, SD: Standard deviation, Min: Minimum, Max: Maximum

When evaluating the relationship between the patients' existing chronic diseases and the total score of DSSI, no statistically significant relationship was found (p=0.48). However, a statistically significant correlation was observed between smoking and the DSSI, including total score, dysmotility-like, reflux-like, and ulcer-like findings (respectvly, p=0.01, 0.02, <0.01, <0.01).

Gender was also assessed in relation to the subgroup and total scores obtained with the DSSI. It was found that the median score for dysmotility-like findings was significantly higher in girls compared to boys (p=0.02). However, no statistically significant difference was observed between girls and boys in other parameters (p>0.05).

Furthermore, a comparison was made between the endoscopy findings of the patients and the total score of DSSI. It was found that the DSSI total score was significantly higher in patients with ulcers detected during UGE (p<0.01). However, there was no statistically significant difference in DSSI total score concerning antral gastritis, pangastritis, alkaline reflux gastritis, nodularity, hyperemia, edema, LES laxity, erosional area, and flattening of pleats observed in UGE (Table 2).

Table 2. Comparison of DSSI total score and endoscopy findings

		DSSI total score-median		
Upper gastrointestinal tract sign	n	Yes	None	p
Antral gastritis	134	0.99	0.89	0.72
Pangastritis	16	1.17	0.95	0.90
Alkaline reflux gastritis	12	1.07	1.08	0.73
Ulcer	21	1.42	0.90	<0.01
Nodularity	34	0.89	0.99	0.74
Hyperemia	95	0.99	0.78	0.09
LES laxity	11	0.84	0.97	0.77
Erosional area	33	0.95	0.97	0.38
Flattening of pleats	18	0.70	0.99	0.16
Edema	98	0.99	0.96	0.27
Fragility	7	1.36	0.95	0.15

DSSI: Dyspepsia Symptom Severity Index, LES: Lower esophageal sphincter

The pathology findings of the patients were compared to the total score of DSSI. The study examined whether there were any statistically significant differences between *H. pylori* infection, esophagitis, duodenitis, and crypt hyperplasia in relation to GER. However, no significant differences were detected (p>0.05).

When comparing antral pathologies with the DSSI total score, no statistically significant difference was observed. (p>0.05).

The study also evaluated the relationship between the median score of DSSI subgroups (dysmotility, reflux, and ulcer-like findings) and UGE findings (Table 3). The median score for dysmotility-like findings was 1.18 in patients with ulcers detected during UGE, compared to 0.90 in patients without ulcers. This difference was found to be statistically significant (p=0.01).

Furthermore, in patients with pangastritis observed during UGE, the median score for ulcer-like findings was 1.18, compared to 0.90 in patients without ulcer-like findings. This difference was statistically significant (p=0.009). In patients with ulcers detected during UGE, the median score for ulcer-like findings was 2.00, compared to 1.00 in patients without ulcers. This difference was also found to be statistically significant (p=0.001). Additionally, in patients with erosional areas observed during UGE, the median score for ulcer-like findings was 1.66, compared to 1.00 in patients without ulcer-like findings. This difference was statistically significant (p=0.008). Similarly, the median score for ulcer-like findings was 1.66 in patients with fragility observed during UGE, compared to 1.00 in patients without fragility. This difference was statistically significant (p=0.008).

The study examined the relationship between the scores of dysmotility-like, reflux-like, and ulcer-like findings in patients and the pathology findings (Table 4). It was found that the median score for reflux-like findings was 1.10 in patients with esophagitis detected in the pathological findings of biopsies performed during UGE, compared to 0.90 in patients without esophagitis. This difference was statistically significant (p=0.04). Additionally, the median score for ulcer-like findings was 1.66 in patients with crypt hyperplasia observed in the pathological findings of biopsies performed during UGE, compared to 1.00 in patients without crypt hyperplasia. This difference was also statistically significant (p=0.04).

Table 3. Comparison of dysmotility-like, reflux-like, and ulcer-like findings with endoscopy signs

		Dysmotility-like symptoms, median			Refluxlike symptoms, median			Ulcerlike symptoms, median		
UGE signs	n	Yes	None	p	Yes	None	p	Yes	None	p
Antral gastritis	134	0.90	0.90	0.18	1.00	0.80	0.39	1.00	1.00	0.23
Pangastritis	16	0.90	0.90	0.59	0.90	1.00	0.89	1.66	1.00	0.009
Alkaline reflux gastritis	12	0.90	0.90	0.93	1.10	1.00	0.29	0.66	1.00	0.25
Ulcer	21	1.18	0.90	0.01	1.00	1.00	0.31	2.00	1.00	<0.001
Nodularity	34	0.90	0.90	0.84	1.00	1.00	0.93	0.83	1.00	0.60
Hyperemia	95	0.90	1.00	0.44	1.00	1.00	0.48	1.00	0.62	0.05
LES laxity	11	0.81	0.90	0.34	0.67	1.00	0.85	1.00	1.00	0.89
Erosional area	33	0.90	0.90	0.98	0.80	1.00	0.27	1.66	1.00	0.008
Flattening of pleats	18	0.90	0.90	0.51	0.40	1.00	0.15	0.66	1.00	0.39
Edema	98	0.95	0.90	0.32	1.00	1.00	0.92	1.00	1.00	0.38
Fragility	7	0.90	0.90	0.55	0.80	1.00	0.91	1.66	1.00	0.008

UGE: Upper gastrointestinal system endoscopy findings, LES: Lower esophageal sphincter

Table 4. Comparison of dysmotility-like, refluxlike, and ulcerlike findings with pathology signs

		Dysmotility-like symptoms-median			Refluxlike symptoms-median			Ulcerlike symptoms-median		
Pathology signs	**n**	**Yes**	**None**	**p**	**Yes**	**None**	**p**	**Yes**	**None**	**p**
Helicobacter pylori infection	94	0.90	0.90	0.89	1.00	1.00	0.53	1.00	1.00	0.28
Esophagitis	70	0.95	0.90	0.57	1.10	1.00	0.04	1.00	1.00	0.27
Duodenitis	77	1.00	0.90	0.58	1.00	1.00	0.97	1.00	1.00	0.23
Crypt hyperplasia	39	1.09	0.90	0.55	1.20	1.00	0.45	1.66	1.00	0.04
GER compatible finding	8	1.00	0.90	0.55	1.20	1.00	0.31	1.00	1.00	0.58

GER: Gastroesophageal reflux

DISCUSSION

Dyspeptic complaints are a common issue in both adults and children. However, there is still no consensus on the diagnosis and management of FD in children. Various scales have been developed to assess the severity of dyspeptic symptoms and differentiate between functional and organic dyspepsia in adults, but their reliability and validity are not yet fully established.[2-4]

There is no generally accepted scale that assesses the severity of dyspepsia in children, suggests organic causes, and directs them to UGE. In this study, we evaluated the findings from UGE performed on children aged 8-17 who presented with dyspepsia complaints, using data obtained from the DSSI and the histopathological results of biopsy materials taken during endoscopy.

Smoking has been reported to increase gastric acid secretion and decrease pancreatic bicarbonate secretion, and it is implicated in the pathogenesis of gastric and duodenal ulcers.[13,14] Koivisto et al.[15] studied the effect of *H. pylori* infection and smoking on the gastric mucosa in adults. They found that inflammation in the gastric mucosa decreased in the smoking group, but smoking increased the severity of *H. pylori* infection by reducing the humoral immune response, thereby raising the frequency of duodenal ulcer development. In our study, 22.6% of the patients were smokers, and we observed higher DSSI subgroup and total scores in these smoking patients. This suggests that smoking may increase the severity of dyspepsia, and the scores obtained in the smoking group in our study might have been elevated as a result.

Previous studies have reported varying frequencies of specific endoscopic findings in children with dyspeptic complaints. For instance, Uğraş and Alan[16] found nodular gastritis in 59.6% of children aged 5-18 years who underwent UGE for abdominal pain, while esophagitis, pangastritis, lower esophageal sphincter laxity, and flattened duodenal folds were observed at lower frequencies. In our study, nodular gastritis was less frequent (21%) in children aged 8-17 years with dyspeptic complaints. The discrepancy in findings could be attributed to differences in study populations and age ranges.

The relationship between nodular gastritis and *H. pylori* infection has been highlighted in previous studies. BahúMda et al.[17] reported a specificity of 98.5% between nodular appearance and *H. pylori* infection in children with chronic abdominal pain. Zhang et al.[18] detected nodular gastritis in 17.8% of children with dyspeptic complaints and recurrent upper quadrant abdominal pain, and 86% of these patients were found to have *H. pylori* infection. Similarly, in our study, *H. pylori* infection was detected in 79% of patients with nodular appearance on UGE, indicating a significant correlation between nodular gastritis and *H. pylori* infection.

The dyspepsia symptom severity index a scale commonly used in adults with dyspeptic complaints. Leidy et al.[11] applied the DSSI to both dyspeptic patients and healthy individuals and found significantly higher DSSI total scores and subcategory scores in the dyspeptic group compared to the control group. Additionally, this study demonstrated that the applicability of the DSSI is high, showing that it can be repeatedly used in patient groups. As a result, the researchers concluded that the assessment obtained through the DSSI and its subcategories is a suitable test for determining the severity of dyspepsia in patients being monitored for functional dyspepsia.

In our study, we observed significant increases in certain parameters of the scoring systems we utilized, particularly in patients with organic dyspepsia. However, we also found evidence that these scoring systems could not completely differentiate between organic and functional dyspepsia. Based on these findings, our aim was to provide appropriate management and treatment guidance for children with dyspepsia, and to avoid unnecessary upper gastrointestinal endoscopy. Unfortunately, there are limited studies on dyspepsia management planning and cost-effectiveness analysis specifically in children.

Limitations

The lack of significant differences between pathological findings and dyspepsia symptoms suggests that this part of the study may have limitations. More in-depth analysis and additional research are needed to better understand the relationship between these factors.

For instance, Olson et al.[19] conducted a study comparing the cost and clinical effectiveness of various treatment modalities in dyspeptic children. These modalities included biopsy-guided endoscopy for *H. pylori* infection, endoscopy without biopsy, *H. pylori* therapy based on *H. pylori* serology screening results, empirical antisecretory therapy, and empirical antibiotic combined with antisecretory therapy for *H. pylori*. Their study showed that empirical antisecretory treatment management was the most cost-effective approach, reducing the need for endoscopy by 40%. However, cost-effectiveness studies on the treatment and management of childhood dyspepsia, both in our country and worldwide, are limited and insufficient.

Currently, another treatment approach applied primarily in adults is to determine the need for endoscopy based on dyspeptic symptom scores. This approach involves assessing the severity and characteristics of dyspeptic complaints to

determine the necessity of endoscopy.[20,21] However, studies in the pediatric population are scarce and the results are contradictory. Therefore, in future studies, it may be beneficial to modify the DSSI scale used in our study or apply other scoring systems to a larger sample of dyspeptic patients, with a revised definition of organic-functional dyspepsia. The use of pre-endoscopy scoring systems in the pediatric age group holds potential benefits. Further research, particularly cost-effectiveness studies, are needed to address this subject comprehensively.

CONCLUSION

This study examines the relationship between dyspepsia symptom severity and endoscopic findings in pediatric patients. Using the DSSI and UGE, significant correlations were identified between dyspepsia symptoms and organic findings such as ulcers and pangastritis. The results suggest that the DSSI can be a useful tool for distinguishing between functional and organic dyspepsia in children.

The study also highlights the impact of smoking on dyspepsia severity, with smokers exhibiting higher DSSI scores. This emphasizes the importance of integrating smoking cessation efforts into the treatment of dyspeptic symptoms.

However, DSSI alone may not fully differentiate between functional and organic dyspepsia in children, indicating the need for comprehensive diagnostic approaches, including UGE and histopathological examination. Future research should focus on refining dyspepsia symptom scales for pediatric populations and assessing the cost-effectiveness of different treatment strategies. The ultimate goal is to improve diagnosis and management while ensuring patient safety and comfort.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was produced from the thesis study conducted in 2015.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Investigation of the frequency of wheezing and airway resistance using the interrupter technique in children born premature and over 3 years old

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ABSTRACT

Aims: The term wheezy child is a complex condition that includes different phenotypes, differences in duration and course, and a group of diseases with distinct pathophysiology. Prematurity is a risk factor for early transient wheezing. However, its restrictive effect on respiratory function tests may also predispose to persistent wheezing. This study aimed to investigate the frequency of wheezing phenotypes and their effect on airway resistance in children born prematurely and over the age of 3.

Methods: Prematurely born children over the age of 3 who were followed up in our hospital were included in our study. The effect of neonatal risk factors, especially prematurity, on persistent wheezing and increased airway resistance has been investigated. The presence of persistent wheezing and asthma in patients was investigated with the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. To evaluate respiratory functions, airway resistance was measured with the interrupter technique.

Results: There was no significant correlation between Rint values indicating airway resistance and week of gestation, birth weight, gender, mechanical ventilation, oxygen therapy, presence of BPD, and smoking exposure at home ($p>0.05$).

Conclusion: Although there are studies in the literature showing a relationship between recurrent preschool wheezing and prematurity. Airway resistance was successfully measured and interpreted with Rint in preschool children who could not comply with the respiratory function test. Although prematurity is expected to increase airway resistance, it is interesting that we did not detect this effect in our patients, which may be due to the limited number of extremely premature patients.

Keywords: Prematurity, persistent wheezing, airway resistance

INTRODUCTION

Prematurely-born children (<37 weeks) experience many problems, especially respiratory problems, in the later stages of their life. Normal lung development begins on the 26th day of the embryological period. After the 36th week, the alveolar developmental stage begins. In preterm babies younger than 28 weeks, respiratory problems occur due to the incompleteness of the canalicular and saccular stages, and therefore the lack of surfactant production. In addition to these issues, exposure of preterm babies to oxygen during their postnatal follow-up, other environmental factors, and intensive care follow-up also increase the effects of the increased bronchial muscles and collagen tissue in their lungs.[1]

Due to such risk factors in children born prematurely, it causes an increase in wheezing and coughing attacks and airway resistance in the later stages of their lives.

Wheezing is a high vibration polyphonic musical sound produced by rapid air vibration due to narrowing of the lower airways. The definition of 'wheezing child' is a complex condition that includes heterogeneous phenotypes, differs in duration and course, and includes a group of diseases with separate pathophysiology. Prematurity, nursery care at an early age, cigarette smoking of the mother during pregnancy, and low maternal age are the most important risk factors associated with the development of 'transient early wheezing' fenotype. On the other hand, persistent wheezing phenotype may also be seen due to the restrictive effect of premature delivery on pulmonary function tests. Perinatal characteristics such as low birth weight (<2500 g) and premature history (<33 weeks of gestation) are among the important factors that facilitate wheezing in childhood. Many studies have found a relationship

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between prematurity and wheezing.[2] In this study, it was aimed to investigate the frequency of wheezing infants and wheezing phenotypes and their effects on airway resistance in children born prematurely and completed 3 years of age.

METHODS

The study was carried out with the permission of İzmir Dr Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.10.2015, Decision No: 2015/14-06). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study, 54 patients were included, who were followed up in our hospital, born in <37 weeks, completed the age of 3. Detailed histories of the patients were obtained at the outpatient clinic control. Gestational week, birth weight, length of stay on mechanical ventilator, duration of oxygen intake, length of hospital stay, surfactant use, bronchopulmonary dysplasia treatment information were recorded in the case report form from patient files. Detailed physical examination of the patients was performed at the outpatient clinic control; patients with pathological findings in the upper and lower respiratory tract examination were not included in the study. Those with structural anomalies, especially in the upper and lower respiratory tract, and those with underlying genetic diseases such as primary ciliary dyskinesia or cystic fibrosis were not included in the study. For these reasons, 8 patients were not included in the study.

Definition of Wheezy Child or Asthma

Questions about smoking at home and the questions in the International Study of Asthma and Allergies in Childhood (ISAAC) research protocol questions were asked to the relatives of the patients the answers were recorded in the case report form.

Detailed physical examination of the patients was performed under the control of the outpatient clinic, and patients with pathological findings in the upper and lower respiratory tract examinations were not included in the study.

Pulmonary Function Test

Airway resistance kit (Rocc, Rint kit) was attached to the Cosmed Pony FX portable spirometry device. Since the patients were under the age of 5, an "airway resistance kit" was used to evaluate respiratory functions. Children under 4 years of age were studied using a face mask, and those over 4 years old using a mouthpiece (nostrils were closed). By adjusting the parameters of the device, Rint was measured in the expiratory phase during the tidal breathing of the patients [Rint (e)]. At least 5 measurements were made on the patients. If there was crying or talking during the measurement, that measurement was excluded from the evaluation. The median value of the 5 correct measurements was accepted as the child's Rint value.[3]

In the evaluation the findings, SPSS (statistical package for social sciences) for Windows 20.0 software was used for statistical analysis.

RESULTS

Of the 54 subjects included in the study, 30 (55.6%) were female and 24 (44.4%) were male. The age distribution range of all patients ranged from 3 to 4 years. Birth weights were found to be 1777±550 gr, minimum 770 gr, maximum 3400 gr. Considering the distribution of the cases according to their gestational weeks, it was found that 8 patients were at the 28th week or less (14.8%), 20 patients were between the 28th-32nd weeks (37%), 26 patients were at the 32nd-36th weeks (48.2%).

In the first 1-year period of the cases whose nutritional histories were questioned, it was found that 8 (14.8%) cases were fed only with breast milk, 42 (77.8%) cases were fed with formula in addition to breast milk, and 4 (7.4%) cases were fed only with formula.

Neonatal histories of the patients were investigated, 43 (79.6%) of the cases included in the study needed oxygen and 12 (27.9%) of these patients were followed up with only nasal continous positive airway pressure (CPAP), 23 (53.4%) were followed up with mechanical ventilation and then n-CPAP.

21 (38.9%) patients needed surfactant during their follow-up, 33 (61.1%) patients did not need surfactant. Bronchopulmonary dysplasia (BPD) developed in 4 (19%) of 21 patients who were administered surfactant. It was determined that patients who were not given surfactant treatment did not have BPD.

The presence of wheezy child and asthma was investigated by ISAAC. The results of the ISAAC asthma research questionnaire administered to the patients in our study are given in Table 1.

Table 1. ISAAC asthma research survey findings

ISAAC asthma research questions	Yes n/%	No n/%
Having a wheezing or whistling sound in the chest since birth	34/63	20/37
Wheezing attacks in the past 12 months	12/22.2	42/77.8
Dry cough at night since birth (non-infectious)	14/25.9	40/74.1
Dry cough at night in the last 12 months (non-infectious)	10/18.1	44/81.5
History of hay fever or eczema	5/9.3	49/90.7
Receiving more than 3 courses of antibiotics for upper and lower respiratory tract infections since birth	17/31.5	37/68.5
Receiving more than 3 courses of antibiotics for upper and lower respiratory tract infections respiratory tract infections since birth	7/13	47/87
Wheezing during or after exercise since birth	13/24.1	41/75.9
Wheezing during or after exercise in the past 12 months	5/9.3	49/90.7
Waking up with wheezing since birth	14/25.9	40/74.1
Awakening from sleep with wheezing in the past 12 months	7/13	47/87
Consulting a physician for wheezing since birth	34/63	20/37
Consulting a doctor for wheezing in the past 12 months	14/25.9	40/74.1
Coughing severe enough to limit speech since birth	4/7.4	50/92.6
Coughing severe enough to limit speech in the past 12 months	1/1.9	53/98.1

ISAAC: International Study of Asthma and Allergies in Childhood

According to ISAAC results, 34 (63%) of 54 patients described wheezing attack at least once. Wheezing persisted in 22% of these. In the comparison of the patient group with wheezing according to the week of gestation, no statistically significant difference was found (p=0.326).

No statistically significant difference was found when the birth weights of the patients were compared with the findings of non-infectious dry cough (p=0.808). When the gestational week and non-infectious dry cough findings were compared, no statistically significant difference was found (p=0.824). When gender and non-infectious dry cough findings were compared, no statistically significant difference was found (p=0.627).

Awakening from sleep with wheezing was detected in 14 of 54 cases included in the study, and the mean gestational week was found to be 31.5 (±3.15) weeks. There was no statistically significant difference between the two groups (p=0.480). The mean birth weight of the cases with wheezing and waking from sleep was 1807 (±570) g; no statistically significant difference was observed (p=0.512). No statistically significant difference was observed when wheezing and waking up from sleep were compared with gender (p=0.627).

When the oxygen intake of the patients, wheezing, non-infectious dry cough, eczema, use of three consecutive courses of antibiotics, wheezing after exercise, waking up from sleep with wheezing and coughing severe enough to restrict speech are evaluated; no statistically significant difference was found (p>0.05) (Table 2).

Table 2. Correlation between ISAAC questions and oxgygen receiving

Oxgygen receiving (n)	Yes	No	p
Wheezing	5	29	0.178
Dry cough	3	11	0.909
Eczema	2	6	0.659
Receiving more than 3 courses of antibiotics	8	9	0.394
Wheezing during or after exercise	3	1	1.0
Awakening from sleep with wheezing	1	13	0.153
Coughing severe enough to limit speech	0	4	0.571

ISAAC: International Study of Asthma and Allergies in Childhood

When the parameters of wheezing, non-infectious dry cough, eczema, use of three consecutive courses of antibiotics, wheezing after exercise, waking up from sleep with wheezing and coughing severe enough to restrict speech are evaluated with the mechanical ventilator monitoring of the patients; no statistically significant difference was found (p>0.05).

Of a total of 54 patients, 34 (63%) had wheezing since birth and 20 (37%) did not. No statistically significant difference was found when the patient group with wheezing was compared according to gestational week (Table 3).

Table 3. Relationship between wheezing and week of gestation

	Wheezing		p
Gestation week	Yes	No	
26	4	0	
27	3	0	
28	1	1	
29	2	0	
30	1	4	
31	4	3	0.326
32	3	1	
33	0	3	
34	6	3	
35	5	1	
36	5	4	
Total	34	20	

When the family history of the cases was questioned, there was a history of asthma in the 1st degree relatives of 5 (9.3%) cases, and in the 2nd degree relatives of 13 (24.1%) cases, while 36 (66.7%) had no family history of asthma.

The mean Rint value of all patients in our study was 0.53 kPa.L-1.s. It was found to be higher than the mean Rint value of children in the same age group. The median Rint value of 23 patients with mechanical ventilation was 0.618, and the median Rint value of 31 patients without mechanical ventilation was 0.420, and there was no significant difference in Rint values between the two groups (p=0.055). The median Rint value of 43 patients who received oxygen therapy was 0.552, and the median Rint value of 11 patients who did not receive oxygen therapy was 0.394, and there was no significant difference in Rint values between the two groups (p=0.114). The mean Rint value of 21 patients who received surfactant treatment was 0.576 (±0.208), and the mean Rint value of 33 patients who did not receive surfactant treatment was 0.506 (±0.214), and there was no significant difference in Rint values between the two groups (p=0.242). No significant correlation was found between Rint value and week of gestation (p=0.15, r=-0.19), mechanical ventilation time (p=0.33, r=0.21), oxygen uptake time (p=0.42, r=0.12) (Figure).

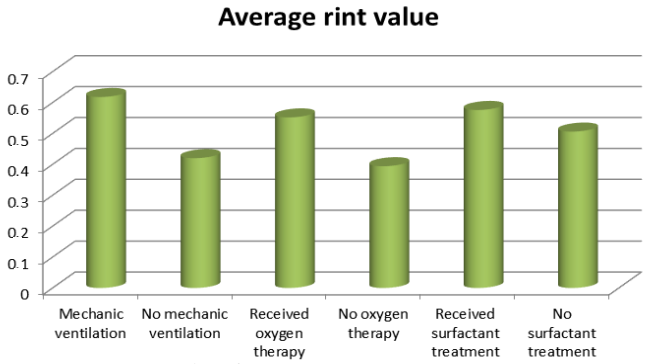

Figure. AvaregeRint value of patients

DISCUSSION

In our study, variables that create a predisposition for persistent wheezing risk in children born prematurely were questioned, and contrary to some views in the literature, no significant relationship with prematurity was found.

Recurrent respiratory diseases are a common cause of hospital admissions, and are more common in children born prematurely (<37 weeks) in the first year of life. It is difficult to distinguish which of the children who experience wheezing attacks in the first years of life will become asthmatic in the future. For this reason, the relationship between wheezing in infancy and later development of asthma has been investigated for many years. Since the mid-1990s, applications to hospitals with the complaint of wheezing have increased considerably, especially in industrialized countries. In international study of ISAAC conducted in 56 countries and 155 centers, the prevalence of wheezing was found to be 4-32% in different countries.[4]

Three different wheezing phenotypes were determined according to the age of wheezing, the atopic background in the child, the change in respiratory functions and the risk factors carried by the patient. These are transient early wheezing, non-atopic persistent wheezing, and atopic wheezing.[5] Prematurity, nursery care at an early age, cigarette smoking of the mother during pregnancy, and low maternal age are the most important risk factors associated with the development of temporary early wheezing.[6] In the study of Elder et al.,[7] recurrent wheezing attacks occurred in the first year of life in 14.5% of

525 premature babies born before the 33rd gestational week, while this rate was found to be only 3% in term newborns. In the cohort study conducted by Harju et al.[1] with 44173 patients between 1989 and 2008, it was found that the prevalence of asthma increased significantly in children born under 32 weeks. In a study by Leps et al.,[8] which included the follow-up of 18118 cases at the age of 3, 5, 7 and 11 years, a significant relationship was found between the week of miscarriage and the frequency of wheezing, and it was stated that there was also the use of drugs related to this. In our study, unlike the literature, no significant difference was observed when the patient group with wheezing was compared according to the week of gestation.

Gender also has an important role in wheezing phenotypes. In the study of Guilbert et al.,[9] wheezing was found more frequently in all three phenotypes in males, and while wheezing was more severe in males, a more rapid deterioration was also detected in pulmonary function test. Possible reasons for this may be relative airway stenosis, delay in immune maturation, low lung volume, high airway resistance, hormonal differences, or vascular/bronchial tone difference. In the study of Hennessy et al.[10] performed on 197 prematurely born 30-month-old children, no significant difference was found between the presence of wheezing, waking up with wheezing at night, and gender. Similar to the literature, no significant difference was found in our study between waking up with wheezing at night and gender.

In the study conducted by Elder et al.[7] in children born under 33 weeks of age and followed up in the neonatal intensive care unit of King Edward Memorial Hospital between 1990 and 1991, it was found that the frequency of recurrent wheezing in preterm infants was 14.5%. The relationship between the history of having oxygen therapy in the neonatal period and the frequency of wheezing was found in the children in this group, and in our study, the relationship between having oxygen therapy and future wheezing attacks was evaluated, but no significant difference was found.

In a study by Useman et al.[8] in which term and preterm early infants were included, the mean Rint value was found to be higher in term infants. It was thought that the reason for this was due to the incompleteness of fetal lung developmental stages. In our study, although the mean Rint value of preterm patients was found to be lower than that of term-born healthy children, no statistically significant difference was found. Although we think that the small number of our patients affected this data, our finding of a significant difference also supports the transient wheezing phenotype.

Measurement of lung volumes by spirometry and bronchial hypersensitivity tests have taken their place as diagnostic criteria in asthma in children older than 6 years and adults. However, the application of these techniques in pre-school children is limited due to the difficulty of breathing. Some techniques that can be applied in clinical practice continue to be developed for the diagnosis of asthma in the pre-school age group. Measuring airflow resistance with the interrupter technique is one of them. This technique can be easily used in the infant age group because it requires minimal patient compliance. The working principle of the interrupter technique is based on the assumption that the alveolar pressure equals the mouth pressure with an interruption made by the device during passive breathing. Thus, the pressure measured from the mouth shows us the resistance of the airways.[11] This technique can be easily applied to the portable pulmonary function test device by attaching the apparatus containing the flow meter and pressure transmitter parts. Although it is sufficient for the patients to be calm and preferably asleep for the technique to be applied, many studies have been conducted regarding the applicability of the test in clinical practice.[12] The airway resistance value (Rint) measured with this technique varies depending on its measurement in expiration or inspiration. In a study, it was observed that while an increase was detected in Rint [Rint (e)] measured during expiration in healthy children with mild respiratory tract infection compared to the control group, there was no change in Rint [Rint (i)] measured during inspirium. Likewise, many studies have shown that there is a more significant increase in Rint (e) than Rint (i) when airway obstruction develops, therefore it has been found that Rint (e) value better reflects airway resistance.[3] In our study, Rint values were measured in the expiratory phase of tidal respiration by adjusting the parameters of the device. In the study of Özek et al.,[13] consisting of term born, healthy 28 males (56%), 22 females (44%) a total of 50 patients with a mean age of 3.2±1.8 years, the mean Rint value was found to be 0.489 kPa. L-1.s and the mean Rint value was found to be 0.53 kPa.L-1.s in our study. The data we obtained does not meet the expectation of increased airway resistance in prematurity.

In the study conducted by VR Kairamkonda et al.[14] in children born prematurely between the ages of 2-4 years, Rint values of patients with chronic lung disease (n: 28) and healthy patients (n: 18) were compared, and the Rint value in the preterm control group was found to be 1.16 (1.03-1.32) kPa. .L-1.s in the group with chronic lung disease, and 1.33 (1.21-1.42) kPa.L-1.s was found to be in the group with chronic lung disease. In the study conducted by Vrijlandt ET et al.[15] with patients born premature, aged 3-5 years, with and without BPD, no significant difference was found in Rint values between the two groups. In our study, no significant difference was found between the group with and without BPD.

Limitations

There are also some limiting features in our study. One of the most important limiting factors is the low number of patients who were born premature (<37 weeks), completed the age of three, and included in the study. Therefore, the parameters found to be related to each other in similar studies were not found significant in our study. Although the Rint value indicating airway resistance increased as the gestational week decreased, statistically significant data could not be obtained. There is a need for studies with larger patient groups in order to detect airway resistance in pre-school children born prematurely with the interrupter technique.

CONCLUSION

In conclusion, although transient wheezing is an expected condition in preschool children, we wanted to determine whether premature birth and subsequent intensive care follow-up contribute to this condition. Although there are reports with similar results in the literature, studies with a larger patient population are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of İzmir Dr Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.10.2015, Decision No: 2015/14-06).

Informed Consent

All relatives of the patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Effect of lipoic acid on cisplatin-induced cardiotoxicity and inflammation in cardiomyocytes

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ABSTRACT

Aims: Cisplatin (CPL) is a potent chemotherapeutic agent widely used to treat various cancers. However, CPL causes toxicity in various tissues, including the heart. Lipoic acid (LPA) is a thiol compound with antioxidant, anti-inflammatory, and anti-apoptotic properties. Although LPA has been reported to have protective effects in various cardiac diseases, the mechanisms underlying its cardio-protective effects have not been elucidated. This study aimed to establish a CPL-induced cardiotoxicity model in the H9c2 cardiomyocyte cell line, to understand the mechanisms underlying this cardiotoxicity, and to investigate the effect of LPA on cardiotoxicity.

Methods: H9c2 cardiomyocyte cells as control (CNT), CPL (40 µm), and LPA-1 (300 µm LPA, and 40 µm CPL), LPA-2 (500 µm LPA, and 40 µm CPL) in combination along with CIS were used. In the analyses made, glutathione (GSH) and glutathione peroxidase (GSHPx) enzyme activity, lipid peroxidation [malondialdehyde, (MDA)] levels, inflammation markers interleukin (IL) -1β, IL-6, and tumor necrosis factor (TNF) -α levels, total oxidant/antioxidant (TOS and TAS) status levels, reactive oxygen species (ROS) and caspase activity (Casp 3 and 9) in the cells were determined.

Results: CIS treatment caused cardiomyocyte cell toxicity and increased Casp 3, Casp 9, ROS, IL-1β, IL-6, TNF-α, TOS, and MDA levels while decreasing GSHPx, GSH, and TAS levels. Increased inflammation and impaired oxidant/antioxidant balance in cardiomyocyte cells after CPL treatment were regulated by LPA treatment.

Conclusion: LPA treatment was found to have a protective effect against CPL-induced cardiotoxicity in cardiomyocyte cells.

Keywords: Apoptosis, lipoic acid, cardiotoxicity, cisplatin, oxidative stress

INTRODUCTION

Cisplatin (CPL) is a platinum based compound widely used as a chemo-therapeutic agent against various human cancers.[1] However, despite the anticancer efficacy of CPL, its toxicity in various tissues limits its safety in chemotherapy.[2] CPL, which has anti-cancer activity by inducing reactive oxygen species (ROS) that trigger cell death and DNA damage, causes toxicity by inducing the same effects on non-cancer cells.[3-5] As it is known that CPL treatment has significant side effects such as cardiotoxicity, ototoxicity, nephrotoxicity, and hepatotoxicity, intensive experimental and clinical studies are underway to discover new agents to reduce toxicity in these tissues.[1,3,4,6] Although CPL-induced cardiotoxicity is not frequently observed as an acute effect, it is an important side effect observed in the long-term survival of patients receiving CPL chemotherapy.[7] Therefore, the identification of agents that reduce drug toxicity during and after chemotherapy is very important for patients. CPL treatment can cause cardiotoxic effects in patients, such as congestive heart failure or even sudden cardiac death.[4] By clarifying the multifactorial physio-pathological mechanisms underlying the cardiotoxic effects of CPL, it may be able to reduce its side effects during treatment. In the literature, the results of studies related to CPL-induced cardiotoxicity have not fully elucidated the mechanisms of damage. Evidence suggests that inflammation[7,8] oxidative stress (OS)[6,9,10] and apoptosis[11] are the main factors in CPL toxicity. CPL has been shown to induce apoptosis by depleting glutathione (GSH) and deactivating glutathione peroxidase (GSHPx).[7] It has been reported that CPL may cause mitochondrial dysfunction and, consequently, activate the apoptotic pathway by increasing intracellular ROS levels.[2,4] The effects of adding compounds with anti-apoptotic, antioxidant, and anti-inflammatory properties to CPL chemotherapy on slowing CPL-induced myocyte damage have been investigated. Still, experimental studies should be continued as the results are uncertain.

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Lipoic acid (LPA), known to have anti-apoptotic, antioxidant, and anti-inflammatory properties, is a thiol compound found naturally in plants and animals.[12] As LPA is an important factor in enzymes that scavenge reactive oxygen species, the antioxidant properties of LPA have recently attracted considerable interest.[13] LPA has been reported to be effective in preventing and treating OS in many models or clinical conditions.[12,14] In addition, recent studies have shown that LPA is also protective against cardiac oxidative damage induced by cardiovascular disease and cardiotoxic drugs.[14,15] Therefore, LPA may serve as a protective agent against the risk factors of cardio-vascular disease. Although the ability of LPA to directly scavenge ROS appears to be partly responsible for its cardio-protective effects, it is not known whether the cardio-protective effects of LPA also occur through other mechanisms, such as the induction of endogenous antioxidant enzymes such as GSH and GSHPx in the myocardium, the reduction of inflammatory markers such as tumor-necrosis-factor-alpha (TNF-α), interleukin (IL) -1β, and IL-6, and caspase activation.

The limited number of studies in the literature showing that CPL-induced myocardial damage is improved by LPA application focused more on oxidative parameters. In contrast, the present study analyzed inflammatory markers, apoptotic caspase pathways, and OS parameters, providing more reliable results. In this study, H9c2 cells were used as an experimental model of CPL-induced cardiotoxicity, which was induced by CPL in these cells. CPL-induced damage in H9c2 cells and the regulatory effects of LPA on this damage were evaluated by analyzing caspase activation (Casp 3 and 9) and inflammation markers (TNF-α, IL-1β, and IL-6 levels). In addition to GSH and GSHPx levels, total antioxidant/oxidant status (TAS and TOS) was analyzed to investigate OS. Moreover, lipid peroxidation as malondialdehyde (MDA) levels were analyzed to determine lipid peroxidation.

METHODS

The current study has no study with human and human participants. The study is not subject to ethics committee approval. All procedures were carried out in accordance with the ethical rules and the principles.

Chemicals

LPA (Cat; 437692) and CPL (Cat; PHR1624) were purchased from Sigma Aldrich C. (USA). Caspase 3 (Cat; SRBT-81638), Caspase 9 (Cat; SRBT-82090), IL-1β (Cat; SRBT-83324), IL-6 (Cat; SRBT-83168), reactive oxygen species (Cat; 201-11-0305), and TNF-α (Cat: SRBT-82883) were obtained from Sun. Red Biotech Comp (SRB) Ltd (China). Total antioxidant/oxidant capacity (TAS-Pro No: RL0017 and TOS-Pro No: RL0024) ELISA kit was purchased from RelAssay (Turkiye).

Cell Culture

The manufacturer's instructions prepared the growth medium for the cells used in the study. Dulbecco's-modified-eagle's-medium (DMEM, Cat; L0064, Biowest, France) was supplemented with 10% Fetal-bovine-serum (FBS, Cat; SV30160.03, Cytiva, Turkiye) and 1% antibiotics (Cat; LMA 4118, Biosera, Turkiye). Cells previously purchased from ATCC company and reached 6-8 passages were used. The growth medium of the cells was prepared following the experimental procedure for the H9c2 embryonic cardiomyocyte cells taken from the nitrogen tank. The H9c2 embryonic cardiomyocyte cells were passaged and divided into four groups after reaching 80-85% confluence, and then this process was repeated. Cells in T25 (flask with 25 cm^2 surface area) culture flasks were cultured in an incubator (95% air, 5% CO2, and 37 °C). According to the experimental procedure, treatments were applied to the cells according to the groups. Depending on the experimental group, the following treatment procedure was used. Cells were washed with fresh 1x phosphate-buffered saline (PBS) (Cat; LM-S2043/500, Biosera, Turkiye) at the end of the incubation period, and trypsin-EDTA (0.25%) (Cat; LM-T1720/100, Biosera, Turkiye) was used to detach the cells from the bottom of the flask. Analyses were performed for all groups after completion of the experimental steps.

Experimental Groups

The cardiomyocyte cell line was divided into four groups.

CNT (n: 6), H9c2 cells in this group were not treated with any treatment and were incubated (24 h).

CPL (n: 6), H9c2 cells in this group were treated with 40 µm CPL and were incubated (24 h).[4]

LPA-1 (n: 6), H9c2 cells in this group were pre-treated with 300 µm LPA[16,17] 3 hours before 40 µm CPL treatment, followed by 40 µm CPL treatment and were incubated (24 h).

LPA-2 (n: 6), H9c2 cells in this group were pre-treated with 500 µm LPA[18] 3 hours before 40 µm CPL treatment, followed by 40 µm CPL treatment and were incubated (24 h).

Cell Homogenate Preparation Steps

Following the kit instructions, the cells for each group were added to separate Eppendorf tubes and centrifuged (1000 RPM, 5 min). The following steps were followed: Using a pipette, the supernatants were removed from the top of the Eppendorf tubes, and the cell pellets underneath were diluted in PBS (pH 7.4) to a concentration of $1x10^6$ cells/ml. The H9c2 embryonic cardiomyocyte cell structure was lysed by freeze thaw repetition, and the mixture was centrifuged at 4 °C (3000 RPM, 20 min.) after removing the cytoplasmic components. Any supernatants were removed by automated pipetting and transferred to new sterile tubes for further analysis.

Analysis

Caspase, reactive oxygen species, and inflammation markers levels in the cardiomyocyte cells: Caspase, ROS, and inflammation markers (TNF-α, IL-1β, and IL-6) levels in cardiomyocyte cell supernatants were determined (ELISA kit). For analyses according to the kit protocol following the instructions of the commercially purchased company, the following steps were followed: supernatants were incubated (37°C) according to the specified protocols, using a pipette, the supernatant and standard samples were transferred into 96-well plates, standard and supernatant samples placed on 96-well plates were incubated (60 min), washing steps were applied and staining solutions were added and incubated (15 min). At the end of all these procedures, a stop solution was added, and an ELISA spectrophotometer was used to read the absorbance values (Bio Tek EL808™).[19,20]

Total antioxidant/oxidant status levels in the cardiomyocyte cells: Supernatants of the samples were used for TAS analyses, and the following steps were followed for TAS analyses according to the kit protocol and the instructions of the

commercially purchased company. The method is based on reducing the colored azinobis radical by antioxidants to a colorless reduced form. Sample supernatants, kit standard, and dH20 were mixed with 200 µl Reagent 1 buffer in 96 well plates and incubated according to the protocol (5 min). The first absorbance of the sample was measured at 660 nm with an ELISA reader, then 30 µl of Reagent-2 buffer was added, and the mixtures were incubated (37°C, 5 min). After incubation, the second absorbance value of the sample was measured at 660 nm with an ELISA reader. The kit standard equivalent to 1 mmol/L Trolox was used to calculate the data for each sample.

Supernatants of the samples were used for TOS analyses, and the following steps were followed for TOS analyses according to the kit protocol and the instructions of the commercially purchased company. The ferrous ion-dianisidine complex is oxidized to ferric ions by oxidizing agents in the sample. A coloured complex is produced by the ferric ion in an acidic medium with xylenol orange, which is related to the amount of oxidant molecules (colour intensity associated with the amount of oxidant molecules). For the dilution step, Standard-2 (5 µl) and distilled water (1 ml) were added to an Eppendorf tube, vortexed (20 seconds), then 5 µl of this solution was added to another Eppendorf tube, and by adding 1 ml of distilled water, 20 mm H2O2 was prepared. Afterward, 200 µL of Reagent-1 buffer was transferred to each well of 96-well plates, and the first TOS absorbance of the sample was measured at 530 nm with an ELISA reader. Next, 10 µl Reagent-2 was added, and samples were incubated (37°C, 5 min). After incubation, the second TOS absorbance value of the sample was measured at 530 nm with an ELISA reader. The kit standard (µmol H2O2 equivalents/L) was used to calculate the data for each sample.[19]

Glutathione, glutathione peroxidase, and lipid peroxidation, levels in the cardiomyocyte cells: Lipid peroxidation (malondialdehyde, MDA) levels of cardiomyocyte cells were analyzed by spectrophotometer according to the method described by Placer et al.[21] In the experiment, cardiomyocyte cell groups were diluted 1/9 (2.25 ml) with thiobarbituric acid (TBARS) solution. A mix of 1/9 of TBARS and 0.25 ml phosphate buffer was used as a blind. The samples and the blind were kept in boiling water at 100°C in a water bath for 20 minutes.[22] Then they were then cooled with tap water. Afterwards, 3500 RPM centrifugation was performed for 5 min. After centrifugation, the top pink coloured liquid was collected with a pipette (500 µl). The liquid was read against the blind in a spectrophotometer (V-730 UV, spectrophotometer Japan) at 532 nm wavelength in a cuvette with 1 cm light transmission. The standard used was 1,1,3,3,3 tetraethoxypropane solution prepared in the same proportions. The results were given as µmol/g protein.

Cardiomyocyte cell GSH levels were determined using the Sedlak and Lindsay[23] technique. Cardiomyocyte cell GSHPx levels were measured by the Lawrence and Burk[24] technique (V-730 UV spectrophotometer Japan). The solutions required for GSH determination were 10% trichloroacetic acid (TCA) solution and Tris-II buffer. Tris-II buffer (pH: 8.9 and 0.4 M) was prepared by dissolving 48.46 grams of tris-hydroxymethyl-aminomethane in 1 L of distilled water (final volume 1 L), and the pH was adjusted to 8.9 with hydrochloric acid (HCl).

A pipette added cells to falcon tubes for GSH analysis (10^6 cells per ml). Afterwards, 0.1 ml cardiomyocyte cell homogenate fluid and 0.4 ml trichloro-acetic-acid (TCA) solution were transferred to a separate Eppendorf tube. Then, it was mixed on a vortex for 20 seconds and centrifuged (3000 RPM, 5 min). Centrifugation was performed to separate proteins. Then, the following steps were followed: After centrifugation, 0.4 ml supernatant was taken into a clean glass tube, and 2,0 ml Tris-II buffer and 0.1 ml DTNB (0.099 g dissolved in 25 ml methanol) solution were added. The yellow color formed after the added solutions were read with a spectrophotometer at a wavelength of 412 nm in a cuvette with a light transmission of 1 cm against distilled water. And GSH analyzed values were µmol/g protein calculated as.

Solutions required for GSHPx determination: Tris-I buffer solution (pH: 7.6 and 50 mm,), GSH solution, CHPO (cumene hydro peroxide) solution, 10% TCA solution, Tris-II buffer (pH: 8.9 and 0.4 M), DTNB [5.5 dithiobis (2 nitro–benzoic-acid)] solution. Tris-I buffer (pH: 7.6 and 50 mm) was prepared by dissolving 6,057 grams TRIS-hydrochlorid and 0,372 grams EDTA in 1 litre of distilled water (final volume 1 litre), and the pH was adjusted to 8.9 with hydrochloric acid (HCl).

In the experiment, 0.5 ml cardiomyocyte cell homogenate fluid, 0.3 ml Tris-I HCl buffer, and 0.1 ml CHPO (except control) solution were mixed. 0.1 ml GSH (5 s intervals for each tube) was added (in an Eppendorf tube) and kept at room temperature for 10 minutes, and 1.0 ml TCA (5 s intervals for each tube) was added. Centrifuged at 2500 RPM for 5 minutes. After centrifugation, the upper 0.1 ml supernatant was taken into a clean glass tube, and 2 ml Tris-II buffer and 0.1 ml DTNB were added. Waiting time was 5 minutes at room temperature. The yellow color formed after the added solutions were read with a spectrophotometer at a wavelength of 412 nm in a cuvette with a light transmission of 1 cm against distilled water. The GSHPx content of the samples was determined by spectrophotometry at a wavelength of 412 nm, and GSHPx values were (international units) IU/g protein calculated as.

Statistical Analysis

Data analyses were performed with SPSS (ver. 17.0, software, USA) software, and all data were expressed as mean ± standard deviation (SD). A one-way ANOVA, Post-hoc Tukey test was used to evaluate all data showing statistically significant differences between groups. A value of $p<0.05$ was considered statistically significant.

RESULTS

Effect of LPA on Caspase, Reactive Oxygen Species, Total Oxidant Status Levels in Cardiomyocyte Cells

LPA treatment modulated the increase in ROS, TOS, Casp 3, and Casp 9 levels in CPL-treated cardiomyocyte cells (Figure 1). A significant increase in ROS (Figure 1A), TOS (Figure 1B), Casp 3 (Figure 1C), and Casp 9 (Figure 1D) levels was observed in the CPL-treated group was compared to CNT, LPA-1, and LPA-2 groups ($p\leq0.05$). The increase in ROS, TOS, Casp 3, and Casp 9 levels after CPL treatment in cardiomyocytes was regulated by LPA treatment. Significant results were obtained in H9c2 embryonic cardiomyocytes pre-treated with 300 and 500 µm LPA for ROS, TOS, Casp 3, and Casp 9 levels. However, the CPL-induced and disturbed oxidant/antioxidant balance was further regulated by 500 µm LPA.

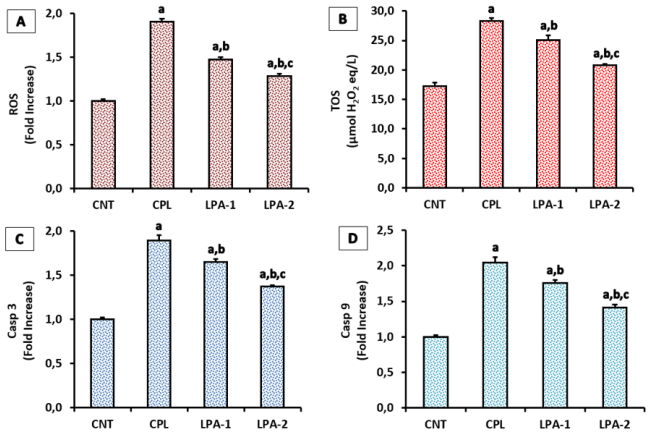

Figure 1. Effect of LPA on ROS (A), TOS (B), Casp 3 (C), and 9 (D) levels in H9c2 embryonic cardiomyocytes after CPL-induced cytotoxicity (mean±SD) ([a]p≤0.001 vs CNT group, [b]p≤0.001 vs CPL group, [c]p≤0.001 vs LPA-1 group)

LPA: Lipoic acid, ROS: Reactive oxygen species, CPL: Cisplatin, SD: Standard deviation, CNT: Cardiomyocyte cells as control

Effect of LPA on Inflammation in Cardiomyocyte Cells

LPA treatment modulated the increase in TNF-α, IL-1β, and IL-6 levels in CPL-treated cardiomyocyte cells (Figure 2). A significant increase in IL-1β (Figure 2A), IL-6 (Figure 2B), and TNF-α (Figure 2C) levels was observed in the CPL-treated group was compared to CNT, LPA-1, and LPA-2 groups (p≤0.05). The increase in TNF-α, IL-1β, and IL-6 levels after CPL therapy in cardiomyocytes was regulated by LPA therapy. Significant results were obtained in H9c2 embryonic cardiomyocytes pre-treated with 300 and 500 μm LPA for TNF-α, IL-1β, and IL-6 levels. However, the CPL-induced and disturbed inflammatory cytokines balance was further regulated by 500 μm LPA.

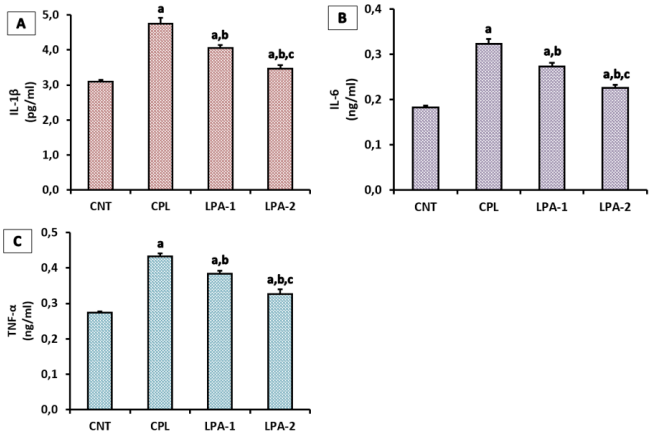

Figure 2. Effect of LPA on IL-1β (A), IL-6 (B), and TNF-α (C) levels in cardiomyocytes after CPL-induced cytotoxicity (mean±SD) ([a]p≤0.001 vs CNT group, [b]p≤0.001 vs CPL group, [c]p≤0.001 vs LPA-1 group)

LPA: Lipoic acid, TNF: Tumor necrosis factor, CPL: Cisplatin, SD: Standard deviation, CNT: Cardiomyocyte cells as control

The LPA therapy regulated the cisplatin-induced changes in total antioxidant status, lipid peroxidation, glutathione peroxidase, and glutathione levels: LPA therapy regulated the increase in lipid peroxidation (MDA) and disturbance of the antioxidant balance (GSH, GSHPx, and TAS) levels in CPL-treated cardiomyocyte cells (Figure 3). A significant decrease in GSH (Figure 3A), GSHPx (Figure 3B), and TAS (Figure 3D) levels was observed in the CPL-treated group compared to CNT, LPA-1, and LPA-2 groups (p≤0.05). A significant increase in MDA (Figure 3C) levels was observed in the CPL-treated group compared to CNT, LPA-1, and LPA-2 groups (p≤0.05). Elevated MDA and reduced GSH, GSHPx, and TAS levels following CPL therapy in cardiomyocytes were regulated by LPA therapy. Significant results have been achieved in cardiomyocytes pre-treated with 300 and 500 μm GAL for GSH, GSHPx, and MDA levels. However, the CPL-induced and disturbed oxidant/antioxidant balance was further regulated by 500 μm LPA.

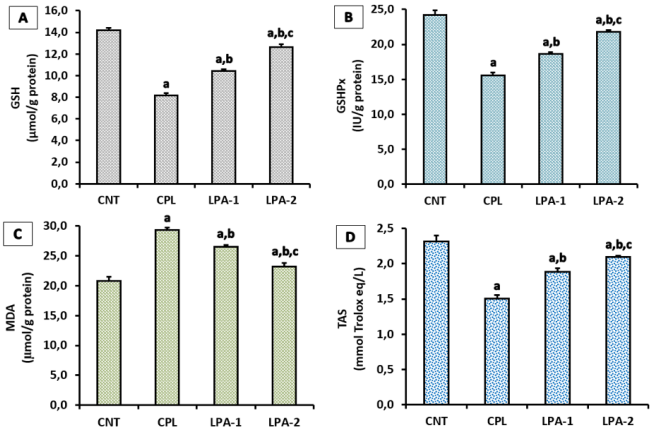

Figure 3. Effect of LPA on GSH (A), GSHPx (B), MDA (C), and TAS (D) levels in cardiomyocytes after CPL-induced cardiotoxicity (mean±SD) ([a]p≤0.001 vs CNT group, [b]p≤0.001 vs CPL group, [c]p≤0.001 vs LPA-1 group)

LPA: Lipoic acid, GSH: Glutathione, GSHPx: Glutathione peroxidase, MDA: Malondialdehyde, TAS: Total antioxidant, CPL: Cisplatin, SD: Standard deviation, CNT: Cardiomyocyte cells as control

DISCUSSION

Although CPL is a potent chemotherapeutic agent, significant side effects such as cardiotoxicity limit its use.[1,4] In this context, it is important to add protective compounds to CPL chemotherapy to reduce toxic effects in patients who need to receive CPL chemotherapy. In this study, H9c2 cells were treated with CPL (40 μm), and drug-induced cardiotoxicity was assessed. In addition to changes in OS parameters and inflammatory markers in CPL-treated cells, whether CPL induces apoptosis in cells was investigated by measuring caspase levels. Recent studies in the literature have reported that CPL therapy is associated with cardiotoxicity.[4,25,26] It has been proposed that CPL may induce ROS and OS, apoptosis, and inflammation in cells, leading to cardiotoxicity.[27,28] CPL has also been reported to react rapidly with thiol containing molecules, leading to depletion of glutathione and related antioxidants and accumulation of ROS.[29] Research has reported that CPL increases ROS levels and lipid peroxidation while decreasing the activity of catalase, GSH, and superoxidedismutase (SOD) enzymes.[30,31] In this study, in agreement with the literature, we showed that MDA levels increased in the CPL-treated groups in H9c2 myocyte cells compared to the CNT group. At the same time, GSH and GSHPx enzyme levels decreased. With the observed decrease in cardiac GSH levels and increase in MDA levels, the reduction in GSHPx enzyme activity may be evidence of OS induced by CPL therapy. Indeed, similar studies have reported a significant decrease in antioxidant capacity with a substantial increase in MDA levels in the heart and other tissues following CPL therapy.[32-35] The increase in MDA levels can be attributed to the rise in ROS caused by CPL.

Several antioxidant molecules have been tested in studies that predict that they may prevent toxicity by reducing CPL-induced OS. In this study, we applied two doses of 300 μM and 500 μm LPA to investigate the efficacy of LPA in preventing cardiotoxicity. Our results showed that CPL treatment led to a significant increase in inflammatory markers, apoptosis, and OS, as well as a decrease in antioxidant capacity. Conversely,

in the H9c2 cardiomyocytes we pre-treated, we found that LPA reduced cardiac damage by regulating these parameters. Cao et al.[12] showed that LPA could induce several endogenous antioxidants in H9c2 cardiomyocytes and that LPA-mediated enhancement of cellular defences significantly conferred resistance to ROS-induced cardiac cell injury. LPA has been reported to have beneficial effects against nephrotoxicity[36] and neurotoxicity[13,37] by suppressing CPL-induced OS. Another study reported that LPA reduced sodium nitroprusside-induced damage in H9c2 cells by downregulating ROS.[18] Consistent with the literature, this study demonstrated that in H9c2 myocyte cells, MDA levels increased in the CPL-treated groups compared to the CNT group. Accordingly, GSH and GSHPx enzyme activities decreased. We found that antioxidant enzyme activities increased and MDA levels decreased in the LPA-1 and LPA-2 groups treated with LPA compared to the CPL group. Thus, our study demonstrated that LPA might protect cardiomyocytes against oxidative damage. There are only a few studies on the effect of LPA on cardiomyocyte damage caused by CPL.[32,36] Hussein et al.[36] found that the CPL-induced cardiotoxicity model in rats caused a significant decrease in GSH and SOD and a significant increase in MDA and NO in cardiac tissue. On the other hand, they reported that LPA administration caused improvement in these parameters. Similarly, El-Awady et al.[32] reported that the CPL-induced decrease in GSH and SOD and the increase in MDA in rat heart tissue were ameliorated by LPA administration. In our study, we observed a significant improvement in the LPA groups (LPA-1 and LPA-2) with two different doses of LPA pre-treatment. The ROS, MDA, and TOS increase with CPL treatment was significantly reduced in both the LPA-1 and LPA-2 groups. This significant improvement was more pronounced in the LPA-2 group. Furthermore, in our study, we found that although TAS, GSH levels, and GSHPx activities decreased in the CPL group compared to the CNT group, these values increased substantially in the LPA groups compared to the CPL group. The limited number of studies in the literature showing that CPL-induced myocardial damage is improved by LPA application focused more on oxidative parameters (two studies).[32,36] In contrast, the present study analyzed inflammatory and apoptotic markers in addition to OS parameters, providing more reliable results.

CPL has been reported to increase the expression of pro-inflammatory signalling molecules such as chemokines and cytokines by stimulating certain cellular signalling pathways.[38] These increased signaling molecules have also been reported to mediate CPL toxicity in many tissues.[1,2,6,8] Most previous publications have found that the increase in CPL toxicity is significantly paralleled by an increase in TNF-α, IL-1β, and IL-6 values.[1,6,27,38] In the physio pathological process of CPL-induced cardiotoxicity, we predict the activation of pro-inflammatory cytokines in cardiomyocytes. To this end, we examined the levels of inflammation markers after the application of CPL to H9c2 embryonic cardiomyocytes. In this study, we found a significant increase in TNF-α, IL-1β, and IL-6 values in the CPL treatment groups compared to the CNT group. The effects of LPA in reducing inflammation-related damage have been reported in many tissues.[13,22,39] In this study, we have shown that LPA can protect cardiomyocytes from inflammatory damage. In our study, we observed that TNF-α, IL-1β, and IL-6 values were markedly decreased in the LPA pre-treated LPA-1 and LPA-2 groups compared to the CPL group. We also found that a dose of 500 μM LPA was more effective. These results suggest that the cardiotoxic effects of CPL chemotherapy may be reduced by LPA treatment.

It has been reported that the accumulation of CPL in the cell during chemotherapy reduces the activity of the antioxidant system, increases ROS production and lipid peroxidation, and also promotes cell apoptosis through the activation of various pro-apoptotic pathways.[4,9,11] Previous studies have shown that mitochondrial dysfunction due to increased ROS and subsequent activation of the apoptotic pathway is involved in the pathogenesis of CPL toxicity.[11,28] Casp 3 and 9 activation is an irreversible step that induces apoptosis. Therefore, these caspases are often used in studies to assess apoptosis.[19,20] Inflammatory responses, OS, and apoptosis were detected after CPL treatment in this study. We examined Casp 3 and 9 levels after CPL treatment of cardiomyocyte cells. We found a significant upregulation of Casp 3 and 9 in the CPL-treated groups compared to the CNT group. Previous studies suggested that CPL caused upregulation of Casp 3 and downregulation of Bcl-2.[40,41] Another study found that Casp 9 and Casp 3 activity was significantly increased after CPL application in H9c2 cells.[11] LPA has been shown to have pharmacological potential in the regulation of various cellular and molecular processes, such as apoptosis and autophagy.[17,27] LPA is a potent regulator of different molecular and cellular processes, including apoptotic and autophagic processes.[17] Qi et al.[42] found that LPA decreased the expression of inflammation markers (TNF-α, IL-1β, and IL-6 levels), increased cell viability in an in vitro model, and decreased ROS and apoptosis in cardiac ischemia/reperfusion model in vivo/in vitro models. They also reported that it increased the expression of anti-apoptotic protein Bcl-2 and suppressed the levels of apoptotic protein Bax. In our study, we observed a significant improvement in the LPA pre-treatment groups (LPA-1 and LPA-2 groups). Casp 3 and 9 levels were significantly reduced in the LPA-1 and LPA-2 groups compared to the CPL group. The improvement was more pronounced in the LPA-2 group. As a result, using the H9c2 embryonic cardiomyocyte cell line, we were able to show that LPA prevents a CPL-induced increase in OS and inflammation in cardiac tissue and prevents the induction of caspases.

CONCLUSION

In conclusion, this study showed that LPA could increase antioxidant capacity in CLP-induced injury in cultured cardiomyocytes, which is consistent with the literature. However, it is also the first study to report that LPA could reduce the levels of inflammatory markers and down-regulate caspase 3 and 9 levels in CLP-induced cardiotoxicity. By establishing the protective effects of LPA, such as suppression of inflammation and apoptosis and enhancement of antioxidant capacity, using LPA for cardio-protection in various forms of drug toxicity-induced cardiac damage, including CPL toxicity, can be recommended.

ETHICAL DECLARATIONS

Ethics Committee Approval

The current study has no study with human and human participants. The study is not subject to ethics committee approval.

Informed Consent
Because the study has no study with human and human participants, no written informed consent form was obtained.

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

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Evaluation of the immature granulocyte count in idiopathic sudden sensorineural hearing loss

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ABSTRACT

Aims: The purpose of our study was to show whether the immature granulocyte count (IGC) can be used as a prognostic marker in idiopathic sudden sensorineural hearing loss (ISSNHL).

Methods: This study is a retrospective case-control clinical study. Patients presenting to our clinic between June 2019 and June 2022, diagnosed with ISSNHL, and receiving the same treatment protocol were investigated. Preoperative complete blood count values of 40 normal individuals with normal hearing who presented to our clinic due to nasal septum deviation were adopted as the control group. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) (platelet×neutrophil/lymphocyte) values were calculated in addition to IGC values in complete blood counts from the patient and control groups. The patient group was classified into treatment-responsive and non-responsive subgroups according to the results of audiological examinations performed after one month based on Siegel's criteria. IGC, SII, NRL, and PLT values were compared between all groups.

Results: Comparison of the patient and control group's complete blood count data revealed higher leukocyte and neutrophil counts, IGC and also NLR, PLR, and SII values in the patient group compared to the control group. However, lymphocyte counts were lower in the patient group. None of the parameters previously emerging as significant in the data of patients with healing and non-healing idiopathic sudden hearing loss were statistically significant, and IGC is of no prognostic value in ISSNHL.

Conclusion: IGC may be a novel and inexpensive indicator of ISSNHL and one easily determined with complete blood count, but it is of no prognostic value in the disease.

Keywords: Idiopathic sudden sensorineural hearing loss, immature granulocyte, prognosis

INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSNHL) is an acute, unilateral, sensorineural loss of hearing with no definite cause involving sudden onset loss of hearing, greater than 30 decibels (dB) at three consecutive frequencies, usually within three days.[1,2]

The etiology of ISSNHL is not yet fully understood. Prognostic indicators and biomarkers are therefore important for appropriate treatment selection. Studies have shown that parameters such as hypertension, hyperlipidemia, diabetes mellitus, presence of metabolic syndrome, advanced age, delayed treatment, vertigo, alcohol, vasculopathy and hearing loss at high frequencies adversely affect prognosis,[3-5] while younger age, having tinnitus and early treatment have a positive impact on prognosis.[6]

Various different approaches have been recommended in the treatment of ISSNHL, such as steroids, hyperbaric oxygen, vasodilator agents, antiviral agents, and diuretics, although treatment remains controversial. In addition, spontaneous recovery at rates of up to 60% may occur in ISSNHL without treatment.[7] This means that greater efforts are required to identify prognostic factors or factors affecting the nature of the disease for the treatment of ISSNHL.

The neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and Systemic Immune Inflammation Index (SII) (platelet×neutrophil/lymphocyte) can be easily calculated from peripheral complete blood counts. Various hematological indices, such as NLR and PLR have recently been found to be associated with prognosis in patients with ISSNHL.[8] These have also been shown to be capable of use as inflammatory markers.[9]

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Immature granulocytes (IGs) consisting of promyelocytes, myelocytes and metamyelocytes are not present in peripheral blood under normal physiological conditions.[10] However, the immature granulocyte count (IGC) in peripheral blood can indicate bone marrow activation in periods of infection and inflammation.[11] IGC is easy to obtain in complete blood counts with automatic hematological analyzers. There are studies in the literature showing that IGC increases earlier than CRP and leukocyte count in inflammatory conditions such as sepsis and infection.[10,11]

We encountered no previous studies investigating the relationship between ISSNHL and the IGC. The purpose of our study was therefore to investigate the prognostic value of the IGC in ISSNHL.

METHODS

This retrospective study was performed in accordance with the principles of the Declaration of Helsinki. Approval of the study was received from Kastamonu University Clinical Researches Ethics Committee (Date: 06.07.2022, Decision No: 2022-KAEK-38). Patients aged 18-65 presenting to our clinic between June 2019 and June 2022, diagnosed with ISSNHL, and treated and follow-up on an outpatient basis were included.

The inclusion criteria were sensorineural hearing loss of at least 30 decibels (dB) at three consecutive frequencies within three days, presentation within a week of onset, no previous steroid use, blood specimens being collected at the first presentation, pure tone hearing tests being performed, and no abnormal findings that would cause loss of hearing at magnetic resonance imaging. Patients with any previous otological disease, history of acoustic trauma, any acute inflammation, hypertension, coronary diseases, chronic obstructive pulmonary disease, renal diseases, connective tissue diseases, liver diseases, diabetes mellitus or regularly taking medications for any disease were excluded from the study. Pre-operative complete blood count specimens from 40 individuals with no health problems who presented to the ear, nose, and throat clinic due to nasal septum deviation and with normal hearing were employed as the control group. There was no significant age or sex difference between the patient and control group.

All patients' complete blood count and pure tone audiometry thresholds at 250, 500, 1000, 2000, 4000, and 8000 Hz before and after treatment were recorded. All patients were evaluated according to their recovery status during a one-month follow-up period. All were started on 1 mg/kg oral methylprednisolone, treatment being completed in 14 days with gradual dose reductions. Siegel's hearing recovery criteria were used to assess the patients' response to treatment (Table 1). According to these criteria, types 1, 2 and 3 were defined as the recovery group and type 4 was defined as the non-recovery group.

Table 1. Siegel's criteria

Type	Description	Details
1.	Complete recovery	Final hearing level 25 dB
2.	Partial recovery	More than 15 dB hearing gain dB and a final haring level of 25-45 dB
3.	Slight recovery	More than 15 dB hearing gain and a final hearing level >45 dB
4.	No recovery	Hearing gain less than 15 dB

Statistical Analysis

This study data were retrieved from the hospital information management system. Complete blood count parameters in the patient group and control group requested at the time of presentation to hospital and measured using an XN-1000 (Sysmex Corporation, Kobe, Japan) automatic hematological analyzer were examined retrospectively. NLR, PLR, SII, IGC, and IG% values were analyzed in addition to standard complete blood count parameters. Blood specimens from the patient group (39) were subsequently subjected to statistical comparisons between those with (23) and without recovery (16).

This study data were analyzed on Statistical Package for Social Sciences version 18.0 for Windows software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as median (25^{th}-75^{th} percentiles) for numerical variables, number and percentage for categorical variables. Since the results were not normally distributed, the Mann-Whitney U test was applied in the comparison of data between the control and ISSNHL groups and the recovery and non-recovery subgroups. The chi-square test was applied to determine whether there was any gender difference between groups. Area under the curve (AUC), cut-off, sensitivity and specificity values were determined by receiver operating characteristic (ROC) analysis and Youden index. p value <0.05 were regarded as statistically significant (Figure).

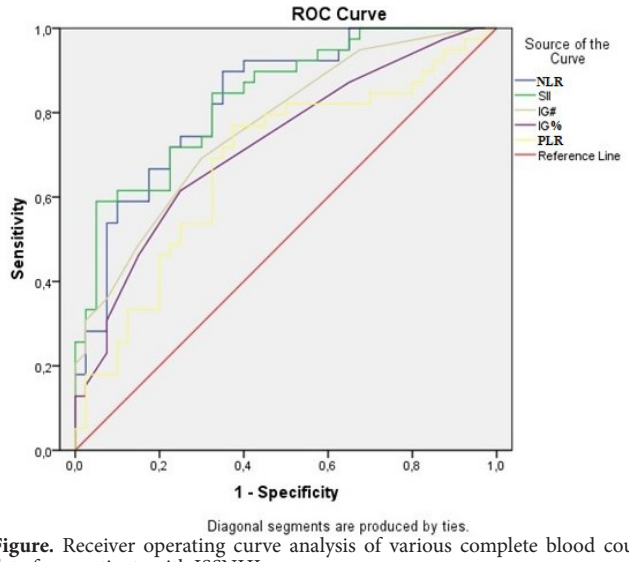

Figure. Receiver operating curve analysis of various complete blood count data from patients with ISSNHL

ROC: Receiver operating characteristic, ISSNHL: Idiopathic sudden sensorineural hearing loss, NLR: Neutrophil lymphocyte ratio, SII: Systemic Immune Inflammation Index, PLR: Platelet lymphocyte ratio

RESULTS

Comparison revealed higher IG, leukocyte, and neutrophil counts, as well as NLR, PLR, and SII values in the patient group than in the control group, while lymphocyte counts were lower than in the control group (Table 2).

SII and NLR were found to be of high predictive value in distinguishing the idiopathic sudden hearing loss and control groups. Additionally, IGC, IG%, and PLR exhibited moderate predictive value (Table 3).

None of the parameters previously reported to be significant in the data for recovering and non-recovering patients emerged as statistically significant, and IGC was of no prognostic value in ISSNHL (Table 4).

Table 2. A comparison of the patient and control groups

	Control (40)	Patient (39)	
	Median (IQR)		p
WBC (×10³/µl)	7.1 (5.4, 7.9)	8.7 (7.4, 11.0)	<0.001
NEU# (×10³/µl)	3.6 (2.6, 4.3)	5.7 (4.1, 7.2)	<0.001
LYM# (×10³/µl)	37.6 (32.3, 45.1)	25.1 (21.6, 33.5)	<0.001
IG# (×10³/µl)	0.02 (0.01, 0.03)	0.03 (0.02, 0.06)	<0.001
IG (%)	0.3 (0.2, 0.37)	0.4 (0.3, 0.6)	<0.001
NLR	1.3 (1.0, 1.7)	2.6 (1.6, 3.3)	<0.001
PLR	102 (90, 126)	126 (112, 151)	0.006
SII	391 (257, 545)	726 (460, 1101)	<0.001

WBC: White blood count, LYM: Lymphocyte, IG: Immature granulocyte, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic Immune Inflammation Index

Table 3. Receiver operating curve analysis of various complete blood count data from patients with ISSNHL

	Cut-off	AUC	95% CI	p	Sensitivity%	Specificity%
SII	638	0.835	0.74-0.92	<0.001	59	95
NLR	Oca.53	0.830	0.75-0.92	<0.001	90	65
IGC	0.025	0.768	0.67-0.87	<0.001	69	70
IG%	0.035	0.725	0.61-0.84	0.001	62	75
PLR	112	0.680	0.56-0.80	0.006	77	63

ISSNHL: Idiopathic sudden sensorineural hearing loss, AUC: Area under the curve, SII: Systemic Immune Inflammation Index, NLR: Neutrophil lymphocyte ratio, IGC: Immature granulocyte count, IG: Immature granulocyte, PLR: Platelet lymphocyte ratio

Table 4. A Comparison of the recovering and non-recovering idiopathic hearing loss groups

	Recovery (23)	Non-recovery (16)	p
	Median (IQR)		
WBC (×10³/µl)	8.28 (7.01, 9.75)	9.93 (8.09, 11.2)	0.077
NEU# (×10³/µl)	5.5 (3.9, 6.07)	6.5 (4.7, 8.9)	0.127
LYM# (×10³/µl)	2.1 (1.7, 2.7)	2.3 (1.5, 2.6)	0.597
IGC (×10³/µl)	0.03 (0.02, 0.05)	0.04 (0.03, 0.09)	0.093
IG (%)	0.4 (0.3, 0.6)	0.5 (0.3, 0.6)	0.165
NLR	2.6 (1.8, 3.1)	2.5 (1.6, 4.9)	0.886
PLR	130 (106, 142)	121 (115, 199)	0.954
SII	726 (444, 889)	797 (497, 1607)	0.356

WBC: White blood count, LYM: Lymphocyte, IGC: Immature granulocyte count, IG: Immature granulocyte, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, SII: Systemic Immune Inflammation Index

DISCUSSION

The purpose of our study was to investigate the importance of IG and various other blood count parameters (WBC, neutrophil count, NLR, PLR, and SII) as predictive and prognostic markers in ISSNHL. Both IGC and other hematological markers were significantly higher in the patients with ISSNHL than in the healthy control group, but none was of any prognostic value.

The etiology of SSINHL is not yet fully understood, but it is thought to be multifactorial. Various mechanisms have been proposed that may contribute to cochlear damage, such as viral infection, vascular disorders, immune-mediated mechanisms, and inflammation.[12] However, there is no definite evidence for any specific hypothesis. Some studies have shown an association between ISSNHL and chronic inflammation.[13] Chronic inflammation is thought to be a risk factor in the development of atherogenesis and microvascular damage, which increase the risk of cochlear ischemia and induce endocochlear immune responses.[14-16] Vascular wall damage increases the risk of ischemia in chronic inflammation and this is important for cochlea supplied by a single artery.[14] Systemic steroid therapy represents the basis of treatment in ISSNHL. However, no improvement has been observed in 20-50% of patients despite two-week oral or intravenous steroid therapy.[15]

WBC and various subtypes are used as inflammatory markers. NLR and PLR values are newly identified inflammatory markers that can be calculated from peripheral blood specimens. Elevation in NLR values is associated with the level of inflammation,[5] while high PLR values are indicative of atherosclerosis.[17] The SII can be used as an inflammatory marker in malignancy and inflammatory states. Some studies have reported that it represents a superior index of systemic inflammation than NLR and PRL values.[18,19] IGs are not present in peripheral blood under normal physiological conditions. Peripheral IGC can indicate increased bone marrow activation in periods of infection and inflammation. This has been shown to rise earlier than CRP and leukocyte counts in infection and sepsis.[10,11] In some studies, significant IGC elevation has been observed in acute appendicitis and pancreatitis.[10]

In this study, both IGC values and NRL, PRL and SII values were higher in patients with ISSNHL than in the control group. No statistically significant difference was observed in IG, NRL, PRL, or SII values between patients with recovery of at least 15 dB according to Siegel's criteria and patients with no recovery. This finding confirms that inflammation is important in the pathogenesis of ISSNHL and supports the idea that IGs are of predictive value in ISSNHL. However, neither IGs nor the SII were of any prognostic significance in ISSNHL.

Our review of the literature revealed no previous studies concerning IGC in patients with hearing loss. However, the NLR and PLR indices have been widely investigated in ISSNHL. Masuda et al.[16] reported that increases in neutrophil counts are an indicating poor prognosis in ISSNHL. Özler[20] reported that NRL was higher in patients with ISSNHL than in the control group. SEO et al.[17] reported that NRL and PRL values were higher in patients with ISSNHL than in the control group. There are studies in the literature reporting that increased NRL values are associated with poor prognosis in ISSNHL.[21,22] In contrast, in a prospective study, Gupta et al.[23] determined no a statistically significant association between the severity of hearing loss in patients with ISSNHL and hematological tests (total leukocyte count and subtypes) and reported no relationship between NRL values and recovery. The number of studies of the prognostic value of the SII in ISSNHL is limited. Ulu et al.[24] reported that the SII, a novel index, may represent an indicator in ISSNHL and is also capable of predicting prognosis. In their retrospective study, Kumbul et al.[25] reported high SII values in patients with ISSNHL, but that it exhibited no prognostic value. We think that the fact that the majority of these studies are retrospective, their low patient numbers, the lack of any universally accepted threshold values for NRL and PRL levels, the use of different criteria to define recovery, the presence or absence of additional diseases that might cause inflammation in patients with ISSNHL, and the use of different devices such as hematological analyzers and audiometers in studies may account for the heterogeneity in the results obtained.

Limitations

To our knowledge, our study is the first study to investigate the prognostic significance of the IGC in ISSNHL and to investigate it to support the role of inflammation in the pathogenesis of ISSNHL.

The limitations of our study are its single-center nature and limited patient numbers. In our study, finding that IGC, NRL and SII values were significantly higher in patients with ISSNHL compared to the healthy control group supports the idea of the involvement of inflammation in the etiopathogenesis in ISSNHL. However, the absence of any significant difference in these values between the recovering and non-recovering patients show that they are of no prognostic significance. Early treatment is important in ISSNHL. Prognostic factors and alternative treatments (hyperbaric oxygen, vasodilator agents, antiviral agents, etc.) should also be considered in addition to standard cortisone therapy at the beginning of treatment.

CONCLUSION

Recently, new inflammatory markers have described to predict inflammatory states. IGC may be a novel and inexpensive indicator of ISSNHL and one easily determined from complete blood count, but it is of no prognostic value in ISSNHL. Nonetheless, in the light of the study limitations, we think that further prospective studies including various inflammatory factors such as CRP, fibrinogen, cytokines, and interleukins in larger numbers of patients with ISSNHL are needed to confirm our findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Clinical Researches Ethics Committee (Date: 06.07.2022, Decision No: 2022-KAEK-38).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Nonoperative management of blunt splenic injury: a rural hospital experience

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ABSTRACT

Aims: Nonoperative management (NOM) of blunt splenic injuries in adults has become a standard approach in hemodynamically stable patients. We aimed to investigate the reliability of NOM and the risk factors for failure of NOM.

Methods: Included in the present study were 97 patients who underwent NOM for blunt splenic trauma between 2014 and 2022, whose computed tomography (CT) images, treatment, number of transfused erythrocyte suspensions, complications, duration of hospital stay and mortality data were evaluated retrospectively. The cases that underwent laparotomy due to NOM failure (group OP, n: 20), and those in whom NOM was successful (group NOM, n: 77) were statistically compared.

Results: Among the patients, nine were female and 88 were male, with a mean age of 23.7 years. The CT grade was higher in the OP group than in the NOM group (p: <0.001); the number of patients with multiple organ injuries was significantly higher in the OP group (p: 0.026); the number of ES transfused patients was significantly higher in the OP group (p<0.001); and the duration of hospital stay was longer in the OP group (p<0.001). The CT grade and number of ES transfusions (cut off >0.5 units) were determined as risk factors for NOM failure based on a receiver operating characteristic analysis (p<0.001). There were no differences between the groups in terms of complications, ICU admissions and mortality

Conclusion: Non-operative management is a safe and effective protocol in cases of blunt splenic trauma. High grade injury and the quantity of transfused erythrocyte suspensions (>0.5 units) were found to be predictive for NOM failure.

Keywords: Blunt trauma, computerized tomography, non-operative management, splenic injury

INTRODUCTION

The spleen is one of the most commonly injured organs following blunt abdominal trauma. The treatment of blunt splenic trauma has been subject to much discussion in recent decades, and protocols have changed substantially. Nonoperative management (NOM) is accepted as the standard care approach in some centers.[1,2] The accepted criteria for the application of NOM are hemodynamic stability, absence of signs of peritonitis and absence of no other injury requiring laparotomy. The single absolute contraindication for NOM is the presence of hemodynamic instability, although polytrauma, high grade splenic injury and the presence of a large hemoperitoneum have also been reported to be risk factors for NOM failure.[3,4]

Besides these criteria, factors such as the experience of the surgeon, the type of hospital and access to the required blood products are effective in decisions to follow a NOM approach, while the feasibility, indications and risks in selecting NOM in such instances are less clear. The present study evaluates the results of NOM in blunt splenic trauma, and analyzes the risk factors for NOM failure.

METHODS

The study was carried out with the permission of the Dicle University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 12.12.2022, Decision No: 27). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Retrospective analysis was performed on patients who were hospitalized between January 2014 and September 2022 at the Şırnak State Hospital. A total of 97 patients, all of whom were over the age of 18 years, with blunt splenic trauma and who were applied NOM at admission were included in the study. Excluded from the study were patients with penetrating traumas, those below the age of 18 years, those operated on with an urgent laparotomy at admission, those who died before the total diagnostic work-up was completed, those with non-survivable brain injuries and those with missing data in their medical records (n: 14).

The patient demographics, computed tomography (CT) images, treatment approaches, number of transfused blood products, duration of hospital stay and mortality data were recorded. The

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NOM group and the group of patients who were operated on due to failure of NOM (group OP) were statistically compared to determine the risk factors for surgery. In addition, the grade of splenic injury on CT and the intraoperative injury grade in the patients who underwent surgery were compared and correlations were analyzed.

The CT images of all patients were evaluated retrospectively by the same radiologist, who had 8 years of experience. The splenic injury grade was determined based on the American Association for the Surgery of Trauma (AAST) splenic injury scale.[5] An increase of at least 50% in hemoperitoneum in a follow-up CT was considered a sign of progression. NOM failure was defined as the need for laparotomy in patients initially admitted to the ICU or ward for nonoperative treatment. Mortality was accepted as death within 30 days of the trauma. The number of transfused erythrocyte suspensions (ES) was calculated taking into account only the preoperative ES replacements, while intraoperative and postoperative ES replacements were excluded.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.). A histogram analysis and Kolmogorov-Smirnov test were used to evaluate whether the variables were normally distributed. Descriptive statistics were expressed as mean, standard deviation, median, and min-max. Categorical variables were compared with a Pearson's Chi-square test. A Mann-Whitney U test was used for a between-group comparison of variables with a non-normal distribution (nonparametric). A Spearman's Correlation test was used to analyze numerical data. The values with the potential to predict the OP group were evaluated with a ROC analysis. The correlations between the intraoperative and CT grades of splenic trauma were assessed with a Kappa correlation analysis. The level of statistical significance was set at $p<0.05$.

RESULTS

Among the patients, nine were females and 88 were male, with a mean age of 23.77±9.54 years. Of the total, 33 had signs of multiple traumas. A total of 83 patients underwent a second CT evaluation, with a mean interval between the first and follow-up CT of 12.75±4.17 hours. NOM failure was recorded for 20 patients who underwent surgery (group OP) while 77 patients were recorded as successful NOM. Among the patients, 46 were admitted to the ICU. The mean duration of hospital stay in the total series was 4.64±2.05 days with a mortality rate of 4.1% (n: 4) (Table 1).

No significant differences were noted in age or gender between the NOM and OP groups. The CT grade of splenic injury was significantly lower in the NOM group ($p<0.001$). The patients in the NOM group had mostly grade 2 injuries, while grade 3 injuries were most common in the OP group. The number of patients with a "sign of progression on follow-up CT" was significantly higher in the OP group ($p<0.001$), and another significant parameter in the OP group was presence of multiple traumas (p:0.026). The most common injury other than splenic injury was, in descending order, the thorax (n: 14) followed by the liver (n: 11). The mean number of ES transfused preoperatively was 1.25±0.85 and 0.31±0.57 in the OP and NOM groups, respectively ($p<0.001$). The most commonly observed complications were pulmonary complications and infective complications (n: 4, each) (Table 2). No significant difference was noted in the rate of complications between the two groups. No overwhelming post-splenectomy infection (OPSI) or sepsis developed in any of the cases in the OP group. The duration of hospital stay was shorter in the NOM group ($p<0.001$), while there was no significant difference in the mortality rates of the two groups (Table 3). All four patients who died had multiple traumas, and the cause of death was secondary to other organ injuries.

Table 1. Main demographic. clinical and radiological data (n: 97)

		n (%)/mean±SD
Age		23.77±9.54
Gender	Male	88 (90.7)
	Female	9 (9.3)
CT grade	1	20 (20.6)
	2	52 (53.6)
	3	20 (20.6)
	4	5 (5.1)
Control CT		83 (85.6)
Control CT interval (hour)		12.75±4.17
Progression in control CT		21 (25.3)
Multiple trauma		33 (34.0)
Complications		10 (10.3)
Number of ES		0.51±.74
Intraoperative grade	1	0 (0)
	2	1 (5)
	3	15 (75)
	4	4 (20)
ICU admission		46 (47.4)
Length of hospital stay (day)		4.64±2.05
Mortality		4 (4.1)

SD: Standard deviation, CT: Computed tomography. ES: Erythrocyte suspension. ICU: Intensive care unit

Table 2. Type of complications

Type of complication	OP group, n (%)	NOM group, n (%)
Pulmonary	1 (5)	3 (3.9)
Infective	2 (10)	2 (2.6)
Hemorrhagic shock	1 (5)	-
Ileus	1 (5)	-

OP: Postoperative, NOM: Nonoperative management

The CT grade and the number of ES transfused were identified as significant predictive factors for NOM failure ($p<0.001$) (Table 4). The CT grade cut-off value was determined to be >2.5, with 85% sensitivity and 89.61% specificity. The cut-off value for the number of ES transfused was determined to be >0.5, with 80% sensitivity and 74.03% specificity.

The CT grade and intraoperative grade in the OP group was evaluated, and a positive correlation was noted between them (r: 0.764), and a significant correlation was found between the two grades (Ḱ: 0.657) (Table 5).

Table 3. Comparison of demographic, radiological and clinical features between NOM and OP groups

		OP group n/mean±SD	NOM group n/mean±SD	p
Age		25.65±9.57	23.29±9.53	0.1291
Gender (Male/Female)		18/ 2	70/7	0.9012
CT grade	1		20	<0.001
	2	3	49	
	3	14	6	
	4	3	2	
Control CT		18	65	0.5272
Progression in control CT		14	7	<0.0012
Multiple trauma		11	22	0.0262
Complication		4	6	0.1102
Number of ES		1.25±0.85	0.31±0.57	<0.0011
ICU admission		13	33	0.0772
Length of hospital stay (day)		7.95±1.90	3.78±0.88	<0.0011
Mortality		2	2	0.1382

[1]Mann-Whitney U test, [2]Chi-square test, OP: Postoperative, NOM: Nonoperative management, SD: Standard deviation, CT: Computed tomography, ES: Erythrocyte suspension, ICU: Intensive care unit

Table 4. ROC analysis of predictive parameters for failure of NOM

				95% CI						
	Area	SD error	p	Lower	Upper	Cut-off	SEN	SPE	PPV	NPV
CT grade	0.889	0.041	<0.001	0.810	0.969	>2.5	(85.00)	(89.61)	(68.00)	(95.83)
Number of ES	0.803	0.060	<0.001	0.685	0.920	>0.5	(80.00)	(74.03)	(44.44)	(93.44)

ROC: Receiver operating characteristic, NOM: Nonoperative management, SD: Standard deviation, SEN: Sensitivity, SPE: Specifitiy, PPV: Positive predictive value; NPV: Negative predictive value

Table 5. The relationship and compliance between CT grade and intraoperative grade in the OP group

		Intraoperative grade		
		2	3	4
CT grade	2	1	2	-
	3		13	1
	4			3

Grade 2	Grade 3	Grade 4	Total	r[1]	Ḱ[2]	p
100%	86.67%	75%	85%	0.764	0.657	<0.001

[1]Spearman correlation test, [2]Kappa compliance analysis, CT: Computed tomography, OP: Postoperative

DISCUSSION

The spleen is the most commonly damaged organ in blunt abdominal traumas, and is affected in around 33% of patients with traumatic abdominal injuries.[6,7] The standard treatment of splenic injury has been splenectomy for the last 100 years, while NOM has gained popularity since the late 1980s. Currently, more than 80% of adult patients with blunt splenic traumas are managed nonoperatively.[3]

The spleen is a highly efficient immunological organ, and contributes substantially to the development of primary and secondary immune responses through antibody production against antigens, mediated by the T and B lymphocytes that are present intensely in its white pulp. Furthermore, macrophages in the spleen perform phagocytosis, and remove foreign antigens and immune complexes though phagocytosis. The spleen is an organ with regulatory functions affecting plasma volume and albumin synthesis, and has a rich reticular structure and a large reservoir function. The most feared complication of splenectomy is therefore OPSI, which develops in 3-5% of splenectomy cases.[8] Most infectious complications are caused by encapsulated bacteria (*Meningococcus*, *Pneumococcus and Hemophilus)*, and there is a further tendency for thrombosis to develop due to the increase in platelet, fibrinogen and tissue plasminogen activator inhibitor-type 1 levels following splenectomy.[9] Thrombotic complications frequently include pulmonary embolism, porto-mesenteric system thrombosis and caval system thrombosis.

Surgeons tend to opt for spleen-preserving methods due to the vital functions of the spleen and the complications secondary to splenectomy. Partial splenectomy, splenorrhaphy and splenic artery embolization as para-surgical treatment methods may be applied, while NOM is accepted as the standard treatment for blunt splenic trauma in some centers. Consensus on the contraindications for NOM have been reached, being hemodynamic instability and peritonitis.[10,11] Franseva et al.[1] reported NOM to be inappropriate for patients with an Abbreviated Injury Scale >3, while Godley et al.[12] reported NOM to be contraindicated in patients aged >55 years.[13] The failure rate for NOM was reported to be 2.5 times greater in patients aged >55 years than in those aged <55 years in a multicenter study of 1,488 patients, while Cocanour et al.[14] concluded in their retrospective study reported similar rates of NOM failure in those aged >55 years and younger patients. Age was found not to be a risk factor for NOM failure in the present study.

Smith et al.[4] reported high-grade splenic injury and large hemoperitoneum to be risk factors of NOM failure. In a study of 94 cases with grade 4 splenic trauma, NOM was suggested to be safe for the treatment of such cases, provided a rigid protocol was followed.[15] The CT grade in the OP group was higher in the present study and the CT grade was determined to be a risk factor for NOM failure. Also revealed in the present study was that CT grading in cases of splenic trauma was compatible with actual intraoperative grading. The reliability of CT in this area and the experience of the radiologist with the CT signs of splenic trauma are important in planning the optimal treatment.

Generally, the NOM failure rate is accepted to be increased in multiple solid organ injuries in literature.[10] Malhotra et al.[16] reported higher rates of NOM failure, a greater transfusion requirement and more frequent mortality in patients with multiple organ injuries. In contrast, Sartorelli et al.[17] reported the outcome of NOM in patients with multiple parenchymal trauma to be no different to that of NOM in unique splenic injury. In the present study, multi-organ injury was found not to be a risk factor for NOM failure, although the ratio of patients with multiple organ trauma was higher in the OP group.

A transfusion of 2 units of blood to keep the hemoglobin level above 8 g/dl in the first 48 hours may be sufficient for successful NOM, although a ≤4 unit blood transfusion has been reported as the standard criteria for NOM in some studies.[14,18,19] The amount of blood transfused was found to be significantly higher in the OP group, with a blood transfusion of >0.5 units (above the cut-off number) being a significant risk factor for NOM failure in the present study.

Treatment with angioembolization in blunt spleen traumas is a widely applied method in the last 2-3 decads. To avoid surgery

and preserve splenic parenchyma, selective splenic artery embolization is increasingly being used in haemodynamically stable patients with evidence of ongoing haemorrhage on contrast-enhanced computed tomography. It has been reported in the literature that it can be applied in grade 3-4-5 splenic injuries.[20] Sclafani believes that this procedure is compatible with the maintenance of splenic immune function and even if surgery is necessary, splenorrhaphy is facilitated.[21] Since there is no interventional radiology department in our hospital, splenic angioembolization could not be performed.

A review of the current literature reveals that there are numerous predictive scoring systems for identifying NOM failure.[22] One such system, which incorporates variables such as Glasgow coma scale, systolic blood pressures, abdominal injury score and injury severity score (ISS) at the time of patient presentation, has demonstrated that a score of 5 or higher is predictive of NOM failure.[23] Since these parameters were not included in our study, the predictive value of these scoring systems could not be evaluated in our research.

Limitations

The study has some significant limitations, the first of which is its retrospective, single center study design the low number of patients. Second, several patients (n: 14) were excluded from the study due to missing data in their medical records, and ISS, Glascow coma scale score parameter, which has been evaluated in most studies on the subject in literature, was not included in the analysis for the same reason. Another limitation is the absence of an evaluation of the long-term outcome of the patients.

CONCLUSION

Nonoperative management can be considered a safe and effective protocol in cases of blunt splenic trauma. AAST CT grade, frequency of multiple organ injury and blood transfusion amounts were found to be higher and the duration of hospital stay to be longer in patients with NOM failure, which was also predicted by high-grade injury and transfused erythrocyte suspension amounts exceeding 0.5 units.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dicle University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 12.12.2022, Decision No: 27).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Impact of the COVID-19 pandemic on breast cancer biopsies: a retrospective comparative study

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ABSTRACT

Aims: The purpose of this study is to evaluate and compare the quantity and pathological outcomes of diagnostic breast biopsy procedures performed in our interventional radiology unit before, during, and after the COVID-19 pandemic. This study aims to examine the influence of the COVID-19 pandemic on the quantity of biopsies performed and the rates of detecting malignancies during different time periods.

Methods: This retrospective study examined 365 patients who underwent diagnostic breast biopsies between January 2019 and January 2023. The study was approved by the hospital's ethics committee. After excluding 19 patients with inconclusive pathology results, a total of 346 patients were analyzed. Biopsies were performed utilizing 14-18 G tru-cut needles with the assistance of ultrasound guidance. Patients were classified into the following periods: pre-pandemic, pandemic, and post-pandemic. The histopathological findings were categorized as either benign or malignant. Statistical comparisons were conducted using the SPSS software, and a significance level of $p<0.05$ was used.

Results: The average age of the patients was 53.7±15.7 years. Out of the total of 346 biopsies, 165 (47.7%) were determined to be malignant, while 177 (51.2%) were found to be benign. The distribution of biopsies was as follows: 76 (22.0%) were conducted before the pandemic, 13 (3.8%) were conducted during the pandemic, and 257 (74.3%) were conducted after the pandemic. There was a substantial decline in the number of biopsies during the pandemic compared to before the pandemic, and a significant rise in the post-pandemic period compared to both the pandemic and pre-pandemic periods ($p=0.024$ and $p=0.041$, respectively). The incidence of malignancies during the post-pandemic period was significantly greater compared to both the pre-pandemic period ($p=0.045$) and the pandemic period ($p=0.027$).

Conclusion: The COVID-19 pandemic caused substantial disruptions in breast cancer diagnostics, as indicated by a decrease in the number of biopsies performed and delays in the detection of malignancies. Following the pandemic, there was a significant rise in the incidence of malignancies, which can be attributed to the delays in diagnosing and treating these conditions during the pandemic. These findings indicate the significance for stronger healthcare strategies to reduce the effects of future crises on cancer management.

Keywords: Breast cancer, COVID-19, biopsy, malignancy, diagnosis, pandemic

INTRODUCTION

The World Health Organization (WHO) officially declared the outbreak of COVID-19, caused by the SARS-CoV-2 virus, a public health emergency of international concern on January 30, 2020. Subsequently, on March 11, 2020, the WHO officially announced that COVID-19 had become a global pandemic.[1,2] The COVID-19 pandemic has significantly challenged the medical community in numerous areas, notably affecting access to cancer diagnosis and treatment. One of the primary factors contributing to delays in cancer diagnosis and treatment has been the fear of infection while utilizing healthcare facilities amidst the rising number of COVID-19 cases. During the COVID-19 pandemic, there was a significant decline in cancer diagnoses, with the most pronounced decrease observed in breast cancer diagnoses (51.8%).[3]

Breast cancer accounts for 14% of all cancer diagnoses and 30% of cancer cases diagnosed in women. The prevalence of breast cancer in our country is 47.7 cases per 100,000 women. Early diagnosis is critical in reducing breast cancer prognosis and mortality, and this is possible with screening programs.[4,5]

Routine screening methods for breast cancer, such as mammography and breast ultrasound (US), are procedures

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that inherently require close physical contact, providing little opportunity to maintain physical distance. During these examinations, the patient's face can be as close as 20-30 cm to the radiologist's face. Similarly, during breast procedures guided by US, stereotactic, or MRI, such as biopsies, drainages, and clip placements, the interventional radiologist can be only 30 cm away from the patient's face. The risk of COVID-19 infection has been reported to increase with close physical proximity and prolonged contact.[6-8]

Moreover, during the COVID-19 pandemic, many patients have been hesitant to visit healthcare facilities due to concerns about infection risks and the imposition of movement restrictions, such as curfews and lockdowns. This has led to delays in routine screening and necessary breast procedures, potentially impacting early diagnosis and treatment outcomes.

Due to these reasons, unfortunately, breast cancer screening activities were suspended during the pandemic in our country, as in many other countries. Only urgent cancer-related medical activities were carried out.[9]

The aim of this study is to compare the number and pathological results of diagnostic breast biopsy examinations performed in our interventional unit during the pre-pandemic, pandemic, and post-pandemic periods. Additionally, this study seeks to investigate the impact of the COVID-19 pandemic on the number of biopsies conducted and the rates of malignancy detection across these different periods.

METHODS

This study received approval from the Kastamonu University Clinical Researches Ethics Committee (Date: 08.03.2023, Decision No: 2023-KAEK-27) and was designed as a retrospective analysis. A total of 365 patients who underwent diagnostic breast biopsies between January 2019 and January 2023 were reviewed. Patient demographics, BI-RADS data from mammography and ultrasound, and histopathology results were documented. 19 patients with unclear pathology results were excluded, leaving 346 patients in the final analysis. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Diagnostic breast biopsy procedures were performed using multiple biopsies with 14-18 G fully automatic tru-cut biopsy needles under ultrasound guidance. Additionally, tru-cut and fine-needle aspiration biopsies on pathological lymph nodes in the axilla were included. Patients were categorized into three groups: pre-pandemic, pandemic, and post-pandemic periods. Histopathological results were classified as benign or malignant.

The date of the first diagnosed COVID-19 case in Turkiye marked the beginning of the COVID period, while the start of controlled normalization measures in March 2021 signified the onset of the post-COVID period. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 23 software (IBM SPSS Inc., Chicago, IL, USA). Normal distribution of the data was assessed using the Kolmogorov-Smirnov test. Numerical variables with a normal distribution are presented as mean±standard deviation (SD) values. Categorical variables are reported as the number (n) and percentage (%). For group comparisons, the independent samples t-test was used for data with a normal distribution, and the Mann-Whitney U test was used for data without a normal distribution. The Chi-square test was employed to compare categorical variables. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 53.7±15.7 years. Among the 346 biopsies included in the study, 165 (47.7%) were malignant, and 177 (51.2%) were benign. The distribution of biopsies was as follows: 76 (22.0%) were performed in the pre-pandemic period, 13 (3.8%) during the pandemic, and 257 (74.3%) in the post-pandemic period. During the pandemic period, the number of diagnostic biopsy procedures significantly decreased compared to the pre-pandemic period, whereas in the post-pandemic period, there was a statistically significant increase in the number of biopsies compared to both the pandemic and pre-pandemic periods (Figure 1, Table 1). The malignancy rates in the post-pandemic period were statistically significantly higher compared to the pre-pandemic and pandemic periods (Figure 2, Table 2).

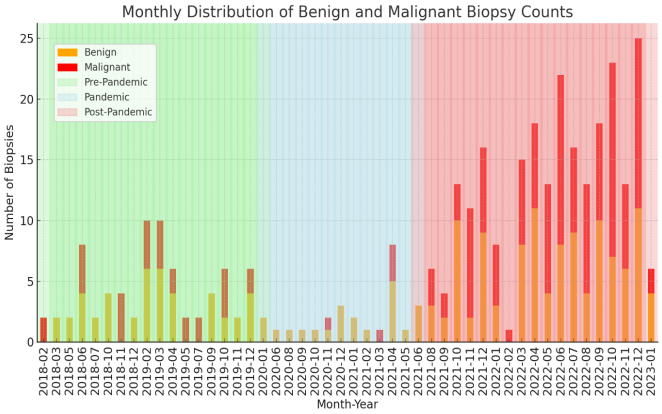

Figure 1. Monthly distribution of benign and malignant biopsy counts by periods

In the analysis performed to demonstrate the concordance between BI-RADS categories and histopathology results, we showed that 9.5% of patients categorized as BI-RADS 4A had malignant lesions, while the malignancy rate increased to 48.3% in the BI-RADS 4B category, 94.4% in the BI-RADS 4C category, and 99.0% in the BI-RADS 5 category (Figure 3, Table 3).

Table 1. Distribution of biopsy results and age distribution in periods

Period	Age (y)±mean SD	p value	Inadequate (n)	Inadequate (%)	Benign (n)	Benign (%)	Malignant (n)	Malignant (%)	Total (n)	Total (%)	p value
Prepandemic	53.26±15.7	0.94	0	0	46	60.5	30	39.5	76	22	0.041
During pandemic	53.0±11.2	0.81	0	0	11	84.6	2	15.4	13	3.8	0.024
Postpandemic	53.7±15.9		4	1.6	120	46.7	133	51.8	257	74.3	
Total	53.6±15.7		4	1.2	177	51.2	165	47.7	346	100	

Notes: "p-values" indicate the significance of comparisons between the postpandemic period and the prepandemic and pandemic periods, Abbrevations: SD: Standard deviation

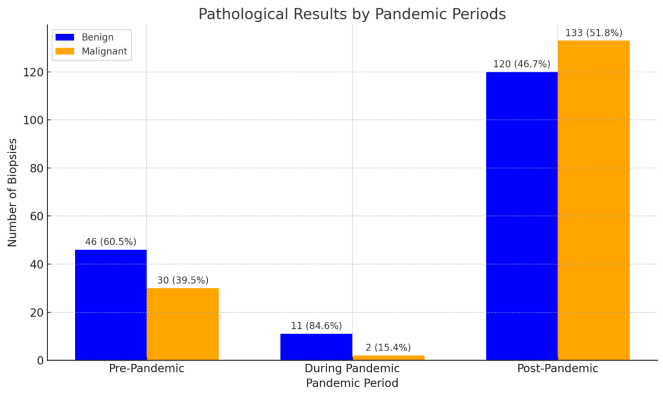

Figure 2. Pathological results by pandemic periods

Table 2. Comparison of benign and malignant biopsy outcomes in periods

Comparison	Benign (n)	Benign (%)	Malign (n)	Malign (%)	p value
Prepandemic vs postpandemic	46 vs 120	13.4 vs 35.0	30 vs 133	8.7 vs 38.8	0.045
During pandemic vs postpandemic	11 vs 120	84.6 vs 35.0	2 vs 133	15.4 vs 38.8	0.021

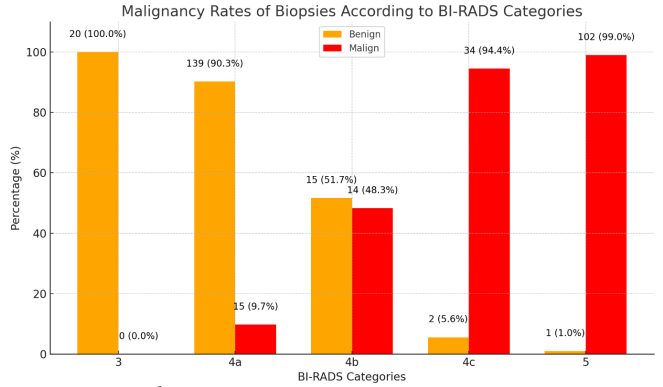

Figure 3. Malignancy rates across BI-RADS categories in biopsy results

Table 3. Malignancy rates of biopsies performed on patients according to BI-RADS categories

BI-RADS	Inadequate (n)	Inadequate (%)	Benign (n)	Benign (%)	Malign (n)	Malign (%)	Total (n)
3	0	00	20	100	0	0	20
4A	4	2.5	139	88.0	15	9.5	158
4B	0	0	15	51.7	14	48.3	29
4C	0	0	2	5.6	34	94.4	36
5	0	0	1	1.0	102	99.0	103
Total	4	1.2	177	51.2	165	47.6	346

BI-RADS: Breast imaging reporting and data systems

In a comparison of mammography rates in patients over 40 years of age, the mammography rate in the pre-pandemic period was 18.7%, significantly lower than the 37.5% observed in the post-pandemic period (p=0.008), indicating a significant increase in mammography screening in the post-pandemic period. In the comparison of mammography outcomes, the proportion of patients with BIRADS 4 and above (including categories 4A, 4B, 4C, and 5) did not significantly differ between the pre-pandemic and post-pandemic periods (p=0.129). Specifically, BIRADS 4 and above were observed in 50.0% of cases pre-pandemic and 52.6% post-pandemic (Table 4).

Table 4. Comparison of mammography rates in patients over 40 years

Period	n (>40y)	MMG (n)	MMG (%)	p value	>BI-RADS 4 (n)	>BI-RADS 4 (%)	p value
Prepandemic	64	12	18.7	0.008	6	50.0	0.129
Postpandemic	208	78	37.5		40	51.2	

Abbrevations: MMG: Mammography, BI-RADS: Breast imaging reporting and data systems

DISCUSSION

During the COVID-19 pandemic, challenges in breast cancer management extended beyond surgery delays to include issues in performing biopsies and evaluating histopathological results. The number of emergency and elective surgical interventions, as well as patient admissions to hospitals, significantly decreased compared to the pre-pandemic period. For instance, Filipe et al.[10] observed a general reduction in the number of patients undergoing breast cancer surgery. Similarly, Dauti Işıklar et al.[11] reported a decrease in the number of patients visiting oncology clinics. Bulbul et al.[4] demonstrated a significant reduction in breast cancer screening, especially in the initial months of the pandemic. Consistent with these findings, our study also identified a significant decline in the number of diagnostic breast biopsy procedures performed at our center during the COVID-19 pandemic.

Considering the doubling time of breast cancer, a certain period is required to observe the outcomes of delayed diagnosis and treatment. Citgez et al.[12] found in their study that the challenges faced in breast cancer management during the pandemic led to an increase in malignancy rates. In our study, statistically significant results were obtained due to the more than two-year period after the pandemic. The higher detection of malignancies in the post-pandemic period compared to both the pandemic and pre-pandemic periods indicates delays in diagnosis.[13]

The rise in mammography rates among individuals aged 40 and above following the pandemic (from 18.7% to 37.5%) could be explained by alterations in public health policies, increased awareness, or an accumulation of routine screenings caused by temporary disruptions caused by the pandemic. The observed increase was statistically significant, indicating a notable shift in screening practices or accessibility following the pandemic. The rise in the identification of BI-RADS 4 and higher lesions after the pandemic is in line with findings from other studies that have noted an increase in the number of advanced-stage cases and uncertain results after the resumption of regular screenings following pandemic-related lockdowns. For instance, a study conducted by Patt et al.[14] observed a similar trend and attributed it to the delay of screening and diagnosis during the pandemic. This delay may have resulted in an accumulation of cases where the disease had progressed to more advanced stages by the time regular mammography screening resumed.[15]

Additionally, our study compared the concordance between US BI-RADS categories and histopathology results (Figure 3, Table 3). According to the results, 9.5% of patients in the BI-RADS 4A category were found to be malignant, compared to 48.3% in the BI-RADS 4B category, 94.4% in the BI-RADS 4C category, and 99% in the BI-RADS 5 category. These findings are consistent with the literature, further validating the reliability of the BI-RADS classification system in assessing the malignancy risk of breast lesions.[16]

Limitations

The main limitations of our study include the limited number of patients and its retrospective design. Another limitation is that it was a single-center study. Patient groups were classified as malignant/benign, but subtypes, disease grade, tumor size, stage, and survival rates were not evaluated. Therefore, multicenter studies with larger patient populations are needed.

CONCLUSION

In conclusion, the malignancy detection rate during the pandemic period was low, but it was significantly higher in the post-pandemic period compared to other periods. Due to delays in the diagnosis and treatment of breast malignancies during the pandemic, there was an increase in the malignancy detection rate not only compared to the pandemic period but also to the pre-pandemic period. We attribute this to the backlog of patients and delays in treatment approaches during the pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Clinical Researches Ethics Committee (Date: 08.03.2023, Decision No: 2023-KAEK-27).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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A comprehensive analysis of demographics, comorbidities, and laboratory findings in adult celiac disease patients: a single center experience

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ABSTRACT

Aims: This study aims to evaluate the demographics, comorbidities, and laboratory findings of patients with Celiac disease in our clinic.

Methods: A total of 91 celiac patients who were followed in our centre between January 2020 and September 2023 were included in the study. Demographic, laboratory and comorbidities data were analysed retrospectively.

Results: 72 (79.1%) patients were female, and the mean age of the participants was 42.3±15.1 years. Deficiency of iron was observed in 46 (50.6%) participants, vitamin B12 in 9 (9.9%) participants, folat in 11 (12.1%) participants, and vitamin D in 37 (40.7%) participants. Hypothyroidism and diabetes mellitus were found to be the two most common comorbidities of celiac disease. In addition, liver enzymes were demonstrated to be elevated in the 9 (9.9%) patients.

Conclusion: Celiac disease is associated with mineral and vitamine deficiency. In addition, mildly elevated liver enzymes may be observed in the clinical course. Notably, extraintestinal manifestations, especially hypothyroidism and diabetes, may accompany the disease.

Keywords: Celiac disease, iron deficiency, hypothyroidism, autoimmune disease

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune condition triggered by the consumption of gluten, primarily affecting the small intestine.[1] In genetically predisposed individuals, gluten intake leads to inflammation, villous atrophy, and subsequent malabsorption of key nutrients.[2] The clinical presentation of CD can vary widely, from classic gastrointestinal symptoms like diarrhea and abdominal pain to more subtle signs due to malabsorption of nutrients such as anemia, osteoporosis etc.[3] Due to the lack of disease-specific signs and symptoms, along with the presence of asymptomatic patients, the diagnosis of CD is frequently delayed.[4]

The diagnosis of CD is typically established through a combination of serological tests and histopathological examination of duodenal biopsies. The presence of specific antibodies, such as anti-endomysium IgA, tissue transglutaminase IgA, and anti-gliadin IgA, is indicative of CD and is used as a preliminary screening tool.[4] Confirmatory diagnosis is made using the Marsh-Oberhuber classification, where patients with Marsh 3 pathology (showing villous atrophy) are diagnosed with CD.[5]

In addition to gastrointestinal involvement, CD is associated with a range of comorbid conditions, particularly other autoimmune diseases.[6] The relationship between CD and conditions like autoimmune thyroid disease, type 1 diabetes, and rheumatoid arthritis suggests a broader systemic immune dysregulation in these patients.[7] The aim of this study is to provide a detailed analysis of the demographic characteristics, comorbid conditions, serological markers, and laboratory findings in a cohort of adult patients diagnosed with CD at a tertiary medical center in Ankara, Turkiye.

METHODS

The presented study was a retrospective study conducted in Gastroenterology Unit of Yenimahalle Training and Research Hospital, a tertiary medical center in Ankara, Turkiye. All adult patients diagnosed with CD between January 2020-Semptember 2023 were included in the study. Patients with malignancy, severe chronic liver and kidney diseases, altered GI anatomy, and younger than 18 years old were excluded. In addition, patients with missing data were also

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excluded. This study was conducted in accordance with the principles of the Declaration of Helsinki, reviewed ethically, and approved by the Medical and Health Researches Ethics Committee of Yenimahalle Training and Research Hospital (Date: 22.11.2023, Decision No: E-2023-60). Informed consent was not required due to the retrospective nature of the study.

Demographic data, comorbidity status, Celiac serology, laboratory results such as liver enzymes, lipid profiles, parameters for vitamin and iron deficiency, renal and thyroid function were collected from the electronic and printed files of the patients.

The diagnosis of CD was made based on the GI endoscopy with duodenal biopsy due to suspicion of CD or other indications.

Cut-off values for vitamin and iron deficiency was determined as 200 pg/ml for vitamin B12, 4 ng/ml for folate, 20 ng/mL for vitamin D, 15% for transferrin saturation and 20 ml/ng for ferritin levels. The values below the cut-off level were considered as deficiency for the corresponding parameter. Both for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, cut-off was considered as 35 U/L. Serologic parameters such as anti-endomysium IgA, tissue transglutaminase IgA, and anti-gliadin IgA was recorded as either positive or negative. Selective IgA deficiency was excluded by confirming that the patients' total IgA levels were within the normal range.

Statistical Analysis

Statistical analysis was performed using 24th version of Statistical Package for the Social Sciences (SPSS; IBM SPSS Statistics, United States). Categorical variables were described using as numbers and percentages. For continuous variables were tested with the Kolmogorov–Smirnov test for scattering pattern. Data were presented as median and standard deviation for continues variables with normal distribution, and median and minimum-maximum values (min-max) for non-parametric values. No comparative statistical analysis was performed in the study.

RESULTS

A total of 91 participants were included in the study, of whom 72 (79.1%) were female. The mean age of the participants was 42.3±15.1 years, and the median disease duration was 11.1 years, ranging from 1 to 42 years. The mean body-mass index (BMI) was 25.3±2.0 kg/m². Comorbid disease profiles were given in Table 1 with other demographic features. Of the study population, hypothyroidism was the most common comorbidity, observed in 18 (19.8%) participants. Other comorbidities included diabetes mellitus in 6 (6.6%) participants, Sjögren's disease in 3 (3.3%) participants, asthma and rheumatoid arthritis in 2 (2.2%) participants each, and inflammatory bowel disease, familial Mediterranean fever, and Graves' disease in 1 (1.1%) participant each.

The serological test results for celiac disease were given in Table 1. Anti-endomysium IgA antibody positivity was observed in 60 (65.9%) participants. Tissue transglutaminase IgA antibodies were positive in 71 (78.0%), and anti-gliadin IgA antibodies were detected in 49 (53.9%) participants.

Laboratory results other than serology for Celiac disease were given in Table 2. The median hemoglobin level was 13.1 g/dl (range: 8.6-16.5), and the median white blood cell count was 6.2×10³/µl (range: 3.3-13.5). Platelet counts had a median of

Table 1. Demographic characteristics, comorbid diseases and celiac test results of the participants

Parameter	n=91
Sex (female), n (%)	72 (79.1)
Age, mean (SD)	42.3 (15.1)
Disease duration, years, median (min-max)	11.1 (1.0-42.0)
BMI, kg/m², mean (SD)	25.3 (2.0)
Anti-endomysium IgA	
Negative, n (%)	31 (34.1%)
Positive, n (%)	60 (65.9%)
Tissue transglutaminase IgA	
Negative, n (%)	20 (22.0%)
Positive, n (%)	71 (78.0%)
Anti-gliadin IgA	
Negative, n (%)	42 (46.1%)
Positive, n (%)	49 (53.9%)
Comorbid disease	
Hypothyroidism, n (%)	18 (19.8%)
Diabetes mellitus, n (%)	6 (6.6%)
Sjögren disease, n (%)	3 (3.3%)
Asthma, n (%)	2 (2.2%)
Rheumatoid arthritis, n (%)	2 (2.2%)
Inflammatory bowel disease, n (%)	1 (1.1%)
Famillial mediterranean fewer, n (%)	1 (1.1%)
Graves disease, n (%)	1 (1.1%)

SD: Standard deviation, BMI: Body-mass index, IgA: Selective immunoglobulin A

Table 2. Laboratory results of the participants

Hemoglobin (g/dl), median (min-max)	13.1 (8.6-16.5)
White blood cell count (×103/µl), median (min-max)	6.2 (3.3-13.5)
Platelet (×103/µl), median (min-max)	283.0 (145.0-550.0)
Ferritin (ml/ng), median (min-max) <20 ml/ng, n (%)	17.7 (2.0-158.0) 46 (50.6%)
Transferrin saturation (%), median <15%, n (%)	18.0 (1.0-120.0) 38 (41.8%)
Vitamin B12 (pg/ml), median (min-max) <200 pg/ml, n (%)	319.0 (130.0-924.0) 9 (9.9%)
Folate (ng/ml), median (min-max) <4 ng/ml, n (%)	8.0 (1.5-44.0) 11 (12.1%)
Vitamin D (ng/ml), median <20 ng/ml, n (%)	22.0 (4.0-49) 37 (40.7%)
ALT (U/L), median (min-max) >35 U/L, n (%)	17.1 (5.0-83.0) 9 (9.9%)
AST (U/L), median >35 U/L, n (%)	20.0 (12.0-80.0) 7 (7.7%)
Creatinine (mg/dl), mean (SD)	0.70 (0.19)
Albumin (g/dl), mean (SD)	4.13 (0.23)
Calcium (mg/dl), mean (SD)	9.58 (0.51)
TSH (mIU/L), median (min-max)	2.0 (0.01-65.0)
Total cholesterol (mg/dl), mean (SD)	181.3 (39.6)
Triglyceride (mg/dl), median (min-max)	124.0 (45.0-459.0)
HDL (mg/dl), mean (SD)	50.9 (12.7)
LDL (mg/dl), mean (SD)	104.4 (37.1)
Glucose (mg/dl), mean (SD)	86.4 (12.2)

Min: Minimum, Max: Maximum, SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TSH: Thyroid-stimulating hormone, HDL: High density lipoprotein, LDL: Low density lipoprotein

283.0×10³/µl (range: 145.0-550.0). The median ferritin value of the study population was 17.7 ng/ml (range: 2.0-158.0) for ferritin and 18.0% (range: 1.0-120.0) for transferrin saturation. While ferritin levels were below 20 ng/ml in 46 (50.6%) participants, transferrin saturation was below 15% in 38 (41.8%) participants. The median (min-max) levels of vitamin B12, folate and vitamin D were 319.0 pg/ml (130.0-924.0), 8.0 ng/ml (1.5-44.0), and 22.0 ng/ml (4.0-499.0), respectively. Among the study population, 9 (9.9%) participants had vitamin B12 levels below 200 pg/ml, 11 (12.1%) participants had folate levels below 4 ng/ml, and 37 (40.7%) participants had vitamin D levels below 20 ng/ml.

The median ALT level was 17.1 U/L (range: 5.0-83.0), and 9 participants (9.9%) had ALT levels above 35 U/L. The median aspartate aminotransferase (AST) level was 20.0 U/L (range: 12.0-80.0), with 7 participants (7.7%) having elevated AST levels. Creatinine levels had a mean of 0.70±0.19 mg/dl albumin levels had a mean of 4.13±0.23 g/dl, and calcium levels had a mean of 9.58±0.51 mg/dl. The median thyroid-stimulating hormone (TSH) level was 2.0 mIU/L, ranging in between 0.01 and 65. The mean total cholesterol level was 181.3±39.6 mg/dl, the median triglyceride level was 124.0 mg/dl (range: 45.0-49.0), and the mean HDL cholesterol level was 50.9±12.7 mg/dl. The mean LDL cholesterol level was 104.4±37.1 mg/dl. The mean glucose level was 86.4±12.2 mg/dl.

DISCUSSION

This study demonstrated that CD is associated with iron deficiency and vitamin deficiency including vitamin B12, folat, and vitamin D. Notably, it has also been demonstrated that many chronic inflammatory diseases may accompany CD.

In this study, the study population is predominantly female with a rate of 79.1%. According to the literature, it has been also observed that celiac disease is predominantly female in gender distribution, thus our findings is consistent with the literature.[8] The predominance of the female population in celiac disease suggests an autoimmune basis for the disease.[9] This autoimmune background also explains the occurrence of other autoimmune and inflammatory diseases in the clinical course of celiac disease.[10,11] In this study, hypothyroidism and diabetes mellitus were found to be the two most common comorbidities with a rate of 19.8% and 6.6%, respectively. This result is consistent with the findings of Freeman et al.,[12] which also demonstrated that the most common comorbid disease are hypothyroidism and diabetes mellitus in patients with CD. Although the rate was low in the study, it is noteworthy that autoimmune and inflammatory diseases such as Sjögren's disease, asthma, rheumatoid arthritis, IBD, inflammatory bowel disease, famillial mediterranean fewer and Graves' disease were also observed in some patients. However, the comorbidities associated with CD are not limited to our findings but can also be accompanied by many extraintestinal manifestations.

CD disease mainly involves small intestine. The chronic inflammatory condition caused by gluten sensitivity leads to damage to small intestinal cells. This damage causes disruption of the architecture of the villus structure and consequently malabsorption of key nutrients.[13] In this study, iron deficiency was observed in 46 (50.6%) participants according to ferritin results, and in 38 (41.8%) participants according to transferrin saturation results. The second most common deficiency was found in vitamin D with a rate of 40.7%. Folat and vitamin B12 deficiency was also absorved in participants with a rate of 12.1% and 9.9%, respectively. This study demonstrated that majority of the participants has vitamine and mineral deficiency. It should be emphasised that the literature shows that subclinical inflammation may persist even in diet-compliant patients.[14] Therefore, all patients should be screened for vitamin and mineral deficiencies in clinical controls, regardless of dietary compliance.

Another important finding of the current study was high ALT and AST levels with a rate of 9.9% and 7.7%, respectively. Previous studies have also shown that mild elevation of liver enzymes can be observed in celiac patients.[15,16] These findings emphasise the importance of the possibility of celiac disease in the etiology of patients investigated with elevated liver enzymes. In addition, it has been shown that in some patients a gluten-free diet induces normalisation of liver enzymes, so patients should be monitored in this respect.[17]

Limitations

The major limitation of the present study is its retrospective design. In addition, the study has a relatively small sample size since it is a single center study. Lastly, the effects of dynamic dietary adaptation changes on these data could not be analyzed.

CONCLUSION

In conclusion, this study demonstrated that vitamin and mineral deficiencies are present in the majority of patients with celiac disease. In addition, inflammation in celiac disease is not limited to the small intestine and may be accompanied by various inflammatory and autoimmune diseases in the clinical course of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Medical and Health Researches Ethics Committee of Yenimahalle Training and Research Hospital (Date: 22.11.2023, Decision No: E-2023-60).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Use of ultrasonography in the diagnosis of pneumonia in intensive care patients

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ABSTRACT

Aims: A significant portion of respiratory system infections seen in intensive care units is ventilator-associated pneumonia, which has a high mortality rate and diagnosis may be delayed. Bedside lung ultrasonography (USG) offers the advantages of standard diagnostic methods as chest radiography or thorax computed tomography (CT). We aim to evaluate the bedside lung USG correlation with the chest radiography or thorax tomography.

Methods: It was conducted prospectively on 60 patients between the ages of 18-85 who were admitted to intensive care with respiratory failure within an 8-month period. Anterioposterior chest radiographs were taken on the first day of mechanical ventilation for the patients included in the study. Ultrasonographic examination was performed separately for both hemithoraxes and recorded digitally. Simultaneously with the ultrasonographic examination, PEEP, FiO2, blood gas examination results and the highest body temperatures in the last 24 hours were recorded. The quality and quantity of tracheal secretions were evaluated, and sampling was performed for complete blood examination and tracheal aspirate culture-antibiogram. Lung Injury Score (LIS) and Clinical Pulmonary Infection Score (CPIS) were calculated from the data obtained. In this process, independent of the research, the same day examination results of patients who required CT for diagnosis and treatment planning were evaluated together with USG and chest radiography. Tomographic examinations were evaluated by a radiologist.

Results: In the examination of 120 hemithoraxes of 60 patients we included in the study, we were able to detect 74.17% of the pathological images obtained with chest radiography and ultrasonographic examination with bedside USG and 70.84% with chest radiography. Of the 20 patients who underwent tomographic evaluation, pathology was observed in 40 hemithoraxes in 82.5% by tomography, in 85% by USG, and in 75% by chest radiography. 82.7% of the consolidations detected by tomography and 77.5% of the infiltrations detected by chest radiography were shown by USG, and 12.5% of the consolidations that could not be detected by lung radiography were also detected. 58.8% of the patients with consolidation detected by CT, we observed that there was growth in the tracheal aspirate of 56.2% of the patients whose ultrasonographic examination revealed consolidation. In the examination of 120 hemithoraxes of 60 patients we included in the study, we were able to detect 74.17% of the pathological images obtained with chest radiography and ultrasonographic examination with bedside USG and 70.84% with chest radiography. Of the 20 patients who underwent tomographic evaluation, pathology was observed in 40 hemithoraxes in 92.5% by tomography, in 85% by ultrasonography, and in 75% by chest radiography. While isolated consolidation was detected equally on USG and CT imaging, there was a high false-positive rate of 48% on chest radiography. 58.8% of the patients with consolidation detected by CT, we observed that there was growth in the tracheal aspirate of 56.2% of the patients whose ultrasonographic examination revealed consolidation.

Conclusion: Bedside lung USG is a fast, non-invasive, repeatable and reliable diagnostic method in patients followed in intensive care, and is compatible with traditionally used laboratory and clinical parameters. This reveals that USG, which is known to have other advantages such as cost, applicability, and not using radiopaque, will become an indispensable examination for ICU.

Keywords: Bedside lung ultrasonography, chest radiography, thorax tomography, consolidations, pneumonia, intensive care unit

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INTRODUCTION

Infection and infection-related sepsis are among the main problems such as morbidity, mortality (the main cause of non-cardiac deaths), hospital stay and cost (40% of the total intensive care cost) in patients treated in intensive care unit (ICU).[1,2] Among these infections, respiratory system infections rank first with a rate of 63.5%.[3] A significant portion of respiratory system infections seen in ICUs is ventilator-associated pneumonia, which has a high mortality rate and diagnosis may be delayed. On the other hand, ALI-ARDS is a common condition in intensive care patients. Although one of the factors in the development of ALI-ARDS is pneumonia, pneumonia may also develop in patients with ALI-ARDS. Pleural effusion can often accompany pneumonia or ALI-ARDS. Pleural effusion is frequently observed in intensive care patients who are under mechanical ventilator support and using sedative, analgesic and paralytic drugs and can often be difficult to diagnose it through routine physical examination and to visualize it on a chest X-Ray.[4] Since the coexistence of pneumonia, ARDS, ALI/ARDS, consolidation and pleural effusion is frequently encountered in intensive care unit patients, it has been understood that it is difficult to distinguish these intertwined pathologies from each other and their correlation with computed tomography (CT) is low.[5-7] CT, on the other hand, can only be applied to a limited number of patients due to restrictions such as the high radiation dose received, high cost, and the need to transport patients out of ICU, so it cannot become standard practice. When the transfer risk of intensive care patients is high, it is not always possible to perform gold standard examinations such as CT, which has the potential to give us more guidance compared to chest radiography, and to perform them repeatedly.[8]

Bedside lung USG offers the simple use of traditional diagnostic methods and the advantages of gold standard diagnostic methods.[8] It appears as an alternative that allows rapid and accurate diagnosis in a limited time in intensive care, is the basis for monitoring the treatment process and making strategy changes when necessary, is easy to apply and can be learned by intensive care physicians.

This prospective study examines the usability, reliability, contribution to clinical diagnosis, and the traditional and gold standard acceptance of bedside lung USG in the diagnosis of pneumonia and/or pleural effusion in patients with respiratory failure and invasive mechanical ventilator support that we follow in our ICU. We aim to evaluate its correlation with the methods given.

METHODS

Study Design

The study was conducted in accordance with the Declaration of Helsinki, ethics committee approval was obtained from the Ankara University Clinical Researches Ethics Committee (Date: 09.06.2009, Decision No: 154-4941). The personal information of the patients was not used, only the data obtained from the medical records were evaluated. Therefore, permission was obtained from the hospital manager for the examination of records, and there was no need to obtain individual patient consent.

Data Collection

This research was conducted by Ankara University Faculty of Medicine Department of Anesthesiology and Reanimation. It was conducted prospectively on 168 patients between the ages of 18-85 who were admitted to intensive care with respiratory failure within an 8-month period (between 09.2010 and 04.2011). Patients with breast deformity or who were pregnant were not included in the study. Of these patients, 100 patients who needed invasive mechanical ventilation were included in the study and 68 patients who did not need it were excluded from the study. Anterioposterior chest radiographs were taken on the first day of mechanical ventilation for the patients included in the study. Chest radiographs were evaluated by a specialist who worked in the intensive care unit but was not involved in the study. In his graphs; 60 patients with infiltration and/or pleural effusion were included in the study and each hemithorax was evaluated separately. Bedside lung USG was performed by a specialist within the first 6 hours following the detection of infiltration/pleural effusion on chest radiography. For USG examination, Sono Site M-Turbo (Sono Site Inc. USA) portable USG device and convex and linear probes were used. For chest wall examination; a high-frequency linear probe (5-7.5 mHz) was used, and a low-frequency (3.5 mHz) convex probe was used to detect pleural and pulmonary pathologies.[9] Ultrasonographic examination was performed separately for both hemithoraxes and recorded digitally. Simultaneously with the ultrasonographic examination, PEEP, FiO2, blood gas examination results and the highest body temperatures in the last 24 hours were recorded. The quality and quantity of tracheal secretions were evaluated, and sampling was performed for complete blood examination and tracheal aspirate culture-antibiogram.

Lung Injury Score (LIS) and Clinical Pulmonary Infection Score (CPIS) were calculated from the data obtained. In this process, independent of the research, the same day examination results of patients who required thorax CT for diagnosis and treatment planning were evaluated together with USG and chest radiography. Tomographic examinations were evaluated by a radiologist. USG examinations were performed by an anesthesiologist who received USG training.

Statistical Analysis

Data analysis was done using SPSS 11.5 package program. While number and frequency (percentage) were used as descriptive statistics for variables obtained by counting, mean±standard deviation value was used for variables obtained by measurement.

RESULTS

Demographic characteristics, body-mass index (BMI), LIS, CPIS of a total of 60 patients, 27 of whom were admitted to intensive care for surgical and 33 for non-surgical reasons, were included in the study. and tracheal aspirate growth results are shown in Table 1. CPIS>6: There is pulmonary infection; CPIS≤6: No pulmonary infection; lung injury score; LIS>2.5: ARDS; It was evaluated as LIS<2.5 ALI). With these results, 11 patients had ARDS (18.3%) and 49 patients had ALI (81.7%). According to CPIS scoring, the clinical picture was in favor of lung infection in 47 patients (78.3%), while it was not in favor of lung infection in 13 patients (21.7%). In the comparison of

chest X-Ray and USG, the comparative chest X-Ray and USG results of a total of 120 hemithoraxes in 60 patients included in the study with a preliminary diagnosis of pneumonia and/or pleural effusion are shown in Table 2.

Table 1. Demographic data and BMI, LIS, CPIS, tracheal aspirate reproductive results

Demographic data (n=60)		
Age (mean±SD)		55.5±18.4
Gender (F/M)	Female	24
	Male	36
Reason for ICU admission	Surgical	27
	Non-surgical	33
BMI (mean±SD)		26.8±7.2
LIS (mean±SD)		1.82±0.7
CPIS (mean±SD)		7.7±1.6
Growth in tracheal aspirate	Yes	27
	No	33

BMI: Body-mass index, LIS: Lung Injury Score, CPIS: Clinical Pulmonary Infection Score, SD: Standard deviation, F: Famele, M: Male

Table 2. Comparison of chest radiography and ultrasonography (percentages are given as a ratio of 120 hemithoraxes)

	Chest radiography	Ultrasonography
Effusion	5 (4.16%)	22 (18.33%)
Infiltration	71 (59.16%)	29 (24.16%)
Effusion+infiltration	9 (7.5%)	38 (31.66%)
Pathology	85 (70.84%)	89 (74.17%)
Normal	35 (29.16%)	31 (25.83%)
Total	120 (100%)	120 (100%)

In the ultrasonographic examination of 35 hemithoraxes that were evaluated as normal on chest radiography, consolidation was detected in 1 hemithorax (2.85%), pleural effusion was detected in 7 (20%), and pleural effusion with consolidation was detected in 2 (5.71%). In other words, 28.57% of the hemithoraxes that were considered normal on chest radiography had a pathology that could be detected ultrasonographically, and 90% of these pathologies were isolated or combined effusion with consolidation.

Comparison of Lung Radiography and Computed Tomography

40 hemithoraxes of 20 patients evaluated by computed tomography tomographic and chest radiography results are shown in Table 3. While pathological findings were detected in 37 of 40 hemithoraxes (92.5%) by computed tomography, pathological findings were detected by chest radiography in only 30 of these hemithoraxes (75%). In other words, the rate of not being able to see tomographic pathology on chest radiography was 17.5% 18.9 %.

Pathological findings were demonstrated by tomography in 70% of the hemithoraxes, which were thought to be normal by chest radiography. While the probability of detecting tomographic effusion by chest radiography was 20.8%, in other words, 79% of existing effusions were missed by chest radiography.

Table 3. Comparison of chest radiography, ultrasonography and computed tomography: (percentages are given as the ratio of 40 hemithoraxes)

	Chest radiography	Ultrasonography	Computed tomography
Consolidation	25 (62.5%)	13 (32.5%)	13 (32.5%)
Consolidation+effusion	4 (10%)	10 (25%)	16 (40%)
Effusion	1 (2.5%)	11 (27.5%)	8 (20%)
Pathology	30 (75%)	34 (85%)	37 (82.5%)
Normal	10 (25%)	6 (15%)	3 (7.5%)

Comparison between Ultrasonography and Computed Tomography

Tomographic and ultrasonographic results of 40 hemithoraxes of 20 patients evaluated by CT are shown in Table 3. While pathology was detected tomographically in 37 (92.5%) of 40 hemithoraxes, pathology was found ultrasonographically in 34 (85%). In other words, the rate of not detecting tomographic pathology in USG was 8.1%. In total, the probability that tomographically detected consolidation could not be demonstrated by USG was 20.68%. Compared to the results of CT in detecting consolidation or consolidated area under effusion, it was determined that the rate of false negativity in USG was 20.6%. In the tomographic examination of 6 hemithoraxes that were found to be normal ultrasonographically, 3 were found to be normal and 3 were found to be consolidation/consolidation+effusion. Of the 29 hemithoraxes in which consolidation was detected by CT, infiltration was detected in 29 of them (100%) when evaluated by chest radiography, while consolidation was detected in 23 of them (79.31%) by ultrasonographic examination. While effusion could be detected by chest radiography in 5 (20.8%) of 24 hemithoraxes where effusion was detected, effusion was observed in 21 (87.5%) of the same hemithoraxes when examined by USG.

Comparison of Tracheal Aspirate Results with Ultrasonography

Patients included in the study, the results of tracheal aspirate gram staining and ultrasonographic examination are as shown in Table 4. Among the total number of patients, all 27 patients with growth in their tracheal aspirates, consolidation was detected by ultrasonographic examination in 21 of 33 patients (63.6%) whose tracheal aspirate showed no growth.

Table 4. Tracheal aspirate results, comparison of CPIS and ultrasonography

	Ultrasonography				
Tracheal aspirate	**Effusion**	**Consolidation**	**Consolidation +effusion**	**Normal**	**Total**
Growth	0	7	20	0	27
Non-growth	8	8	13	4	33
Total	8	15	33	4	60
CPIS	**Effusion**	**Consolidation**	**Consolidation +effusion**	**Normal**	**Total**
Negative (CPIS<6)	7	1	1	4	13
Positive (CPIS>6)	1	14	32	0	47
Total	8	15	33	4	60

CPIS: Clinical Pulmonary Infection Score

Comparison of Clinical Pulmonary Infection Score and Ultrasonography

Patients included in the study, the relationship between the calculated clinical pulmonary infection score and the USG performed is as shown in Table 4. In 2 of 13 patients (15.3%) whose infection score was considered negative, consolidation was also detected by ultrasonographic examination in 46 of 47 patients (97.8%) whose infection score was considered positive.

Comparison of Clinical Pulmonary Infection Score and Tracheal Aspirate

There was growth in tracheal aspirate examination in 27 of 47 patients (57.4%) with a positive calculated infection score, in all 13 patients with a negative infection score; no growth was found in tracheal aspirate examination. In other words, while it was clinically supported in favor of infection, the number of patients who had no growth in tracheal aspirate and were considered to have pneumonia was 20 (60.6%). Of the 20 patients who underwent tomography imaging, 10 of whom had growth in tracheal aspirate sampling had infiltration in 4, infiltration and pleural effusion in 6, while in the tomographic examination of 10 patients without growth, 3 had infiltration, 3 had effusion, and 4 had infiltration and effusion together. In other words, of the 17 patients in whom infiltration was detected by CT, which is considered the gold standard in diagnosis, the number of patients with growth in their tracheal aspirates was 10 (58.8%). Moreover, again, there was no growth in the tracheal aspirate in any of the 3 patients whose infiltration was not detected on CT. As a result, tomographic infiltration was detected in all patients (n: 10) with growth in tracheal aspirate, while 7 of the patients without growth in tracheal aspirate cultures had tomographic infiltration (Table 5).

Table 5. Comparison of tracheal aspirate reproduction results with CT and ultrasonographic evaluation

	Effusion	Consolidation	Consolidation +effusion	Total
Tracheal aspirate growth	CT/USG	CT/USG	CT/USG	CT/USG
Yes	3/5	3/3	4/2	10/10
No	0/0	4/5	6/5	10/10
Total	3/5	7/8	10/7	20/20

CT: Computed tomography, USG: Ultrasonographic

In comparing the clinical pulmonary infection score and Computed Tomography results, the relationship between the calculated clinical pulmonary infection score and computed tomography results of the patients included in the study is as shown in Table 6. Clinical infection score was positive in 15 of 17 patients (88.2%) with consolidation detected on computed tomography.

Table 6. Comparison of clinical pulmonary infection score and computed tomography results

	Computed tomography				
CPIS	Effusion	Consolidation	Consolidation +effusion	Normal	Total
Negative	3	0	2	0	5
Pozitive	0	7	8	0	15
Total	3	7	10	0	20

CPIS: Pulmonary infection score

DISCUSSION

In the examination of 120 hemithoraxes of 60 patients we included in the study, we were able to detect 74.17% of the pathological images obtained with chest radiography and ultrasonographic examination with bedside USG and 70.84% with chest radiography. Of the 20 patients who underwent tomographic evaluation, pathology was observed in 40 hemithoraxes in 92.5% by tomography, in 85% by USG, and in 75% by chest radiography. While isolated consolidation was detected equally on USG and CT imaging, there was a high false-positive rate of 48% on chest radiography. 58.8% of the patients with consolidation detected by CT, we observed that there was growth in the tracheal aspirate of 56.2% of the patients whose ultrasonographic examination revealed consolidation.

In the correlation between CPIS and USG, in 95.8% of the patients whose ultrasonographic examination revealed consolidation; had positive CPIS. We calculated the CPIS as negative in all patients in whom no consolidation was observed on ultrasonography. In the comparison of CPIS and computed tomography, 88.2% of the patients with consolidation detected in CT had a positive CPIS Score. CPIS has high false positivity and negativity.

The most valuable examination for identifying lung pathologies is CT. Other disadvantages of tomographic examinations are that patients followed in intensive care require a risky transport procedure by a monitored and trained team, limited use of contrast material in patients with multiple organ dysfunction, high radiation dose received by CT, and limited reproducibility of the procedure to the patient.[10,11] Under these conditions, lung USG has been prioritized. Compared to CT, which directly displays lung morphology; since USG can visualize artifacts resulting from lung damage, it inevitably contributes less to the diagnosis. However, the fact that it is a technique that can be applied at the bedside, is cheap, repeatable, suitable for recording and re-examination and comparison, is easy to learn and compare, and eliminates radiation exposure makes this method valuable. Additionally, an advantage of this technique compared to CT is that the intravenous contrast material given for diagnosis in CT may be harmful to the damaged lung.[12]

In a study conducted by Gazon et al.,[13] chest radiography and USG were used in intensive care patients; Considering its consistency in diagnosing pleural effusion and alveolar consolidation, it has been concluded that USG detects a higher rate of abnormalities. It has been clearly shown in our study that the infiltrations detected in chest radiography are detected in USG to a large extent.

In their study, Marco et al.[14] confirmed this diagnosis with USG in 92% of the patients diagnosed with pneumonia by chest radiography, and they were able to detect pleural effusion in 111 patients with chest radiography and in 120 patients with USG. The reason why the diagnosis of pneumonia can be detected better in USG in this study than in our study may be that the patients included in the study had community-acquired pneumonia and that there was an experienced radiologist in the study.

Parliament et al.[15] also demonstrated the superiority of USG in the diagnosis of pleural effusion in their study.

In the clinical study conducted by Reissig et al.,[16] the effectiveness of X-Ray and USG in the diagnosis and follow-

up of pneumonia in intensive care patients has been examined and it has been shown that USG can be used in this field.

We were able to detect all of the pleural effusions detected on chest radiography by USG, and in addition, we were able to detect pathology by USG examination of the hemithoraxes where infiltration and/or pleural effusion could not be detected on chest radiography. The compatibility of USG with tomography in detecting effusion was significantly higher than chest radiography. Indeed, in our literature review, the success of USG, especially in detecting effusion, has been shown in many studies.[17-19] The reason for this is that USG is more sensitive than chest radiography in distinguishing small pleural effusions.[20] In the study conducted by Xirouchaki et al.,[21] in which bedside chest radiography and USG were compared in intensive care patients, the superiority of USG, especially in diagnosing pleural effusion, was clearly demonstrated. In the study conducted by Zanobetti et al.,[22] USG showed more sensitivity than chest radiography, especially in detecting pleural effusion.

In the clinical study of Lichtenstein et al.[23] in which they compared auscultation, chest radiography and USG in ARDS on 119 patients, alveolar consolidation; the diagnostic accuracy of chest radiography and USG was found to be 75% and 97%, respectively, and the diagnostic accuracy of pleural effusion was found to be 47% and 93%, respectively. The success they attribute to USG in detecting consolidation may be due to the fact that all the patients they included in their studies had ARDS.

Lung USG in patients who are obese, have multiple trauma, are accompanied by subcutaneous emphysema, and have pathological conditions related to the thorax wall and pleura, imaging of centrally located lesions will be difficult, requiring specialized practitioners. In such cases, examinations should be carried out by experienced people. In terms of ultrasonographic evaluation, Although BMI was calculated for all patients with the idea that increasing BMI would create difficulty in evaluation, the values of the patients with the lowest and highest BMI among the patients we included in the study were 13.36 and 66.6, respectively. We observed that BMI values within these limits do not pose a difficulty in performing lung USG.

Consolidation seen with pleural effusion in intensive care patients on mechanical ventilation is easy to detect and can be achieved in a short time by practitioners who have received this training.[24] In our study, we concluded that it may be easier to detect consolidated lung areas ultrasonographic ally in the presence of accompanying pleural effusion.

One of the aims of this study is to reduce the need for chest radiography and tomography in patients followed up with respiratory failure in ICUs. In the study conducted by Peris et al.,[25] it is stated that there may be a relationship between the routine use of lung USG in intensive care and the decrease in the number of scans with chest radiography and CT. At the same time, it is to reduce the cost of patient care in ICU and to ensure accurate, reliable and timely diagnosis. In this context, lung USG may be a new and good alternative for lung monitoring.

Some researchers reported that condolitation will be visualized better if it has a connection with the lung surface area. Because the consolidated area is rich in water and therefore sonographic waves are transmitted better.[26,27] With this; small consolidations are less common due to poor echogenicity and lack of surface connection. However, early detection of small consolidated areas may be associated with early diagnosis. In our opinion, imaging by users with good intensive care experience and the choice of USG devices equipped with advanced technology will increase success.

In intensive care patients, in a study, the diagnostic rate of tracheal aspirate sampling, which is used to diagnose ventilator-associated pneumonia, was found to be 52%, and in the same study, CPIS was found to have high sensitivity in diagnosing ventilator-associated pneumonia.[28] The results of our study are similar.

In our literature review, false positivity was higher in tracheal aspirate, whereas false negativity was higher in ours.[29,30] While this shows the success of our culture technique in terms of not causing contamination, it also reveals the disadvantage of being non-selective. In this case, USG-guided selective tracheal aspirate culture may be recommended. However, if instead of blind tracheal aspirate, sampling was done from the infiltration area with bronchoscopic mini-BAL or protected brush for culture, the results might have been different. Meanwhile, the possibility of selective culture sampling after detection of infiltration localization by USG may be an approach that may make its use in intensive care more important.

When CPIS and tracheal aspirate reproduction results are compared; while all patients with growth in tracheal aspirate were clinically supported in favor of infection, we observed growth in 57.4% of the patients who were clinically considered to have pneumonia (CPIS>6) in the tracheal aspirate examination.

We also compared the ease of use, side effects, and diagnostic performance of chest radiography and USG. Chest radiography, which we routinely use in our ICU; in patients with respiratory failure, it is considered a reference to evaluate lung status. However, the limited diagnostic performance and effectiveness of this method have been reported in various clinical studies.[31,32] In our study, bedside lung USG; we observed that it has superior performance both in diagnostic terms and in patient follow-up, as it is easily repeatable and has the ability to store data digitally.

Limitations

Our study has some limitations. It is single-centered, the examinations were performed in the supine position (the apex and retrocardiac area were not clearly visualized), and not every patient had a tomography image. Studies with larger patient populations are needed.

CONCLUSION

Bedside lung USG is a fast, non-invasive, repeatable and reliable diagnostic method in patients followed in intensive care, and is compatible with traditionally used laboratory and clinical parameters. This reveals that USG, which is known to have other advantages such as cost, applicability, and not using radiopaque, will become an indispensable examination for ICU.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara University Clinical Researches Ethics Committee (Date: 09.06.2009, Decision No: 154-4941).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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