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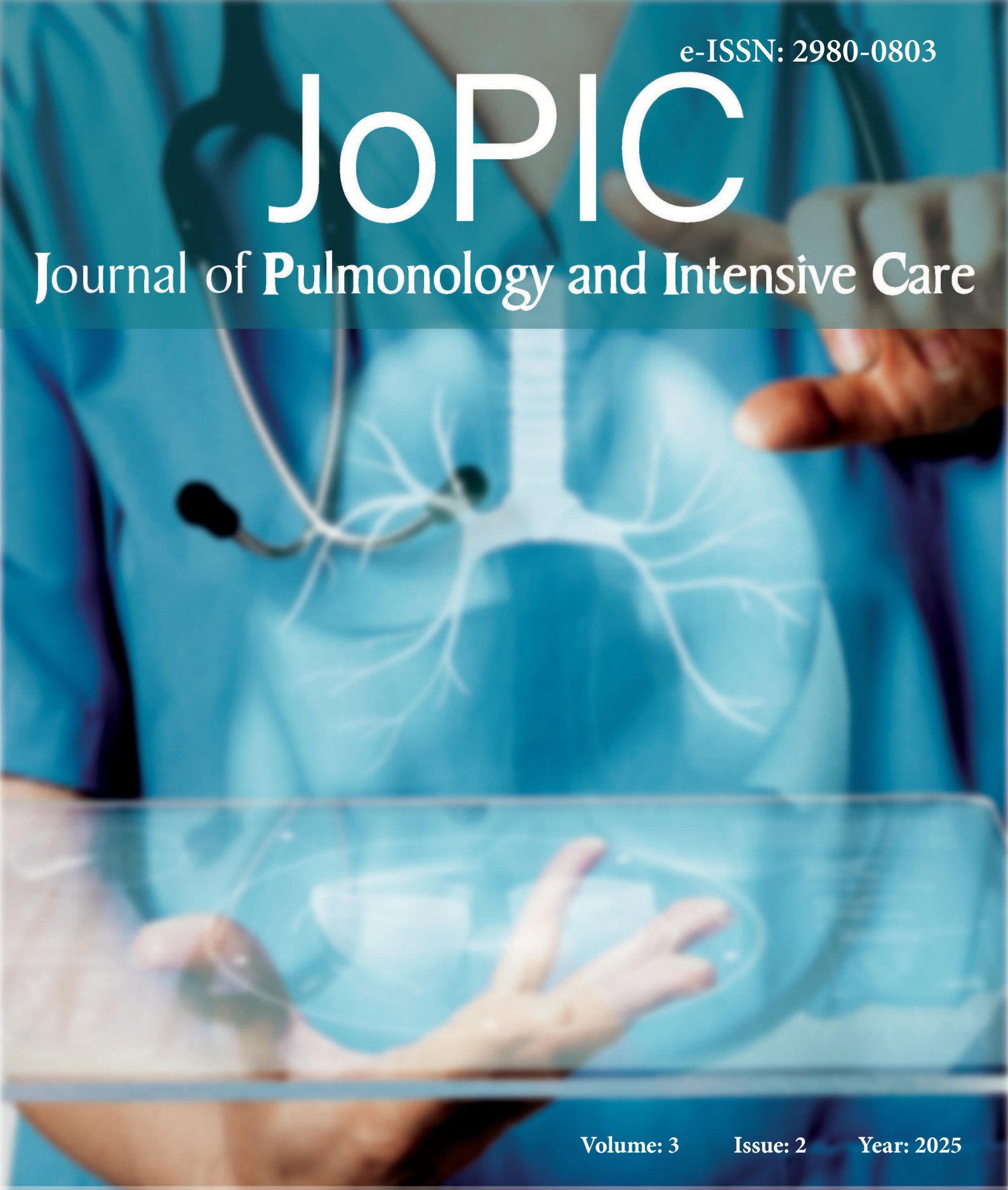

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The impact of coexisting metabolic syndrome on asthma control in patients diagnosed with asthma

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ABSTRACT

Aims: Asthma is a disease characterized by diffuse and reversible narrowing of the airways, affecting approximately 300 million people worldwide. Metabolic syndrome, on the other hand, is a fatal endocrinopathy that begins with insulin resistance. Numerous studies have investigated the impact of metabolic syndrome on airway inflammation in patients with asthma. In this study, we aimed to investigate the coexistence of metabolic syndrome in patients followed up with a diagnosis of asthma and its impact on asthma control using the asthma control test (ACT).

Methods: A total of 50 patients, including 10 men and 40 women aged between 18 and 70 years, who presented to the asthma outpatient clinic of Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital and were diagnosed with asthma, were included in the study. Participants completed a questionnaire assessing demographic characteristics and medical history. Subsequently, height, weight, waist circumference, and triceps skinfold thickness measurements were taken. Arterial blood pressure was measured, and blood samples were collected after 12 hours of fasting to evaluate serum triglyceride (TG), HDL, and fasting glucose levels, along with a complete blood count. Pulmonary function tests were performed, and participants responded to the short form of the International Physical Activity Questionnaire (IPAQ).

Results: Upon evaluation, 30% of the cases were diagnosed with metabolic syndrome. Metabolic syndrome was diagnosed in 40% of male and 27.5% of female patients. Among the 50 participants, 16 (32%) were diagnosed with obesity, 19 (38%) with hypertension, and 1 (2%) with diabetes mellitus. The average duration of asthma follow-up was calculated as 10.8±8.7 years. The prevalence of metabolic syndrome was found to be higher in postmenopausal women compared to premenopausal women, whereas among women using oral contraceptives, the diagnosis of metabolic syndrome was lower than in non-users; however, this was not statistically significant ($p>0.05$). However, waist circumference measurements were significantly higher in those with metabolic syndrome compared to those without ($p<0.05$). A significant association was found between serum TG levels and metabolic syndrome diagnosis, while no significant relationship was observed for fasting blood glucose and serum HDL levels. Both systolic and diastolic blood pressure values were found to be higher in individuals with metabolic syndrome, with a statistically significant association between blood pressure values and the diagnosis of metabolic syndrome. According to the ACT results, 4 patente (8%) were under control, 17 (34%) were partially controlled, and 29 (58%) were uncontrolled. Among patients with metabolic syndrome, the forced expiratory volume in 1 second (FEV_1) was found to be lower with borderline values. No significant association was found between physical activity levels and metabolic syndrome. Both groups, with and without metabolic syndrome, had low ACT scores, and no significant relationship was found between metabolic syndrome and ACT scores.

Conclusion: Nonetheless, based on the findings of this study, we believe that metabolic syndrome should also be considered when planning treatment for asthmatic patients.

Keywords: Asthma, metabolic syndrome, asthma control test

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways, characterized by recurrent symptoms such as wheezing, shortness of breath, chest tightness, and coughing, particularly during the night or early morning hours. These symptoms are associated with variable and often reversible airway obstruction. Affecting approximately 300 million individuals worldwide, the prevalence of asthma has increased—especially in Western countries—during the second half of the 20th century, making it a significant public health concern.[1]

Obesity is a major individual risk factor associated with the development of asthma. Studies have demonstrated that asthma is more prevalent among individuals with a high

body-mass index (BMI), and that obese individuals have a 2.7-fold higher risk of developing asthma compared to their non-obese counterparts.[1]

Since the early 20th century, cardiovascular diseases have ranked among the leading causes of morbidity and mortality in developed countries. In 1988, Dr. Gerald Reaven first introduced the concept of metabolic syndrome, characterized by a cluster of risk factors including insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol, and elevated triglyceride (TG) levels. Today, the World Health Organization (WHO) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) provide widely accepted clinical criteria for the diagnosis of metabolic syndrome.[2]

To diagnose metabolic syndrome, the presence of at least three of the following five criteria is required:

1. Abdominal obesity: Waist circumference >102 cm in men and >88 cm in women
2. Serum TG level: ≥150 mg/dl
3. HDL cholesterol level: <40 mg/dl in men and <50 mg/dl in women
4. Blood pressure: ≥130/80 mmHg
5. Fasting blood glucose: ≥110 mg/dl

The prevalence of metabolic syndrome increases with advancing age and weight gain, and may vary depending on the diagnostic criteria used and the characteristics of the studied population. According to the definition and data provided by the WHO, the prevalence of metabolic syndrome in the United States has been reported as 23.7% in the general population and 43.5% among individuals over 60 years of age.[3]

Beyond the increased risk of cardiovascular disease and diabetes, metabolic syndrome has also been associated with a higher prevalence of other conditions, including polycystic ovary syndrome, gallstones, asthma, sleep disorders, and certain types of cancer.[4]

Obesity has also been identified as a risk factor for asthma.[5] Studies have demonstrated that individuals with higher BMI are more likely to develop asthma, with obese individuals showing a 2.7-fold increased risk compared to their non-obese counterparts.[1] Moreover, certain mediators such as leptin may influence airway function and contribute to increased susceptibility to asthma.[6]

Studies conducted on animal models have demonstrated that a high-cholesterol diet can exacerbate allergic airway inflammation. For instance, in one study, mice fed a high-cholesterol diet exhibited increased eosinophil counts in bronchoalveolar lavage fluid, elevated interleukin-5 levels, and upregulation of other pro-inflammatory markers. Moreover, it was reported that statin therapy attenuated this inflammatory response.[7]

To assess asthma control, clinical guidelines recommend using criteria such as symptom frequency, use of rescue medications, and impact on daily activities. Based on these, a five-item questionnaire known as the asthma control test (ACT) has been developed. The ACT demonstrates low sensitivity but high specificity at lower cut-off scores. Its reliability and validity have been established.[5,6] The ACT comprises five questions evaluating daytime and nighttime symptoms, rescue medication use, and the degree to which asthma interferes with daily life. Each item is scored on a scale from 0 to 5, with the total score ranging from 5 to 25. A score of 25 indicates well-controlled asthma; scores between 20 and 24 suggest partially controlled asthma; and a score of 19 or below reflects poorly controlled asthma.[8]

The aim of this study was to investigate the presence of metabolic syndrome in patients diagnosed with asthma and to evaluate its effect on asthma control using the ACT.

METHODS

Ethics

This article is derived from a thesis study before 2020 (Project No: 832904) and was conducted with institutional approval. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

Study Design and Participants

The study included 50 patients (10 males, 40 females) aged between 18 and 70 years who had been diagnosed with asthma. Inclusion criteria comprised: a diagnosis of asthma according to the Global Initiative for Asthma (GINA) 2010 guidelines, compatible pulmonary function test (PFT) results, no history of smoking more than 10 pack-years, absence of comorbidities requiring steroid therapy, no signs of respiratory failure, non-pregnancy status in female participants, and absence of additional diseases that could affect metabolic rate (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism).

Data Collection

Patients with an anamnesis consistent with a diagnosis of asthma underwent PFT in the respiratory function laboratory. The measured parameters included forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), the FEV1/FVC ratio, and the forced expiratory flow during the 25–75% portion of the forced vital capacity (FEF 25–75). A reversibility test was also performed. The diagnosis of asthma was established based on the criteria of the GINA guidelines.

Subsequently, a structured questionnaire was administered to collect data on sex, age, place of birth, occupation, family and allergy history, smoking status, menopausal status, weight status between ages 0–15, presence of comorbid conditions, asthma treatment history, and oral contraceptive (OC) use in female participants.

Blood samples were collected from patients who completed the questionnaire after a 12-hour fasting period to evaluate TG, HDL cholesterol, glucose, and complete blood count

(CBC) parameters. Height and weight measurements were recorded to calculate BMI. Waist circumference was measured at the midpoint between the lower margin of the 12th rib and the top of the iliac crest. Arterial blood pressure was measured using a standard manual sphygmomanometer with a cuff, and triceps skinfold thickness was also assessed.

Following the collection of all relevant data, the ACT was administered. ACT scores were interpreted as follows: a score of 25 indicated well-controlled asthma, scores between 20–24 indicated partially controlled asthma, and scores ≤19 indicated uncontrolled asthma. In addition, the International Physical Activity Questionnaire (IPAQ-short form) was used to assess the physical activity levels of the participants.

Statistical Analysis

Data analysis was performed using SPSS for Windows version 11.5. Descriptive statistics were expressed as mean±standard deviation or median (minimum–maximum) for continuous variables, and as frequencies and percentages for categorical variables. Patients who met at least three of the metabolic syndrome criteria were classified as having metabolic syndrome; those who did not were classified as not having metabolic syndrome. Comparisons between groups were conducted using the Mann–Whitney U test, T-test, and Chi-square test, as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 50 patients included in the study, 20% were male and 80% were female. Metabolic syndrome was identified in 4 of the male patients (26.7% of those diagnosed with metabolic syndrome) and in 11 of the female patients (73.3% of those diagnosed with metabolic syndrome). Overall, 15 patients (30%) were diagnosed with metabolic syndrome (**Figure**).

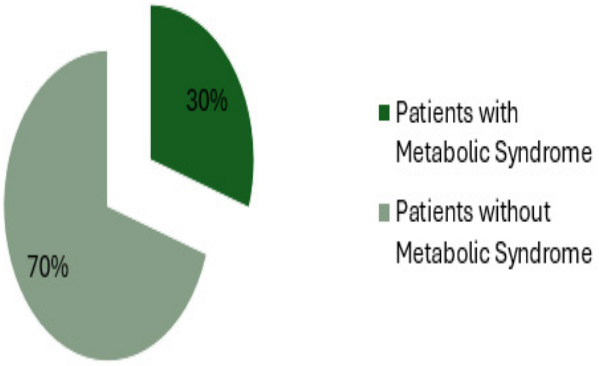

Figure. Rate of metabolic syndrome in patients

Among female patients, the mean height was 161.2±6.2 cm, mean weight was 75.2±12.5 kg, and mean BMI was 28.6±4.6 kg/m². For male patients, the mean height was 170.2±6.8 cm, mean weight was 71.7±15.9 kg, and mean BMI was 24.8±5.3 kg/m². No statistically significant association was found between BMI and the presence of metabolic syndrome (p=0.126).

When evaluating family history, 60% of the patients reported a family history of asthma. Among those diagnosed with metabolic syndrome, 73.3% had a positive family history of asthma (**Table 1**). However, when comparing the presence or absence of metabolic syndrome with family history, no statistically significant relationship was found (p>0.05).

Table 1. Distribution of patients by family history and presence of metabolic syndrome

	Metabolic syndrome		
	Present	**Absent**	**Total (N)**
Present (n)	11 (73.3%)	19 (54.3%)	30 (60%)
Absent (n)	4 (26.7%)	16 (45.7%)	20 (40%)
Total (N)	15	35	50

N: Total number of individuals, n: Number of individuals

Among the female patients diagnosed with metabolic syndrome, 45.5% were premenopausal and 54.5% were postmenopausal (**Table 2**). No statistically significant association was found between menopausal status and the presence of metabolic syndrome (p>0.05).

Table 2. Distribution of female cases according to menopausal status and metabolic syndrome

		Metabolic syndrome		Total	p
Menopausal status		**Present**	**Absent**		
Premenopause	Number	5	21	26	0.147
	Percentage of MS (%)	45.5	72.4	65	
Post menopause	Number	6	8	14	
	Percentage of MS (%)	54.5	27.6	35	
Total	Number	11	29	40	
	Percentage of MS (%)	100	100	100	

MS: Metabolic syndrome

Considering all participants, cigarette consumption was assessed in pack-years, with a mean value of 4.3±8.6 pack-years. Among patients with metabolic syndrome, the mean was 5.2±10.1 pack-years, while it was 4.0±8.0 pack-years in those without metabolic syndrome (**Table 3**). No statistically significant relationship was observed between cigarette consumption and the presence of metabolic syndrome (p>0.05).

Table 3. Distribution of cases according to mean cigarette consumption (pack/year)

Metabolic syndrome	**Number**	**Mean cigarette consumption value (±) (pack/year)**	**p**
Present	15	5.2±10.1	1.000
Absent	35	4.0±8.0	
Total	50	4.3±8.6	

Patients were also asked to self-report their body weight status (underweight, normal weight, overweight) during ages 0–15. Among those diagnosed with metabolic syndrome, 20% reported being underweight, 66.7% normal weight, and 13.3% overweight during childhood (**Table 4**). No statistically significant association was found between childhood weight status and the presence of metabolic syndrome (p>0.05).

The mean waist circumference was 98.4±20.6 cm in males and 95.1±15.0 cm in females. Among patients with metabolic syndrome, the mean waist circumference was 112.7±26.5

Table 4. Distribution of cases according to weight status between ages 0–15

Weight status in the 0–15 age range		Metabolic syndrome		Total	p
		Present	Absent		
Underweight	Number	3	13	16	0.474
	Percentage of MS (%)	20	37.1	32	
Normal weight	Number	10	17	27	
	Percentage of MS (%)	66.7	48.6	54	
Overweight	Number	2	5	7	
	Percentage of MS (%)	13.3	14.3	14	
Total	Number	15	35	50	
	Percentage of MS (%)	100	100	100	

MS: Metabolic syndrome

cm in males and 101.1±8.6 cm in females (**Table 5**). A statistically significant association was found between waist circumference and the presence of metabolic syndrome (p=0.011).

Tablo 5. Distribution of mean waist circumference values according to gender and metabolic syndrome diagnosis

Metabolic syndrome	Gender	Number	Mean waist circumference value (cm)
Present	Male	4	112.7±26.5
	Female	11	101.1±8.6
	Total	15	104.2±15.2
Absent	Male	6	88.8±8.4
	Female	29	92.9±14.4
	Total	35	92.2±13.5
Total	Male	10	98.4±20.6
	Female	40	95.1±13.5
	Total	50	98.8±15.0

The average triceps skinfold thickness was 41.0±6.9 mm in males and 45.4±7.4 mm in females. In patients diagnosed with metabolic syndrome, the mean triceps skinfold thickness was 45.0±5.7 mm in males and 47.0±7.2 mm in females (**Table 6**). No statistically significant relationship was found between triceps skinfold thickness and the presence of metabolic syndrome (p>0.05).

Table 6. Distribution of mean triceps skinfold thickness values according to gender and metabolic syndrome diagnosis

Metabolic syndrome	Gender	Number	Mean TSF (±)
Present	Male	4	45.0±5.7
	Female	11	47.0±7.2
	Total	15	46.5±6.7
Absent	Male	6	38.3±6.8
	Female	29	44.8±7.5
	Total	35	43.7±7.7
Total	Male	10	41.0±6.9
	Female	40	45.4±7.4
	Total	50	44.5±7.5

TSF: Mean triceps skinfold thickness

Among the patients diagnosed with metabolic syndrome, the mean serum TG level was 186.0±84.7 mg/dl, fasting blood glucose (FBG) level was 89.7±12.4 mg/dl, and mean serum HDL cholesterol level was 43.9±12.9 mg/dl (**Table 7**). A statistically significant association was observed between serum TG levels and the presence of metabolic syndrome (p=0.006), while no significant associations were found for FBG or HDL cholesterol levels (p>0.05).

Table 7. Distribution of mean triglyceride (TG), HDL, and fasting blood glucose (FBG) levels in patients with and without metabolic syndrome

Metabolic syndrome	Number (n)	Mean values (±SD)		
		TG (mg/dl)	HDL (mg/dl)	FBG (mg/dl)
Present	15	186.0±84.7	43.9±12.9	89.7±12.4
Absent	35	119.7±93.9	49.8±11.3	89.5±13.1
Total	50	139.6±95.4	48.0±12.0	89.5±12.7

SD: Standard deviation, HDL: High-density lipoprotein

The mean systolic blood pressure of males diagnosed with metabolic syndrome was 131.3±8.5 mmHg, and the mean diastolic pressure was 87.5±5.0 mmHg. For females with metabolic syndrome, the mean systolic blood pressure was 127.2±18.3 mmHg, and the mean diastolic pressure was 79.0±16.4 mmHg (**Table 8**). A statistically significant relationship was found between the presence of metabolic syndrome and both systolic and diastolic blood pressure values (p=0.008, p=0.044, respectively).

Table 8. Distribution of systolic and diastolic blood pressure in individuals with and without metabolic syndrome

Metabolic syndrome	Gender distribution	Number	Mean values (±SD)	
			Systolic (mmHg)	Diastolic (mmHg)
Present	Male	4	131.2±8.5	87.5±5.0
	Female	11	127.2±18.3	79.0±16.4
	Total	15	128.3±16.1	81.3±14.5
Absent	Male	6	120.0±13.7	73.3±10.3
	Female	29	115.8±13.7	74.6±11.6
	Total	35	116.5±13.6	74.4±11.2
Total	Male	10	124.5±12.7	79.0±11.0
	Female	40	119.0±15.7	75.8±13.0
	Total	50	120.1±15.2	76.5±12.6

SD: Standard deviation

The mean FEV_1 percentage in patients diagnosed with metabolic syndrome was 74.6±24.0%, the mean FEV_1/FVC ratio was 76.4±10.1, and the mean PEF percentage was 72.6±28.8. In patients without metabolic syndrome, these values were 75.9±16.6%, 75.6±13.0, and 70.7±18.4, respectively (**Table 9**). No statistically significant associations were observed between metabolic syndrome status and the mean values of FEV_1 percentage, FEV_1/FVC ratio, or PEF percentage (p>0.05).

Among female patients diagnosed with metabolic syndrome, 27.3% reported a history of OC use (**Table 10**). However, no significant relationship was found between metabolic syndrome status and OC use (p>0.05).

Table 9. Distribution of mean FEV_1 percentage, mean FEV_1/FVC ratio, and mean PEF percentage in individuals with and without metabolic syndrome

		Mean values (±SD)		
Metabolic syndrome	**Number**	**FEV_1 (%)**	**FEV_1/FVC**	**PEF (%)**
Present	15	74.6±24.0	76.4±10.1	72.6±28.6
Absent	35	75.9±16.6	75.6±13.0	70.7±18.4
Total	50	75.5±18.9	75.9±12.1	71.3±21.7

SD: Standard deviation, FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity

Table 10. Distribution of oral contraceptive use among female cases with and without a diagnosis of metabolic syndrome

			Metabolic syndrome		Total
			Present	**Absent**	
OC	Present	Number	3	7	10
		Percentage of MS (%)	27.3	24.1	25.0
	Absent	Number	8	22	30
		Percentage of MS (%)	72.7	75.9	75.0
Total		Number	11	29	40
		Percentage of MS (%)	100.0	100.0	100.0

OC: Oral contraceptive, MS: Metabolic syndrome

Regarding physical activity, 80% of patients with metabolic syndrome were classified as having low activity levels, and 20% had moderate activity levels (**Table 11**). No statistically significant association was found between physical activity status and metabolic syndrome diagnosis (p>0.05).

Table 11. Distribution of physical activity assessment in cases with and without a diagnosis of metabolic syndrome

			Metabolic syndrome		
			Present	**Absent**	**Total**
Physical activity assessment	Low	Number	12	34	46
		Percentage of MS (%)	80	97.1	92
	Moderate	Number	3	1	4
		Percentage of MS (%)	20	2.9	8
Total		Number	15	35	50
		Percentage of MS (%)	100	100	100

MS: Metabolic syndrome

The mean ACT score of patients with metabolic syndrome was 19.3±4.1, while it was 17.8±4.7 in those without metabolic syndrome (**Table 12**). However, no statistically significant relationship was identified between metabolic syndrome status and ACT scores (p>0.05).

Table 12. Distribution of mean asthma control test (ACT) scores in patients with and without metabolic syndrome

Metabolic syndrome	**Number (n)**	**Mean ACT score (±SD)**
Present	15	19.3±4.1
Absent	35	17.8±4.7
Total	50	18.2±4.5

SD: Standard deviation

DISCUSSION

Asthma is a chronic inflammatory disease of the airways characterized by recurrent wheezing, shortness of breath, chest tightness, and coughing, especially during the night or early morning hours. These symptoms are associated with variable and typically reversible airway obstruction.[1] The primary goal of asthma treatment is to achieve and maintain asthma control. To evaluate asthma control, the ACT was developed, consisting of five questions assessing daytime and nighttime symptoms, rescue medication use, and limitations in daily activities. The ACT demonstrates low sensitivity but high specificity at lower score thresholds and has been validated and shown to be reliable.[9,10]

In this study, we aimed to investigate the presence of metabolic syndrome in patients diagnosed with asthma and the impact of metabolic syndrome on asthma control using the ACT.

The mean age of patients diagnosed with metabolic syndrome in our study was 46.8±9.7 years. In contrast, according to data from the Turkish Metabolic Syndrome Study (METSAR), metabolic syndrome is most prevalent in the 60–69 age group, with a prevalence of 62% in this cohort.[11] Our study observed that both female and male patients with metabolic syndrome had higher BMI values compared to those without metabolic syndrome, although this difference was not statistically significant. Conversely, Demir et al.[12], in a study conducted on a homogeneous population, reported significantly higher BMI values in individuals diagnosed with metabolic syndrome (p=0.005). The lack of a similar finding in our study may be explained by the limited sample size.

When examining individuals with a history of asthma, the proportion of cases with a family history in our study was found to be 60%. In the current literature, a family history of asthma is emphasized as one of the strongest risk factors for the development of asthma in childhood, supporting the findings of our study. Regarding allergy history, 42% of our cases had a positive family history. This rate generally varies between 30–50% in the adult population, and our findings are consistent with the literature.[13]

When evaluating the menopausal status of female cases, 65% were premenopausal and 35% postmenopausal. Metabolic syndrome was diagnosed in 19.2% of premenopausal and 42.9% of postmenopausal cases. This finding is noteworthy as it aligns with a study conducted by the Department of Nutrition and Dietetics at Gazi University, which also reported a higher prevalence of metabolic syndrome among postmenopausal women.[14]

Regarding smoking habits, the average consumption in our study population was calculated as 4.3±8.6 pack-years. This indicates an increasing trend in tobacco use within the society. This observation is supported by the study conducted by the International union against cancer (UICC), which reported tobacco use rates in Turkiye as 54% among men and 20% among women, with the highest usage in the 30–44 age group. Additionally, a study by Uzun et al.[15] reported an

average smoking consumption of 1.4±0.5 packs/day among asthma patients. Weight loss achieved through appropriate nutrition and exercise programs positively affects metabolic disturbances observed in metabolic syndrome, while smoking cessation supports this process. This approach may contribute to reducing overall and cardiovascular mortality. In our study, the average smoking consumption was 5.2±10.1 pack-years in individuals diagnosed with metabolic syndrome and 4.0±8.0 pack-years in those without. The higher smoking rate among those with metabolic syndrome supports the notion that smoking is a risk factor for metabolic syndrome.

In the evaluation of weight status between ages 0 and 15, metabolic syndrome was diagnosed in 18.8% of underweight cases, 37% of normal-weight cases, and 28.6% of overweight cases. These findings are similar to those reported in the literature. Research indicates that approximately 29% of overweight adolescents develop metabolic syndrome. Furthermore, from a public health perspective, about one-third of overweight preschool children and nearly half of overweight adolescents progress to overweight adulthood.[16]

In our study, the average waist circumference was 112.7±26.5 cm in males and 101.1±8.6 cm in females diagnosed with metabolic syndrome. The relationship between waist circumference and metabolic syndrome was found to be statistically significant (p=0.011), indicating a strong association between abdominal obesity and metabolic syndrome. According to the literature, waist circumference measurements exceeding 89 cm in women and 102 cm in men define individuals requiring interventions against obesity.[13] Abdominal obesity is considered a risk type of obesity for metabolic syndrome and has been highlighted in many studies as an important risk factor for metabolic syndrome, diabetes, and cardiovascular diseases.[17-21]

In our study, the mean triceps skinfold thickness was calculated as 45.0±5.7 mm in male cases diagnosed with metabolic syndrome and 47.0±7.2 mm in female cases. These values are consistent with the classification of triceps skinfold thicknesses above 23 mm in males and 30 mm in females as indicative of obesity. The final report from the U.S. National Institutes of Health (NIH) states that the sum of triceps and subscapular skinfold thicknesses exceeding 38 mm in men and 52 mm in women is defined as a sign of obesity.[18]

The mean serum TG level in cases diagnosed with metabolic syndrome was 186.0±84.7 mg/dl, the mean FBG level was 89.7±12.4 mg/dl, and the mean serum HDL level was 43.9±12.9 mg/dl. The average TG level was found to be elevated in individuals with metabolic syndrome, and this association was statistically significant. A FBG level ≥110 mg/dl is accepted as a diagnostic criterion for metabolic syndrome.[2] The lower mean value observed in our study may be attributed to the limited sample size.

Recent studies emphasize that, in addition to fasting TG levels, postprandial TG levels are also important risk factors. A study examining the relationship between lipid levels and gender showed that abdominal obesity is the most important factor affecting lipid levels. Blackburn et al.[25] reported that as waist circumference and fasting TG levels increase, postprandial TG levels significantly rise. Guerci et al.[26], comparing individuals with abdominal obesity to normal controls, reported a significant difference in postprandial TG levels.[22-26]

In our study, the mean systolic and diastolic blood pressures in individuals diagnosed with metabolic syndrome were found to be elevated. This finding reflects the well-established strong association between obesity and hypertension in the literature. Globally, particularly in industrialized societies, the prevalence of obesity and hypertension is rapidly increasing. At least one-third to two-thirds of hypertensive patients are obese, and the likelihood of hypertension is three times higher in obese individuals.[27,28] According to the Framingham heart study, 70% of hypertensive men and 60% of hypertensive women are obese. The same study reported that hypertension risk increases eightfold in individuals with body weight exceeding 20% above ideal.[29,30] A blood pressure ≥130/80 mmHg is one of the diagnostic criteria for metabolic syndrome.

The mean FEV_1 percentage in patients with metabolic syndrome was 74.6±24.0%, the mean FEV_1/FVC ratio was 76.4±10.1, and the mean PEF percentage was 72.6±28.8. In patients without metabolic syndrome, the mean FEV_1 percentage was 75.9±16.6%, the mean FEV_1/FVC ratio was 75.6±13.0, and the mean PEF percentage was 70.7±18.4. However, no statistically significant relationship was found between metabolic syndrome diagnosis and FEV_1, FEV_1/FVC ratio, or PEF percentage ($p>0.05$).

Two cross-sectional population-based studies conducted on individuals of Asian descent examined the relationship between pulmonary function impairment and metabolic syndrome and found a significant association with a restrictive respiratory pattern, but no association with an obstructive pattern.[31,32] A small study on elderly patients similarly reported an association between respiratory functions and metabolic syndrome.[33] In our study, PFT parameters were borderline low, but no statistically significant relationship was identified between these results and metabolic syndrome diagnosis. This may be explained by the small number of cases included in the study.

Among the female participants using OC drugs included in the study, 30% were diagnosed with metabolic syndrome. However, no statistically significant association was found between metabolic syndrome diagnosis and OC use ($p>0.05$). In a study by Macsali et al.[34], it was shown that women using OCs had a higher prevalence of asthma, which was related to BMI. In Turkiye, the use of contraceptive methods is generally low, with the OC usage rate being only 6.5%.[35] Therefore, the low rate of OC use among cases diagnosed with metabolic syndrome in our study can be explained by the overall low usage rate.

In our study, a higher frequency of metabolic syndrome diagnosis was observed among those performing moderate levels of physical activity. This may be due to the small sample size included in the study. Physical activity is widely recognized to play a significant role in the prevention of metabolic syndrome and diabetes. It may confer benefits through one or more mechanisms, such as reducing abdominal obesity, blood pressure, low-grade

chronic inflammation, or LDL cholesterol. Additionally, improvement of TG/HDL cholesterol dyslipidemia may also be an important factor.[36-38]

The mean ACT scores of individuals diagnosed with metabolic syndrome in our study were 19.3±4.1, while those without metabolic syndrome had mean scores of 17.8±4.7. Although ACT scores were low in both groups, no statistically significant relationship was found between metabolic syndrome diagnosis and ACT scores. Barros et al.[39], in a study involving 508 patients based on the ACT, reported that severe asthmatic patients with obesity had poorer asthma control compared to asthmatics with normal BMI. The discrepancy between our findings and those of Barros et al.[39] may be explained by the limited number of cases included in our study.

Limitations

Our study demonstrates that metabolic syndrome is a significant comorbidity in patients with asthma, and the coexistence of these two conditions may affect individuals' overall health status and treatment responses. The study found significant associations between metabolic syndrome and factors such as abdominal obesity, elevated TG levels, and high blood pressure. Moreover, there are limited but noteworthy findings suggesting that metabolic syndrome may negatively impact asthma control.

CONCLUSION

As a result, when metabolic syndrome and asthma are considered together, it is evident that a more effective treatment approach is required for both conditions. The management of these patients necessitates a multidisciplinary approach; that is, not only controlling asthma symptoms but also addressing the adverse effects of metabolic syndrome to contribute to a healthier life. Asthma treatment, when approached holistically without neglecting metabolic syndrome, can lead to more successful and sustained outcomes. This approach will improve individual health and contribute to public health overall.

ETHICAL DECLARATIONS

Ethics Committee Approval

This article is derived from a thesis study before 2020 (Project No: 832904) and was conducted with institutional approval.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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

REFERENCES

1. Global Strategy for Asthma Management and Prevention. 2009 update. Accessed May 20, 2025. https://www.ginasthma.org
2. Karcıer S, Onat A, Aksoy M. Türkiye klinikleri, Dahili Tıp Bilimleri; Kardiyoloji, Hiperlipidemi Özel Sayısı. 2006;7:21-57.
3. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med*. 2003; 163(4):427-436. doi:10.1001/archinte.163.4.427
4. Reaven G. Role of insulin resistance in human disease. *Diabetes*. 1988; 37(12):1595-607. doi:10.2337/diab.37.12.1595
5. Global Strategy for Asthma Management and Prevention. 2007 update. Accessed May 20, 2025. https://www.ginasthma.org
6. Guler N, Kirerleri E, Ones U, Tamay Z, Salmayenli N, Darendeliler F. Leptin: does it have any role in childhood asthma? *J Allergy Clin Immunol*. 2004;114(2):254-259. doi:10.1016/j.jaci.2004.03.053
7. Ramaraju K, Krishnamurthy S, Maamidi S, Kaza AM, Balasubramaniam N. Is serum cholesterol a risk factor for asthma? *Lung India*. 2013;30(4):295-301. doi:10.4103/0970-2113.120604
8. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65. doi:10.1016/j.jaci.2003.09.008
9. Schatz M, Sorkness CA, Li JT, et al. Asthma control test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol*. 2006;117(3):549-556. doi:10.1016/j.jaci.2006.01.011
10. Schatz M, Zeiger RS, Drane A, et al. Reliability and predictive validity of the asthma control test administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol*. 2007;119(2):336-343. doi:10.1016/j.jaci.2006.08.042
11. Kozan O, Oguz A, Abaci A, et al. Prevalence of the metabolic syndrome among Turkish adults. *Eur J Clin Nutr*. 2007;61(4):548-553. doi:10.1038/sj.ejcn.1602554
12. Demir D. Comparison of sociodemographic, anthropometric and biochemical characteristics of individuals with metabolic syndrome, type 2 diabetes mellitus and healthy subjects. *Konuralp Med J*. 2010;2(1): 12-19.
13. Karakaya G. Atopy, allergy and asthma. In: Karakaya G, Kalyoncu AF, eds. Asthma and Accompanying Conditions. Ankara: Bilimsel Tıp Yayınevi; 2004.
14. Akbulut G. Does the prevalence of metabolic syndrome differ between pre- and post-menopausal women according to ATP III and IDF criteria? *Turk Klin J Med Sci*. 2011;31:1463-1470.
15. Uzun K, Özbay B, Ceylan E. Smoking frequency among lung patients. *Tuberk Toraks*. 2000;48:40-46.
16. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the Third National Health and Nutrition Examination Survey, 1988-1994. *Arch Pediatr Adolesc Med*. 2003;157(8):821-827. doi:10.1001/archpedi.157.8.821
17. Gokcel A, Ozsahin AK, Sezgin N, et al. High prevalence of diabetes in Adana, a southern province of Turkey. *Diabetes Care*. 2003;26(11):3031-3034. doi:10.2337/diacare.26.11.3031
18. Erem C, Arslan C, Hacihasanoglu A, et al. Prevalence of obesity and associated risk factors in a Turkish population (Trabzon City, Turkey). *Obes Res*. 2004;12(7):1117-1127. doi:10.1038/oby.2004.140
19. Yumuk VD, Hatemi H, Tarakci T, et al. High prevalence of obesity and diabetes mellitus in Konya, a central Anatolian city in Turkey. *Diabetes Res Clin Pract*. 2005;70(2):151-158. doi:10.1016/j.diabres.2005.03.030
20. Onat A, Avcı GŞ, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes*. 2004;28(8):1018-1025. doi:10.1038/sj.ijo.0802695

21. Varlıbaş F, Gencer M, Örken C, Çakal N, Tireli H. Metabolic syndrome in cerebrovascular diseases. *J Neurol Sci Turk*. 2006;23(2):93-101.
22. Ginsberg HN, Jones J, Blaner WS, et al. Association of postprandial triglyceride and retinyl palmitate responses with newly diagnosed exercise-induced myocardial ischemia in middle-aged men and women. *Arterioscler Thromb Vasc Biol*. 1995;15(11):1829-1838. doi: 10.1161/01.atv.15.11.1829
23. Meyer E, Westerveld HT, de Ruyter-Meijstek FC, et al. Abnormal postprandial apolipoprotein B-48 and triglyceride responses in normolipidemic women with greater than 70% stenotic coronary artery disease: a case-control study. *Atherosclerosis*. 1996;124(2):221-235. doi: 10.1016/0021-9150(96)05832-7
24. Couillard C, Bergeron N, Prud'homme D, et al. Gender difference in postprandial lipemia: importance of visceral adipose tissue accumulation. *Arterioscler Thromb Vasc Biol*. 1999;19(10):2448-2455. doi:10.1161/01.ATV.19.10.2448
25. Blackburn P, Lamarche B, Couillard C, et al. Postprandial hyperlipidemia: another correlate of the "hypertriglyceridemic waist" phenotype in men. *Atherosclerosis*. 2003;171(2):327-336. doi:10.1016/S0021-9150(03)00069-9
26. Guerci B, Paul JL, Hadjadj S, et al. Analysis of the postprandial lipid metabolism: use of a 3-point test. *Diabetes Metab*. 2001;27(4 Pt 1):449-457.
27. King DS, Wofford MR. Obesity and hypertension. *Drug Topics*. 2000;3:59-67.
28. Narkiewicz K. Obesity-related hypertension: relevance of vascular responses to mental stress. *J Hypertens*. 2002;20(7):1277-1278. doi:10.1097/00004872-200207000-00009
29. Swales JD. Manual of Hypertension. Oxford: Blackwell Science; 1995.
30. Sharma AM, Engeli S. Managing big issues on lean evidence: treating obesity hypertension. *Nephrol Dial Transplant*. 2002;17(3):353-355. doi:10.1093/ndt/17.3.353
31. Lin WY, Yao CA, Wang HC, Huang KC. Impaired lung function is associated with obesity and metabolic syndrome in adults. *Obesity (Silver Spring)*. 2006;14(9):1654-1661. doi:10.1038/oby.2006.190
32. Nakajima K, Kubouchi Y, Muneyuki T, Ebata M, Eguchi S, Munakata H. A possible association between suspected restrictive pattern as assessed by ordinary pulmonary function test and the metabolic syndrome. *Chest*. 2008;134(4):712-718. doi:10.1378/chest.07-3003
33. Fimognari FL, Pasqualetti P, Moro L, et al. The association between metabolic syndrome and restrictive ventilatory dysfunction in older persons. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):760-765. doi:10.1093/gerona/62.7.760
34. Macsali F, Real FG, Omenaas ER, et al. Oral contraception, body mass index, and asthma: a cross-sectional Nordic-Baltic population survey. *J Allergy Clin Immunol*. 2009;123(2):391-397. doi:10.1016/j.jaci.2008.11.016
35. Hacettepe University Institute of Population Studies. Turkey Demographic and Health Survey (TDHS). Ankara; 2003.
36. Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P. Joint effects of physical activity, body-mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. *Eur Heart J*. 2004;25(24):2212-2219. doi:10.1016/j.ehj.2004.10.018
37. Park S, Rink LD, Wallace JP. Accumulation of physical activity leads to a greater blood pressure reduction than a single continuous session, in prehypertension. *J Hypertens*. 2006;24(9):1761-1770. doi:10.1097/01.hjh.0000242400.37967.54
38. Kelley GA, Kelley KS, Tran ZV. Walking, lipids, and lipoproteins: a meta-analysis of randomized controlled trials. *Prev Med*. 2004;38(5):651-661. doi:10.1016/j.ypmed.2003.12.012
39. Barros LL, Souza-Machado A, Corrêa LB, et al. Obesity and poor asthma control in patient with severe asthma. *J Asthma*. 2011;48(2):171-176. doi:10.3109/02770903.2010.536594

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Current diagnostic criteria, therapeutic approaches, and long-term outcomes in acute respiratory distress syndrome

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a common condition in intensive care units, characterized by severe hypoxemic respiratory failure. It typically develops following triggering factors such as pneumonia or sepsis. Diagnosis is based on clinical and radiological findings in conjunction with oxygenation parameters, and the syndrome is classified as mild, moderate, or severe. Key management strategies include low tidal volume ventilation, appropriate positive end-expiratory pressure, prone positioning, and extracorporeal membrane oxygenation in selected cases. Corticosteroids and neuromuscular blocking agents should be used with caution in specific patient groups. Since survivors of ARDS are at risk for long-term physical, cognitive, and psychological impairments, rehabilitation and long-term follow-up are of paramount importance. This article provides an updated overview of the diagnosis, differential diagnosis, treatment strategies, and long-term management of ARDS.

Keywords: ARDS, alveolar damage, hypoxemia, intensive care

DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a severe clinical condition characterized by hypoxemic respiratory failure affecting both lungs, and it was first described in the 1960s. Initially referred to as "shock lung" or "adult respiratory distress syndrome," the terminology later evolved to "ARDS" upon recognition that the condition can affect individuals of all age groups.[1] Technological advancements such as high-flow nasal oxygen (HFNO), pulse oximetry, and thoracic ultrasonography have prompted the need for revisions in the definition of ARDS.

ARDS is an acute, widespread inflammatory lung injury that develops following triggers such as pneumonia, sepsis, trauma, or aspiration.[2] Clinically, it presents within the first 7 days with dyspnea and hypoxemia; tachypnea, bilateral crackles, and, in advanced cases, cyanosis and confusion may also be observed. The hallmark of pathogenesis is diffuse alveolar damage.[3] Elevated pro-inflammatory cytokines activate neutrophils, and the released mediators injure the capillary endothelium and alveolar epithelium.[4] This damage leads to the leakage of protein-rich fluid into the alveolar spaces, surfactant depletion, and atelectasis. Consequently, arterial hypoxemia, increased shunt fraction, dead space ventilation, and reduced lung compliance occur; hypercapnia may develop in the later stages.[5,6]

LABORATORY TESTS

Although there is no specific laboratory test diagnostic for ARDS, certain abnormalities can provide guidance in identifying the underlying cause and assessing disease severity. Complete blood count may reveal leukocytosis or leukopenia. Biochemical tests may indicate renal or hepatic dysfunction secondary to hypoxemia or shock. In cases of severe inflammation, coagulation abnormalities such as prothrombin time, activated partial thromboplastin time, and elevated D-dimer levels may be observed. While arterial blood gas (ABG) analysis usually shows hypoxemia and respiratory alkalosis, hypercapnic acidosis may develop in advanced stages and this may be an indicator of poor prognosis.

IMAGING FINDINGS

Radiologic imaging plays a crucial supportive role in the diagnosis of ARDS. The most common finding on chest radiographs is the presence of diffuse alveolar opacities affecting both lungs. These opacities are typically centrally located and predominantly involve the lower lobes, rather than being peripheral. More detailed findings can be identified through thoracic ultrasonography or chest computed tomography (CT). These modalities often reveal diffuse and patchy opacities, interstitial thickening, and an increase in B-lines.

DEFINITION AND CLASSIFICATION OF ARDS ACCORDING TO BRITISH THORACIC SOCIETY (BTS) GUIDELINES

The guidelines supported by the BTS adopt the Berlin Definition for the characterization of ARDS. ARDS is defined as a condition marked by acute onset hypoxemia, bilateral pulmonary infiltrates, and non-cardiogenic pulmonary involvement.[7] To confirm the diagnosis, imaging studies must demonstrate bilateral widespread infiltrates, and cardiac etiologies must be excluded. The BTS guidelines particularly recommend chest radiography or thoracic CT for diagnostic confirmation.

The Berlin Definition classifies ARDS into three categories based on the severity of hypoxemia: mild, moderate, and severe. This classification is grounded in oxygenation parameters and serves as a crucial guide in determining clinical management strategies.

CORE DIAGNOSTIC CRITERIA FOR ARDS APPLICABLE ACROSS ALL SUBGROUPS

The diagnosis of ARDS relies on the comprehensive evaluation of clinical, radiologic, and pathophysiologic findings. Several fundamental criteria have been established to define the condition across all subcategories:

Risk Factors

ARDS is typically triggered by acute-onset predisposing conditions such as pneumonia, sepsis, extrapulmonary systemic infections, trauma, massive transfusion, aspiration, or shock. Differentiating pulmonary involvement from cardiogenic pulmonary edema is essential; therefore, cardiogenic causes such as congestive heart failure or left ventricular dysfunction must be excluded. Moreover, the primary cause of hypoxemia and impaired ventilation should not be solely attributed to atelectasis.

Timing

The onset of ARDS usually occurs within one week of exposure to an identifiable risk factor or is characterized by a significant worsening of existing respiratory symptoms. In some cases, such as viral infections like COVID-19, the onset may be more gradual, making this temporal criterion particularly relevant.

Imaging Findings

Radiological assessment is a cornerstone in the diagnostic process. Chest radiography, CT, or thoracic ultrasonography typically reveal newly developed bilateral consolidations. These findings must not be fully explained by alternative causes such as massive pleural effusion, unilateral atelectasis, or progressive nodular/mass lesions. Particularly in settings where radiography or CT is unavailable, thoracic ultrasonography serves as a viable alternative diagnostic modality and has been incorporated into the diagnostic criteria.

ASSESSMENT OF ARDS SEVERITY

After confirming the clinical, radiological, and temporal criteria for ARDS, the diagnosis is finalized based on the presence of refractory hypoxemia. Recent guidelines have re-evaluated the oxygenation parameters used to classify the severity of the syndrome.[8]

Traditionally, the PaO_2/FiO_2 ratio obtained via ABG has been used as the standard parameter in ARDS diagnosis and staging. However, in settings where ABG is not available or is costly, the SpO_2/FiO_2 ratio, based on pulse oximetry, offers a practical alternative.

HFNO has become an accepted respiratory support strategy for non-intubated ARDS patients and is now included in diagnostic criteria. Severity is determined by the level of positive end-expiratory pressure (PEEP) applied during: HFNO at ≥30 L/min flow, noninvasive ventilation (NIV) at ≥5 L/min, or continuous positive airway pressure. The classification is summarized in the following **Table.**

Table. Classification of ARDS severity based on oxygenation parameters

ARDS severity	PaO_2/FiO_2 ratio (with PEEP ≥5 cm H_2O)	SpO_2/FiO_2 ratio (when SpO_2 ≤97%)
Mild	200-300 mmHg	235-315 mmHg
Moderate	100-200 mmHg	148-235 mmHg
Severe	≤100 mmHg	≤148 mmHg

ARDS: Acute respiratory distress syndrome

EXCLUSION OF ACUTE CARDIOGENIC PULMONARY EDEMA IN THE DIFFERENTIAL DIAGNOSIS

Before confirming a diagnosis of ARDS, it is essential to exclude acute cardiogenic pulmonary edema, particularly in intensive care and emergency settings.[9] Common causes include left ventricular dysfunction, valvular heart disease, malignant hypertension, and advanced renal failure. Differential diagnosis should involve transthoracic echocardiography and measurement of BNP or NT-proBNP levels. Chest radiographs showing cardiomegaly, pleural effusion, or Kerley B lines support a cardiac origin. Additional clinical signs such as an S3/S4 gallop, jugular venous distention, and peripheral edema can aid in differentiation. A rapid response to diuretic therapy may further confirm a cardiogenic cause retrospectively.

PRIMARY CAUSES OF ARDS

ARDS may develop as a result of various pulmonary and extrapulmonary triggers. Although its pathophysiology varies depending on the etiology, the clinical and radiological manifestations are often similar across different causes. Below are the primary causes of ARDS: Sepsis, aspiration, pneumonia, severe trauma, massive transfusion, substance and alcohol use.

COVID-19-ASSOCIATED ARDS

COVID-19 is one of the major viral infections that can lead to the development of ARDS. SARS-CoV-2 infection results in diffuse alveolar damage, interstitial edema, and microthrombosis within the lungs. The pathophysiology of COVID-19-associated ARDS differs in certain aspects

from classical ARDS, most notably with more pronounced vascular pathology, widespread endothelial injury, capillary dilation, and in-situ microthrombosis.[10]

Additionally, a distinctive feature of COVID-19 ARDS is "silent hypoxemia," where patients experience severe hypoxemia without noticeable respiratory distress.[11] Imaging findings typically begin with peripheral and basilar ground-glass opacities, progressing to characteristic consolidations as the disease advances.

In terms of clinical management, low tidal volume ventilation, prone positioning, and moderate levels of PEEP are recommended. Furthermore, due to the hypercoagulable state specific to COVID-19, anticoagulant therapy has become an integral component of the management strategy.[12]

MANAGEMENT OF ARDS AND PHARMACOTHERAPEUTIC APPROACH

Due to its complex pathophysiology, ARDS is a severe clinical condition that necessitates a multidisciplinary approach. The primary therapeutic goals include improving oxygenation, supporting ventilation, maintaining hemodynamic stability, and addressing the underlying cause. As there is no disease-specific pharmacological treatment proven to be effective, management largely relies on supportive care strategies. Given the high risk of non-cardiogenic pulmonary edema resulting from increased capillary permeability and hydrostatic imbalance, meticulous fluid management is essential.[13]

ROLE OF NEUROMUSCULAR BLOCKERS IN THE MANAGEMENT OF ARDS

Neuromuscular blockers (NMBs) may be used as an adjunctive therapy in severe ARDS cases to improve patient-ventilator synchrony and reduce ventilator-induced lung injury (VILI).[14] Despite potential benefits such as reducing oxygen consumption and systemic inflammation, current clinical guidelines do not recommend the routine use of NMBs, as meta-analyses have failed to demonstrate significant improvements in mortality or duration of mechanical ventilation. Contemporary recommendations support the short-term use of NMBs (up to 48 hours) only in the early phase of disease and in severe cases; however, this recommendation is based on low-quality evidence.[15] Furthermore, the therapeutic benefit of NMBs has predominantly been observed when used in conjunction with deep sedation; comparable outcomes have not been demonstrated with light sedation. Therefore, the use of NMBs should be restricted to carefully selected patients.

SYSTEMIC GLUCOCORTICOID THERAPY IN ARDS

Systemic glucocorticoids exert anti-inflammatory effects by inhibiting the synthesis of proinflammatory mediators involved in the pathogenesis of ARDS. Traditionally used in the treatment of secondary conditions such as refractory septic shock or pneumonia, these agents have recently gained attention for their mortality-reducing effects, particularly in COVID-19–related ARDS.[16] In line with this, the 2024 ATS guidelines conditionally recommend the use of systemic corticosteroids in all patients diagnosed with ARDS. The duration of glucocorticoid therapy should not exceed 14 days. Recommended dosing regimens include dexamethasone at 20 mg/day for the first 5 days followed by 10 mg/day for the next 5 days, and methylprednisolone initiated at 1 mg/kg/day with gradual tapering.[16,17] Close monitoring for potential adverse effects such as infection, hyperglycemia, and muscle weakness is essential throughout the treatment course.

USE OF INHALED PULMONARY VASODILATORS IN ARDS

In cases of ARDS with persistent refractory hypoxemia despite standard ventilation strategies, case series and small-scale studies have reported on the use of inhaled pulmonary vasodilators, such as nitric oxide or prostacyclin. These agents have been shown to temporarily improve oxygenation, particularly in patients with right ventricular dysfunction or concomitant pulmonary arterial hypertension.[18] The primary mechanism of action of inhaled vasodilators is enhancing ventilation-perfusion matching by promoting vascular dilation in ventilated alveoli. This selective pulmonary vasodilation occurs with minimal impact on the systemic circulation.

However, there is no robust clinical evidence demonstrating a significant improvement in morbidity or mortality with the use of these agents. The therapeutic response is generally assessed within the first 24 hours following administration. If no clinical benefit is observed, continuation of the therapy is not recommended. Prior to initiation, it is essential to carefully evaluate the potential benefits, as well as the cost and risk of adverse effects.

SUPPORTIVE CARE APPROACHES IN ARDS

Mortality in ARDS is not solely attributable to respiratory failure but also results from multiple organ dysfunction and secondary complications. Therefore, supportive care strategies are critical components of management.

Supportive care in ARDS includes careful fluid management with hemodynamic monitoring, targeting a central venous pressure (CVP) of less than 4 cmH_2O. Early initiation of enteral nutrition is recommended to meet metabolic demands and support immune function.[19] Blood glucose levels should be closely regulated to prevent hyperglycemia-related complications. Infection control measures are crucial to prevent nosocomial and ventilator-associated pneumonia (VAP).[20] Routine pharmacologic prophylaxis should be implemented to reduce the risk of venous thromboembolism (VTE) associated with immobility and mechanical ventilation. Additionally, proton pump inhibitors or H_2 receptor blockers should be used for stress ulcer prophylaxis.

VENTILATION STRATEGIES AND RESPIRATORY SUPPORT IN ARDS

The choice of ventilation mode in patients with ARDS varies depending on the underlying pathology and individual respiratory mechanics.[21] In most clinical scenarios, volume-

controlled ventilation is preferred due to its ability to guarantee a consistent tidal volume and ensure adequate ventilation. However, due to the commonly observed decreased lung compliance in ARDS, even low tidal volumes may exceed inspiratory capacity, leading to elevated airway pressures. This can increase the risk of VILI. Therefore, pressure-controlled volume-guaranteed ventilation-which incorporates pressure-limiting features while maintaining volume targets-is frequently recommended as a safer and more protective mode of ventilation in ARDS management.[22]

In patients with severe ARDS, invasive mechanical ventilation is frequently required.[8] In contrast, for patients with non-severe ARDS, the use of HFNO has been suggested, as it may reduce the need for intubation. However, it is also emphasized that HFNO has not demonstrated a significant impact on mortality outcomes.[15]

In patients with acute hypoxemic respiratory failure (AHRF) who are not receiving invasive mechanical ventilation, and after excluding specific conditions such as cardiogenic pulmonary edema, obesity hypoventilation syndrome, or acute exacerbation of COPD, there is no conclusive evidence that NIV reduces intubation rates or mortality. Nevertheless, particularly in AHRF cases associated with COVID-19, NIV has been shown to reduce the need for intubation compared to conventional oxygen therapy, and its use has been recommended in this context.[15]

LOW TIDAL VOLUME VENTILATION IN ARDS

Low tidal volume ventilation (LTVV), also known as lung-protective ventilation, is a key strategy in the management of ARDS. Its main aim is to provide effective respiratory support while reducing alveolar overdistension and preventing VILI.

Guidelines recommend setting the tidal volume between 4-8 ml/kg of predicted body weight (PBW), with 6 ml/kg PBW being the usual starting point in clinical practice.[23]

Because lung compliance is reduced in ARDS, even low tidal volumes may result in high airway pressures. For this reason, plateau pressure should be kept below 30 cmH_2O. The respiratory rate is usually set between 14–22 breaths per minute, and should not exceed 35 breaths per minute.[24]

ROLE OF POSITIVE END-EXPIRATORY PRESSURE AND RECRUITMENT MANEUVERS IN THE MANAGEMENT OF ARDS

PEEP is a fundamental ventilatory parameter used in ARDS to prevent alveolar collapse and improve oxygenation. The 2017 guidelines recommend the use of high PEEP and recruitment maneuvers in moderate to severe ARDS cases; however, there is no standardized algorithm for determining the optimal PEEP-FiO_2 combination.[16] High PEEP may enhance gas exchange by reducing intrapulmonary shunting and may offer protection against oxygen toxicity. On the other hand, it may also increase plateau pressure, leading to potential adverse effects such as barotrauma and decreased cardiac output. Considering these risks, meta-analyses have not demonstrated a significant difference in mortality between high and low PEEP strategies.[25] Current guidelines support the use of high PEEP in moderate to severe ARDS cases without routine recruitment maneuvers, while no definitive recommendation is provided for mild ARDS. Although LTVV is generally well tolerated, it may result in permissive hypercapnia, which should be carefully managed, especially in patients with elevated intracranial pressure.

PERMISSIVE HYPERCAPNIA AND VENTILATION STRATEGIES

Permissive hypercapnia is a foreseeable and generally tolerable consequence of LTVV. While LTVV aims to reduce alveolar overdistension and ventilator-associated lung injury (VILI), it can lead to arterial hypercapnia due to alveolar hypoventilation.[26] In efforts to maintain adequate minute ventilation, increasing the respiratory rate may shorten the expiratory phase, potentially resulting in the development of auto-PEEP. This complication can be avoided through careful adjustment of ventilatory parameters. Moreover, high-frequency ventilation has not demonstrated a significant impact on mortality in patients with moderate to severe ARDS, and thus its routine use is not recommended.[15]

OXYGENATION-SUPPORTIVE THERAPIES IN ARDS

In moderate to severe ARDS, especially when LTVV fails to provide adequate oxygenation, additional oxygen support strategies become critical. The main goals are to enhance oxygen delivery and reduce systemic oxygen consumption.

Supportive Measures to Reduce Oxygen Consumption

Fever, anxiety, pain, and increased work of breathing can elevate oxygen demand. The use of antipyretics, sedatives, and analgesics is recommended to help maintain the balance between ventilation and oxygenation, particularly in patients with high oxygen requirements.

Prone Ventilation

Prone positioning enhances perfusion and ventilation-perfusion matching in the dorsal regions of the lungs by reducing both cardiac and diaphragmatic compression. This intervention can lead to a significant improvement in oxygenation levels. It is particularly recommended for patients with moderate to severe ARDS who exhibit inadequate oxygenation despite LTVV, provided there are no contraindications, such as spinal instability.

The optimal period for prone positioning is within the first seven days of disease onset. It is advised to implement prone positioning early and maintain it for at least 16 consecutive hours. This duration and timing are crucial for not only improving oxygenation but also potentially reducing mortality rates.

Extracorporeal Membrane Oxygenation (ECMO)

In ARDS patients where adequate oxygenation cannot be achieved through conventional ventilation strategies, ECMO emerges as a therapeutic option. Specifically, venovenous ECMO can be utilized to support oxygenation in cases of severe ARDS. Current guidelines classify the use of

venovenous ECMO as a "conditional recommendation" with a low level of evidence.[15]

For optimal effectiveness, early initiation of ECMO is crucial, ideally within the first seven days following symptom onset. The highest success rates are typically observed when ECMO is commenced during this early phase. Therefore, it is recommended that patients in centers without ECMO capabilities be transferred promptly to specialized reference centers where this intervention is available.

LONG-TERM MORBIDITY ASSOCIATED WITH ARDS

ARDS poses not only a significant risk of acute mortality but also represents a major clinical concern due to the long-term morbidity observed in survivors. These individuals frequently experience cognitive impairments (including deficits in attention, memory, and executive function), psychological disorders (such as anxiety, depression, and post-traumatic stress disorder), and physical complications (including muscle weakness, exercise intolerance, and neuromuscular dysfunction).[27,28] These sequelae are collectively described under the term post-intensive care syndrome and are known to substantially impair quality of life. Additionally, the post-ARDS period is often associated with reduced rates of return to work, income loss, and social isolation, further exacerbating the burden of illness. Therefore, the implementation of multidisciplinary and long-term rehabilitation programs for ARDS survivors is of critical importance for improving both clinical outcomes and overall quality of life.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The author declares that they solely conducted the design, execution, analysis, and writing of the manuscript, and approved the final version.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet.* 1967;2(7511):319-323. doi:10.1016/s0140-6736(67)90168-7
2. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med.* 2012;38(10):1573-1582. doi:10.1007/s00134-012-2682-1
3. Hughes KT, Beasley MB. Pulmonary manifestations of acute lung injury: more than just diffuse alveolar damage. *Arch Pathol Lab Med.* 2017;141(7):916-922. doi:10.5858/arpa.2016-0342-RA
4. Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *Lancet Respir Med.* 2015;3(1):24-32. doi:10.1016/S2213-2600(14)70291-7
5. Kiiski R, Takala J, Kari A, Milic-Emili J. Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1992;146(5 Pt 1):1131-1135. doi:10.1164/ajrccm/146.5_Pt_1.1131
6. Roupie E, Dambrosio M, Servillo G, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;152(1):121-128. doi:10.1164/ajrccm.152.1.7599810
7. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res.* 2019;6(1):e000420. doi:10.1136/bmjresp-2019-000420
8. Grasselli G, Calfee CS, Camporota L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med.* 2023;49(7):727-759. doi:10.1007/s00134-023-07050-7
9. Schwarz MI, Albert RK. "Imitators" of the ARDS: implications for diagnosis and treatment. *Chest.* 2004;125(4):1530-1535. doi:10.1378/chest.125.4.1530
10. Dorward DA, Russell CD, Um IH, et al. Tissue-specific immunopathology in fatal COVID-19. *Am J Respir Crit Care Med.* 2021;203(2):192-201. doi:10.1164/rccm.202008-3265OC
11. Swenson KE, Swenson ER. Pathophysiology of acute respiratory distress syndrome and COVID-19 lung injury. *Crit Care Clin.* 2021;37(4):749-776. doi:10.1016/j.ccc.2021.05.003
12. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med.* 2020;383(2):120-128. doi:10.1056/NEJMoa2015432
13. Silversides JA, Major E, Ferguson AJ, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med.* 2017;43(2):155-170. doi:10.1007/s00134-016-4573-3
14. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;363(12):1107-1116. doi:10.1056/NEJMoa1005372
15. Qadir N, Sahetya S, Munshi L, et al. An update on management of adult patients with acute respiratory distress syndrome: an official American thoracic society clinical practice guideline. *Am J Respir Crit Care Med.* 2024;209(1):24-36. doi:10.1164/rccm.202311-2011ST
16. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Intensive Care Med.* 2017;43(12):1751-1763. doi:10.1007/s00134-017-4919-5
17. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(3):267-276. doi:10.1016/S2213-2600(19)30417-5
18. Karam O, Gebistorf F, Wetterslev J, Afshari A. The effect of inhaled nitric oxide in acute respiratory distress syndrome in children and adults: a cochrane systematic review with trial sequential analysis. *Anaesthesia.* 2017;72(1):106-117. doi:10.1111/anae.13628
19. Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine and american society for parenteral and enteral nutrition: executive summary. *Crit Care Med.* 2009;37(5):175. doi:10.1097/CCM.0b013e3181a40116
20. Zampieri FG, Póvoa P, Salluh JI, et al. Lower respiratory tract infection and short-term outcome in patients with acute respiratory distress syndrome. *J Intensive Care Med.* 2020;35(6):588-594. doi:10.1177/0885066618772498
21. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA.* 2016;315(8):788-800. doi:10.1001/jama.2016.0291
22. Umoh NJ, Fan E, Mendez-Tellez PA, et al. Patient and intensive care unit organizational factors associated with low tidal volume ventilation in acute lung injury. *Crit Care Med.* 2008;36(5):1463-1468. doi:10.1097/CCM.0b013e31816fc3d0
23. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1301-1308. doi:10.1056/NEJM200005043421801

24. de Durante G, del Turco M, Rustichini L, et al. Lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002;165(9):1271-1274. doi:10.1164/rccm.2105050
25. Santa Cruz R, Villarejo F, Irrazabal C, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev.* 2021;3(3):CD009098. doi:10.1002/14651858.CD009098.pub3
26. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER. Hypercapnic acidosis and mortality in acute lung injury. *Crit Care Med*. 2006;34(1):1-7. doi:10.1097/01.ccm.0000194533.75481.03
27. Hiser SL, Fatima A, Ali M, Needham DM. Post-intensive care syndrome (PICS): recent updates. *J Intensive Care.* 2023;11(1):23. doi:10.1186/s40560-023-00670-7
28. Ilias I, Mantziou V, Vamvakas E, et al. Post-traumatic stress disorder and burnout in healthcare professionals during the sars-cov-2 pandemic: a cross-sectional study. *J Crit Care Med (Targu Mures).* 2021;7(1):14-20. doi:10.2478/jccm-2020-0042

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Case Report

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A rare case of "inhalation fruit hypersensitivity"

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ABSTRACT

Allergies to vegetables and fruits develop as a primary sensitization to pollen allergens followed by cross-reactive secondary sensitization to foods or as a direct sensitization to foods via the gastrointestinal tract. Although much focus has been placed on food hypersensitivity reactions following oral ingestion, reactions resulting from skin contact and inhalation are slowly gaining attention. A 34-year-old female patient, who had no known history of chronic disease and was a teacher by profession, applied to our outpatient clinic with airway symptoms (dyspnea and cough) triggered by apple odor for 5 years. In our test room, where there are equipment that can intervene in a possible anaphylaxis, the patient was provoked with the smell of an apple. The patient was made to smell the apple cut in half for 10 seconds. The patient developed a dry cough that started as mild and then gradually became more severe, and mild urticarial lesions on the anterior chest wall. The patient was diagnosed with inhalation fruit hypersensitivity. An epinephrine auto-injectorwas prescribed and an IKS-LABA dry powder inhaler was prescribed for use when necessary. She was told to stay away from apples.

Keywords: Fruit, hypersensitivity, inhalation

INTRODUCTION

Food hypersensitivity reactions typically present as skin, gastrointestinal and respiratory symptoms such as urticaria, atopic dermatitis, nausea, vomiting, diarrhea, cough and asthma.[1] However, systemic anaphylactic reactions can also be observed in some cases. Fruits and vegetables account for a significant proportion of food hypersensitivity reactions. Sensitization to these foods may develop as a result of cross-reaction caused by allergy to the pollen of the relevant fruit or vegetable. Another route of sensitization is the direct ingestion of fruit or vegetables through the gastrointestinal tract.[2,3] These allergic reactions may develop after exposure to various components of the plant. For example, there are several published case reports describing allergic reactions to apple seeds without allergy to the pulp or peel of the fruit.[4-6] Reactions that develop only to the smell of the fruit can also be given as an example of this situation. Reactions that develop through skin contact and inhalation have recently attracted attention. Inhalational food hypersensitivity can cause significant morbidity in affected individuals. Exposure is usually more pronounced in occupational settings but can also occur during daily life. Clinical manifestations may range from a benign respiratory or skin reaction to a life-threatening systemic reaction.

CASE

A 34-year-old female patient, who has no known history of chronic disease and is a teacher, applied to our polyclinic with airway symptoms (dyspnea and cough) due to apple odor for 5 years. It was learned from the patient's anamnesis that this complaint developed after intense pepper spray exposure, that she had no such complaint until that period of her life, and that her complaints arose with apple odor or oral intake, whether she was aware of it or not. She stated that she had similar symptoms with oral intake compared to inhalation exposure, but their severity was greater.

The skin prick test performed with aeroallergens was found to be negative. The prick to prick test performed with apple, apple and pollen specific IgE and tryptase resulted in negative. The basal respiratory function test was within the normal range and reversibility was found to be negative. The patient was provoked with apple odor in our test room, which has equipment that can intervene in a possible anaphylaxis. The patient was made to smell the apple cut in half for 10 seconds. The patient developed a dry cough that started as mild and then became increasingly severe, and mild urticarial lesions on the anterior chest wall. During the physical examination, normal breath sounds were detected. While TA and SpO_2 values were measured as normal in vital signs, the pulse was between 120-140/min. During this time, a respiratory function test could not be performed due to severe cough. After the patient was given antihistamine and nebules (SABA+SAMA and IKS), the urticarial lesions regressed within 10 minutes, and the cough completely regressed within 30 minutes. The patient was diagnosed with food

hypersensitivity developing through the respiratory tract. An epinephrine auto-injector was prescribed and an IKS-LABA dry powder inhaler was prescribed for use when necessary. She was told to stay away from apples.

DISCUSSION

Post-inhalation reactions to fruits have been linked to the PR protein family found in plants. These proteins are synthesized by plants in response to various biotic and abiotic stresses and accumulate in edible parts such as fruits, seeds and pollen grains. When ingested or inhaled, these proteins interact with IgE, which triggers an immunological response through antigen-antibody interaction, leading to the development of symptoms such as oral allergy syndrome, allergy, asthma, anaphylaxis, conjunctivitis, rhinitis, nausea.[7]

It was interesting to note that the prick and specific IgE test results against apple and pollen were negative, while the objective symptoms appeared with the apple inhalation test. Similarly, a 7-month-old boy who had anaphylaxis after being fed bananas despite a negative prick test with bananas is available in the literature.[8] The exposure of the patient to intense toxic gas in a part of his life may have caused damage to the mucosal defense mechanisms of the respiratory system. We think that this may have resulted in a reaction with a much lower dose of allergen even though it was not detected in the tests. It is also known that allergy may develop against lipid transfer protein (LTP) found in fruits grown especially in the Mediterranean region.[9] Although apple-specific IgE was negative in this case, it is also possible that an apple LTP-specific IgE-mediated allergic reaction developed.

Several published reports have highlighted cases of food hypersensitivity reactions following inhalation of airborne food allergens. In the literature, there are cases of allergic reactions to the odor of foods such as fish, eggs and cow's milk.[10-12] Sensitization may develop not only from childhood as in our case, but also after intense inhalation exposure to non-specific irritants at any period of life.[13]

CONCLUSION

Oral ingestion is the primary route of exposure to food allergens, which can cause or worsen allergic symptoms. However, an increasing number of published studies have highlighted allergic reactions to foods after inhalation. This case report provides an example of a food allergic reaction triggered by ingestion of the food as well as inhalation exposure to airborne food allergens. Patients with a history of allergic reaction after inhalation exposure to the relevant food should be considered. It should be kept in mind that environmental exposures to non-specific irritants (pepper spray), as in this case, may subsequently increase the reactivity of the respiratory tract. In addition to strict avoidance of the causative agent, such hypersensitive persons should carry an epinephrine auto-injector and identification indicating their allergic status. More publications are needed both to determine the accuracy and sensitivity of diagnostic tests and to determine the incidence of inhaled food allergy.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

REFERENCES

1. Sampson HA: Food allergy. Part 1: immunopathogenesis and clinical disorders. *J Allergy Clin Immunol*. 1999;103(5 Pt 1):717-728. doi:10.1016/s0091-6749(99)70411-2
2. Ballmer-Weber BK, Hoffmann-Sommergruber K. Molecular diagnosis of fruit and vegetable allergy. *Curr Opin Allergy Clin Immunol*. 2011;11(3):229-235. doi:10.1097/ACI.0b013e3283464c74
3. Yun J, Katelaris CH. Food allergy in adolescents and adults. *Intern Med J*. 2009;39(7):475-478. doi:10.1111/j.1445-5994.2009.01967.x
4. Wang ET. Anaphylaxis caused by tangerine seeds but not tangerine fruit. *Ann Allergy Asthma Immunol*. 2008;101(5):553-554. doi:10.1016/S1081-1206(10)60299-2
5. Zhu SL, Ye ST, Yu Y. Allergenicity of orange juice and orange seeds: a clinical study. *Asian Pac J Allergy Immunol*. 1989;7(1):5-8.
6. Turner PJ, Gray PE, Wong M, et al. Anaphylaxis to apple and orange seed. *J Allergy Clin Immunol*. 2011;128(6):1363-1365. doi:10.1016/j.jaci.2011.07.005
7. Suriyamoorthy P, Madhuri A, Tangirala S, et al. Comprehensive review on banana fruit allergy: pathogenesis, diagnosis, management, and potential modification of allergens through food processing. *Plant Foods Hum Nutr*. 2022;77(2):159-171. doi:10.1007/s11130-022-00976-1
8. Ricci A, Avanzini MA, Scaramuzza C, et al. Toll-like receptor 2-positive and toll-like receptor 4-positive cells in adenoids of children exposed to passive smoking [1]. *J Allergy Clin Immunol*. 2005;115(3):631-632. doi:10.1016/j.jaci.2004.11.044
9. Gülsen A, Jappe U. Lipid transfer protein sensitization in an apple-allergic patient: a case report from northern Europe. *Eur Ann Allergy Clin Immunol*. 2019;51(2):80-83. doi:10.23822/EurAnnACI.1764-1489.63
10. Crespo JF, Pascual C, Dominguez C, Ojeda I, Muñoz FM, Esteban MM. Allergic reactions associated with airborne fish particles in IgE-mediated fish hypersensitive patients. *Allergy*. 1995;50(3):257-261. doi:10.1111/j.1398-9995.1995.tb01143.x
11. Quirce S, Díez-Gómez ML, Eiras P, Cuevas M, Baz G, Losada E. Inhalant allergy to egg yolk and egg white proteins. *Clin Exp Allergy*. 1998;28(4):478-485. doi:10.1046/j.1365-2222.1998.00253.x
12. Olaguibel JM, Hernandez D, Morales P, et al. Occupational asthma caused by inhalation of casein. *Allergy*. 1990;45(4):306-308. doi:10.1111/j.1398-9995.1990.tb00500.x
13. Zuskin E, Kanceljak B, Schacter EN, Mustajbegovic J. Respiratory function and immunologic status in workers processing dried fruits and teas. *Ann Allergy Asthma Immunol*. 1996;77(5):417-422. doi:10.1016/S1081-1206(10)63341-8

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Thromboembolic complication of nephrotic syndrome: a case of pulmonary embolism

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ABSTRACT

Pulmonary thromboembolism (PTE) is a common, potentially fatal condition that can be challenging to diagnose. While risk factors like lower extremity fractures, myocardial infarction, immobilization, and malignancy are well known, nephrotic syndrome is a rare secondary cause. We present a 28-year-old male hospitalized with suspected nephrotic syndrome. On the second day of admission, he developed sudden chest pain and shortness of breath. Although he was hemodynamically stable, chest X-ray showed increased opacity in the right lower lung zone, suggesting infarction. Elevated D-dimer levels and right heart enlargement on bedside echocardiography raised suspicion of PTE, and anticoagulant treatment was initiated. CT pulmonary angiography confirmed thrombi in the right pulmonary artery and infarct areas. This case illustrates the rare coexistence of nephrotic syndrome and acute PTE in a young adult and underscores the importance of recognizing radiological signs and considering prophylactic anticoagulation.

Keywords: Nephrotic syndrome, membranous nephropathy, pulmonary thromboembolism, venous thromboembolism, young adult

INTRODUCTION

Venous thromboembolism (VTE) includes pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT).[1]

VTE is more common in older adults. Studies show a mean age above 50, with over half of cases occurring after age 65.[2]

PTE has high mortality and morbidity. Early diagnosis is essential and depends on clinical signs and identification of risk factors. These include genetic (primary) and acquired (secondary) causes. Nephrotic syndrome is a less frequent secondary cause.[2]

Patients with nephrotic syndrome have a well-known tendency for thromboembolic events. These events can involve both veins and arteries. PTE occurs in 1% to 20% of cases, with membranous nephropathy being particularly high-risk.[3]

There are no prevalence studies showing how often nephrotic syndrome appears in patients with PTE. The coexistence of both conditions is rare and needs further study.

This report presents a young adult who developed PTE while hospitalized for nephrotic syndrome.

CASE

A 28-year-old male with no known comorbidities or medication history presented to the internal medicine outpatient clinic with complaints of fatigue and bilateral leg swelling. Laboratory results revealed serum albumin of 18.9 g/L, urine protein 3+, and a spot urine protein/creatinine ratio of 20.573 mg/g. The patient was hospitalized by the nephrology department with a preliminary diagnosis of nephrotic syndrome. Further evaluation showed 6.613 mg/day of albumin and 8.432 mg/day of total protein in 24-hour urine collection. A renal biopsy was planned to investigate the underlying etiology. On the second day of hospitalization, the patient experienced sudden onset dyspnea, chest pain, and sharp back pain.

Postero-anterior chest radiograph taken in hospital application is provided in **Figure 1a**. Additionally, **Figure 1b** presents the anteroposterior chest radiograph of the patient, demonstrating the area of infarction (a pleural-based, irregular opacity in the right lower lung zone).

D-dimer was elevated at 2.4 µg/mL, while troponin levels were within normal limits, and ECG showed no ischemic changes. Arterial blood gas was pH 7.39, pCO_2 40 mmHg, HCO_3 24

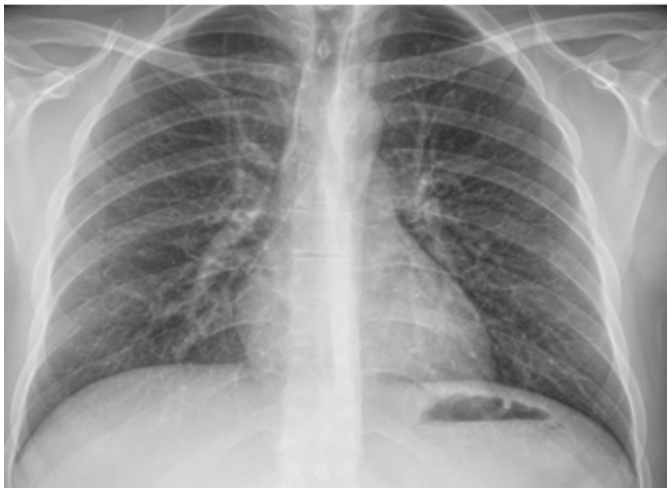

Figure 1a. Postero-anterior chest radiograph taken in hospital application

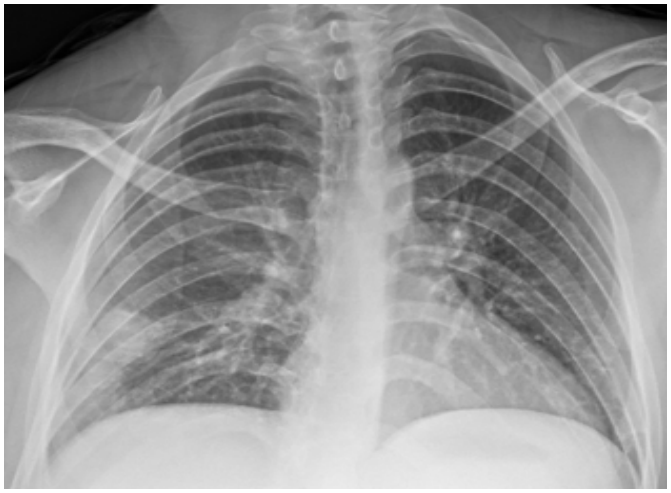

Figure 1b. Antero-posterior chest radiograph withdrawn when complaints started

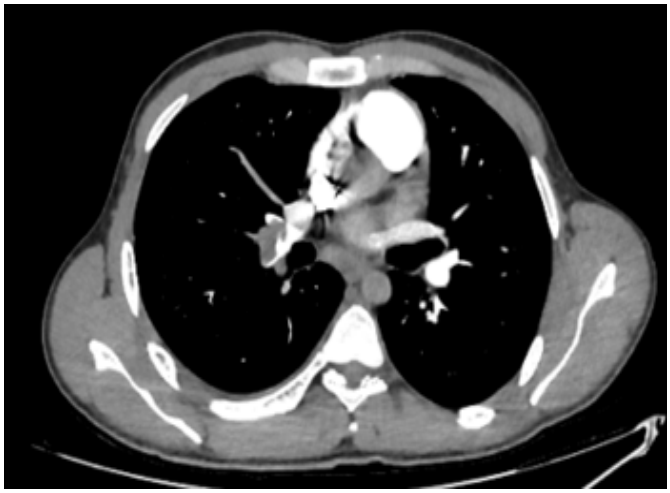

Figure 2a. Intraluminal thrombus in right main pulmonary artery middle lobe

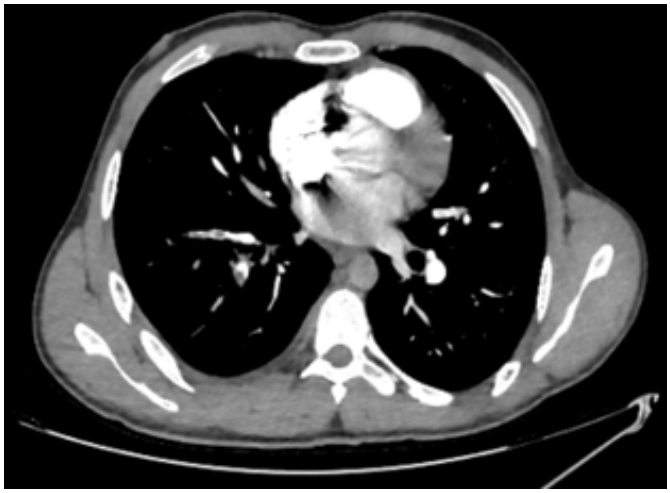

Figure 2b. Intraluminal thrombus in right main pulmonary artery lower lobe

mmol/L, and lactate 1.1 mmol/L. Acute phase reactants were unremarkable. Echocardiography showed an ejection fraction (EF) of 60%, systolic pulmonary artery pressure (sPAP) of 35 mmHg, and mild right chamber dilation. No thrombus was detected on bilateral lower extremity doppler ultrasound. The pulmonary embolism severity index (PESI) score was 1, and sPESI was 0, classifying the patient as low-risk PTE based on early mortality criteria. Anticoagulation was initiated with enoxaparin 0.6 ml twice daily, considering renal function and bleeding risk. CT pulmonary angiography (CTPA) performed 48 hours later revealed filling defects in the distal right main pulmonary artery extending to segmental branches of the middle and lower lobes (**Figure 2a, 2b**). Additionally, peripheral ground-glass consolidation with lobulated margins at the right lower lobe's basal segments suggested infarction (**Figure 3**).

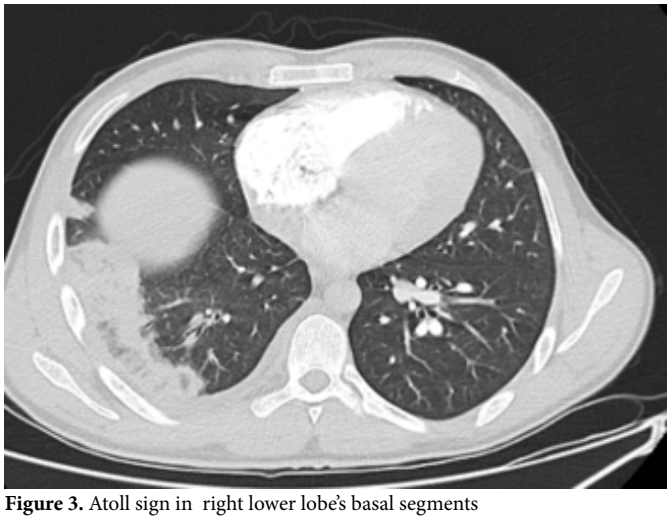

Figure 3. Atoll sign in right lower lobe's basal segments

This finding is known as the "reverse halo" or "atoll sign," a radiologic marker occasionally associated with PTE. Enoxaparin sodium and warfarin were administered concomitantly for 5 days. Once the INR reached the therapeutic range (2.0–3.0), enoxaparin was discontinued, and warfarin was continued. The warfarin dose was adjusted to maintain the INR within this range. The patient was planned to receive warfarin therapy for at least 6 months and is currently still on warfarin treatment. The patient will be followed up at regular intervals, and future decisions regarding anticoagulation will be based on clinical status and imaging to assess the risk of PTE.

Due to the patient's young age, thrombophilia screening was performed, revealing heterozygous mutations in factor V Leiden and factor C, and a homozygous mutation in MTHFR; no mutations were detected in protein C, protein S, or antithrombin III.

Based on hematology recommendations, anticoagulation was planned for a minimum of six months. The renal biopsy

was postponed, and anti-PLA2R antibodies were detected, confirming a diagnosis of membranous glomerulonephritis. In the treatment of membranous glomerulonephritis, the patient received 1.000 mg of intravenous rituximab on days 1 and 15. Pre-treatment infection screening was conducted, and premedication was administered to prevent infusion-related reactions. Clinical response was monitored via proteinuria and serum albumin levels. The treatment was well tolerated. In case of relapse during follow-up, additional dosing was planned.

DISCUSSION

Nephrotic syndrome is a hallmark of glomerular disease characterized by increased glomerular permeability to macromolecules, especially albumin, resulting in nephrotic-range proteinuria (>3.5 g/day). The classic clinical manifestations include hypoalbuminemia, hyperlipidemia, edema, and a hypercoagulable state. These features significantly contribute to the morbidity and mortality associated with nephrotic syndrome. Thromboembolic risk is a well-documented complication in nephrotic syndrome. The incidence of venous thrombosis has been reported around 15%, pulmonary embolism between 10–30%, and renal vein thrombosis in 25–37% of cases.[4,5] The hypercoagulable state is attributed to multiple mechanisms including increased hepatic synthesis of procoagulants (e.g., fibrinogen, factor V, factor VIII), heightened platelet activity and aggregation, reduced fibrinolytic activity, local activation of coagulation within the kidney, and urinary losses of natural anticoagulants such as antithrombin III.

However, the role of prophylactic anticoagulation in patients with nephrotic syndrome remains controversial.[6] In a retrospective study evaluating 298 patients with primary and secondary nephrotic syndrome, the risk of thromboembolism was found to be eight times higher than the general population over a 10-year period. The highest risk was observed within the first six months and was strongly associated with the degree of proteinuria and hypoalbuminemia.[6] A 2023 study published in Medicina Clinica explored the predictive value of phospholipase A2 receptor (PLA2R) antibodies in membranous nephropathy. Anti-PLA2R positivity, a marker of disease activity in primary membranous nephropathy, was associated with a significantly higher risk of VTE compared to anti-PLA2R negative cases.[7] According to the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, anticoagulation should be considered in membranous nephropathy patients with serum albumin levels below 2.0–2.5 g/dl and additional risk factors, albeit with a low level of evidence (2C). The guideline recommends full-dose anticoagulation in nephrotic syndrome patients who develop a thromboembolic event.[7] Limited data exists on outcomes of patients receiving prophylactic anticoagulation. The only controlled study on this topic was a retrospective analysis by Kelddal et al.[9], suggesting a cautious use of anticoagulation—especially in patients with serum albumin <2 g/dl—in combination with aspirin may be beneficial. Similarly, a 2024 meta-analysis by de Pascalini[8] reported that, although associated with a non-negligible risk of bleeding, prophylactic anticoagulation significantly reduces the risk of VTE in adult patients with primary nephrotic syndrome. In this case, the patient presented with nephrotic syndrome and respiratory symptoms suggestive of thrombosis. The diagnosis of PTE was supported by imaging findings showing thrombi in the pulmonary arteries and the presence of a “reverse halo” sign in the lung parenchyma. The patient responded well to anticoagulation therapy, initially with enoxaparin and subsequently with warfarin. This case highlights the importance of considering PTE in young patients with nephrotic syndrome who develop respiratory complaints and raises the issue of whether prophylactic anticoagulation should be routinely considered in such high-risk individuals.

CONCLUSION

Nephrotic syndrome is a significant risk factor for VTE. Patients should be systematically evaluated for thromboembolic complications. In young individuals with nephrotic syndrome presenting with chest pain and dyspnea, the possibility of pulmonary embolism must be promptly considered and investigated.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

REFERENCES

1. Dickson BC. Venous thrombosis: on the history of Virchow’s triad. *Univ Toronto Med J.* 2004;81(3):166-171.
2. Turkish Thoracic Society. Pulmonary thromboembolism diagnosis and treatment consensus report. 2021.
3. Yang Y, Lv J, Zhou F, et al. Risk factors of pulmonary thrombosis/embolism in nephrotic syndrome. *Am J Med Sci.* 2014;347(1):33-37. doi: 10.1097/MAJ.0000000000000315
4. Sagripanti A, Barsotti G. Hypercoagulability, intraglomerular coagulation and thromboembolism in nephrotic syndrome. *Nephron.* 1995;70(3):271-281. doi:10.1159/000188604
5. Ikeda S, Takaya Y, Takahashi K, et al. A case of nephrotic syndrome associated with pulmonary infarction and renal vein thrombosis. *Nippon Jinzo Gakkai Shi.* 1989;31(8):883-889.
6. Gordon-Cappitelli J, Choi MJ. Prophylactic anticoagulation in adult patients with nephrotic syndrome. *Clin J Am Soc Nephrol.* 2019;14(10):1592-1600. doi:10.2215/CJN.05250419
7. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int.* 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021

8. De Pascali F, Brunini F, Rombolà G, Squizzato A. Efficacy and safety of prophylactic anticoagulation in patients with primary nephrotic syndrome: a systematic review and meta-analysis. *Intern Med J.* 2024; 54(2):214-223. doi:10.1111/imj.16227
9. Kelddal S, Nykjær KM, Gregersen JW, Birn H. Prophylactic anticoagulation in nephrotic syndrome prevents thromboembolic complications. *BMC Nephrol*. 2019;20(1):139. doi:10.1186/s12882-019-1336

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Case Report

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Chest wall pilomatrixoma

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ABSTRACT

Pilomatrixoma is a rare soft tissue tumor of generally benign nature that originates from pluripotent matrix cells and does not present specific radiological findings. It most commonly occurs in the second decade of life and in female individuals. Approximately half of the cases are localized in the head and neck region, and the main treatment method is surgical resection. In this report, we aimed to present two cases of chest wall pilomatrixoma in middle-aged male patients which were treated surgically.

Keywords: Pilomatrixoma, chest wall, soft tissue tumor

INTRODUCTION

Pilomatrixoma or Malherbe's calcifying epithelioma was first described in 1880 and named pilomatrixoma by Forbis and Helwig in 1961. Pilomatrixoma originates from hair follicle cells. Most of these tumors exhibit a mutation in the CTNNB1 gene (3p22-p21.3), leading to overexpression of beta-catenin, which stimulates cell growth and proliferation.[1] Beta-catenin functions in Wnt signaling pathways as a cellular signaling and cytoskeletal protein. The presence of mutations is thought to increase the potential for transformation from benign pilomatrixoma to malignant pilomatrix carcinoma.[2] Although larger benign lesions have been reported in the literature, they are generally benign soft tissue tumors smaller than 3 cm. While most of these tumors are tend to be benign, cases of metastatic malignant pilomatrixoma have also been reported.[1-3] Nearly 50% occur in the head and neck region, but they can also be found on the thorax, trunk, and extremities. They are usually solitary nodules and rarely multiple. Cystic nodules may harden over time due to calcification. Their growth is slow, and they are more commonly seen in females by a 3:2 ratio in the first two decades of life.[3,4] Although the etiology is not fully understood, these tumors, which may be hereditary, have been found to be associated with Gardner syndrome, Steinert's disease, and sarcoidosis.[5] Additionally, post-vaccination (e.g., COVID-19, influenza) and trauma-associated cases have been reported.[6] Clinical and radiological features are non-specific. Ghost or shadow cells observed pathologically are diagnostic for pilomatrixoma.[7]

CASE

In our study, we present two cases that were admitted to our clinic with complaints of a gradually growing and painful swelling on the chest wall. Both patients were male, aged 36 and 43 years, respectively. Both had nearly 2 cm in diameter, palpable lesions on the right anterior chest wall. Neither patient had a history of significant trauma, infection, or comorbidities. Both of the patients were active smokers. One patient reported that he had noticed the lesion for 4 months, and the other reported that he had noticed it for 6 months. Both patients reported that the lesion, which had been growing, had recently started to cause pain. Both patients were evaluated with ultrasonography and thoracic computed tomography (CT) [**Figure**]. It was reported as a solid, well-circumscribed lesion on the chest wall, with no radiological findings to suggest a specific diagnosis. Both patients underwent surgical excision with clear surgical margins. They were discharged the same day. The final histopathological examination revealed benign pilomatrixoma.

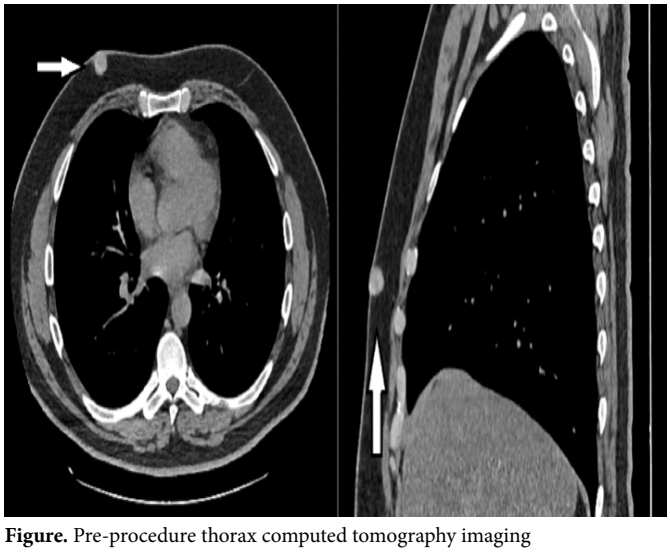

Figure. Pre-procedure thorax computed tomography imaging

CONCLUSION

Considering gender and age, our cases do not align with the literature. While pilomatrixomas are typically observed as single lesions in the head and neck region in 50% of cases, our cases had single lesions localized in the right anterior chest wall. In this regard, the number and location of lesions in our cases deviate from general literature findings. Consistent with the literature, the lesion size in both patients was under 3 cm, and there were no specific clinical or radiological findings. In conclusion, pilomatrixoma is a rarely seen pathological diagnosis that is often not considered in differential diagnosis and is generally benign. Chest wall lesions should also consider pilomatrixoma in the differential diagnosis alongside dermoid cysts, calcified hematomas, giant cell tumors, foreign body reactions, and lipomas. Surgical excision with clear margins remains the primary treatment, and generally, no additional treatment or follow-up is needed. However, the rare possibility of transformation into malignant pilomatrix carcinoma should not be overlooked.

ETHICAL DECLARATIONS

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

REFERENCES

1. Poch G, Vokuhl C, Klapper W, Erkens AS, Fölster-Holst R. Enlarging tumor of the lateral chest wall in a 14-year-old boy. *J Dtsch Dermatol Ges*. 2018;16(5):640-643. doi:10.1111/ddg.13428
2. Briley T, Sobiesk JL, Chu Q. Pilomatrix carcinoma: a rare hair cell tumor. *Am Surg*. 2020;86(1):e38-e39.
3. Nikolaidou E, Papadopoulou S, Tzimorota Z, Pipinia A, Stampou P, Karagergou E. Giant pilomatrix carcinoma of the thorax: an uncommon and clinically misdiagnosed tumor. *Plast Reconstr Surg Glob Open*. 2023;11(7):e5101. doi:10.1097/GOX.0000000000005101
4. Jones CD, Ho W, Robertson BF, Gunn E, Morley S. Pilomatrixoma: a comprehensive review of the literature. *Am J Dermatopathol*. 2018; 40(9):631-641. doi:10.1097/DAD.0000000000001118
5. Ciriacks K, Knabel D, Waite MB. Syndromes associated with multiple pilomatricomas: when should clinicians be concerned? *Pediatr Dermatol*. 2020;37(1):9-17. doi:10.1111/pde.13947
6. Nakazono M, Kawai M, Mizukami A, Kondoh A, Yamaoka H, Mabuchi T. Case of pilomatricoma after coronavirus disease 2019 vaccination. *Tokai J Exp Clin Med*. 2023;48(1):10-12.
7. Fu H, Shen C, Wu B, et al. Clinical and pathological features of pilomatrixoma in children: a retrospective study. *Dermatology*. 2024; 240(4):543-552. doi:10.1159/000538802

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Letter to the Editor

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Chronic cough and Sjogren's syndrome

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Keywords: Cough, Sjogren's syndrome, allergy

Dear Editor,

This year, i presented a study evaluating patients who presented with chronic cough in immunology allergy clinic.[2] Among the 106 patients evaluated, 11 were identified as experiencing cough secondary to Sjogren's syndrome. This represents a noteworthy proportion. Accordingly, i deemed it appropriate to compose this letter to provide a more detailed presentation of the clinical characteristics and findings observed in these patients

Cough is a defensive reflex for protect the lung from aspirationin normaly. It develops as a symptom in some diseases. If a cough lasts longer than eight weeks, it is considered a chronic cough. In some cases, it can be excessive, uncomfortable and take a long time. Chronic cough has many cause and the causes are different in children and adults. In adults most of them; astma, chronic obstructive pulmonary disease (COPD), seconder after viral enfections, gastroesophageal reflux disease/laryngopharyngeal reflux disease, tobacca use and etc. Despite extensive research, the cause may not be identified and this condition is mentioned in idiopathic chronic cough.[1]

Sjogren's syndrome have dry mouth and dry eye symptoms, especially due to lymphocyte infiltration in the exocrine glands. It can also occur with systemic involvement. The diversity of disease symptoms and differences in the course of the disease cause difficulties in the diagnosis of SS. There is no single gold standard diagnostic method such as pathology or laboratory findings. An attempt has been made to standardize diagnosis using criteria. The American College of Rheumatology and the European League Against Rheumatism (ACR-EULAR) updated the diagnostic criteria in 2017. According to these criteria, the diagnosis is established by scoring a combination of tests, including results of ocular dryness assessments (schimmer test), the presence of specific autoantibodies, histopathological evaluation of salivary gland tissue, and measurements of salivary flow rate. Salivary gland histopathological classification in SS was made by Chisholm and Mason[3] in 1968.

These diagnostic criteria are applied if certain conditions for the disease are met. These requirements include that in people with dry eye or mouth symptoms, the symptoms must last for at least three months, the need to use tear drops more than three times a day, a feeling of sand in the eyes, the need to eat dry foods with liquids, and the desire to drink water at night due to dry mouth. Diseases such as amyloidosis, sarcoidosis and hepatitis C should be excluded along with dry mouth due to anticholinergic drug use.[4]

In our study; in patients with chronic, long-standing cough of unknown etiology particularly when symptoms worsen during eating, when assistance with swallowing using liquids is required, and when physical examination reveals a dry, dehydrated tongue we considered the possibility of Sjogren's syndrome and proceeded with investigations in that direction.

The evaluation was performed in collaboration with the rheumatology department, using the diagnostic criteria recommended by the ACR-EULAR. Only two patients had a prior diagnosis of Sjogren's syndrome, while the initial clinical presentation in the remaining nine patients was chronic cough. In our study, the diagnosis rate of Sjogren's syndrome was determined to be 8.5%.[2] None of the patients showed evidence of systemic involvement. Among those previously diagnosed, clinical signs of arthritis were present. The other patients reported nonspecific arthralgia predominantly in small joints. None of the patients had elevated acute phase reactants. The clinical findings of these patients are presented in **Table**.

There were four patients with a history of hypertension. Two of the patients were using ACE inhibitors. Despite the switch to ARB blockers, their complaints continued, and dry mouth and eye symptoms were present, prompting further investigation and diagnosis.

All patients were female, with a mean age of 53 years. The most notable finding was the absence of systemic

Table. Clinical findings in patients with Sjogren's syndrome presenting with chronic cough

Patients	Age	Gender	Duration of symtoms (year)	Comorbidity	RF	ANA pattern	ENA	Schimmer test	Chisholm-Mason score
Patient-1	56	Female	3	-	47	++ Reticular	-	8/10	2
Patient-2	44	Female	2	-	20	++ Centromere	Anti-Ssa++	4/5	Not done
Patient-3	50	Female	20	Hypertension	14	++ Granulare	Anti Ssa ++ AntiSm/RNP ++	3/2	Not done
Patient-4	44	Female	4	Hypothyroidis	10	+++ Homageneous	AntiSSb:++ Anti Ssa ++	2/2	Not done
Patient-5	60	Female	2	Hypertension	147	+ spotted	AntiSSa:++ AntidsDNA:+	5/5	Not done
Patient-6	55	Female	30	Hypertension	10	++ Homageneous	-	4/2	3
Patient-7	56	Female	1	-	8	+++ Centromere	-	4/4	2
Patient-8	45	Female	4	-	12	++ Nucleolar	-	-/-	2
Patient-9	54	Female	2	Hypertension	40	++ Homogeneous	AntiDsDNA +	4/2	Not done
Patient-10	52	Female	2	-	58	++ Granulare	-	2/-	Not done
Patient-11	58	Female	3	-	34	++ Granulare	-	-/-	3

involvement and arthritis symptoms in this cohort. Although symptoms of dry mouth and dry eyes were present, dryness and inflammation were confirmed through Schirmer's test and labial salivary gland biopsy. These patients had mild symptoms such as skin and oral dryness, which may not have significantly impacted their daily comfort, and thus likely did not prompt them to seek medical attention. However, due to their persistent cough, they were referred to the allergy clinic, where further investigations led to the diagnosis. It is known that there is a subset of Sjogren's syndrome patients without systemic involvement; however, even in such cases, arthritis is commonly observed.[4] In our patient group, arthralgia was present, but the lack of more extensive systemic symptoms suggests either that these patients were identified at an early stage of the disease or that they may represent a subclinical phenotype of Sjogren's syndrome, manifesting only with dryness of the mouth, eyes, and skin. There is no study in the literature describing the relationship between chronic cough and Sjogren's syndrome. Data related to Sjogren's syndrome is more commonly associated with systemic involvement. Pulmonary involvement is reported to be at a rate of 23% in the study by Kabasakal et al.[5] However, cases of cough due to mucosal dryness without pulmonary involvement have been reported in case series. This is presented in our study.[1] During the treatment, patients were warned about adequate daily fluid intake and advised to chew gum to stimulate salivary gland function. Antimuscarinic drugs such as pilocarpine have been recommended to increase salivation in patients whose daily lives are affected by dry mouth and cough. Only two patients required anticholinergic treatment. In the remaining patients, symptoms significantly improved but did not completely resolve after being informed about the treatment. Anticholinergic therapy was planned in case of symptom exacerbation. This letter was written to emphasize that this condition should be considered in the differential diagnosis of chronic cough, and that patients with Sjogren's syndrome may initially present with cough before a rheumatologic diagnosis is established.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

REFERENCES

1. Aksakal Ş, Evaluation of chronic cough in an immunology and allergy clinic in the Black Sea region: causes, prevalence and outcomes. *Experimental Biomedical Research*. 2025;8(2):72-79. doi:10.30714/j-ebr.2025.238
2. Chung KF, McGarvey L, Song WJ, et al. Cough hypersensitivity and chronic cough. *Nat Rev Dis Primers*. 2022;8(1):45. doi:10.1038/s41572-022-00370-w
3. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjogren's disease. *J Clin Pathol*. 1968;21(5):656-660. doi:10.1136/jcp.21.5.656
4. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis*. 2017;76(1):9-16. doi:10.1136/annrheumdis-2016-210571
5. Kabasakal Y, Kitapçıoğlu G, Karabulut G, et al. Criteria sets for primary Sjogren's syndrome are not adequate for those presenting with extraglandular organ involvements as their dominant clinical features. *Rheumatol Int*. 2017;37(5):675-684. doi:10.1007/s00296-017-3691-8