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ABOUT

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Thoracic Research and Practice is a bimonthly journal that is published in English in January, March, May, July, September, and November.

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Thoracic Research and Practice started its publication life following the merger of two journals which were published under the titles "Turkish Respiratory Journal" and "Toraks Journal" until 2008. From 2008 to 2022, the journal was published under the title "Turkish Thoracic Journal". Archives of the journals were transferred to Thoracic Research and Practice.

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Thorac Res Pract. 2025;26(5):217-223 DOI: 10.4274/ThoracResPract.2025.2025-1-2

Original Article

An Important Question: Can Serum Chitotriosidase Enzyme Predict the Activity and Clinical Course of Sarcoidosis Disease?

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Abstract

OBJECTIVE: Serum chitotriosidase (CHIT) is a promising biomarker that has shown high specificity and sensitivity in patients with sarcoidosis. Our study aimed to evaluate the CHIT enzyme concerning the activity, prognosis, and treatment decision of sarcoidosis.

MATERIAL AND METHODS: The patients with the following characteristics were included in our single-center study as long as they agreed to participate. These patients were newly or previously diagnosed with sarcoidosis according to American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders and consulted the outpatient clinic of chest diseases in our university hospital between August 2020 and April 2021. The patients with sarcoidosis were categorized into 3 groups: 1) diagnosed as sarcoidosis but not having the treatment indication; 2) previouslytreated or currently receiving treatment; and 3) newly diagnosed and having a treatment indication.

RESULTS: A total of 126 sarcoidosis patients and 43 healthy volunteers were included. The median value of serum CHIT enzyme levels in patients with sarcoidosis was determined to be 9.8 ng/mL, while it was 5.1 ng/mL in the control group. It was determined that the serum CHIT levels were notably higher in patients with sarcoidosis ($P = 0.000$). In the serum CHIT levels of the newly-treated patient, a significant reduction was observed after the 6-month treatment ($P = 0.008$), in comparison with these levels noted at the time of diagnosis.

CONCLUSION: Our study demonstrated that the serum CHIT has a high sensitivity and high specificity in the diagnosis of sarcoidosis and a reduction in the level of that enzyme occurs upon treatment.

KEYWORDS: Sarcoidosis, biomarker, chitotriosidase, disease activity, clinical course

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by a heterogeneous clinical course and unpredictable outcomes.[1] It affects multiple organ systems, particularly the lungs and lymphatic system.[2] The natural course and prognosis of sarcoidosis are highly variable. The disease may spontaneously remit, but progression is also a potential outcome. Spontaneous remission occurs in approximately two-thirds of patients.[1]

Even though many biomarkers have been studied to determine disease activity, a biomarker with high sensitivity, specificity, and satisfactory prognostic value has yet to be identified. Angiotensin-converting enzyme (ACE) is the most frequently used laboratory test in sarcoidosis and is considered an indicator of the total granuloma burden in the body.[3,4] Despite its frequent use in assessing sarcoidosis activity, the diagnostic and prognostic values of ACE remain uncertain. In their study, Gungor et al.[5] (2015) reported that the sensitivity and specificity of serum ACE levels in diagnosing sarcoidosis are 72% and 60%, respectively. The weak correlation between serum ACE levels and sarcoidosis activity or response to treatment has been observed.[6]

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The human chitotriosidase (CHIT) enzyme, a chitinase secreted by activated macrophages and neutrophils, is considered responsible for the degradation of chitin and chitin-like substrates and associated with defense against chitin-containing pathogens.[7,8] This enzyme is secreted by pulmonary macrophages and neutrophils in response to the stimulation of toll-like receptors by interferon-γ, tumor necrosis factor (TNF), and granulocyte/macrophage colony-stimulating factor.[9] The procedure for measuring serum CHIT levels in patients with sarcoidosis is based on the direct involvement of activated macrophages and granulomatous inflammation in the disease's pathogenesis.[10-13] The first report evaluating serum CHIT activity in patients with sarcoidosis was published in 2004 by Grosso et al.[10] The report determined that significantly high chitinase activity was present in sarcoidosis patients compared to the control group.

The aim of our study is to evaluate the significance of the CHIT enzyme in sarcoidosis regarding activity, prognosis, and treatment decisions.

MATERIAL AND METHODS

Study Subjects

Our study is prospective, single-centered and cross-sectional. According to the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders (ATS/ERS/WASOG) guidelines, patients who presented to Kocaeli University Faculty of Medicine Chest Diseases Outpatient Clinic between August 2020 and April 2021, with either a prior or new diagnosis of sarcoidosis, were included in the study upon providing informed consent. Patients with sarcoidosis were divided into three groups: those diagnosed with sarcoidosis but without a treatment indication (treatment-naive group), those previously treated or currently receiving treatment (treated group), and those newly diagnosed with a treatment indication (newly-treated group). There were 57 patients in the treatment-naive group, 60 patients in the treated group, and 9 patients in the newly treated group. The control group consisted of 43 healthy volunteers with the following criteria: being over the age of 18, having no comorbidities or history of drug use, being non-smokers, and consenting to participate in our study. The study was initiated after approval from Kocaeli University Medical Faculty Hospital Ethics Committee (project number: GOKAEK-2020/14.06, 2020/243, approval date: 20/08/2020). Informed consent was obtained. This is my thesis study, which I conducted while I was a resident at the Department of Pulmonary Diseases, Faculty of Medicine Kocaeli University, Kocaeli.

Main Points

- Serum chitotriosidase (CHIT) is a promising biomarker that has shown high specificity and sensitivity in patients with sarcoidosis.
- This study demonstrated that serum CHIT has high sensitivity and specificity in diagnosing sarcoidosis, and that a reduction in enzyme levels occurs with treatment.
- Multicenter studies involving a larger patient population and performing serial CHIT measurements with extended follow-up times may be planned.

For all patients with sarcoidosis, demographic data [sex, age, height, weight, body mass index (BMI)], comorbidities, pulmonary function test results (FVC liters, FVC%, FEV1 liters, FEV1%, FEV1/FVC ratio, DLCO, DLCO%), symptoms, radiological findings [lung radiography and high-resolution computed tomography (CT)], presence of extrapulmonary involvement, laboratory findings (serum calcium, albumin, CHIT enzyme level, serum ACE levels, and 24-hour urine calcium), the 6-minute walk test results, and modified Medical Research Council (mMRC) dyspnea scale scores were recorded. The serum CHIT enzyme levels of patients who were newly diagnosed and were to be treated were measured twice: once before treatment and again in the sixth month of treatment. At the sixth month, respiratory function tests, carbon monoxide diffusion tests, 6-minute walking tests, and mMRC dyspnea scores were repeated and recorded. The serum CHIT enzyme levels were measured once for the other sarcoidosis patient groups and the control group.

Chitotriosidase Measurement

Blood samples collected from patients and the control group were kept at room temperature for approximately 30 minutes and then centrifuged at 3000 rpm for 10 minutes to obtain serum. They were stored frozen at -80 °C until needed. CHIT (human chitinase 1 enzyme, Cat. No. E4540Hu) levels were measured using the enzyme-linked immunosorbent assay. The plates in the assay have been coated with CHIT antibodies, and the addition of CHIT to these plates allows the binding of the enzyme to the antibodies. The markers, the samples, and the standards were prepared. 40 microliters of serum sample, followed by 10 microliters of anti-CHIT antibody and 50 microliters of streptavidin-HRP, was transferred into each sample well. The plates were sealed with covers and incubated at 37 °C for 1 hour, followed by washing with wash buffer five times. 50 µL of substrate solution A, followed by 50 µL of substrate solution B, was placed in each well. The plates were covered and incubated in the dark at 37 °C for 10 minutes. 50 µL of stop solution was added to each well, and the rapid change from blue to yellow was observed. Ten minutes after adding the stop solution, the optical density values were determined at 450 nm using a microplate reader. Serum CHIT concentrations were expressed in ng/mL.

Pulmonary Function Tests

The pulmonary function tests were carried out according to the ATS criteria using a ZAN brand (Germany) pulmonary function test device. Spirometry was automatically calibrated with the flow sensor on a daily basis. Before the test, each participant was informed about the test protocol. After the participants rested for 15 minutes, at least three tests were performed in a sitting position. The test was repeated up to eight times to ensure three acceptable maneuvers, with the difference between the two best FVC and FEV1 measurements being ≤200 mL. Nevertheless, the test was terminated if a valid maneuver could not be obtained or if the patient became tired.

The parameters of FVC, FEV1, FEV1/FVC, and DLCO were evaluated in pulmonary function tests.

Computed Tomography

CT images were obtained at our center using 64-slice CT (Toshiba Aquilion Medical Systems, Japan) and 16-slice CT (Toshiba Alexion Medical Systems, Japan). The parameters used in imaging with the 64-slice CT device were as follows: pitch 0.8-1.5, rotation time 0.5 sec, tube voltage 120 kV, tube current 50-220 mAs (with automatic exposure control), and slice thickness 1-5 mm. In comparison, the parameters used in imaging with the 16-slice CT device were as follows: pitch 0.6-1.7, rotation time (0.75 sec), tube voltage (120 kV), tube current (50-300 mAs) (with automatic exposure control), and slice thickness (1-5 mm).

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences 20.0 software package (IBM Corp., Armonk, NY, USA). In determining the power and sample volume of the study, the G*Power version 3.1.9.2 software package (Kiel University, Kiel, Germany) was used. The test for conformity to normal distribution was evaluated using the Kolmogorov-Smirnov test. Numerical variables were presented as median (25^{th} to 75^{th} percentile), and categorical variables as frequency (percentage). Using the Kruskal-Wallis one-way analysis of variance and Dunn's multiple comparison test, the differences between groups/materials were compared for numerical variables that did not have a normal distribution. The Pearson chi-square test was used to evaluate the differences between groups for the categorical variables. The relationship between numerical variables was evaluated using Spearman's correlation analysis. $P < 0.05$ was considered sufficient for statistical significance in two-way tests.

RESULTS

A total of 126 sarcoidosis patients and 43 healthy volunteers were included in the study. The patterns of the patient profiles in the study are as follows: 57 (45.2%) patients had no indication (treatment-naive group); 60 (47.6%) patients were previously diagnosed with sarcoidosis and either received treatment or were receiving treatment (treated group); and 9 (7.1%) were newly diagnosed with a treatment indication (newly treated group). Forty-three healthy volunteers were included in the control group.

The mean ages of patients in these groups were 44.1±10.9 years in the treatment-naive group, 49±9.6 years in the newly treated group, and 47.6±11.6 years in the treated group. The mean age of the control group was 36.6±10. In the treatment-naive group, 77.2% (n = 44) of patients were female, while 70% (n = 42) of those in the treated group were female, and 77.8% (n = 7) of the newly treated patients were female. In contrast, 62.8% (n = 27) of the healthy control group were female. There was no significant difference in gender distribution between the groups, as determined by the Pearson chi-square test. Additionally, there was no notable difference in comorbidities among the sarcoidosis patient groups.

The median serum CHIT enzyme levels were 9.8 ng/mL in patients with sarcoidosis, compared to 5.1 ng/mL in the control group; the serum CHIT level was significantly higher ($P < 0.001$). The comparison of the groups' CHIT values indicates a significant difference between the three patient groups and the control group ($P < 0.001$). However, no significant difference was detected between the patient groups. Changes in serum CHIT levels were assessed in the newly-treated group by comparing levels at diagnosis to levels at the sixth month of treatment. A significant decrease in serum CHIT levels was observed after six months of treatment ($P = 0.008$). Comparison of CHIT value, mMRC and pulmonary function test parameters at the time of diagnosis and the 6th month of treatment is shown in Table 1. The number of cases and the distribution of serum CHIT levels in the sarcoidosis patient group and the control group are shown in Table 2.

Prior to treatment, nine patients in the newly treated group were classified as having stage 2 radiological disease. After six months of therapy, all patients remitted to stage 0 radiological disease ($P = 0.03$).

Table 1. Comparison of CHIT value, mMRC and pulmonary function test parameters at the time of diagnosis and the 6^{th} month of treatment

Newly-treated group	The time of diagnosis Median (25-75%)	The 6^{th} month of treatment Median (25-75%)	*P* value
CHIT value	10.5 (9.5-14.0)	7.1 (5.5-7.9)	0.008
FEV1 (L)	2.02 (1.78-3.26)	2.05 (1.7-3.16)	0.86
FEV1 (%)	90 (74.5-101.5)	82 (76-97)	0.106
FVC (L)	3 (2.735-3.44)	2.64 (2.34-3.295)	0.05
FVC (%)	99 (86-106)	93 (82-96)	0.058
FEV1/FVC	76 (69-85)	78	0.151
DLCO (L)	7.47 (6.005-7.93)	7 (5.525-7.295)	0.314
DLCO (%)	93 (73-99)	85 (72.5-92)	0.312
mMRC	1 (0-2)	1 (0-1)	0.83

CHIT: chitotriosidase, mMRC: modified Medical Research Council

The serum CHIT values of all 126 sarcoidosis patients were examined according to the stages, and no significant difference was found between the stages and serum CHIT values (P = 0.844). Table 3 presents the serum CHIT median, the percentile values (25^{th} to 75^{th} percentiles) of the patients based on their stages, and the P value. The distribution of the number and percentage of patients according to the stages is shown in Figure 1.

In the examination of serum ACE, calcium, and urine calcium values among 126 sarcoidosis patients according to the stages (shown in Table 4), no significant difference was observed for any of these. In the evaluation of patients based on their extrapulmonary involvement (shown in Table 5), the only involvement that showed a significantly higher serum CHIT level was eye involvement (P = 0.03). The median serum CHIT value and percentile range (25^{th}-75^{th}) for patients with eye involvement were 12.1 ng/mL (10.2-17.4), while these values for patients without eye involvement were 9.8 ng/mL (7.6-12.1), respectively. No relationship was found between serum CHIT levels and the ages, heights, weights, or BMIs of the sarcoidosis and control groups.

In the receiver operating characteristic (ROC) analysis, the area under the curve (AUC) was calculated. The diagnostic cutoff value of the CHIT enzyme for sarcoidosis was determined to be 6.7 within a 95% confidence interval, with a sensitivity of 86.51% and a specificity of 93.02%. ROC analysis data are summarized in Tables 6 and 7. The ROC curve is shown in Figure 2.

Treatment indications are present in symptomatic patients, individuals with impaired pulmonary function test results, and those exhibiting signs of organ dysfunction. All patients in the treated group (n = 60) received corticosteroid therapy. Ten of them required the addition of methotrexate as a

Table 2. The number of patients and the distribution of serum CHIT levels according to the sarcoidosis patient group and the control group

Groups	Serum CHIT Median (25-75%)
Treatment-naive group (n = 57)	10.1 (7.3-12.4)
Treated group (n = 60)	9.8 (8-11.8)
Newly-treated group (n = 9)	10.5 (9.5-14)
Control group (n = 43)	5.1 (4.7- 6.2)

CHIT: chitotriosidase

Table 3. Serum CHIT values of patients according to stages and the p value

Stages	Serum CHIT median (25-75%)	*P* value
0	10.3 (8.8-13.8)	
1	9.5 (7.0-11.4)	
2	9.9 (7.9-12.4)	0.844
3	10.1 (7.0-17.4)	
4	10.0 (8.3-14.1)	

CHIT: chitotriosidase

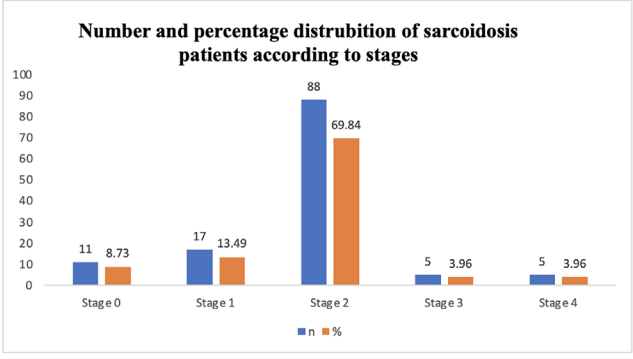

Figure 1. The graph showing the number and percentage distribution of sarcoidosis patients according to the stages

Table 4. Serum ACE, calcium and urine calcium values

Parameters	Treatment naive group	Newly-treated group	Treated group	*P*
sACE	42 (26.5-66)	40 (29-56.5)	38.5 (27.5-55)	0.329
Serum calcium	9.8 (9.5-10)	9.7 (9.25-10.35)	9.8 (9.5-10)	0.803
Urinary calcium	152 (82.75-229.85)	223.2 (117.4-491.6)	131.5 (91.8-259.15)	0.601

ACE: angiotensin-converting enzyme

Table 5. Extrapulmonary involvement

Organ involvement	Number of patient (n)	Percentile (%)
Arthritis	41	32.5
Erythema nodosum	16	12.7
Peripheral lymph node	15	11.9
Ocular	8	6.3
Bone marrow	5	4

Table 6. ROC analysis of CHIT level

	Under the curve area	95% confidence interval	*P* value
Serum CHIT	0.954	0.911-0.980	<0.0001

CHIT: chitotriosidase, ROC: receiver operating characteristic

Table 7. The sensitivity and specificity of CHIT level

Serum CHIT level (ng/mL)	Sensitivity (%)	Specificity (%)
6.6	88.1	88.37
6.733	86.51	93.02
8.521	67.46	100

CHIT: chitotriosidase

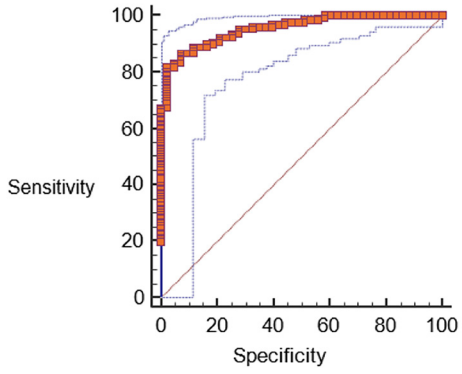

Figure 2. The graph that shows CHIT level and the ROC curve

CHIT: chitotriosidase, ROC: receiver operating characteristic

second-line therapy. Only one patient was treated with an anti-TNF agent.

DISCUSSION

In our study, we found that serum CHIT enzyme levels were significantly elevated in patients with sarcoidosis when compared to healthy individuals in the control group. Thus, the sensitivity and specificity are high for the diagnosis of sarcoidosis. This supports the potential use of CHIT enzyme levels as an auxiliary biomarker for diagnosing sarcoidosis. Moreover, its use in monitoring treatment response may be considered beneficial due to the reduction in serum CHIT enzyme values in patients with sarcoidosis, and the regression of radiological stages from 2 to 0 who have recently initiated treatment. The initial report indicating that serum CHIT enzyme levels are significantly elevated in sarcoidosis patients compared to healthy controls was published by Grosso et al.[10] in 2004, and these findings was subsequently confirmed by Bargagli et al.[14] in further research.

The results of our study are consistent with the literature, which demonstrates that serum CHIT enzyme levels are notably higher in sarcoidosis patients compared to the control group.

The relationship between radiological stage and serum CHIT levels yields varying results in the literature. In two separate studies by Bargagli et al.,[14] conducted in 2008 and 2013, serum CHIT enzyme levels were found to be significantly higher in sarcoidosis patients at radiological stages 3 and 4, compared to those at stages 0 and 1. Additionally, a correlation was observed between radiological stages and enzyme levels.[12,14] In their study, Popević et al.[15] observed the highest serum CHIT levels in stage 2 disease. They discussed that the high level of CHIT enzyme in stage 3 pulmonary disease is due to the induction of overexpression of profibrotic type-2 (Th2) cytokines. Therefore, this elevation may also be observed in stage 2 disease due to the presence of active granulomas.[15] However, Lopes et al.[16] reported the highest serum CHIT levels in radiological stages 0, 1, and 2 disease. Harlander et al.[17] did not detect any correlation between the radiological stages and serum CHIT levels.

In accordance with the aforementioned studies, no correlation was observed between the radiological stages and serum CHIT levels in our study. This result may be attributed to the predominance of stage 1 and 2 patients, coupled with the limited number of patients in stages 3 and 4. A frequent polymorphism in the *CHIT* gene, which results in a CHIT enzyme deficiency, may occur due to a 24 bp duplication in exon 10, leading to an abnormal deletion and splicing of 87 nucleotides.[18] Lee et al.[19] investigated the allele frequency of this polymorphism in different populations and reported the results as 7-64%. The prevalence of this polymorphism in the Turkish population is unknown. The absence of a significant relation between the radiological stages and the serum CHIT levels in our study may be due to the *CHIT* gene polymorphism. However, a definite conclusion cannot be drawn about this phenomenon as this polymorphism has not been examined in our study.

The calculation of the AUC was conducted using ROC analysis in our study. A cutoff value of 6.7 ng/mL was established for diagnosing sarcoidosis, yielding a sensitivity of 86.51% and a specificity of 93.02%, with a 95% confidence interval. Similarly, Bargagli et al.[14] calculated the sensitivity as 88.79% and the specificity as 92.86% for this biomarker. Bergantini et al.[20] observed that serum CHIT levels were higher in sarcoidosis patients with extrapulmonary involvement, and they stated a possible relationship between chitinase activity and the extent of systemic disease. However, in our study, significantly higher serum CHIT levels were observed in cases with ocular involvement. In the literature, Bennet et al.[21] reported that higher CHIT levels were detected in patients with abdominal involvement. Secondly, ocular involvement followed abdominal involvement, and their study revealed that multiorgan sarcoid involvement was associated with higher CHIT levels. In our study, some patients with pulmonary sarcoidosis and ocular involvement also had arthritis. This multiorgan involvement may reflect the presence of highly active granulomas. Conversely, Harlander et al.[17] reported that no notable difference exists in serum CHIT levels in sarcoidosis patients with or without extrapulmonary involvement.

The serum CHIT levels of 9 newly treated patients at the time of diagnosis were compared with their values at the 6th month of treatment. A significant decrease was detected in the CHIT levels of these patients after 6 months of treatment. This supports the possible use of CHIT as a beneficial biomarker in the evaluation of treatment efficacy. Besides, other studies have demonstrated the reduction in serum CHIT levels after corticosteroid or immunosuppressive therapies in sarcoidosis patients.[14,22,23] The significantly reduced CHIT levels were also observed in juvenile sarcoidosis patients after oral corticosteroid treatment, compared to their levels before treatment.[13]

The low sensitivity and specificity of ACE limit its use as both a diagnostic and prognostic tool. The serum levels may also increase in granulomatous diseases such as berylliosis and silicosis.[24,25] In addition, *ACE* gene polymorphism may affect serum ACE values, and the use of genotype-based reference values may improve interpretation.[26] The highest serum ACE values were reported in patients with radiological stages 0, 1 and 2 of the disease.[16] Gungor et al.[5] reported that serum ACE levels did not differ significantly between active and inactive disease, and they also determined the sensitivity and specificity of ACE to be 72% and 60%, respectively. Similar to our study,

which states that no significant difference was found between radiological stage and serum ACE levels, Rust et al.,[27] also reported that no relationship was detected between the initial radiological stage and serum ACE levels, as well as the clinical course of the disease. This may be related to the polymorphism in the *ACE* gene.

The most significant aspect of our study is that to the best of our knowledge, no similar study on sarcoidosis has been published in Türkiye. Another issue is that some studies evaluated serum CHIT only once.[16] In our study, in the newly-treated group, we measured CHIT levels twice.

It would be useful to address some limitations of our study. It was a single-center study, and the number of patient admissions was very low due to the pandemic. This situation could be considered an important reason for the limited number of patients in stages 3 and 4. Furthermore, the short duration of the study limits the sample size. Despite the possible existence of CHIT and ACE variants among our patients, genotyping could not be performed due to inadequate conditions. Serial measurements could not be performed for serum CHIT levels in some groups. The measurement could only be performed once, in patient groups other than the newly-treated group. In addition to these, the small number of patients for whom treatment was started in the sarcoidosis group is also among the limitations of our study.

CONCLUSION

Our study suggests the potentially beneficial use of serum CHIT enzyme levels in the diagnosis of sarcoidosis, as well as in evaluating follow-up and treatment response. Consequently, this enzyme may be considered helpful in differentiating sarcoidosis patients from healthy individuals and in evaluating treatment response. However, its usefulness in predicting disease activity and prognosis may be limited since no significant relation was detected between the radiological stages and serum CHIT levels in our study. Multicenter studies with a larger patient population, serial CHIT measurements, extended follow-up periods, investigations of ACE and *CHIT* gene polymorphisms, and a more uniform distribution of disease stages will yield more conclusive results.

In conclusion, our study indicates that measuring CHIT enzyme levels may help reduce the necessity for radiological examinations when used in combination with other biomarkers like ACE. This, therefore, reduces the patient's exposure to radiation.

Ethics

Ethics Committee Approval: The study was initiated after approval from the Kocaeli University Medical Faculty Hospital Ethics Committee (project number: GOKAEK-2020/14.06, 2020/243, approval date: 20/08/2020).

Informed Consent: Informed consent was obtained.

Presented in: This study was presented as an oral presentation at the 26th Turkish Thoracic Society Congress in 2023.

Footnotes

Authorship Contributions

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Original Article

Attitudes and Practices of Family Physicians and Nurses in Evaluating Their Patients' Smoking Status: A Cross-sectional Study

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Abstract

OBJECTIVE: The low quit rate of smokers without support increases the importance of very brief clinical interventions for smoking cessation. The aim of this study was to determine the attitudes and practices of family physicians and nurses in primary care in evaluating patients' smoking status.

MATERIAL AND METHODS: This cross-sectional survey was conducted in family health centres in Aydın Efeler district between November and December 2020. A questionnaire developed on the basis of the "modified very brief clinical intervention (3A-OR)" model was used. Questionnaires were administered to all participants using the face-to-face method. In addition to descriptive statistical methods, univariate and multivariate analysis were performed. The statistical significance level was accepted as "$P < 0.05$".

RESULTS: Fifty-nine family physicians and 64 nurses participated in the study. Of the participants, 62.6% were female and the mean age was 44.9 years. The most common practices of family physicians and nurses concerning learning their patients' smoking behaviour were to offer assistance to smokers (82.4%) and to recommend that they quit (81.3%). Family physicians and nurses mostly thought that it was their responsibility to refer their smoker patients to stop smoking counselling centres (71.6%) and to offer assistance (61.8%). Family physicians had a 3.12 times more positive attitude than nurses in evaluating the smoking status of the patients ($P = 0.008$).

CONCLUSION: Our study results have revealed that the positive attitudes of family physicians are not fully reflected in practice and that nurses generally do not adopt responsibilities related to evaluating patients' smoking habits, despite their efforts to make better practices.

KEYWORDS: Smoking cessation, family physicians, nurses, behaviour, attitude

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INTRODUCTION

Smoking is one of the most important preventable public health problems of the present.[1] The positive effects of smoking cessation on health and the desire of most smokers to quit are important motivations in the struggle against tobacco use. The low quit rate of smokers without support increases the importance of very brief clinical interventions for smoking cessation. Many national or international stop smoking strategies have been established to improve cessation rates in medical settings and especially in primary care.[2]

The AAR brief clinical intervention method, which has been developed from the 5A approach, is primarily aimed at increasing awareness, offering advice and making referrals.[3] An AAC approach to increase the effectiveness of referrals for stop smoking counseling services is also recommended.[2] These brief clinical interventions do not overemphasize evaluating the smoker's motivation to quit. However, the success of the next steps of an intervention is closely related to knowing the smoker's motivation to quit. From this point of view, we use a modified brief intervention in our family health centres (FHCs) (primary care). This brief intervention, which is defined as 3A-OR, consists of five steps: 1) Learning the smoking status of all patients during the course of a routine consultation (Ask). 2) Evaluating the motivation of smokers to quit smoking (Assess). 3) Providing brief stop smoking advice to those who do not contemplate quitting

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(Advise). 4) Offering assistance with quitting to all smokers regardless of readiness to quit (Offer) and 5) Recording the smoking information to their files (Record).

Studies have shown that joint interventions by healthcare providers are more effective than individual interventions in evaluating and counselling smokers to quit.[4] Although all guidelines recommend that smokers be advised to quit smoking at every opportunity, opportunities to give stop smoking advice are not sufficiently used in primary care.[5] In many countries, non-physician healthcare professionals contribute to the stop smoking services, and there is evidence to suggest that their advice to quit smoking is as effective as that of physicians.[6]

It is known that the frequency of physicians who advise smokers to quit smoking is not sufficient in our country.[7] In FHCs in primary care, family health providers, mostly nurses or midwives, provide reproductive health services such as pregnancy follow-up, family planning and cervical cancer screening, as well as other preventive health services. Although the provision of these services is an important opportunity to assess the smoking status of women, the attitudes and behaviors of the family health providers are not known. On the other hand, the attitudes of primary health care providers towards evaluating patients' smoking status will influence their practices.

The aim of this study was to determine the attitudes and practices of family physicians and nurses in primary care when evaluating the smoking status of patients.

MATERIAL AND METHODS

In this descriptive cross-sectional study, the aim was to reach all 91 family physicians and 79 nurses in 25 FHCs in Aydın Efeler district (330,000 inhabitants) between November and December 2020. No criteria for inclusion or exclusion were determined; volunteering to participate in the study was the only criterion.

Data Collection

A questionnaire developed by the researchers (RS) based on the relevant literature review and the "modified very brief clinical intervention (3A-OR)" model was used as a data collection tool. In addition to some socio-demographic characteristics and habits of the participants, the questionnaire consisted of questions about the evaluation of patients' smoking status by family physicians and nurses. Their attitudes, opinions, and perceptions on self-competency regarding these practices were taken. Questionnaires were administered by one of the RS to all family physicians and nurses who agreed to participate in the study, outside of working hours, taking into account the pandemic conditions. Verbal informed consent was obtained from all participants.

Main Points

- The positive attitudes of family physicians in smoking cessation are not fully reflected in practice.
- Despite efforts to implement better practices, nurses generally do not assume responsibility for assessing patients' smoking habits.
- The lack of education among primary care professionals and their lack of competence seem to prevent them from assuming responsibility for smoking cessation.

Ethical approval for the study was received from the Aydın Adnan Menderes University Faculty of Medicine Non-interventional Research Ethics Committee (protocol number: 2020/156, date: 20.08.2020). Administrative permission to conduct the study in FHCs obtained from the Aydın Provincial Health Directorate (number: 44021967-605.01, date: 03.11.2020).

Statistical Analysis

The data were analyzed using the IBM Statistical Package for the Social Sciences 20.0 (Armonk, New York, USA) statistical program. In addition to the use of descriptive statistical methods for data analysis, the Shapiro-Wilk test for the normality distribution of the variables, the independent samples t-test, the Mann-Whitney U test, and the chi-square test for comparisons between groups, and the Spearman correlation test for correlation analyses between variables were used. ROC analysis was conducted to categorize the total attitude score and multiple logistic regression analysis was conducted to determine the independent variables affecting attitudes. Statistical significance level was accepted as $P < 0.05$.

RESULTS

In the study, 88 of 91 family physicians and 77 of 79 nurses working in 25 FHCs in the Efeler district were reached. Out of the family health staff reached, 59 family physicians (response rate 67.1%) and 64 nurses (response rate 83.1%) agreed to participate in the study (total 123 participants; total response rate 74.5%).

Socio-demographic Characteristics of the Participants

Of the participants, 77 (62.6%) were female, and the mean age was 44.9±10.3. Female family physicians (47.9±6.6), were younger than male family physicians (52.6±6.9), ($P = 0.003$). The mean working time in the profession was 22.8±9.6 years, and 7.8±3.4 years in FHCs.

Thirty-three (26.8%) of the participants were smokers. Almost one third (32.5%; n = 40) of the participants stated that they received training on "stop smoking counselling." Some socio-demographic characteristics and habits of family physicians and nurses participating in the study are comparatively shown in Table 1.

The most common practices of family physicians and nurses concerning learning their patients' smoking behaviour were to offer assistance to smokers (82.4%) and to recommend them to quit (81.3%). Nearly two-thirds of the participants (67.5%) considered themselves competent to refer smokers to smoking cessation counseling centers, while 56.1% of them considered themselves competent to advise smokers to quit smoking.

The practices of the participants regarding the patients' smoking behaviors and their views on their self-competency are shown comparatively in Table 2.

Nurses were more likely to know if patients were smoking than family physicians (P = 0.001). After removing the confounding effect of gender (P = 0.002), this relationship persisted (forward LR, odds ratio (OR)=3.872; P = 0.001).

In univariate analyses, it was found that family physicians offered more assistance to smokers than nurses (P = 0.027). However, after removing the confounding effect of male (OR=2.903; P = 0.011) and non-smokers (OR=2.594; P = 0.028), it was

Table 1. Some socio-demographic characteristics and habits of family physicians and family health workers participating in the study, n = 123

Socio-demographic characteristics and habits		Participants			Statistics*
		FP	FHW	Total	
Age Mean±SD (median; interquartiles)		51.5±7.0 (52; 29-68)	38.7±8.9 (42; 21-58)	44.9±10.3 (46; 40-52)	Z=7.618 P < 0.001
Working years in the profession, Mean±SD (median; interquartiles)		27.2±7.2 (28; 5-42)	18.7±9.9 (20.5; 1-39)	22.8±9.6 (25; 18-30)	Z=5.227 P < 0.001
Working years at FHC, Mean±SD (median; interquartiles)		8.6±3 (10; 1-14)	7.1±3.5 (9; 1-13)	7.8±3.4 (10; 5-10)	Z=2.924 P = 0.003
		Number (%)	**Number (%)**	**Number (%)**	
Gender	**Woman**	14 (23.7)	63 (98.4)	77 (62.6)	χ^2=70.030 P < 0.001
Marital status	**Married**	51 (86.4)	48 (75.0)	99 (80.5)	P > 0.05
Smoking status	**Yes**	15 (25.4)	18 (28.1)	33 (26.8)	P > 0.05

FP: family physicans, FHW: family health worker, FHC: family health center, SD: standard deviation

Table 2. The practices and self-competency perceptions of the participants in learning smoking behaviors of the patients comparatively (univariate analyses)

Interventions		Practice number (%)		Perceptions of self-competency, number (%)	
		Always	Statistics*	Competant	Statistics*
ASK if you smoke	FP	27 (45.8)	**χ^2=11.064 P = 0.001**	29 (49.1)	P > 0.05
	FHW	49 (76.6)		38 (59.4)	
	General	76 (61.8)		67 (54.5)	
ASSESS smokers' motivation	FP	20 (33.9)	P > 0.05	33 (55.9)	**χ^2=14.451 P = 0.001**
	FHW	18 (28.1)		16 (25.0)	
	General	38 (30.9)		49 (39.8)	
ADVISE smokers to quit	FP	49 (83.1)	P > 0.05	38 (64.4)	**χ^2=6.518 P = 0.041**
	FHW	51 (79.6)		31 (48.4)	
	General	100 (81.3)		69 (56.1)	
ATTEMPT to improve motivation	FP	36 (61.0)	P > 0.05	32 (54.2)	P > 0.05
	FHW	30 (46.9)		25 (39.1)	
	General	66 (53.7)		57 (46.3)	
ASSIST when they want to quit	FP	42 (71.2)	**χ^2=4.899 P = 0.027**	32 (54.2)	P > 0.05
	FHW	32 (50.0)		25 (39.1)	
	General	74 (60.2)		57 (46.3)	
REFER for stop smoking counselling	FP	55 (93.2)	**χ^2=7.146 P = 0.008**	48 (81.4)	**χ^2=9.953 P = 0.005**
	FHW	47 (73.4)		35 (54.7)	
	General	102 (82.9)		83 (67.5)	
RECORD smoking behavior information	FP	18 (30.5)	P > 0.05	28 (47.5)	P > 0.05
	FHW	28 (43.8)		29 (45.4)	
	General	46 (37.4)		57 (46.3)	

FP: family physicans (n = 59), FHW: family health workers (n = 64), *chi-square test

determined that this relationship did not persist (forward LR; $P > 0.05$).

In univariate analyses, it was found that family physicians mostly referred smokers ready to quit for smoking cessation counseling ($P = 0.008$). However, when the confounding effect of age (OR=1.072 for each 1 year increase; $P = 0.003$) was removed, it was determined that this relationship did not persist (forward LR, $P > 0.05$).

Attitudes Towards Learning Patients' Smoking Behavior

Family physicians and nurses mostly thought that it was their responsibility to refer their patients who smoke to stop smoking counseling centers (71.6%) and to offer assistance (61.8%). The least responsibility they assumed was evaluating the motivations of smokers to quit smoking (49.6%). Family physicians assumed more responsibility than nurses for all items of duties related to learning the smoking behaviors of patients ($P < 0.001$) (Table 3).

To determine the factors related to attitudes, a total score out of 7 points was defined by giving 1 point to each attitude statement. Attitude scores increased with increasing age (r = 0.272; $P = 0.002$). Men had more positive attitudes compared to women ($P < 0.001$), and family physicians had more positive attitudes compared to nurses ($P < 0.001$). ROC analysis was performed to categorize the total attitude score variable according to whether the participants were family physicians or nurses. The attitude cut-off point was determined to be 5.5 by ROC analysis [area under the curve=0.224; 95% confidence interval (CI): 0.142-0.307; $P < 0.001$]. Those with a total attitude score above 5.5 were considered to be high-attitude, and multiple logistic regression analysis was performed to determine the variables associated with attitudes (forward LR). In the regression analysis, in which the variables of age, gender, marital status, smoking, profession, and education were considered, only the profession of the participants entered into the model [OR=3.120 (95% CI: 1.349-7.214), $P = 0.008$]. Compared to nurses, family physicians were 3.12 times more likely to have a positive attitude towards evaluating the patients' smoking status.

Opinions of Family Physicians Regarding the Responsibilities of Nurses

Family physicians mostly thought that nurses should take responsibility for the effort against smoking. The most attributed responsibility was that nurses should give advice of quitting smoking to women who do not contemplate to quit smoking (n = 54; 91.5%). The views of the family physicians participating in the study on the responsibilities of family health worker nurses in evaluating the smoking behaviors of the patients are shown in Table 4.

Table 3. Attitudes of the participants regarding their duties in evaluating the smoking behaviors of the patients, n = 123

Attitude statements		Participants n (%)	Statistics
It is the responsibility of the FPs/FHWs to learn smoking status of their patients.	FP	**46 (78.0)**	χ^2=15.150 $P < 0.001$
	FHW	23 (35.9)	
	General	69 (56.1)	
It is the responsibility of the FPs/FHWs to assess motivation of the smokers to quit smoking.	FP	**43 (74.1)**	χ^2=20.905 $P < 0.001$
	FHW	18 (31.6)	
	General	61 (49.6)	
It is the responsibility of the FPs/FHWs to advise smokers to quit who do not consider quitting.	FP	**42 (73.7)**	χ^2=10.997 $P = 0.001$
	FHW	23 (41.1)	
	General	65 (52.8)	
It is the responsibility of the FPs/FHWs to make an attempt to positively change motivation to quit smoking for patients who do not intend to quit smoking.	FP	**46 (83.6)**	χ^2=22.929 $P < 0.001$
	FHW	19 (36.5)	
	General	65 (52.8)	
It is the responsibility of the FPs/FHWs to offer assistance to their smoking patients when they consider quitting.	FP	**47 (82.5)**	χ^2=11.408 $P = 0.001$
	FHW	29 (50.9)	
	General	76 (61.8)	
It is the responsibility of the FPs/FHWs to refer patients who consider or are ready to quit smoking and request support to centers providing stop smoking counseling.	FP	**52 (89.7)**	χ^2=10.593 $P = 0.001$
	FHW	36 (62.1)	
	General	88 (71.6)	
It is the responsibility of the FPs/FHWs to record the information about the smoking behavior of their patients into their files.	FP	**44 (78.6)**	χ^2=13.554 $P < 0.001$
	FHP	25 (43.1)	
	General	69 (56.1)	

FPs: family physicans (n = 59), FHWs: family health workers (n = 64)

Table 4. Opinions of family physicians regarding the responsibilities of family health workers in evaluating the smoking behaviors of patients, n = 59

Family health workers, for women who receive reproductive health services (pregnant follow-up, 'smear', etc.):	
Opinions	**Agree, n (%)**
Should question the smoking behavior of women.	52 (88.2)
Should evaluate motivation of the smokers to quit smoking.	50 (84.8)
Should offer stop smoking advice to the smokers who do not consider quitting.	54 (91.5)
Should attempt to positively change their motivation to quit smoking for women who do not intend to quit smoking.	51 (86.4)
Should offer assistance if they later consider quitting smoking.	50 (84.8)
Should refer women who consider/are ready to quit smoking and request support to centers that provide stop smoking counseling.	53 (89.9)
Should record the information about the smoking behavior of individuals in their files.	46 (77.9)

DISCUSSION

This study aims the attitudes and behaviors of family physicians and nurses in FHCs in evaluating patient smoking behaviors.

According to our study results, the practices of family health care providers are not sufficient in terms of all the tasks related to evaluating the smoking behavior patients On the other hand, although they often feel inadequate about these tasks, they still perform better. Nurses ask more questions about the smoking status of the patients. Family physicians take on more responsibility in evaluating smoking behaviors patients. Family physicians generally believe that nurses should also take responsibility for the evaluation of patients' smoking behaviors.

According to the Health Statistics Yearbook (Turkish Ministry of Health) 2019 data, the average number of patient-doctor encounters per person per year in FHCs is 3.5.[8] These encounters should be seen as valuable opportunities for the struggle against smoking. For this reason, primary healthcare providers are expected to have medical competency in smoking addiction and its treatment. However, according to our study results, FHC staff members do not consider themselves competent at evaluating smoking behaviors of the patients. Studies on the competencies of healthcare providers in evaluating patients' smoking status are limited in the literature. In a study conducted in Jeddah, 69% of physicians were found to be confident in their ability to give smoking cessation counseling to their patients.[9] It has been determined that 31% of physicians and 43% of nurses working in primary care in Bosnia and Herzegovina feel very ready to provide smoking cessation counseling to smokers.[10] The main reason they do not see themselves as sufficiently trained seems to be the lack of training. Notably, three out of five family physicians and four out of five nurses have stated that they are not trained on the issue. There are many national[11-13] and international[9,10,14-18] studies emphasizing the lack of training and inadequacy of family physicians and nurses, working in primary care.

According to our study results, the practice of family physicians and nurses in evaluating the smoking behavior of their patients is not as high as expected and desired. The fact that the participants do not consider themselves competent in this regard and do not receive appropriate training seems to be reflected in their practice. Nurses seem to be active in learning the smoking status of women applying for reproductive health and directing those who want to quit to centers that provide smoking cessation counseling. Evaluating the motivations of smokers and taking initiatives to improve them are the weakest areas. This is understandable, given the general lack of nurse training on the subject. Assessing motivation for behavior change and attempts to improve motivation in individuals requires special interview techniques.

Family physicians, on the other hand, are more effective in advising smokers not ready to quit and in directing those ready to quit to the counseling services. It is recommended that physicians should at least advise smokers to quit, especially in the presence of clinical conditions directly related to smoking.[7] Therefore, the high rate of giving advice to quit should be seen as an expected outcome.

Family physicians and nurses mostly behave similarly when evaluating the smoking habits of patients. Nurses are better at asking whether their patients smoke. It does not seem possible to draw a conclusion explain the difference from our study results.

The practices of primary healthcare providers in evaluating the smoking behaviors of patients vary considerably in different studies conducted in different countries. In studies conducted in our country, the rate of primary care physicians varies between 23-67% for inquiring if their patients smoke, between 45-77% for giving advice to smokers to quit smoking, and between 25-63% for smoking cessation counseling.[7,13,19-22] In national and international studies, smokers' motivation to quit has been less evaluated, and it has been found to be low (25-49%), which is similar to our results.[13,14,23] On the other hand, our results in offering assistance show an improvement of 15-45%.[13-15,19,23,24]

No study investigating the practices of nurses in primary care to evaluate the smoking behaviors of their patients has been found in our country. International studies on this subject are also very limited. In a study conducted in Spain, it has been found that physicians and nurses working in primary care learn the smoking status of their patients, advise smokers to quit smoking, assist and counsel them, and record related information in their files at a higher rate compared to our study results. Similar to our study, nurses have more often asked whether their patients smoke than physicians have. Physicians, on the other hand,

have more often explained and assisted patients, and planned and arranged their patients' smoking cessation treatments.[25]

Attitudes of Family Physicians and Nurses

Family physicians adopt and practice recommending smokers to quit and referring them to smoking cessation counseling. For other tasks, although they know that they are their own resposibilities, they seem reluctant to implement them. This can be explained by the emphasized recommendation that physicians should at least advise smokers to quit.

Regarding attitudes, nurses, differ from family physicians. They generally do not see evaluating their patients' smoking habits as their responsibility, but they are better at asking, advising, and directing, which go beyond their perception of self-competency. The lack of aptitude for other tasks, which is also reflected in practice, can be partially explained by the fact that they have not had the required knowledge and skills for these tasks, and that they have not been adequately trained. In other studies, it has been found that the majority of family physicians (80-97%) think that they should play an active role in the struggle against smoking and that it is important to provide smoking cessation counseling to smokers.[9,13,18]

Opinions of Family Physicians

The family physicians participating in the study believe that evaluating the smoking behaviors of patients is the responsibility of nurses as much as it is theirs. We think that this is important for establishing a team approach in the struggle against smoking in FHCs.

In the literature, studies involving physicians' opinions on the tasks of other healthcare professionals in evaluating the smoking habits of applicants are limited. In a study, 87% of the physicians agree that healthcare professionals should regularly advise their patients who smoke to quit smoking.[16]

To ensure that stop smoking interventions become standard nursing practice, there is a need to improve nurses' attitudes towards their contribution to the patients' stop smoking initiatives.[26]

The study was designed based on a short clinical interview model that we used in our clinic. This provided the opportunity to obtain systematic and near-complete information on the evaluation of patients' smoking behavior. The inclusion of nurses in FHCs into the study is one of its strengths as well. Our study, which we think is the first in our country on this subject, has revealed important results for developing a team approach in the struggle against tobacco use, and has been a guide for future research. Considering that participation in survey studies is generally low, the high level of participation in our study is important for generalizing the results to the related population.

Study data were self-reported. Although their statements about their attitudes are considered to be more realistic, the participants may have overestimated their own practices. Because the study has been carried out only in the central district of Aydın, its results should be carefully generalized.

CONCLUSION

Our study results have revealed that the positive attitudes of family physicians are not fully reflected in practice, and that nurses generally do not adopt responsibilities related to evaluating patients' smoking habits, despite their efforts to improve practices. The most important reason for this seems to be that primary care professionals do not see themselves as competent due to lack of training. There is a need for new studies on qualitative methodology to better understand the attitudes and practices of family physicians and nurses in evaluating patients' smoking behaviors.

Ethics

Ethics Committee Approval: Ethical approval for the study was received from the Aydın Adnan Menderes University Faculty of Medicine Non-interventional Research Ethics Committee (protocol number: 2020/156, date: 20.08.2020). Administrative permission to conduct the study in FHCs obtained from the Aydın Provincial Health Directorate (number: 44021967-605.01, date: 03.11.2020).

Informed Consent: Verbal informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: R.S., O.B., Design: R.S., O.B., Data Collection or Processing: R.S., Analysis or Interpretation: R.S., M.D., O.B., Literature Search: R.S., M.D., O.B., Writing: R.S., M.D., O.B.

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Original Article

Evaluation of Systemic Inflammatory Indices of Earthquake Victims After the 6 February Kahramanmaraş Earthquake

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Abstract

OBJECTIVE: Earthquakes cause many people to lose their lives, get injured and leave their homes. Earthquakes constitute a serious risk factor for physical and mental diseases primarily due to traumatic environmental experiences. Systemic inflammation indices are used to determine prognosis in many diseases. This study aims to investigate the effects of the distance of earthquake victims from the epicentre of the earthquake, whether trapped under debris, and their psychological distress on the systemic inflammatory indices.

MATERIAL AND METHODS: Systemic inflammatory indices were retrospectively calculated for all earthquake victims. Questionnaires were evaluated prospectively among earthquake victims who volunteered.

RESULTS: The systemic inflammation values were aggregate index of systemic inflammation (AISI) median 351.5, systemic inflammation response index (SIRI) median 1.30, and systemic inflammation index (SII) median 677.4. Although the number of earthquake survivors under rubble was lower than the number of earthquake survivors not under rubble, AISI ($P = 0.001$), SIRI ($P = 0.03$), and SII ($P = 0.002$) were found to be statistically significantly higher in those under rubble. Depression scores (mean, 37.8) and anxiety scores (mean, 43.6) were compatible with moderate and severe categories. There was a significant relationship between AISI ($P = 0.018$) and SIRI values ($P = 0.05$) and depression outcome. Similarly, there was a statistically significant relationship between anxiety outcome and SII values ($P = 0.002$).

CONCLUSION: A significant correlation was found between the physical and psychological trauma experienced by the earthquake victims and the high level of systemic inflammatory indices. Rehabilitation and close follow-up of the earthquake victims are of great importance given that systemic inflammation is one of the long-term health effects of earthquakes.

KEYWORDS: Earthquake, inflammation, depression, anxiety

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INTRODUCTION

On February 6, 2023, a magnitude 7.8 Mw earthquake centered in Kahramanmaraş struck 11 provinces in Türkiye, causing 50,738 deaths and 115,353 injuries.[1] It prompted the organized evacuation of 28,044 persons and the displacement of approximately 3,000,000 individuals to other regions.[2] Of these displaced individuals, 7,500 were accommodated in dormitories, hotels, and boarding houses in Isparta.

Natural disasters cause great damage to nature and affect a large number of people worldwide. Earthquakes, one of the natural disasters, cause a large number of casualties, injuries, and losses, and force people to leave their homes. Considering the effects of earthquakes on public health, acute effects can include being under rubble, injuries, dust exposure as a result of collapsed buildings, and increases in infectious diseases due to post-earthquake weather and living space conditions. When the long-term health effects of earthquakes are analysed, increases in cardiovascular diseases, mental diseases, and frequency of metabolic diseases have been reported.[3]

The complete blood count (hemogram) is one of the laboratory tests routinely performed in hospital admissions. It provides insight into the patient's hemoglobin level, erythrocyte count, platelet count, and various immune system cell subtypes. Today, systemic inflammatory indices derived from hemogram parameters are becoming increasingly important

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as prognostic indicators for diseases. Indices such as systemic inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) are easily measurable, quantitative markers that provide a comprehensive assessment of the immune-inflammatory response. Chronic inflammation is recognized as an early hallmark of many chronic diseases.[4] Systemic inflammatory indices are used to determine prognosis in conditions such as cancer, cardiovascular diseases, acute and chronic respiratory system diseases, metabolic diseases and psychiatric diseases.[5-7]

Elevated SII values have been associated with a higher prevalence of chronic obstructive pulmonary disease (COPD). Neutrophils, platelets, and lymphocytes are closely related to the biological mechanism of COPD, and it is thought that the increase in the severity of inflammation during exacerbations may be effective in determining prognosis).[8] "This information predicts poor outcomes in patients with solid tumors and constitutes an adverse prognostic factor in small cell lung cancer. It is well known that cancer and inflammation are linked, and the cellular immune system is key to the inflammatory response.[9]" And have been investigated as a marker for identifying moderate to major depression.[10]

Recent evidence has accumulated linking depression with immune function.[11] Inflammation and depression are mutually reinforcing and exert a substantial impact on overall health. Heightened inflammation is a hallmark of many cardiovascular and immunometabolic diseases.

SIRI and SII have been shown to be independent risk factors for all-cause and cardiovascular mortality in obese populations. The underlying mechanism is that accumulated fat cells may overproduce adipokines, which release proinflammatory cytokines that trigger an inflammatory response, resulting in obese individuals remaining in a state of chronic low-grade inflammation.[12]

Main Points

- The depression scale (mean, 37.8; minimum 18-maximum 59) and anxiety scale (mean, 43.6, minimum 20-maximum 61) scores in the earthquake victims were compatible with moderate and severe categories, respectively.
- Analysis showed that depression score (P = 0.000) and anxiety score (P = 0.000) were significantly higher statistically in earthquake victims who were under rubble.
- There was a significant relationship between aggregate index of systemic inflammation, systemic inflammation response index values, and depression inventory results. Similarly, there was a statistically significant relationship between the anxiety inventory result and systemic inflammation index values.
- When earthquake victims with high depression and anxiety scores, were evaluated according to the rubble group, all three inflammation indices were significantly higher in those trapped under rubble. These data support the conclusion that the inflammatory response was much higher in people who were under rubble.

Elevated SII, SIRI, and AISI values have been shown to predict cardiovascular mortality,[13] and are significant for estimating depression risk,[14] and have prognostic value in idiopathic pulmonary fibrosis.[15]

Exposure to natural disasters has been associated with elevated short-, medium-, and long-term hospital admissions for acute and chronic conditions, yet the underlying mechanisms remain poorly defined. Considering the documented links between systemic inflammatory indices and chronic disease, chronic systemic inflammation may be one mechanism contributing to the morbidities observed among earthquake survivors.

Systemic inflammatory indices were retrospectively calculated for all earthquake victims admitted to the hospital. Questionnaires and the status of being trapped under debris were evaluated prospectively in earthquake victims who were admitted to the pulmonary clinic and volunteered to participate in the study.

This study aims to investigate the effects of the distance of earthquake victims from the epicentre of the earthquake, their status of being trapped under debris, and their psychological distress to the systemic inflammatory indices.

MATERIAL AND METHODS

Our study was cross-sectional, and approval was obtained from the Süleyman Demirel University Faculty of Medicine Ethics Committee (date: 29.12.2023, decision no: 2012-KAEK-38). After excluding those who were followed up due to infection, and those with high acute phase reactant values from the earthquake victims who applied to our hospital with code X39 in the first month after the earthquake, the remaining earthquake victims were retrospectively analysed. They were evaluated for age, gender characteristics, the branches they applied to, concomitant chronic diseases, residence addresses, and systemic inflammation parameters obtained from their current hemograms.

In the calculation of systemic inflammatory indices: neutrophil x platelet/lymphocyte count for SII, neutrophil x monocyte/lymphocyte count for SIRI, and neutrophil x platelet x monocyte/lymphocyte count for AISI were used in the formulae (15).

The earthquake victims who applied to the pulmonology outpatient clinic and participated voluntarily in the study were questioned about their respiratory symptoms, whether they had been under rubble and the duration of their stay, whether their houses had been destroyed, and if they lived in a public area, the duration of their stay. Beck Depression Inventory and Beck Anxiety Inventory Scales were applied to evaluate their psychological status (Figure 1).

Statistical Analysis

Statistical analysis of the data: Statistical Package for the Social Sciences (SPSS) software version 21.00 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) was used to analyse the data collected in the study. The conformity of the variables to normal distribution was analyzed using the Kolmogorov-Smirnov test. The one-way ANOVA test was used for the groups conforming to normal distribution and the Kruskal-Wallis test was used for

the groups not conforming to normal distribution. Data were presented as mean and standard deviation or median and range. Tukey's test was used when variances were equal between groups, and Tamhane's T2 test was used when variances were not equal. Demographic percentages and mean measurements were compared between the two groups using the independent t-test and the Mann-Whitney U test. The relationship between the groups was evaluated by a chi-square test. Correlations between parameters were evaluated using Pearson correlation. Receiver operating characteristic (ROC) analysis was used to calculate optimum cut-off values, sensitivity and specificity for systemic inflammatory markers. A 95% confidence interval and significance levels of $P < 0.05$ and $P < 0.001$ were sought in the evaluation of all data.

RESULTS

Two hundred thirty-nine earthquake victims were admitted to our hospital with code X39 in the first month. Of 239 earthquake victims, 35.1% were admitted to the emergency department, 17.1% to the chest diseases department, 7.1% to the dermatology department, 6.2% to the internal medicine department, and 5.8% to the family medicine department. Of the earthquake victims admitted to our hospital, 59.4% were women. The majority were from Hatay (42.8%). Forty-one patients were from Kahramanmaraş, and twenty-eight patients were from Malatya. There were earthquake victims from 9 provinces, excluding Diyarbakır and Kilis.

When the systemic inflammation values obtained from hemogram data of the patients were examined, the median for AISI was 351.5 [standard error of mean (SEM) 40.6], the median for SIRI was 1.30 (SEM 0.23), and the median for SII was 677.4 (SEM 43.7) (Table 1). When the cities were grouped according to the number of collapsed buildings, AISI, SIRI and SII values were found to be higher in the cities with more collapsed buildings (Hatay, Kahramanmaraş, Gaziantep,

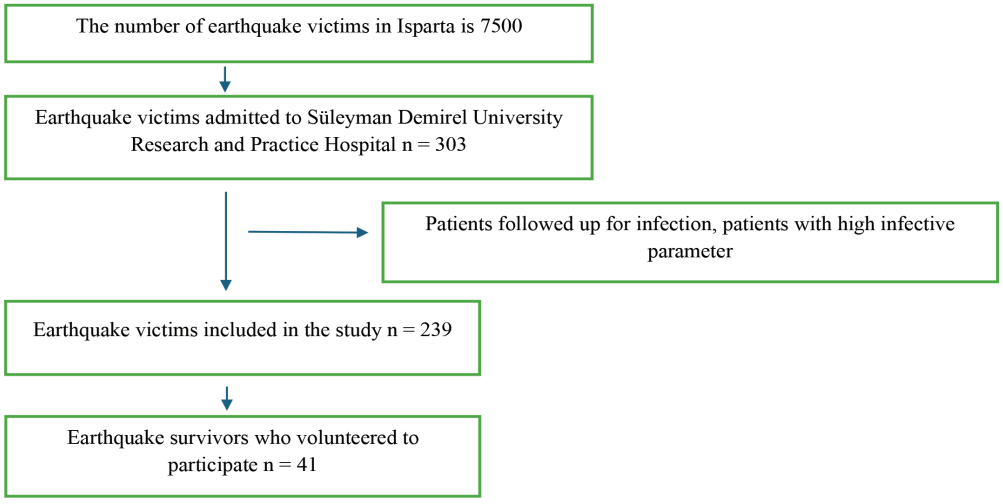

Figure 1. Flow chart of the participants

Table 1. Characteristics of the earthquake victims included in the study

	Earthquake victims admitted to hospital (n = 239)	Earthquake survivors who volunteered to participate in the study (n = 41)
Gender, female	142 (66.4%)	22 (53.6%)
Residence		
Hatay	96	23
Kahramanmaraş	47	8
Malatya	32	5
Gaziantep	16	3
Adıyaman	13	1
Number of people trapped under the rubble	-	14
AISI	Median 351.5 (SEM 40.6)	Median 533.87 (SEM 140.53)
SIRI	Median 1.30 (SEM 0.23)	Median 1.68 (SEM 1.01)
SII	Median 677.4 (SEM 43.7)	Median 760.21 (SEM 138.27)
Beck Depression Score	-	Mean 37.8; min 18-max 59
Beck Anxiety Score	-	Mean 43.6, min 20-max 61

SEM: standard error of mean, SII: systemic inflammatory index, SIRI: systemic inflammatory response index, AISI: aggregate index of systemic inflammation, min: minimum, max: maximum

Malatya, Adıyaman), although not statistically significant ($P > 0.05$). Although there was no statistical significance between the groups, when earthquake survivors without chronic diseases were divided into two groups according to the number of collapsed buildings, those from the provinces where the number of collapsed buildings was high and those from the provinces where the number of collapsed buildings was low, all three systemic inflammation markers were relatively higher in earthquake survivors from the provinces where the number of collapsed buildings was high ($P > 0.05$). When we divided the earthquake victims into 3 groups based on their proximity to the epicentre: group 1 (Kahramanmaraş, Gaziantep), group 2 (Adana, Hatay), group 3 (Malatya, Adıyaman), there was no statistically significant difference in terms of systemic inflammation indices.

Forty-one earthquake survivors who volunteered to answer the questionnaire were evaluated among themselves or by the researchers. The variance distribution of this group was homogeneous in terms of gender, with females (n = 22) and males (n = 19). Respiratory symptoms included shortness of breath in 16 patients, cough in 21 patients, sputum in 20 patients, and flu-like complaints in 16 patients. When we divided the earthquake victims into 3 groups according to the distance from the epicentre, we categorized them as follows: group 1 (Kahramanmaraş, Gaziantep), group 2 (Adana, Hatay), group 3 (Malatya, Adıyaman). There was a significant difference between the groups in terms of being in the collective area (one-way ANOVA $P = 0.001$). Group 1 had a higher frequency of staying in the communal area compared to the other two groups.

The number of earthquake victims trapped under the rubble was 14, and the average duration of being trapped under the rubble was 5 hours (minimum range: 0-57). Twenty-three people stayed in the collective living area after the earthquake, while eighteen people stayed outside the collective living area. The average duration of stay in the earthquake zone was 6.5 days (minimum 0, maximum 15).

Earthquake victims were grouped according to their exposure to rubble, and systemic inflammation indices were evaluated. In the ROC analyses performed for systemic inflammation values, the cut-off value for AISI was 674 (sensitivity 78.6%, specificity 81.5%), the cut-off value for SIRI was 1.88 (sensitivity 78.8%, specificity 74.1%), and the cut-off value for SII was 762.68 (sensitivity 92.9%, specificity 77.8%). Although the number of earthquake victims who were under rubble was lower than those who were not under rubble, AISI ($x^2 = 12$, $P = 0.001$), SIRI ($x^2 = 8.88$, $P = 0.03$), and the SII ($x^2 = 16.53$, $P = 0.002$) was statistically significantly higher in those who were under rubble. A statistically significant relationship was found between AISI, SIRI, SII, and being under rubble (Table 1).

The depression scale values (0-16 mild, 17-29 moderate, 30-63 severe; mean 37.8 minimum 18-maximum 59) were compatible with severe depression, and the anxiety scale values (8-15 mild, 16-25 moderate, 26-63 severe; mean 43.6; minimum 20-maximum 61) indicated severe anxiety. According to the Kruskal-Wallis analysis, the depression score ($P < 0.001$) and the anxiety score ($P < 0.001$) were statistically significantly higher in earthquake victims who were under rubble (Table 2).

When the relationship between the results for depression and anxiety and systemic inflammation values was analysed, there was a significant relationship between AISI ($x^2 = 5.5$, $P = 0.018$), SIRI values ($x^2 = 8$, $P = 0.05$), and depression inventory results. Similarly, there was a statistically significant relationship between the anxiety inventory result and SII values ($x^2 = 9.47$, $P = 0.002$).

DISCUSSION

In recent decades, the frequency of natural disasters has increased markedly, leading to dramatic consequences and huge economic losses. Low-income countries are among the most affected countries. Although data on health effects after earthquakes are available in the literature, unfortunately, political and economic constraints often make long-term epidemiological surveillance in these settings impractical. The Sendai Framework for Disaster Risk Reduction, supported by the United Nations, emphasises that accurate monitoring of the health status of populations exposed to disasters is essential to identify priority interventions and restore previous health conditions.[16]

Looking at the studies on earthquakes to date, it was observed that the Great East Japan (20,896 deaths), Kobe/Hanshin-Awaji (5,530), and L'Aquila (295) earthquakes, which caused the highest loss of life, were the most frequently investigated. The majority of the studies were conducted after the 2000 earthquakes, which may be related to the fact that monitoring the chronic effects of earthquakes was not considered a public health priority or that epidemiological studies were

Table 2. The relationship between systemic inflammation values, Beck Depression and Anxiety Scores and being trapped under rubble

	Number of people above SIRI cut-off value (1.88)	Number of people above the SII cut-off value (762.68)	Number of people above the AISI cut-off value (674)	Beck Depression Scale	Beck Anxiety Scale
History of being trapped under rubble (14 people)	11 people	13 people	11 people	Mean 49.5 min 28-max 59	Mean 53.5 min 49-max 60
No history of being trapped under rubble (27)	8 people	7 people	6 people	Mean 31.7 points min 18-max 58	Mean 38.5 points min 20-max 61
Statistical significance	$x^2 = 8$, $P = 0.05$	$x^2 = 9{,}47$, $P = 0.002$	$x^2 = 5.5$, $P = 0.01$	$P = 0.000$	$P = 0.000$

SII: systemic inflammatory index, SIRI: systemic inflammatory response index, AISI: aggregate index of systemic inflammation, min: minimum, max: maximum

not published in the preceding period. By presenting the data we obtained after the disaster, we wanted to draw attention to the long-term health problems that may be experienced in earthquake victims.

Some studies have reported an increase in a wide range of psychiatric and mood disorders, especially in cases of repeated or high-intensity exposure to earthquakes.[17]

Earthquakes intensify the occurrence of psychiatric health disorders, including depression, anxiety, post-traumatic stress disorder (PTSD), insomnia and drug addiction.[18]

Factors contributing to this situation include physical trauma, loss of relatives, loss of housing, financial hardship, displacement, women's suffering, and low level of education.[19]

Major depressive disorder has been diagnosed in 5.8-54% of adult, 7.5-44.8% of child, survivors of natural disasters, including earthquakes.[20] In post-earthquake studies in Greece, Armenia, Pakistan, and China, it was shown that more than one-fifth of the survivors experienced significant anxiety symptoms.[21]

In our study, the depression scale scores (0-16 mild, 17-29 moderate, 30-63 severe) had a mean of 37.8 (minimum 18-maximum 59), indicating severe levels, while the anxiety scale scores (8-15 mild, 16-25 moderate, 26-63 severe) had a mean of 43.6 (minimum 20-maximum 61), also indicating severe levels. Similar to the literature, our findings showed that earthquake survivors had high depression and anxiety scores. This may suggest that earthquake survivors have a high risk of psychiatric disorders.

Various studies conducted after major earthquakes have shown that the experience of fear, the level of exposure to material and life losses caused by the earthquake (injury, being in a place where people died, death of family members and friends, loss of home and job, etc.), gender (e.g., being female), previous trauma, traumatic distress, lack of social support, being young and old, and low education level are risk factors associated with PTSD, depression and anxiety symptoms.[22]

In our study, Kruskal-Wallis analysis showed that depression score (P = 0.000) and anxiety score (P = 0.000) were significantly higher in earthquake victims who were under rubble. This supports the conclusion that exposure to trauma (injury, material loss, being in a place where people died) is an increased risk factor for depression and anxiety.

Considering the relationship between systemic inflammatory indices and psychiatric diseases, evidence was presented that high SII and SIRI levels were associated with increased risk of depression in a study including 29,000 individuals. They emphasised the potential value of measuring systemic inflammation biomarkers in determining individuals at risk of depression in the general population, especially in those with obesity.[14]

In our study, we found that the median for AISI was 351.5 (SEM 40.6), the median for SIRI was 1.30 (SEM 0.23), and the median for SII was 677.4 (SEM 43.7), all of which were higher than reported in the literature. In a cohort of 312 patients with depressive disorder, certain patterns were observed. In a cohort of 312 patients with depressive disorders, the mean SII was found to be 462.83; the optimal cut-off point of SII was calculated as 540.78 and high SII was stated as a risk factor for moderate/major depression in patients with depressive disorders.[10] It was observed that the median value calculated for SII in our earthquake victims was above the mean values determined in the literature for the risk of depressive disorders. When the cities were grouped according to the number of collapsed buildings, AISI, SIRI, and SII values were found to be higher in such cities, although not statistically significant (P > 0.05). High SII values are identified as a high risk factor for moderate/major depression in the literature, may be associated with the high depression scores caused by the magnitude of the trauma, which we also showed in our study.

Similarly, when the mental health effects of the earthquake on Syrian earthquake victims were examined, it was found that PTSD and generalised anxiety scale scores were significantly higher in severely and moderately damaged areas, than in less damaged areas.[23] This data support that there is a relationship between changes in systemic inflammation indices and mental health.

Considering that chronic diseases may have an effect on systemic inflammatory indices, when the earthquake victims without chronic diseases were divided into two groups according to the number of destroyed buildings—those coming from provinces where the number of destroyed buildings was high and those from provinces where it was low—there was no statistical significance between the groups. However, all three systemic inflammation markers were relatively higher in the earthquake victims from provinces where the number of destroyed buildings was high (P > 0.05).This is important for demonstrating changes in the characteristics of the region, where the earthquake occurred, as reflected on these markers.

When the systemic inflammation indices were evaluated by grouping the earthquake victims according to whether they were under rubble although the number of earthquake victims who were under rubble was lower than the number of earthquake victims who were not under debris, AISI (x^2 = 12, P = 0.001), SIRI (x^2 = 8.88, P = 0.03), SII value (x^2 = 16.53, P = 0.002) were statistically significantly higher in those who were under rubble. When the relationship between depression and anxiety inventory results and systemic inflammation values was analysed, there was a significant relationship between AISI (x^2 = 5.5, P = 0.018), SIRI values, and depression inventory results (x^2 = 8, P = 0.05) (Table 2). Similarly, there was a statistically significant relationship between the anxiety inventory result and SII values (x^2 = 9.47, P = 0.002). This suggests that the psychological stress caused by the earthquake may be related to the increase in systemic inflammatory indices.

When earthquake victims with high depression and anxiety scores were evaluated according to the rubble group, all three inflammation indices were significantly higher in those trapped under rubble. These data supported the finding that the inflammatory response was much higher in people who were under rubble (Table 3).

Table 3. Systemic inflammation indexes of earthquake victims with high depression and anxiety scale scores according to their trapped under rubble

	Earthquake victims trapped under rubble (n = 14)	Earthquake victims not trapped under the rubble (n = 27)	Statistical significance
High Depression Score	SII mean 1820,8 SEM 297.5	SII mean 963.2 SEM 203.8	*P* = 0.028
	SIRI mean 9.17 SEM 2.7	SIRI mean 2.29 SEM 0.60	*P* = 0.026
	AISI mean 1641,4 SEM 311.3	AISI mean 575,3 SEM 169.0	*P* = 0.007
High Anxiety Score	SII mean 1661,1 SEM 307.7	SII mean 800.8 SEM 115.3	*P* = 0.04
	SIRI mean 6.88 SEM 2.11	SIRI mean 2.02 SEM 0.40	*P* = 0.06
	AISI mean 1492,0 SEM 330.8	AISI mean 497.3 SEM 96.9	*P* = 0.01

SEM: standard error of mean, SII: systemic inflammatory index, SIRI: systemic inflammatory response index, AISI: aggregate index of systemic inflammation

In a meta-analysis examining the health effects of earthquakes, there was strong evidence ($P < 0.001$) that mortality from myocardial infarction was 36% higher [95% confidence interval (CI), 19% to 57%] after an earthquake compared with pre-earthquake measurements. Higher mean glycated haemoglobin levels (0.16 percentage points; 95% CI, 0.07 to 0.25) were found in earthquake-exposed people than in non-exposed people. Previous studies have shown that higher rates of diabetes were observed in disaster-exposed individuals concerning the metabolic effects of earthquakes.[3]

Evidence of an overall increase in incidence rates of haemorrhagic gastric ulcers was shown among people exposed to the Kobe earthquake (Japan, 1995).[24]

Examination of studies on the role of systemic inflammatory indices in chronic and immunological diseases has revealed that SII may serve as an important prognostic marker in various tumour types, including small cell lung cancer, metastatic castration-resistant prostate cancer, squamous cell carcinoma of the oesophagus.[9] Furthermore, SII may have potential utility in diagnosing immunological diseases and the presence of active disease.[25] In the general population, SII has been shown to be significantly associated with all-cause cardiovascular mortality, independent of established risk factors (with a cut-off value of 18,284 for SII),[26] and is positively associated with diabetes (with a cut-off value of 588 for SII).[27] Additionally, AISI is effective in predicting the prognosis of idiopathic pulmonary fibrosis.[15] A total of 13 studies involving 152,996 participants showed that higher SII was significantly associated with an increased risk of cardiovascular disease [heart rate (HR) = 1.39, 95% CI: 1.20-1.61, $P < 0.001$]. This increased risk was associated with ischaemic stroke (HR = 1.31, 95% CI: 1.06-1.63, $P = 0.013$), haemorrhagic stroke (HR = 1.22, 95% CI: 1.10-1.37, $P < 0.001$), myocardial infarction (HR = 1.11, 95% CI: 1.01-1.23, $P = 0.027$), and almost all cardiovascular disease subtypes, including peripheral arterial disease (HR = 1.51, 95% CI: 1.18-1.93, $P = 0.001$).[28]

In our study, the finding of median values above the mean values, which are thought to pose a risk for diseases in the literature (588[22] for diabetes, 391[24] for cardiovascular diseases, 390[19] in malignancy), suggests that the inflammatory processes experienced in earthquake victims may pose a risk for cardiovascular, metabolic, immunological, and malignant diseases in the future. Therefore, we think that the long-term health status of earthquake victims should be closely monitored.

The low number of earthquake survivors who volunteered to participate in our study is a limitation. However, the limited data on earthquakes in the literature make each observation valuable.

CONCLUSION

In the light of the data obtained, a relationship was found between the physical and psychological trauma experienced in earthquake victims and the high level of systemic inflammatory indices. Considering the possibility that this inflammation may be effective in the long-term health effects of earthquakes, rehabilitation and close follow-up of earthquake victims are of great importance. We believe that our study will contribute to the literature in terms of psychological rehabilitation and long-term follow-up of earthquake victims after the Kahramanmaraş-centred earthquakes that caused great destruction, and will guide the measures to be taken after possible earthquakes because we live in an earthquake zone.

Ethics

Ethics Committee Approval: Our study was cross-sectional, and approval was obtained from the Süleyman Demirel University Faculty of Medicine Ethics Committee (date: 29.12.2023, decision no: 2012-KAEK-38).

Informed Consent: Retrospective study.

Present in: Presented as an oral presentation at the 27th annual congress of the Turkish Thoracic Society in 2024.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.E., Concept: M.E., Design: M.E., Ö.Ö., Data Collection or Processing: M.E., T.A., H.T.K., Analysis or Interpretation: M.E., Ö.Ö., Literature Search: M.E., Writing: M.E.

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Original Article

Current Status of Cystic Fibrosis in Türkiye: Data from the National Registry

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Abstract

OBJECTIVE: The Cystic Fibrosis Registry of Türkiye (CFRT) was established by the Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society and has provided detailed information on demographic, clinical, genetic, and treatment-related aspects of cystic fibrosis (CF) patients since 2017. We aimed to describe the current status of CF in Türkiye using CFRT's 2023 annual data.

MATERIAL AND METHODS: Demographic, clinical, and treatment data were taken from CFRT's 2023 record.

RESULTS: In 2023, 2,258 patients from 34 centers were recorded. The median age of patients was 9.1 years, and 46.9% were female, with a median age at diagnosis of 0.3 years. Only 14.9% of the patients were older than 18 years. Genetic analyses were completed in 97.3% of patients. The most common variant, F508del, had a total variant frequency of 22.1%. The median percent predicted FEV1 and FVC were 88.0 and 94.0 in those aged 6-17 years 71.0 and 84.0 in those aged ≥18 years, respectively. The median values of body mass index z-scores were -0.5, and -0.5 for patients 2-18 and older than 18 years, respectively. Chronic colonization with *Pseudomonas aeruginosa* was present in 17.2% of the patients. Most patients used inhaled recombinant human DNase (87.1%) and oral pancreatic enzyme replacement treatment (83.0%). CF transmembrane conductance regulator (CFTR) modulators were used by 15.9% of patients. Over the year, 24 patients died, with a median age at death of 13.3 years.

CONCLUSION: The CFRT report provides a valuable resource showing the clinical and laboratory data of patients with CF in the country.

KEYWORDS: Cystic fibrosis, Cystic Fibrosis Registry of Türkiye, annual data

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INTRODUCTION

Cystic fibrosis (CF) is caused by autosomal recessive mutations in the gene that codes for the CF transmembrane conductance regulator (CFTR) protein.[1] CFTR dysfunction causes multi-organ disorders, including chronic sino-pulmonary infections with bronchiectasis, exocrine pancreatic insufficiency, malabsorption, growth failure, distal intestinal obstruction syndrome, and infertility, all of which vary in prevalence.[1,2]

Patient registries are structured systems for gathering comprehensive data, including sociodemographic, clinical, and other important information from various healthcare sources.[3] Registry data fosters partnerships between patients, families, and healthcare providers. They are vital for rare diseases like CF as they unify standardized individual data from various clinics and countries, enabling more robust statistical analyses and optimizing resource use.[4] The first CF registry was launched in the United States of America (USA) in 1966.[5] While many countries established national CF registries,[6-9] international CF patient registry systems were established.[10] Cystic Fibrosis Registry of Türkiye (CFRT) was established by the Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society in 2007.[11] In CFRT, after obtaining written informed consent from parents and patients, each center records patients' demographic and annual data in a software program specifically developed for the CFRT. The first comprehensive results of this national registry were published, with the demographic and laboratory data collected from 1,170 registered patients from 23 centres in 2017.[11,12] The CFRT has been contributing to the European Cystic Fibrosis Society's Patient Registry (ECFSPR) since 2016.[13] Many studies were conducted using CFRT data to evaluate the relationship between follow-up, clinical features, growth, treatment, and complications of patients.[14-21]

This review aims to describe the current status of CF in Türkiye by using the 2023 annual data of CFRT.[22]

MATERIAL AND METHODS

This retrospective study included individuals with CF represented in the 2023 CFRT data. The diagnosis of CF was established based on typical clinical findings, with at least two positive sweat chloride tests and/or two CF-causing CFTR mutations.[23]

Demographic and annual data, including sex, age at diagnosis, current age, z-scores of weight, height, and body mass index (BMI), results of neonatal CF screening, pulmonary function tests, history of meconium ileus, medications, presence of microorganisms, complications, and transplantations, were recorded.

The z-scores of all individuals for weight and height were recorded, while BMI and BMI z-scores were noted for those over the age of 2. The bacterial colonization status is considered chronic if more than 50% of respiratory samples test positive over a 12-month period.[24]

Each center records patient data annually in a specially developed software program for the CFRT. At the end of each year, the CFRT board members review and clean the registry data. After correcting and excluding missing data, CFRT analysts performed a descriptive analysis and provided the variable changes by year. We obtained the descriptive annual data for 2023 from the CFRT database.

The study was conducted after approval from the Hacettepe University Faculty of Medicine Institutional Research and Ethical Committee (reference numbers: GO 23/469, date: 06.06.2023) and according to the Declaration of Helsinki guidelines. Written informed consent from participants' parents and age-appropriate assent from all participants were obtained annually before participants were included in the registration system.

Statistical Analysis

Statistical analysis was performed by the Pleksus company (Türkiye). Missing data were excluded from the analysis. Findings from descriptive analyses were reported as relative and absolute frequencies for categorical variables, and as median and quartile values for quantitative variables.

RESULTS

Demographics

In 2023, 2,258 individuals with CF were registered at 34 centers in Türkiye, which we estimate cover over 70% of CF patients in our country. The number of registered individuals with CF in 2022 was 2,088. One thousand fifty-eight individuals (46.9%) were females, and the patients' median current age was 9.1 years (with a range of 3 months to 48.8 years). Table 1 gives the demographic characteristics of patients. Adults accounted for 14.9% (n = 336) of the CF population.

The number of CF centers contributing to the registry system has increased from 20 to 34 (Figure 1a). The number of patients in the system has gradually increased (Figure 1b), and the number of adult patients reporting has risen from 9 to 336 from 2016 to 2023. Pediatricians still follow most patients with CF in most centers (18/34) in Türkiye, and the transition to adult clinics has just been implemented in many other centers. However, only three adult CF centers (8.8%) contributed data to CFRT. Figure 2 shows a map of cities that contributed data in 2023.

Diagnosis

The median age of our patients at diagnosis was 0.3 years; the oldest was 41 years (Table 1). Seventy-eight percent of patients ≤7 years of age in 2023 were diagnosed through NBS. 4.7% of our patients, currently aged ≤10 years, were diagnosed with meconium ileus.

Genetics

In 2023, genetic analyses of our registered patients were completed in 2196 (97.3%) individuals with CF. Among genotyped patients, two variants were identified in 1916 patients (84.9%), one variant was identified in 155 patients (6.9%), and no variants were found in 125 patients (5.5%). The most common variant was F508del, which had a total allele frequency of 22.1%. The prevalence of the F508del mutation in homozygous form was 12.1% (266 individuals), and in F508del heterozygous form was 15.9% (349 individuals) among individuals whose genetic analyses were completed. The distribution of the 15 most common variants in genotyping is given in Figure 3.

Lung Function

In 2023, the lung function of 1,020 patients (45.2%) was recorded, 755 of whom were between 6 and 17 years old, and 265 were 18 and older. The median percent predicted (pp) FEV1 and FVC were 88.0% and 94.0% in individuals with CF aged between 6 to 17 years and 71.0% and 84.0% in those aged ≥18 years, respectively. Table 2 shows the distribution of categorical pp FEV1 values. The distribution of the median pp FEV1 by age group is given in Figure 4.

Microbiology

Among all patients, 17.2% had chronic infection with *Pseudomonas aeruginosa*, 14.8% with methicillin-sensitive *Staphylococcus aureus*, 10.3% with methicillin-resistant *Staphylococcus aureus*, and 1.3% with *Haemophilus influenzae*. Figure 5 shows the prevalence of chronic and intermittent *Pseudomonas aeruginosa* by year.

The prevalence of *Burkholderia cepacia* complex chronic infection was 0.4%, and intermittent infection was 0.1%. Non-tuberculous mycobacterial infection was seen in 17 (0.8%) patients. The prevalence of patients with chronic infection with *Stenotrophomonas maltophilia* was 0.1%, while intermittent infection was 0.8%. Chronic infection with *Achromobacter* species was reported in 8 (0.4%) patients, and intermittent infection was reported in 13 (0.6%) patients.

Main Points

- Patient registry data fosters partnerships between patients, families, and healthcare providers.
- By 2023, 2,258 registered cases from 34 centers, which we estimate cover over 70% of cystic fibrosis (CF) patients in our country.
- Adults accounted for 14.9% of the CF population. Pediatricians still follow most patients with CF in most centers (18/34), in Türkiye.
- Educating clinicians, patients, and families about the registry's importance in improving CF care and increasing the number of adult CF centers would facilitate greater compliance with the Cystic Fibrosis Registry of Türkiye (CFRT).
- The CFRT report provides a valuable resource showing the clinical and laboratory data of patients with CF in the country.

Table 1. Demographic characteristics of registered patients in 2023

	Female	Male	Total
Total registered patients n (%)	1,058 (46.9)	1,200 (53.1)	2,258 (100.0)
Current age, median (Q1-Q3), years	8.5 (4.6-14.3)	9.7 (5.4-15.4)	9.1 (5.1-14.9)
Age at diagnosis, median (Q1-Q3), years	0.3 (0.2-0.9)	0.3 (0.2-1.0)	0.3 (0.2-1.0)
Number of patients aged ≥18, n (%)	143 (13.5)	193 (16.1)	336 (14.9)
Number of patients who died in 2023, n (%)	17 (1.6)	7 (0.6)	24 (1.1)
Ages at death, median (Q1-Q3), years	14.2 (5.2-19.2)	12.3 (7.6-15.8)	13.3 (5.8-18.8)

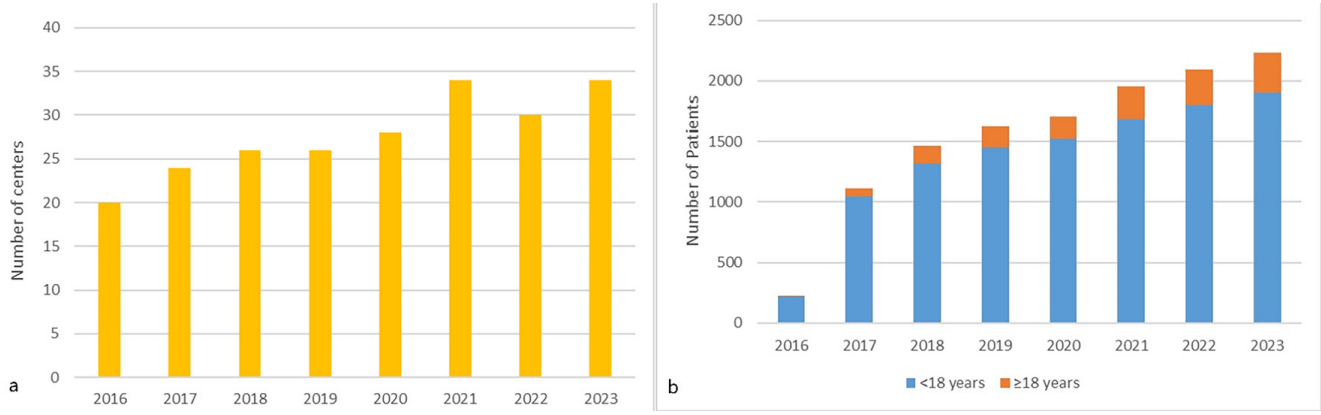

Figure 1. (a, b) Number of CF centers contributing to the registry by year, and number of patients under and over the age of 18 by year

CF: cystic fibrosis

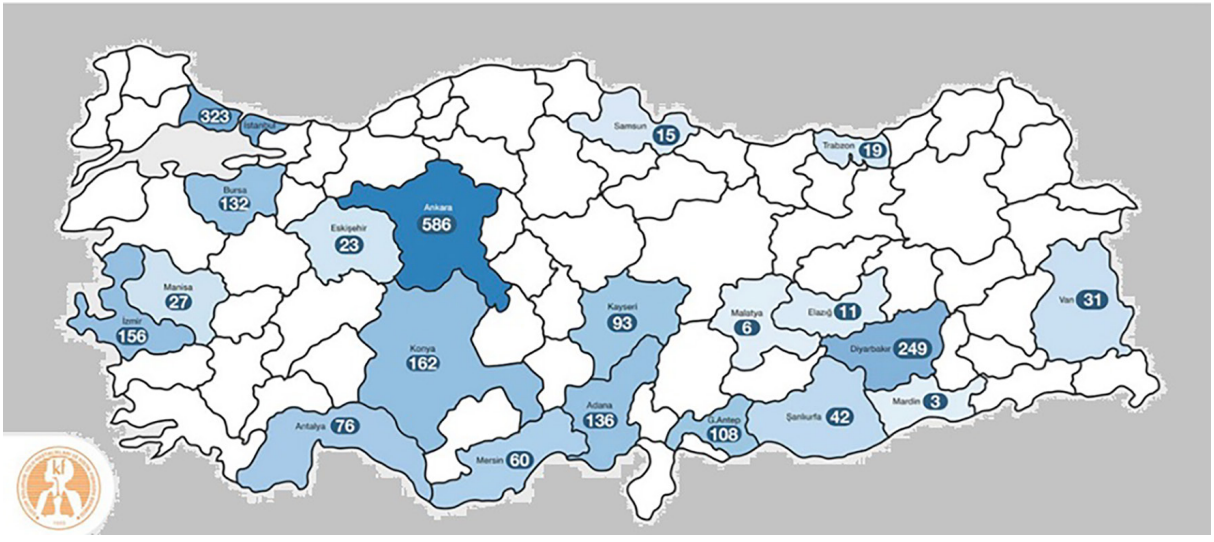

Figure 2. Map of cities that contributed data in 2023

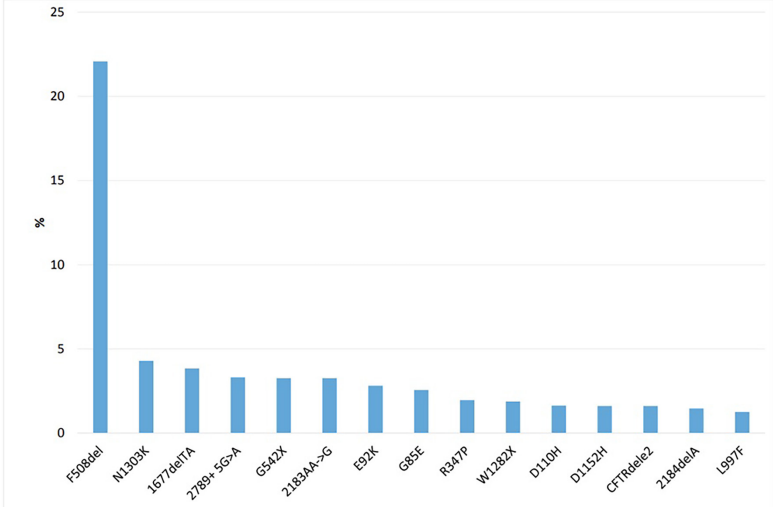

Figure 3. Distribution of the 15 most common variants

Table 2. Distribution of categorical pp FEV1

Age	pp FEV1			
	≤40%	41-59%	60-79%	≥80%
6-17 years n (%)	29 (3.8)	61 (8.1)	162 (21.5)	503 (66.6)
≥18 years n (%)	50 (18.9)	47 (17.7)	63 (23.8)	105 (39.6)

pp: percent predicted

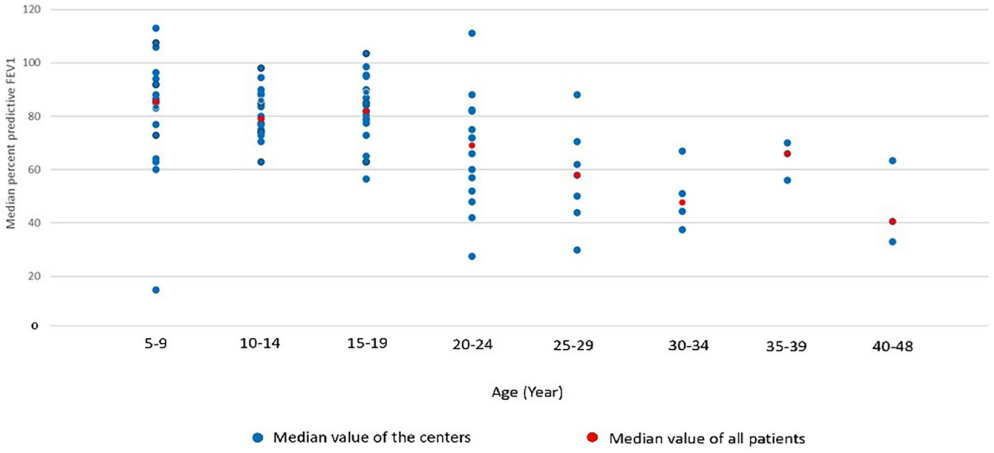

Figure 4. Distribution of the median FEV1 percentage by age group

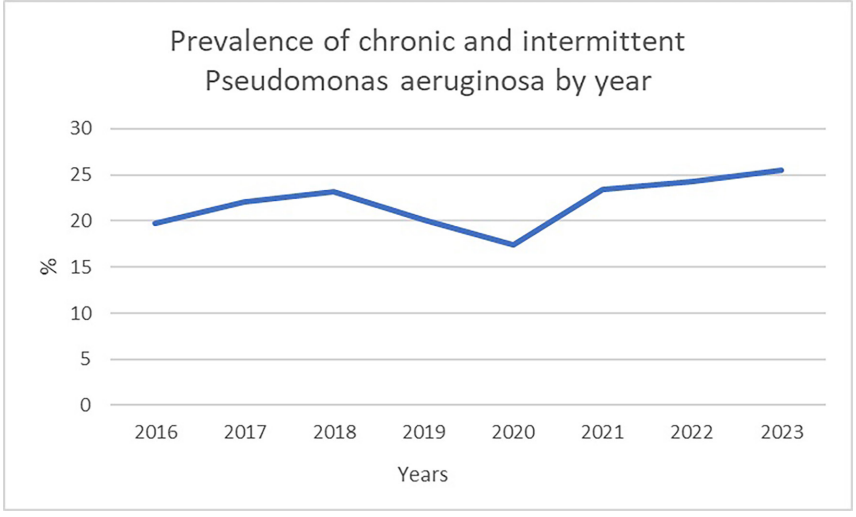

Figure 5. Prevalence of chronic and intermittent *Pseudomonas aeruginosa* by year

Nutrition

In 2023, 83.0% of our registered patients with CF were pancreatically insufficient. The median body weight, height, and BMI z-scores were -0.7 (Q1: -1.3- Q3: 0.0), -0.6 (Q1: -1.6- Q3: 0.3), and -0.5 (Q1: -1.1- Q3: 0.2) in patients under 18 years and -0.7 (Q1: -1.4- Q3: -0.6), -0.6 (Q1: -1.2- Q3: 0.1) and -0.5 (Q1: -1.1- Q3: 0.2) in patients 18 and older, respectively. Figure 6 shows the distribution of median body weight and height z-scores according to age groups and centers. Percutaneous endoscopic gastrostomy was preferred in 12 patients (0.5%) as a feeding and nutritional support route.

Complications and Hospitalizations

Four hundred fifteen patients (18.4%) received intravenous antibiotics for acute pulmonary exacerbations in the hospital for at least one day. Except for routine check-ups, 612 patients (27.1%) spent at least one day in the hospital.

Table 3 summarizes all complications related to CF. The most common complication was liver disease, followed by gastroesophageal reflux.

Treatments

Table 4 summarizes all treatments given to our patients. Most of the patients used recombinant human DNase (87.1%), pancreatic enzyme replacement (83.0%), and multivitamins (71.5%). More than half (58.2%) of the patients received oral nutritional supplements. The prevalence of azithromycin use as a prophylactic antibiotic, and anti-inflammatory treatment was 10.3%. Thirty patients (1.3%) used oral steroids.

CFTR modulators have been used in our country since 2021. Among the patients eligible for modulatory treatment, 358 (15.9%) used CFTR modulators, with elexacaftor/tezacaftor/ivacaftor being the most preferred. The number of patients using CFRT modulator therapy was 35 in 2021 and 358 in 2023. Table 5 shows the number of patients using modulators yearly in all centers. Due to our country's high diversity of mutations and the lack of drug reimbursement, a limited number of patients are eligible for modulator treatments, resulting in a frequency of 15.9% for modulator use.

Transplantation and Mortality

Six CF patients were living in 2023 with transplanted lungs, two with transplanted livers, and one with transplanted kidneys.

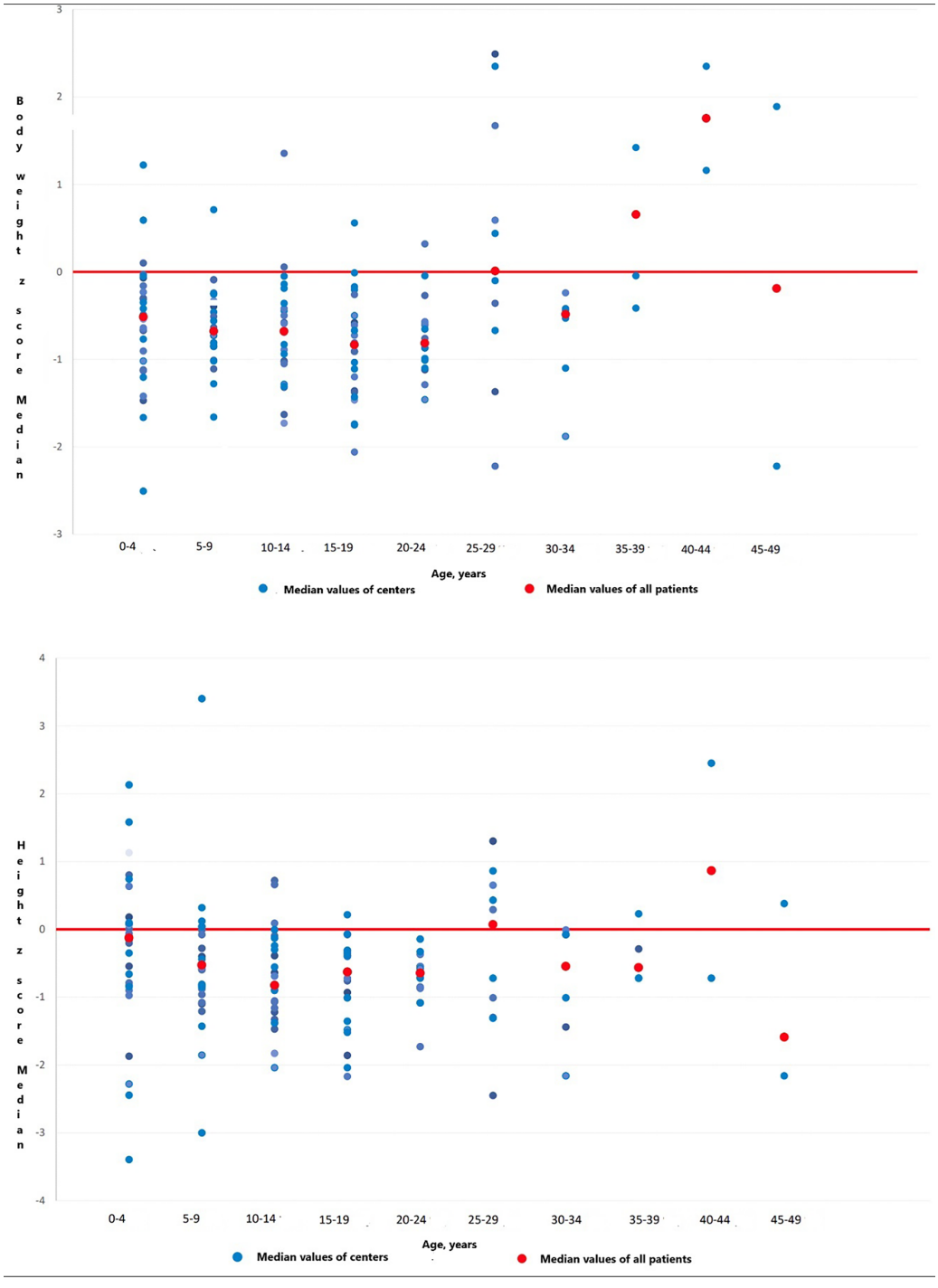

Figure 6. Distribution of median body weight and height z-scores: according to age groups and centers

The deaths of 24 of our patients were documented over the year, all but one of whom died from respiratory problems. Our patients' median age at death was 13.3 years (ranging from 1 to 17 years), and 17 were female.

Table 3. Complications

Complication	n (%)
Pulmonary	
Allergic bronchopulmonary aspergillosis	42 (1.9)
Massive hemoptysis (≥250 mL over the course of a day)	16 (0.7)
Pneumothorax	10 (0.4)
CF-related diabetes	
Using Insulin	96 (4.3)
Only on diet	31 (1.4)
Therapy unknown	4 (0.2)
Liver diseases	
Liver disease without cirrhosis	394 (17.5)
Cirrhosis with portal hypertension/hypersplenism	21 (0.9)
Cirrhosis without portal hypertension/hypersplenism	6 (0.3)
Other complications	
Sinusitis	197 (8.7)
Gastroesophageal reflux	125 (5.5)
Pseudo-Bartter's syndrome	90 (4.0)
Osteoporosis	66 (2.9)
Distal intestinal obstruction syndrome	29 (1.3)
Malignancy	4 (0.2)

CF: cystic fibrosis

Table 4. Treatments for ≥3 consecutive months

Pulmonary treatments	n (%)
rhDNase	1966 (87.1)
Inhaled bronchodilator	700 (31.0)
Hypertonic saline	545 (24.1)
Inhaled antibiotics	455 (20.2)
Inhaled steroids	318 (14.1)
Oxygen support	67 (3.0)
Mannitol	63 (2.8)
Non-invasive mechanical ventilation	56 (2.5)
Gastrointestinal system treatments	
Pancreatic enzyme replacement	1875 (83.0)
Multivitamins	1615 (71.5)
Oral nutritional supplements	1315 (58.2)
Proton pump inhibitors	357 (15.8)
Ursodeoxycholic acid	346 (15.3)
CFTR modulator therapies	
Elexacaftor/tezacaftor/ivacaftor	279 (12.4)
Ivacaftor	55 (2.4)
Lumacaftor/ivacaftor	17 (0.8)
Tezacaftor/ivacaftor	7 (0.3)

CFTR: cystic fibrosis transmembrane conductance regulator, rh: recombinant human

DISCUSSION

This review aims to summarize CFRT 2023's annual data, as it contains the most comprehensive and detailed information about CF patients in our country.[22] The annual data report includes data from individuals diagnosed with CF who have consented to participate in the CFRT and were seen in a CF center during the 2023 calendar year. These data allow us to compare various clinical practices, understand differences, and optimize treatment between CF centers.

It is estimated that there are more than 180,000 people with CF worldwide. CF was initially considered a primary childhood disease. However, improvements in care have led to a substantial and growing adult population. The incidence of CF is the same in female and male individuals.[1-3]

In 2023, the median age of patients with CF in the USA was 22.5, and it was 9.1 in our country.[22,25] According to annual data for 2022-2023, more than half of the people with CF are over 18 years old in the USA and Europe.[25-27] The number of registered patients with CF in the CFRT continues to increase, as does the number of registered adults; however, the proportion of adults is still less than 25%.[22] Only three adult centers (8.8%) care for adult CF patients, who contribute data to CFRT. Pediatricians still follow most patients with CF in most centers (18/34) in Türkiye, and the transition to adult clinics has just been implemented in many centers. The increasing contribution of adult CF care centers in the registry will accurately reflect the number of adult CF patients in the country. Our number of adult patients is low compared to Europe and the USA, and our adult CF centers are also limited. This may be due to insufficient knowledge among adult chest physicians about CF disease and the lack of structured transition programs to support the appropriate shift from pediatric to adult clinics. To address this issue, it is essential to provide training programs for both pediatric and adult chest physicians. Educating clinicians, patients, and families about the registry's importance in improving CF care and increasing adult CF centers would facilitate greater compliance with CFRT.

CFRT includes most CF centers nationwide, except for a few that provide their patients' information directly to the ECFSPR. In our national registry data published in 2020, there were only 1,170 registered patients, and we estimated the coverage rate to be 30% of the entire CF population in the country.[12] By 2023, we had 2,258 registered cases, which we estimate cover over 70% of CF patients in our country.[22]

The diagnosis of CF is based on typical features, a family history of CF, or a positive newborn screening (NBS) test associated with evidence of CFTR dysfunction.[1,2] The CF diagnostic criteria are two sweat tests greater than 60 mmol/L chloride and/or two

Table 5. Patients using modulators by year in all centers

Year	Ivacaftor, n	Lumacaftor-ivacaftor, n	Tezacaftor-ivacaftor, n	Elexacaftor-tezacaftor-ivacaftor, n
2021	3	2	6	24
2022	20	10	8	124
2023	55	17	7	279

identified disease-causing CF variants, one on each parental allele.[1]

The diagnosis of CF is established upon typical clinical findings, with two positive sweat chloride tests and/or two CF-causing CFTR variants.[1,2] The age of diagnosis in many countries has shifted to the first 3 months of life with the implementation of NBS.[22,25-27] NBS for CF has been implemented in our country since 2015, and two repeated immunoreactive trypsinogen (IRT/IRT) tests are used.[10] Meconium ileus at birth is not rare and may be the first symptom of CF detected in newborns.[1,2] Approximately 15% of infants with CF are born with meconium ileus.[2] In CFRT, the rate of meconium ileus in patients under 10 years old is almost 5%. The overall rate is likely higher when considering all patients. However, this difference may be due to limited awareness of CF in some healthcare centers, which can lead to underreporting, especially regarding early-onset manifestations that occur in the neonatal period (patients might die before diagnosis). These cases may not be systematically recorded or linked to later CF diagnoses. Additionally, patients may receive treatment at centers that do not contribute data to the CFRT. Furthermore, false-negative NBS results may frequently arise in patients with meconium ileus, potentially influencing the observed outcome rates.

The *CFTR* gene has been found to contain more than 2,000 variants, some with virtually no CFTR function and others associated with residual function.[23] The most common CFTR variant is F508del in Europe and the USA.[3]

Most individuals with CF have two identified CFTR variants, with the most common mutation being F508del in all registries.[22,25,27] The most common CFTR variant, F508del, is seen in more than 80% of the USA and Europe;[25,27] however, it remains 22% in our country.[22] These differences indicate that Turkish CF patients have a different mutation spectrum from others. Türkiye's high prevalence of consanguineous marriages and geographical location between Asia and Europe has the potential for immigration, and as a result, it contains racially and ethnically diverse populations, which may explain the difference.

Lung disease is the primary cause of morbidity and mortality in CF. The natural course of the disease suggests a 1-2% decline in pp FEV1 annually.[1-3] The median pp FEV1 value is higher in many European countries and the USA than in our country in all age groups.[22,25,27]

Host defense defects in inflammatory cells and impaired mucociliary clearance increase the risk of airway infections in people with CF.[2] The chronic nature of these infections worsens lung disease. One of the most frequent pathogens isolated in the CF airways is *Pseudomonas aeruginosa*, and its chronic colonization is associated with a worse prognosis.[1-3]

Pseudomonas aeruginosa and *Staphylococcus aureus* are still predominant respiratory pathogens in individuals with CF.[22,25-27] The prevalence of *Pseudomonas aeruginosa* infection has decreased in the CF population in Europe and the USA since the increased usage of CFTR modulators.[25,27] However, we did not detect a significant change in the prevalence of *Pseudomonas aeruginosa* infection.[22] The prevalence of intermittent and chronic *Pseudomonas aeruginosa* was lowest in 2020. The Coronavirus disease-2019 pandemic may have contributed to this, as patients did not visit the hospital to provide airway culture samples. The slight increase in the prevalence of intermittent and chronic *Pseudomonas aeruginosa* in recent years can be attributed to the development and maturation of CFRT, the sharing of registry data, heightened awareness among centers about these infections, and improved diagnostic capabilities in their laboratories.

Up to 90% of individuals with CF have exocrine pancreatic insufficiency,[1,2] as most of our patients are pancreatic insufficient.[22] Because of inadequate intake, increased energy expenditure, and malabsorption, patients with CF are at risk of malnutrition. The degree of underweight in CF patients negatively affects survival. Early assessment and management of nutritional status are vital to positively influence lung function in CF patients. Prevention of malnutrition should be a key focus in treating all CF patients.

Most patients with CF (85-90%) have exocrine pancreatic insufficiency. Exocrine pancreatic insufficiency is diagnosed by the presence of low fecal elastase levels, along with typical signs such as fatty stools, flatulence, and poor weight gain.[1,2] It results in maldigestion, malabsorption of nutrients, steatorrhea, fat-soluble vitamin deficiency, and malnutrition. Malnutrition was one of the most important causes of death before pancreatic replacement enzyme therapy.[1,2]

Our patients' height, weight, and BMI values are lower than in many European countries and the USA.[22,25,27] Increased early diagnosis of CF patients through NBS and increased usage of CFTR modulators may allow these patients in our country to have better nutritional metrics, similar to those in Europe and the USA.

Symptomatic treatment, prophylactic treatment, and response to acute events have been applied since the disease was described.[2] With a better understanding of CF, symptomatic treatments and new drugs have steadily been developed. Symptomatic CF treatments include maintaining good nutrition, pancreatic replacement therapy, regular chest physiotherapy, and the inhalation therapy of mucolytic agents to improve mucociliary clearance. They also include prophylactic and aggressive treatment of pulmonary infections with inhaled, oral, and intravenous antibiotics and early identification and treatment of complications.[1,2]

The new treatments that improve CFTR function are called CFTR modulators. CFTR modulators comprise two classes: potentiators and correctors. Ivacaftor was launched as a potentiator in 2012; combinations of potentiators and correctors have emerged, such as lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor. CFTR modulators are currently licensed and used in many countries.[1,2] Those are oral agents that bind to the CFTR protein.[1-3] CFTR modulators have been shown to improve BMI, reduce sweat chloride concentrations, increase predicted FEV1%, quality of life, and decrease pulmonary symptoms.[1,2,28] CFTR modulators are used in patients with eligible genetic variants and who meet age criteria. Approximately 90% of patients in the USA and 73% of patients in Europe are eligible for CFTR modulators;[25,27] however,

less than 20% of our patients can use CFTR modulators in our country due to the diversity of mutations, the limited number of patients eligible for modulator treatments and the lack of drug reimbursement limit our country's frequency of modulator use.[22]

The increased use of modulatory treatments, which have been shown to have many positive effects on the quality of life and life expectancy of CF patients, and the increase in the number of adult CF centers, will improve our patients' outcomes. However, due to our wide range of mutations, new treatment modalities are still needed for our patients, especially those not eligible for modulator treatments.

The incidence of CF is the same in females and males, but there is a survival difference. The lower survival of females with CF compared to males with CF contrasts with the longer survival of females than males in the general population.[2] Most deaths in people with CF occur between the third and fifth decades of life in Europe and the USA. Unfortunately, most deaths are still most common in the first decade in our country.[22,25,27] The limited opportunities for transplantation and limited use of CFTR modulators are among the reasons for earlier deaths in our country. As noted in the literature, the higher mortality rate was observed in females compared to males. This can be attributed to various factors, including physiological, biochemical, nutritional, and behavioral differences. Female lung anatomy may contribute to smaller lung volumes and less effective airway mucus clearance. Pulmonary exacerbations and mortality rates are comparable between boys and girls before puberty, suggesting that female hormones may influence airway pathophysiology. Nevertheless, female sex remains an independent risk factor for death.[29]

The report has several limitations. First, a few CF centers in Türkiye do not provide their data to CFTR. Thus, some CF patients remain unregistered. Second, analyzing registry-based data may not allow us to interpret causality. Additionally, there is no auditing for data accuracy and completeness. However, CFTR has initiated a new program to verify and validate data at its source in participating centers. This program aims to quantify data completeness, consistency, and accuracy. Despite these limitations, the report provides Türkiye's most comprehensive and detailed information on individuals with CF.

CONCLUSION

In conclusion, this study provides our country's most comprehensive and detailed information about individuals with CF. CFRT reports provide critical insights into CF management resources for improvement nationwide.

Ethics

Ethics Committee Approval: The study was conducted after approval from the Hacettepe University Faculty of Medicine Institutional Research and Ethical Committee (reference numbers: GO 23/469, date: 06.06.2023) and according to the Declaration of Helsinki guidelines.

Informed Consent: Written informed consent from participants' parents and age-appropriate assent from all participants were obtained annually before participants were included in the registration system.

Footnotes

Authorship Contributions

Surgical and Medical Practices - Concept - Design - Data Collection or Processing - Analysis or Interpretation - Literature Search - Writing: All authors contributed equally to all contribution sections.

Conflict of Interest: No conflict of interest was declared by the authors.

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Systematic Review

Efficacy of Trikafta (ELX/TEZ/IVA) & Symdeko (TEZ/IVA) in Treating Cystic Fibrosis with F508del Allele: A Systematic Review and Meta-analysis

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Abstract

The objective of the study was to assess and compare the efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) treatment with TEZ/IVA treatment in individuals diagnosed with cystic fibrosis (CF) and carrying the F508del allele. An extensive search of relevant literature was conducted using online resources, namely, PubMed, ScienceDirect, and Google Scholar. The initial search identified 248 articles, and after a careful examination of the full text of 18 articles, 7 met the inclusion and exclusion criteria. These selected reports were then thoroughly examined to perform a comparative analysis of the effectiveness of TEZ/IVA versus ELX/TEZ/IVA in CF patients with the F508del allele. The quality of the selected reports was evaluated using the Cochrane risk-of-bias tool for randomized studies, known as RoB 2. ELX/TEZ/IVA has shown significant improvements in key indicators of CF treatment. It has demonstrated a significant increase in forced expiratory volume in one second levels, indicating improved respiratory capacity and airflow. Additionally, ELX/TEZ/IVA successfully reduced sweat chloride levels and positively impacted Cystic Fibrosis Questionnaire-Revised Respiratory Domain scores, reflecting enhanced respiratory function and improved quality of life for patients. Overall, the study concluded that ELX/TEZ/IVA provided a clinically robust benefit compared to TEZ/IVA alone while maintaining a favourable safety profile.

KEYWORDS: Cystic fibrosis, Phe508del, Symdeko, Trikafta, ivacaftor, tezacaftor, elexacaftor, safety, systematic review

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INTRODUCTION

Cystic fibrosis (CF) is a hereditary disorder characterized by malfunctioning of the CF transmembrane conductance regulator (CFTR) protein.[1] CFTR is found on the apical membrane of epithelial cells, and its absence results in decreased chloride secretion and insufficient fluid transport.[2] A significant reduction in chloride secretion results in mucus impaction in exocrine organs, airways, and gastrointestinal tracts, which progressively leads to pulmonary exacerbations, nutritional deficits, and respiratory failure.[3] It is estimated that more than 70,000 people worldwide are affected by CF.[4]

CFTR mutations are categorized into six groups based on their effect on CFTR protein synthesis, processing, and function. These classes help explain the underlying mechanisms that lead to CF symptoms. Class 2 mutations, which include the most common variant, F508del, result in defective protein folding. This misfolding prevents the CFTR protein from reaching the cell surface, where it would normally regulate chloride ion transport. As a consequence, chloride secretion is impaired, leading to thick mucus buildup in various organs, particularly the lungs and pancreas.[5,6] Approximately 2000 CFTR gene variations have been identified so far,[7] and F508del accounts for the majority of CFTR alleles in individuals with CF.[8]

In recent years, advances in CF research and medical treatments, such as CFTR modulator therapies, have significantly improved outcomes for individuals with CF. These therapies target specific CFTR mutations and aim to correct the underlying defect in CFTR protein function. Ivacaftor (IVA) is a CFTR modulator that is authorized for the treatment

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of people who have CF and at least one of the 33 CF-causing mutations.[9] By enhancing the function of defective CFTR channels at the cell surface, IVA, improves chloride ion transport, leading to improved lung function and reduced respiratory symptoms in CF patients.[10] In individuals with gating mutations, IVA has lowered mortality, lung transplantation rates, and other consequences of CF.[11] Tezacaftor (TEZ) is a broad-acting CFTR corrector that promotes the cellular processing and trafficking of normal CFTR and numerous mutant CFTR forms, including F508del, increasing the quantity of CFTR protein at the cell surface and thereby enhancing chloride transport. It assists in restoring proper folding and trafficking of CFTR protein to the cell surface.[12] When used in combination with IVA, TEZ can significantly enhance CFTR function and clinical outcomes. TEZ in combination with IVA has the potential to address an important unmet need for CFTR modulators, by improving the benefit-to-risk profile of CFTR modulation in patients homozygous for F508del and enhancing the benefit of CFTR modulation in patients with IVA-responsive mutations.[13] Elexacaftor (ELX) is a CFTR corrector that improve CFTR protein processing, stability, and trafficking to the cell surface.[14] By targeting the misfolding issue caused by class 2 mutations, ELX enables the CFTR protein to reach its intended location and function properly as an ion channel.[15] When used in combination with IVA, TEZ and ELX form a novel triple combination therapy.

The gold standard spirometric test for diagnosing and treating CF lung disease involves measuring forced expiratory volume in one second (FEV1).[16] FEV1 measures the volume of air forcibly exhaled in the first second of a forced expiratory maneuver.[17] The percent predicted forced expiratory volume in one second (ppFEV1) compares an individual's FEV1 value to the average FEV1 value of a healthy population of the same age, height, sex, and ethnicity, providing a percentage value. Monitoring ppFEV1 over time helps clinicians evaluate lung function and track disease progression in CF. A decline in ppFEV1 suggests worsening lung disease, while stable or improved ppFEV1 values indicate better respiratory health.[18] Sweat chloride levels are another important diagnostic tool for CF. The sweat test measures the concentration of chloride ions in sweat. CFTR protein dysfunction leads to increased chloride ion levels in sweat, which is the basis for the sweat chloride test.[19] Elevated sweat chloride levels confirm the diagnosis of CF. To gain insights into the respiratory symptoms and quality of life experienced by individuals with CF, the Cystic Fibrosis Questionnaire-Revised Respiratory Domain (CFQ-R RD) is commonly used. It is a validated questionnaire that assesses various aspects of respiratory health, including symptoms, physical functioning, emotional well-being, and social interactions. The CFQ-R RD helps evaluate the impact of CF on a person's daily life, assess treatment efficacy, and identify areas where intervention may be required to improve overall respiratory health and quality of life.[20]

In this systematic review, we assessed and compared the efficacy and safety of TEZ/IVA and ELX/TEZ/IVA as therapies for CF patients and their impact on the quality of life of patients. We evaluated studies reporting ppFEV1, sweat chloride levels, and the CFQ-R RD score, for the assessment of TEZ/IVA / ELX/TEZ/IVA treatment regimens in F508del CF patients.

MATERIAL AND METHODS

The main objective of the systematic review was to formulate a comparative analysis between ELX/TEZ/IVA and TEZ/IVA treatment among CF patients with F508del allele. It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines (Figure 1). The review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) against the registration ID: 444643 (Supplementary Table 1).

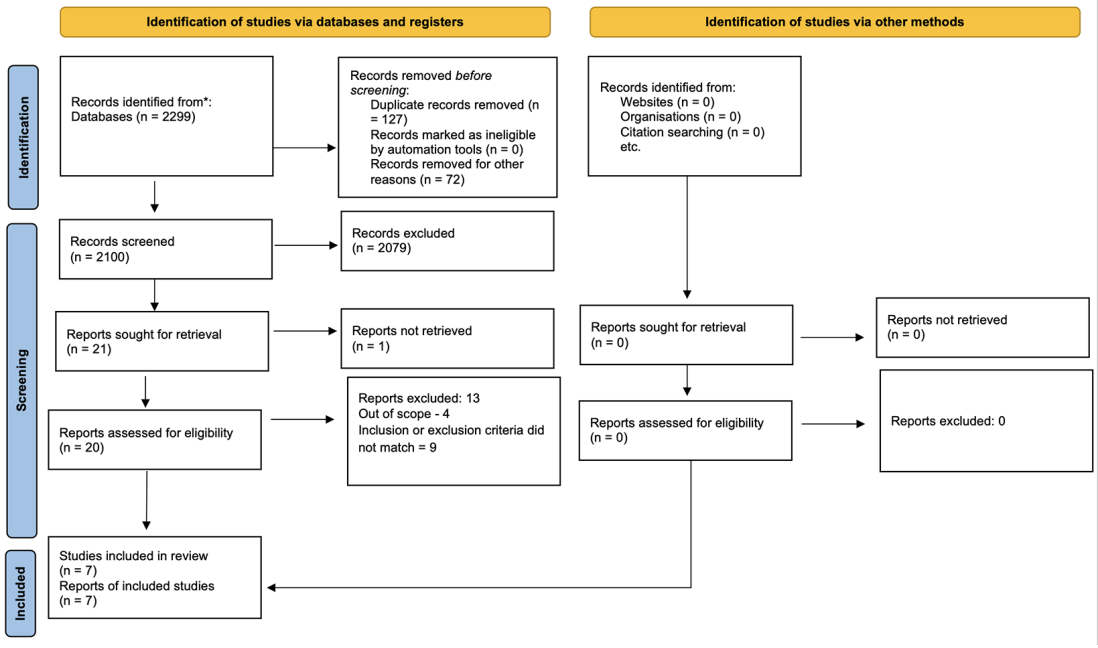

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020-flow diagram for inclusion and exclusion criteria

**PubMed, ScienceDirect, Google Scholar, Cochrane*

Data Sources

Internet databases were searched using key terms to locate randomised controlled trials. Online databases searched included Cochrane Central Register for Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, PubMed, NCBI, ScienceDirect, Google Scholar. We utilized the following key terms to increase sensitivity for discovering CF therapeutic trials: "cystic fibrosis" OR "CFTR", CFTR corrector, CFTR modulator, forced expiratory volume, sweat chloride.

Selection Criteria

Our title-specific search was followed by an abstract-specific screening to exclude extraneous publications. Furthermore, for full-text evaluation, we used the following conditions for inclusion: (1) randomized control trials (2) reports that included patients with CF with the F508del mutation (homozygous or heterozygous), (3) studies reporting predicted FEV1, sweat chloride levels, and CFQ-R RD scores, (4) studies reporting the adverse events of TEZ/IVA / ELX/TEZ/IVA, (5) studies with more than 100 patients recruited, and (6) phase 2 or above randomized studies. We also applied the following exclusion criteria: (1) articles including any CF mutations other than F508del, (2) reports of phase 1 clinical trials, and (3) articles in a language other than English. The whole text was then evaluated using the established qualifying criteria. After several rounds of debate, the authors reached a mutual agreement, with final approval from the principal investigator.

Data Extraction

For data extraction, an authorised tracking sheet (Excel) from the principal investigator, with the mutual agreement of the authors, was utilised. The main outcomes were percentage of predicted FEV1 mean value, sweat chloride levels, CFQ-R RD score, and adverse events. The authors extracted entered the data into the tracking sheet (Excel) for each study's baseline characteristics, clinical data, therapies administered, and findings. The primary investigator double-checked the spreadsheets for any irregularities.

Main Points

- The study aimed to evaluate Trikafta elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and Symdeko (TEZ/IVA) in cystic fibrosis (CF) patients with the F508del allele. A comprehensive literature search was conducted using PubMed, ScienceDirect, and Google Scholar until April 2023. Out of the 248 articles reviewed, 8 met the inclusion criteria and were assessed using the Cochrane risk-of-bias tool.
- Trikafta (ELX/TEZ/IVA) has emerged as a promising treatment option for CF patients carrying the F508del allele. Its efficacy, as demonstrated by significant improvements in FEV1 levels, reduction in sweat chloride levels, and enhanced Cystic Fibrosis Questionnaire-Revised Respiratory Domain scores, suggests superior therapeutic outcomes compared to Symdeko (TEZ/IVA).
- With its favourable safety profile and consistent performance across heterozygous and homozygous F508del patients, Trikafta emerges as a promising and preferred treatment option for enhancing respiratory function and quality of life in CF management.

Risk of Bias Assessment

The chosen research papers underwent an evaluation process to determine their quality using the RoB 2 tool, which is designed for assessing bias in randomized studies (Figure 2). The RoB 2 tool evaluates six areas related to bias, including the randomization process, the impact of assigning participants to interventions, adherence to the intervention, handling of missing outcome data, measurement of outcomes, and selection of reported results. The authors individually assessed the data and then discussed and agreed upon their judgments regarding the risk of bias (Supplementary Table 2).

Statistical Analysis

The statistical analysis for the meta-analysis was performed using RStudio software. Heterogeneity was estimated using the I^2 index. Considering the low heterogeneity of the studies, a fixed effect model was used. The confidence interval of 95% was evaluated for the forest plot. $P < 0.05$ was considered statistically significant.

RESULTS

The studies included in the meta-analysis consisted of seven RCTs with each study recruiting more than 100 patients. The studies were phase 2 and above, which included both heterozygous and homozygous states for the Phe508del mutation. Every study included patients prescribed TEZ 100 mg once daily / IVA 150 mg every 12 hours (TEZ/IVA) or TEZ 100 mg once daily / IVA 150 mg every 12 hours / ELX 200 mg once daily (ELX/TEZ/IVA).

FEV1 Levels

In the case of patients with heterozygous F508 del CF, three studies compared TEZ/IVA with placebo, while one study reported ELX/TEZ/IVA versus placebo. In the phase 3 randomized controlled trial conducted by Taylor-Cousar et al.[21] for evaluating the combination of IVA and TEZ in patients above the age of 12 years, the TEZ/IVA treatment resulted in a mean absolute change in FEV1 level of 3.4±0.7 percentage points as compared to -0.6±0.7. Munck et al.[22] reported a mean FEV1 level of 1±1.2 percentage points and -0.1±1.2 percentage points for placebo. Similarly, the phase 3 crossover study by Rowe et al.[12] giving a combination therapy of TEZ/IVA resulted in a mean change in FEV1 level of 11.1±2.4 percentage points as compared to 4.7±1 in case of placebo.

In the study conducted by Middleton et al.,[23] for evaluating the ELX/TEZ/IVA treatment for a period of 24 weeks, the mean change in FEV1 from baseline was 13.9±1.1, which is higher than the aforementioned values obtained from TEZ/IVA treatment. These findings suggest that both treatments have a positive impact on lung function, but ELX/TEZ/IVA may be slightly more effective.

In the case of homozygous F508del CF patients, Heijerman et al.[24] assessed the effects of TEZ/IVA and ELX/TEZ/IVA on various parameters. The mean change in percentage of predicted FEV1

Table 1. Summary of baseline characteristics, dosage, and associated adverse events in reviewed studies

Author, year	Phase of the study	Type of study	Sample size	F508del (homozygous/ heterozygous)	Treatment group (dose)	Comparator	Adverse events
Taylor-Cousar et al.[21] (2017)	Phase 3	Randomized, double-blind, multicenter, placebo-controlled, parallel group trial	510	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Infective pulmonary exacerbation of CF Cough Headache Nasopharyngitis Increased sputum production Pyrexia Hemoptysis Oropharyngeal pain Fatigue
Rowe et al.[12] (2017)	Phase 3	Randomized, double-blind, placebo-controlled	248	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Infective pulmonary exacerbation of CF Cough Fatigue Hemoptysis Headache Pyrexia Dyspnea Sputum increased Diarrhea Nausea Oropharyngeal pain Nasal congestion Nasopharyngitis Blood CPK increased
Donaldson et al.,[9] (2018)	Phase 2	Randomized, placebo-controlled, double-blind, multicenter	172	Both	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Infective pulmonary exacerbation of CF Cough Headache Increased sputum Fatigue Nausea Diarrhea
Munck et al.,[22] (2020)	Phase 3	Randomized, double-blind, placebo-controlled, multicenter study	168	Heterozygous	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Placebo	Cough Fatigue Hemoptysis Sputum increased
Middleton et al.,[23] (2019)	Phase 3	Randomized, double-blind, placebo-controlled	403	Heterozygous	Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours/ elexacaftor 200 mg once daily	Placebo	Sputum increased Headache Cough Diarrhea Upper respiratory tract infection Nasopharyngitis Oropharyngeal pain Hemoptysis Fatigue
Heijerman et al.,[24] (2019)	Phase 3	Multi-centre, randomised, double-blind, active-controlled trial	113	Homozygous	Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours/ elexacaftor 200 mg once daily	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Cough Nasopharyngitis Oropharyngeal pain Upper respiratory tract infection Headache Hemoptysis
Sutharsan et al.[25] (2022)	Phase 3	Randomized, phase3b controlled trials	176	Homozygous	Tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours/ elexacaftor 200 mg once daily	Tezacaftor 100 mg once daily/ ivacaftor 150 mg every 12 hours	Headache, nazopharyngitis, cough, oropharyngal pain

CF: cystic fibrosis, CPK: creatine phosphokinase

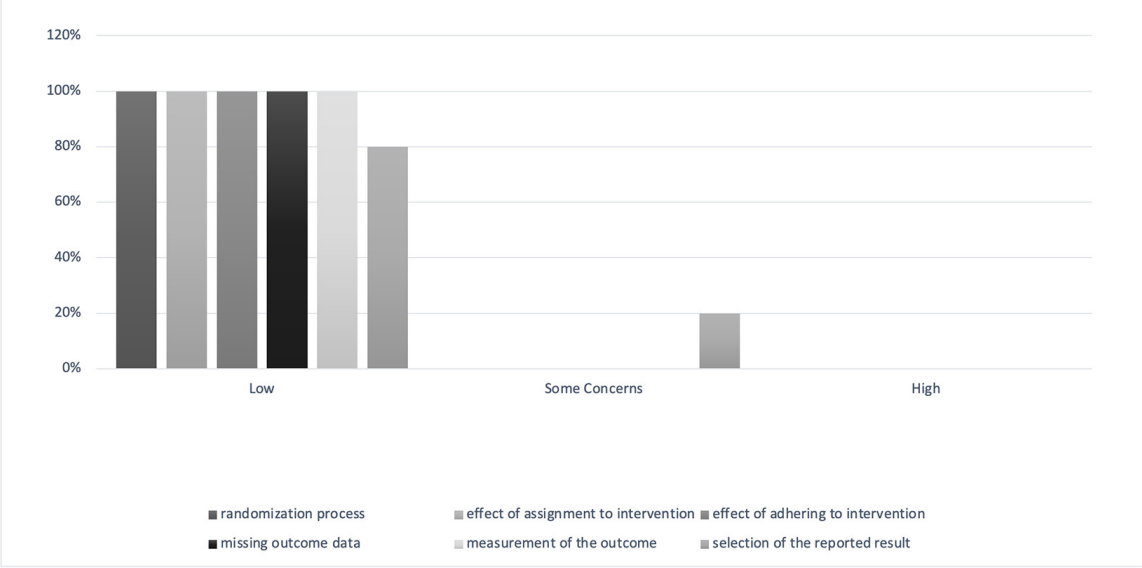

Figure 2. Risk of bias judgement of five included randomized studies by using RoB 2; a revised Cochrane risk-of-bias tool for randomized trials

RoB 2: Risk of Bias 2

was found to be 0.4±1.9 for TEZ/IVA and 10.4±1.8 for ELX/TEZ/IVA. A significant difference in FEV1 levels was observed, with a least square mean change of 10 units from baseline. Similarly, Sutharsan et al.,[25] investigated the effects of TEZ/IVA and ELX/TEZ/IVA on homozygous F508del CF patients at week 24. The change in the percentage of the predicted FEV1 mean value was 1.2±3% for TEZ/IVA and 11.2±1.4% for ELX/TEZ/IVA. The least squares mean change in FEV1 from baseline was 10.2. In the study by Donaldson et al.,[9] homozygous F508del CF patients were assessed at week 4. The TEZ/IVA group showed a change in the mean percentage of predicted FEV1 value of 3.61±1.39.

Sweat Chloride Concentration

For heterozygous F508 del CF patients, Taylor-Cousar et al.[21] reported, at a time point of 24 weeks, the mean sweat chloride level was 101.3±10.9 and the least mean square change was reported to be -10.1 for TEZ/IVA. At a time point of 8 weeks, Rowe et al.[12] reported the mean sweat chloride level was 64.1 (28.9) mmol/liter with a least squares mean change of -9.5 for TEZ/IVA treatment. At a time point of 12 weeks, Donaldson et al.[9] reported that the mean sweat chloride levels were 100.6 (13.0) mmol/liter for TEZ/IVA and the least square mean change was -3.5 for TEZ/IVA. For the ELX/TEZ/IVA treatment, Middleton et al.[23] reported a least square mean change from baseline of -41.8 for a period of 24 weeks. The findings from these studies indicate that while both TEZ/IVA and ELX/TEZ/IVA treatments have shown improvements in sweat chloride levels, ELX/TEZ/IVA demonstrated significant improvement over TEZ/IVA.

In the study conducted by Heijerman et al.[24] homozygous F508del CF patients were assessed at week 4; sweat chloride levels showed an average of 90.0±12.3 mmol/litre for TEZ/IVA, while ELX/TEZ/IVA exhibited 91.4±11.0 mmol/litre. The least square mean change in sweat chloride levels was found to be -45.1. Similarly, Sutharsan et al.[25] reported that sweat chloride levels were 89.8±11.7 mmol/litre for TEZ/IVA and 89.0±12.2 mmol/litre for ELX/TEZ/IVA, with a least square mean change of -42.8. In the study conducted by Donaldson et al.[9], sweat chloride levels for TEZ/IVA were 52.9±19.6 mmol/litre, with a least squares mean change value of -7.02. This also suggests that treatment with ELX/TEZ/IVA shows clinically better results in the case of homozygous F508del CF patients.

CFQ-R RD Score

For heterozygous F508 del CF patients, Taylor-Cousar et al.[21] reported that the CFQ-R RD score for TEZ/IVA was 70.1±16.8 and the least square mean change in the CFQ-R RD score for TEZ/IVA was 5.1, indicating an improvement from baseline for TEZ/IVA treatment. Similar results were reported by Rowe et al.,[12] and Donaldson et al.,[9] who showed that the least square mean change in the CFQ-R RD score for TEZ/IVA was 11.1 and 2.1, respectively. Both studies reported that the TEZ/IVA treatment proved to be efficacious. Notably, Middleton et al.[23] reported a CFQ-R RD score of 68.3±16.9 and a least squares mean of 20.1 for the ELX/TEZ/IVA treatment, which demonstrated better results than TEZ/IVA.

For homozygous F508del CF patients, Heijerman et al.[24] reported that the CFQ-R RD scores were 72.6±17.9 and 70.6±16.2 for TEZ/IVA and ELX/TEZ/IVA, respectively, with a least square mean change of 17.4. Sutharsan et al.[25] showed that TEZ/IVA exhibited a mean score of 73.1±17.6, while ELX/TEZ/IVA had a score of 71.2±19.6. The least square mean change in CFQ-R RD score was 17.1. Donaldson et al.[9] reported that the least-squares mean change for CFQ-R RD scores was 3.79. Collectively, the results show that the ELX/TEZ/IVA regimen is a better alternative to TEZ/IVA regimen.

Table 2. Comparative analysis of FEV1 levels, sweat chloride levels, CFQ-R RD and their respective changes from baseline in heterozygous F508 del CF patients

Author, year	Time of assessment (week)	Absolute change from baseline in percentage of predicted FEV1-percentage points. treatment (Symdeko)	Absolute change from baseline in percentage of predicted FEV1-percentage points. (Placebo)	Absolute change from baseline in percentage of predicted FEV1 mean value treatment (Trikafta)	Least square mean change (95% CI) in FEV1 (difference from baseline)	Absolute change from baseline in sweat chloride (mmol/liter) treatment (Symdeko)	Absolute change from baseline in sweat chloride (mmol/liter) treatment (Placebo)	Absolute change from baseline in sweat chloride (mmol/liter) treatment (Trikafta)	Least square mean change (95% CI) in sweat chloride (difference)	Absolute change from baseline in CFQ-R RD score (Symdeko)	Absolute change from baseline in CFQ-R RD score (Placebo)	Absolute change from baseline in CFQ-R RD score (Trikafta)	Least square mean change (95% CI) in CFQ-R RD score (difference)	Conclusion
Taylor-Cousar et al.,[21] (2017)	24	3.4±0.7	-0.6±0.7	NA	4	-9.9±1	0.2±1	NA	-10.1	5±1.5	-0.1±1.5	NA	5.1	The combination of TEZ/IVA was efficacious and safe
Rowe et al.,[12] (2017)	8	11.1±2.4	4.7±1	NA	6.8	-9.5±2.2	-4.5±2.2	NA	-9.5	11.1±2.4	9.7±2.5	NA	11.1	TEZ/IVA therapy was efficacious
Munck et al.,[22] (2020)	12	1±1.2	-0.1±1.2	NA	1.2	-4.7±1.9	-1.2±1.9	NA	-3.5	5.9±1.2	-0.1±1.2	NA	2.1	TEZ/IVA was efficacious and safe
Middleton et al.,[23] (2019)	24	NA	-0.4±1.1	13.9±1.1	14.3	NA	-0.4±1.8	-42.2±1.8	-41.8	NA	-2.7±1.9	17.5±1.9	20.1	ELX/TEZ/IVA was efficacious in patients with CF

CI: confidence interval, ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor, CF: cystic fibrosis, NA: not applicable, FEV1: forced expiratory volume in one second, CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain

Meta-analysis for FEV1, Sweat Chloride and CFQ-R RD Score

Results showed that the mean change from the baseline level of FEV1 in patients who were heterozygous for the F508 deletion was significantly greater (P = 0.0123) in the Symdeko treated group, compared to the placebo treated group, with an overall effect size, Z=2.5040, and a pooled mean difference of 3.83 [95% confidence interval (CI): 0.83; 6.82] (Figure 3). The data were found to be significantly heterogeneous (I^2=99%; P < 0.01) with overall effect size, Z=-0.6479; P = 0.517. On the other hand, a significant increase in the mean absolute change from baseline value of FEV1 was observed in patients heterozygous for the F508 deletion treated with Trikafta, as compared to placebo-treated patients, with overall effect size Z=130.483, P < 0.001 (Figure 4).

In patients homozygous for the F508 deletion, the mean change from baseline value of FEV1 was found to be significantly increased in patients treated with Symdeko as compared to the placebo-treated group (Figure 5) with overall effect size, Z=11.2006; P< 0.0001. Furthermore, a significantly lower mean difference from baseline in the value of FEV1 level was observed in patients homozygous for the F508 deletion after treatment with Symdeko, compared to Trikafta, with an overall effect size of Z=-39.7555, P < 0.0001. The data was found to be homogeneous (I^2=0%; P = 1.00), with a pooled mean difference of -10.00 (95% CI: -10.49; -9.51) (Figure 6).

The mean change from the baseline value of sweat chloride was found to be significantly (P = 0.0019) decreased in patients heterozygous for the F508 deletion receiving Symdeko compared to the group receiving placebo, with an overall effect size, Z=-3.1003, and a pooled mean difference of -6.21 (95% CI: -10.14; -2.28). The data were found to be significantly heterogeneous with I^2=100%, P < 0.01 (Figure 7). The mean absolute change in sweat chloride from baseline was found to be significantly lower in patients with heterozygous for F508 deletion receiving Trikafta compared to placebo (Figure 8), with overall effect size: Z=-233.0850; P < 0.0001.

In patients with a homogeneous genotype for F508 deletion, a significant increase in the mean difference from baseline of sweat chloride was observed after treatment with Symdeko compared to placebo (Figure 9), with overall effect size, Z=26.7201, P < 0.0001. There was a significantly higher mean change from baseline sweat chloride values in patients homozygous for the F508 deletion receiving Symdeko compared to Trikafta, with a pooled mean difference of 43.88 (95% CI: 41.63, 46.13) (Figure 10) and overall effect size, Z=38, P = 0.9673. The data were found to be homogeneous; I^2=0%; P = 0.45.

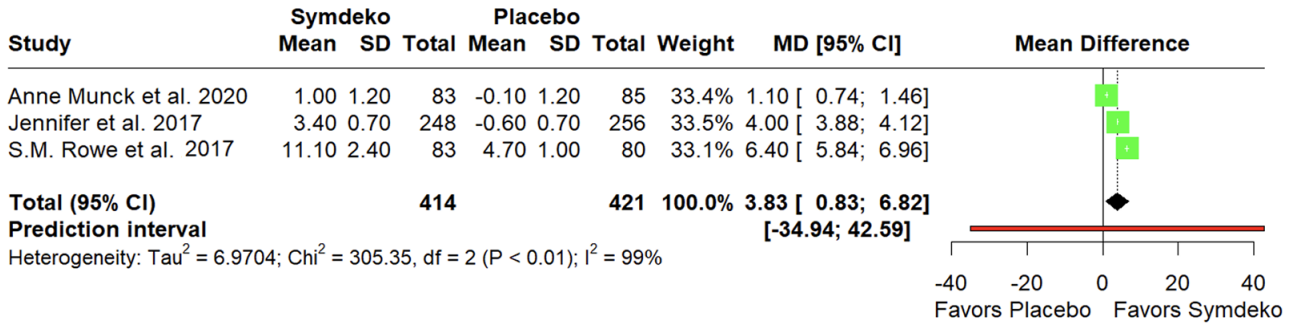

Figure 3. No significant mean difference in FEV1 level was observed in patients with heterogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

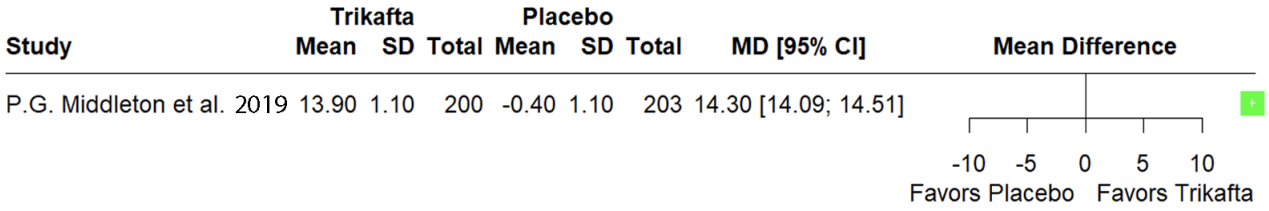

Figure 4. Significant mean difference in absolute change in FEV1 level from baseline was observed in patients with heterogenous for F508 deletion receiving Trikafta compared to placebo

SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

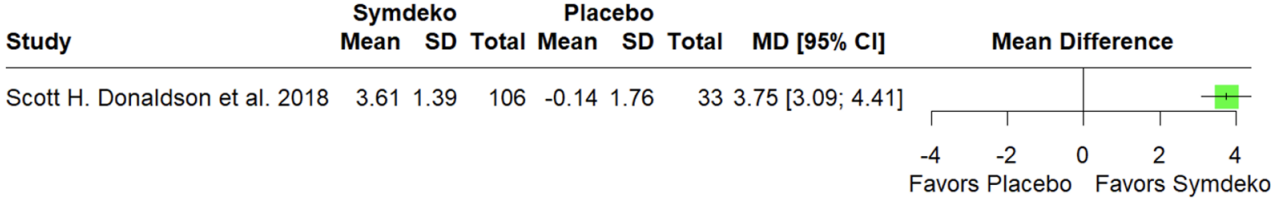

Figure 5. No significant mean difference in FEV1 level was observed in patients with homogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

In patients heterozygous for F508 deletion receiving Symdeko, the mean change from baseline in CFQR value was found to be significantly increased compared to placebo, with an overall effect size, Z=2.9937, $P = 0.0028$, and a pooled mean difference of 4.19 (95% CI: 1.45; 6.93) (Figure 11). The data was found to be homogeneous (I^2=0%; $P = 0.46$) with overall effect size, Z=0.4164; $P = 0.6771$. Furthermore, a significant increase in the mean absolute change of CFQR in patients receiving Trikafta from baseline was observed compared to placebo (Figure 12), with overall effect size, Z=106.7108; $P < 0.001$.

In patients homozygous for F508 deletion, the mean change from baseline value of CFQR was found to be significantly increased in patients receiving Trikafta, compared to Symdeko, with pooled mean difference of -16.52 (95% CI: -17.97; -15.07) (Figure 13) and overall effect size=-22.3503, $P < 0.0001$. The data was found to be heterogeneous (I^2=65%, $P = 0.09$).

Adverse Events

Each study included in the review evaluated the adverse events experienced by the participants during the respective treatment interventions. In a phase 3 randomized, double-blind, multicenter, placebo-controlled trial conducted by Taylor-Cousar et al.[21] adverse events were observed in the treatment group of heterozygous F508del patients receiving TEZ 100 mg once daily and IVA 150 mg every 12 hours. The reported adverse events included infective pulmonary exacerbation of CF, cough, headache, nasopharyngitis, increased sputum production, pyrexia, hemoptysis, oropharyngeal pain, and fatigue. Similar adverse events were reported by Rowe et al.[12], who conducted a phase 3 trial involving heterozygous F508del patients receiving TEZ and IVA. In a similar study conducted by Munck et al.,[22] with heterozygous F508del patients receiving TEZ and IVA, the reported adverse events included cough, fatigue, hemoptysis, and increased sputum production. Middleton et al.[23] evaluated the triple combination treatment and reported

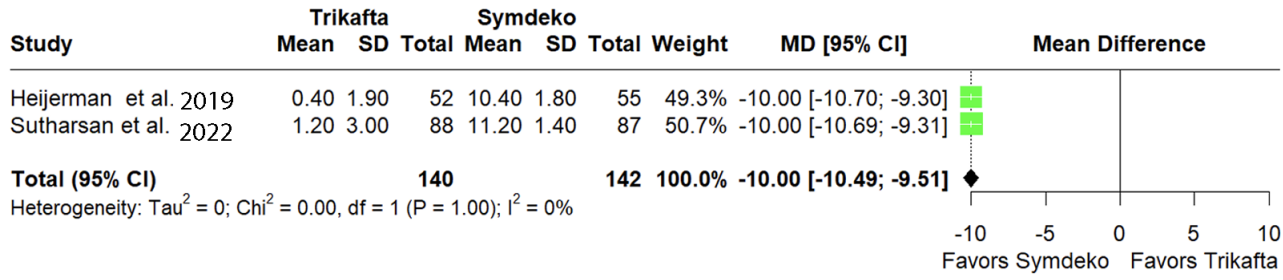

Figure 6. No significant mean difference in FEV1 level was observed in patients with homogenous for F508 deletion receiving Symdeko or Trikafta

SD: standard deviation, CI: confidence interval, FEV1: forced expiratory volume in one second, MD: mean difference

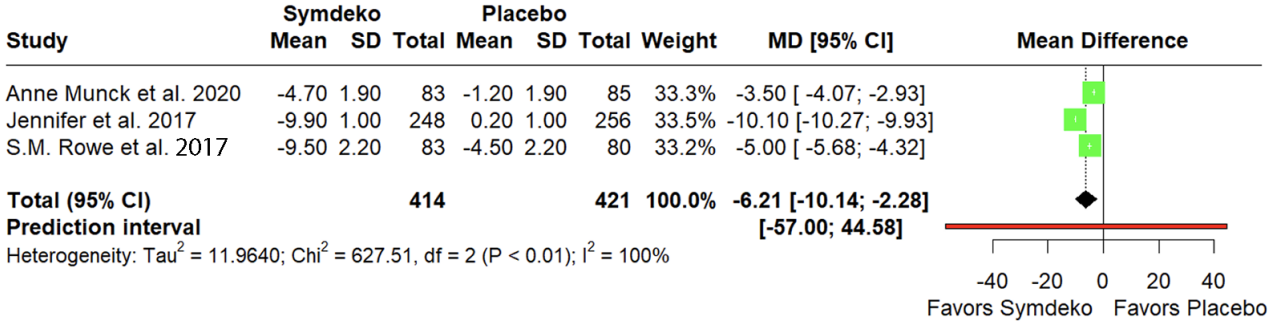

Figure 7. Significant mean difference in sweat chloride level was observed in patients with heterogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, MD: mean difference

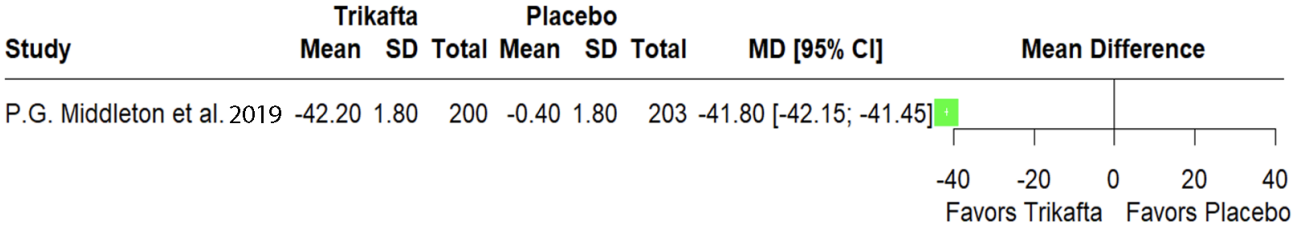

Figure 8. Significant mean difference in absolute change in sweat chloride level from baseline was observed in patients with heterogenous for F508 deletion receiving Trikafta compared to placebo

SD: standard deviation, CI: confidence interval, MD: mean difference

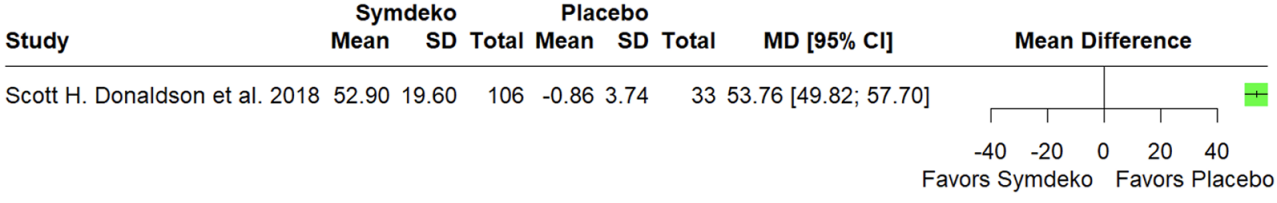

Figure 9. Significant mean difference in sweat chloride level was observed in patients with homogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, MD: mean difference

an increase in sputum production, as well as the occurrence of headache, cough, diarrhea, upper respiratory tract infection, nasopharyngitis, oropharyngeal pain, hemoptysis, and fatigue.

In the phase 2 randomized, placebo-controlled study by Donaldson et al.[9], adverse events were observed in the homozygous F508del patient group receiving TEZ and IVA. These adverse events included infective pulmonary

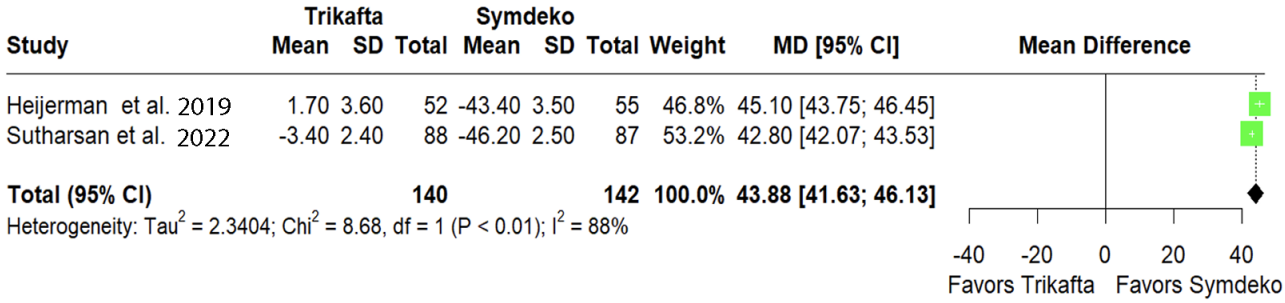

Figure 10. Significant mean difference in sweat chloride level was observed in patients with homogenous for F508 deletion receiving Symdeko or Trikafta

SD: standard deviation, CI: confidence interval

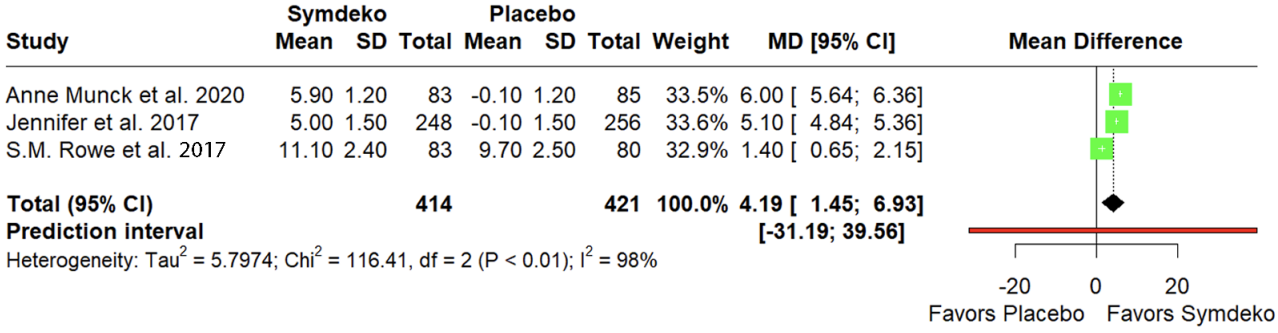

Figure 11. Significant mean difference in CFQ-R level was observed in patients with heterogenous for F508 deletion receiving Symdeko or placebo

SD: standard deviation, CI: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, MD: mean difference

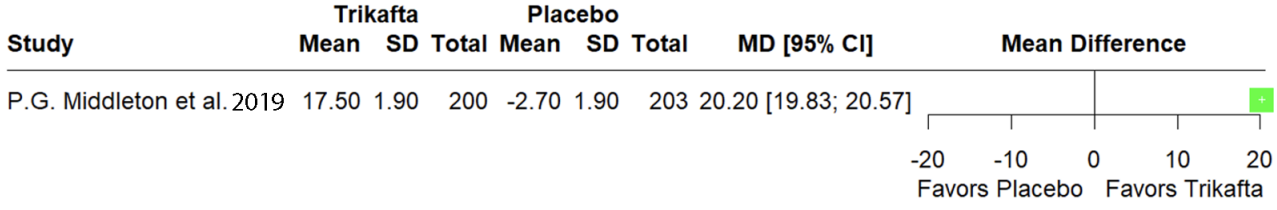

Figure 12. Significant mean difference in absolute change in CFQ-R level from baseline was observed in patients with heterogenous for F508 deletion receiving Trikafta compared to placebo

SD: standard deviation, CI: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised

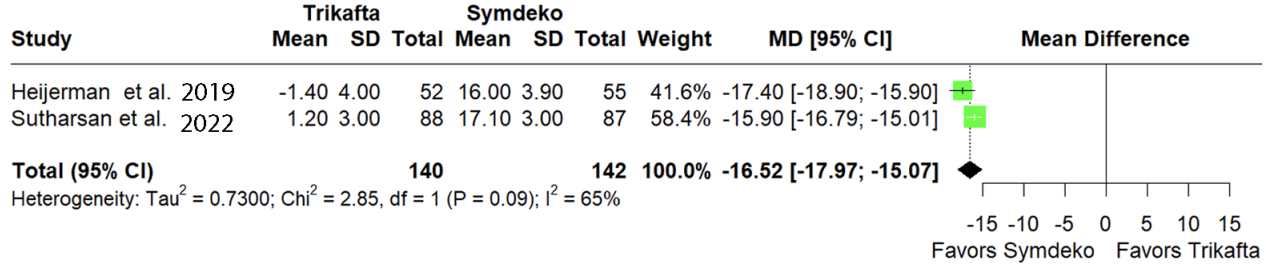

Figure 13. Significant mean difference in CFQ-R level was observed in patients with homogenous for F508 deletion receiving Symdeko or Trikafta

SD: standard deviation, CI: confidence interval, CFQ-R: Cystic Fibrosis Questionnaire-Revised, MD: mean difference

exacerbation of CF, cough, headache, increased sputum, fatigue, nausea, and diarrhea. Heijerman et al.[24] conducted a phase 3 multicentre trial to test triple combination therapy of TEZ, IVA, and ELX. The adverse events included cough, nasopharyngitis, oropharyngeal pain, upper respiratory tract infection, headache, and hemoptysis. Similarly, Sutharsan et al.[25] reported headache, nasopharyngitis, cough, oropharyngeal pain.

Table 3. Comparative analysis of FEV1 levels, sweat chloride levels, CFQ-R RD and their respective changes from baseline in homozygous F508 del cystic fibrosis patients

Author, year	Time of assessment (week)	Absolute change from baseline in percentage of predicted FEV1 mean value treatment (Symdeko)	Absolute change from baseline in percentage of predicted FEV1 mean value treatment (Trikafta)	Least square mean change (95% CI) in FEV1 (difference from baseline)	Absolute change from baseline in sweat chloride (mmol/litre) treatment (Symdeko)	Absolute change from baseline in sweat chloride (mmol/litre) treatment (Trikafta)	Least square mean change (95% CI) in sweat chloride (difference)	Absolute change from baseline in CFQ-R RD score (Symdeko)	Absolute change from baseline in CFQ-R RD score (Trikafta)	Least square mean change (95% CI) in CFQ-R RD score (difference)	Conclusion
Heijerman et al.,[24] (2019)	4	0.4±1.9	10.4±1.8	10	1.7±3.6	-43.4±3.5	-45.1	-1.4±4	16±3.9	17.4	ELX/TEZ/IVA provided clinically robust benefit vs. TEZ/IVA alone with a favourable safety profile
Sutharsan et al.[25] (2022)	24	1.2±3	11.2±1.4	10.2	-3.4±2.4	-46.2±2.5	-42.8	1.2±3	17.1±3	17.1	ELX/TEZ/IVA improved lung function and quality of life
Donaldson et al.,[9] (2018)	4	3.61±1.39	NA	3.61	52.9±19.6	NA	-2.63	NA	NA	3.79	Improved lung function in TEZ/IVA regimen

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain, CI: confidence interval, NA: not applicable, ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor, FEV1: forced expiratory volume in one second

Table 1 summarizes baseline characteristics, dosage, and adverse events reported in the included studies. Table 2 shows comparative analysis of FEV1 levels, sweat chloride levels, CFQ-R RD scores and their respective changes from baseline in heterozygous F508 del CF patients, while Table 3 depicts the same for homozygous F508 del CF patients.

DISCUSSION

The present systematic review aimed to evaluate the comparative effects of TEZ/IVA and ELX/TEZ/IVA on FEV1 levels, sweat chloride concentration, and CFQ-R RD scores, in patients with heterozygous and homozygous F508del CF.

Recent studies comparing the new ELX/TEZ/IVA regimen with older regimens have reported significantly better efficacy of ELX/TEZ/IVA therapy. A recent study on the assessment of blood proteome in patients treated with lumacaftor/IVA (LUM/IVA) vs. ELX/TEZ/IVA therapy reported that ELX/TEZ/IVA is more effective in regulating innate-immune responses, resulting in decreased inflammation both in the airways and throughout the body. This decrease in systemic and airway inflammation is crucial because chronic inflammation contributes significantly to disease progression in CF, exacerbating tissue damage and promoting recurrent infections. By attenuating inflammation more effectively than LUM/IVA or TEZ/IVA, ELX/TEZ/IVA presents a dual benefit in both correcting CFTR function and reducing the inflammatory burden.[26]

The studies included in the present meta-analysis have shown that ELX/TEZ/IVA produces improvements in FEV1 (typically 10-14% increases from baseline), which is greater than the FEV1 improvements achieved with TEZ/IVA alone (approximately 4-6% increases from baseline).[23] This improvement in lung function reflects not only enhanced chloride ion transport but also a likely reduction in mucus viscosity and an overall improvement in airway clearance. Additionally, ELX/TEZ/IVA has been linked to notable reductions in pulmonary exacerbations, hospitalizations, and antibiotic use, highlighting its efficacy in mitigating respiratory complications commonly experienced by CF patients.[24]

Another critical measure in CF therapy efficacy is the reduction in sweat chloride levels, which serves as a direct indicator of CFTR function. ELX/TEZ/IVA achieves an average decrease in sweat chloride levels of around 40-45 mmol/L, considerably greater than the 30 mmol/L reduction typically observed with TEZ/IVA therapy.[21] This larger absolute decrease in sweat chloride corroborates the higher efficacy of ELX/TEZ/IVA in addressing the underlying CFTR defect and aligns with its broader clinical benefits.

In the current study, ELX/TEZ/IVA appears to have a greater impact on sweat chloride reduction and FEV1 levels compared to TEZ/IVA, as indicated by the larger absolute changes reported in the studies. The observed improvements in CFQ-R scores with TEZ/IVA and ELX/TEZ/IVA treatments indicate the beneficial impact of these treatments on the patients' respiratory well-being. While both treatments showed improvements, ELX/TEZ/IVA demonstrated slightly better results in the studies reviewed.

The findings from these clinical trials indicate that the combination therapies of TEZ, IVA, and ELX are generally well-tolerated across diverse patient populations, including those homozygous and heterozygous for the F508del mutation. While adverse events such as cough, nasopharyngitis, fatigue, and headache were frequently reported, they were largely manageable and consistent with the underlying respiratory manifestations of CF. General symptoms like fatigue and headache were consistently noted across trials, alongside occasional reports of pyrexia, which were also manageable. Hemoptysis, a serious but less frequent event, was reported in several studies, along with oropharyngeal pain and nasal congestion. While most trials showed similar profiles of adverse events, variations in their frequency were observed depending on the phase of the study, sample size, and whether the patients were homozygous or heterozygous for the F508del mutation. Three studies reported the incidence of infective pulmonary exacerbation of CF for which the physicians should prescribe necessary medications. The similarity in adverse event profiles across study phases and populations suggests that both therapies have a predictable and manageable safety profile. However, the presence of gastrointestinal symptoms like nausea and diarrhea in some trials highlights the need to further explore strategies to mitigate these effects. Overall, the results support the use of these therapies as an effective treatment option for CF.

The observed differences in the effects of TEZ/IVA and ELX/TEZ/IVA on FEV1 levels in heterozygous F508del CF patients may be attributed to variations in the mechanisms of action and drug compositions. TEZ/IVA, which combines IVA and TEZ, has shown consistent improvements in FEV1 levels across multiple studies. This may be due to the dual action of IVA on the gating defect caused by the G551D mutation and the residual function mutation caused by the F508del allele.[27] TEZ, on the other hand, acts as a corrector by improving CFTR protein processing and trafficking. ELX/TEZ/IVA, a combination therapy containing ELX, TEZ, and IVA, has demonstrated superior efficacy in improving FEV1 levels compared to TEZ/IVA. This may be attributed to the additional action of ELX, which is a potent corrector that enhances the processing and trafficking of CFTR proteins. The presence of ELX in ELX/TEZ/IVA may provide a more comprehensive and effective treatment approach, leading to greater improvements in lung function.

The observed differences in the effects of TEZ/IVA and ELX/TEZ/IVA on FEV1 levels, sweat chloride concentration, and CFQ-R RD scores in patients with F508del CF may be attributed to variations in their compositions, mechanisms of action, and the presence of additional components in ELX/TEZ/IVA. ELX/TEZ/IVA with its triple combination therapy provides greater improvements in lung function and sweat chloride reduction compared to TEZ/IVA, particularly in heterozygous F508del CF patients. However, both treatments demonstrate positive effects in improving the respiratory symptoms and quality of life of CF patients.

The present systematic review has some limitations that should be considered when drawing conclusions. The effects of ELX/TEZ/IVA were not fully reported in all studies. Further studies on ELX/TEZ/IVA regimens are needed to ensure concrete results. Moreover, the duration of treatment varied among the included studies, ranging from short-term evaluations to longer-term assessments. The limited availability of long-term data restricts our understanding of the sustained benefits or potential adverse effects associated with the different treatment options. The number of trials comparing head-to-head ELX/TEZ/IVA to TEZ/IVA is few. Some aspects such as emotional adverse effects should be further studied as this aspect was not compared between the two drugs Further research with extended follow-up periods is necessary to better evaluate the long-term efficacy and safety profiles of these treatments.

CONCLUSION

The systematic review demonstrates that both TEZ/IVA and ELX/TEZ/IVA have shown improvements in FEV1 levels, sweat chloride levels, and CFQ-R RD scores in homozygous F508del CF patients. ELX/TEZ/IVA consistently exhibited significant improvements across all measured parameters. For both heterozygous and homozygous F508del CF patients, TEZ/IVA and ELX/TEZ/IVA demonstrated positive impacts on lung function, with ELX/TEZ/IVA showing slightly better results. Further research with larger sample sizes, standardized study designs, and longer-term follow-up is needed to confirm these findings and gain a more comprehensive understanding of the comparative effectiveness and safety profiles of these treatments.

Ethics

Footnotes

Authorship Contributions

Concept: M.A.K., Design: M.A.K., Data Collection or Processing: K.H., Analysis or Interpretation: S.K., A.G., Literature Search: K.H., Writing: S.K., A.G.

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Click the link to access Supplementary Tables 1, 2: https://d2v96fxpocvxx.cloudfront.net/bda9171a-fae8-4995-8276-2138323f1e16/content-images/06d4a882-a811-492f-9830-555dfe690a9f.pdf

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Letter to the Editor

Comment on: Enhancing Pneumococcal Vaccination Rates Through Family Physicians: Addressing Challenges and Raising Awareness

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DEAR EDITOR,

A very informative article was published in the Thoracic Research and Practice in 2024 titled "Effectiveness of a program to raise awareness about pneumococcal vaccination among physicians and patients with chronic respiratory diseases: a multicenter cohort study".[1] This article highlights that increasing pneumococcal vaccination awareness among physicians and patients with chronic respiratory diseases can raise vaccination rates by up to 75%, thus reducing in-hospital mortality. Family physicians and health workers in Family Health Centers, where most vaccinations are administered, play a key role in this effort.

Pneumococcal vaccination is crucial in family medicine, especially for physicians in primary care. Pneumococcal infections pose a serious risk to those with weakened immune systems, the elderly, and young children, leading to severe diseases like pneumonia, meningitis, and bacteremia. In our country, family physicians administer the conjugated pneumococcal vaccine for free to individuals aged 65 and over. The polysaccharide pneumococcal vaccine is available by prescription to those in at-risk groups, covered by SSI through pharmacies.[2]

The pneumococcal vaccine is crucial for preventing infections, particularly in high-risk groups (over 65, those with chronic diseases, or weakened immune systems). By administering this vaccine and raising public awareness, family physicians play a key role in boosting community immunity, preventing disease spread, and easing the burden on the healthcare system.[3]

In recent years, anti-vaccination sentiment has threatened public health and reduced vaccination rates, including for pneumococcal vaccines. Family physicians can combat this by building communication with individuals, explaining the safety and importance of vaccines. Awareness campaigns by family physicians can effectively increase pneumococcal vaccination rates.[4]

Family physicians play a key role in healthcare for individuals aged 65 and over, yet the demand for free pneumococcal vaccines at family health centers remains low. To increase vaccination rates, awareness must be raised, public concerns addressed, and access to services improved. Training for healthcare workers on adult vaccination is essential, and anti-vaccination campaigns should be countered with media support. Public perception that vaccines are only for children must change, and family physicians should have adequate vaccine supplies, with logistical issues minimized. Vaccination information should be provided during healthcare visits, ensuring free access and availability at all health units.

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Footnotes

Authorship Contributions

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Letter to the Editor

Response to: Effectiveness of a Program to Raise Awareness About Pneumococcal Vaccination Among Physicians and Patients with Chronic Respiratory Diseases: A Multicenter Cohort Study

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DEAR EDITOR,

Regarding our article "Effectiveness of a program to raise awareness about pneumococcal vaccination among physicians and patients with chronic respiratory diseases: a multicenter cohort study" that was published in Thoracic Research and Practice in 2024, we have reviewed your letter to the editor.[1] We firmly believe that a vital part of this endeavor is played by family doctors and other medical staff at family health centers. Considering that vaccination is practiced in our nation, particularly in primary care, we think that raising awareness will result in a rise in vaccination rates and a drop in hospitalizations due to pneumonia. Given the importance of family doctors in family health centers at primary care, we appreciate MD. Uğraş and MD. Şimşek's[2] care and attention.

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