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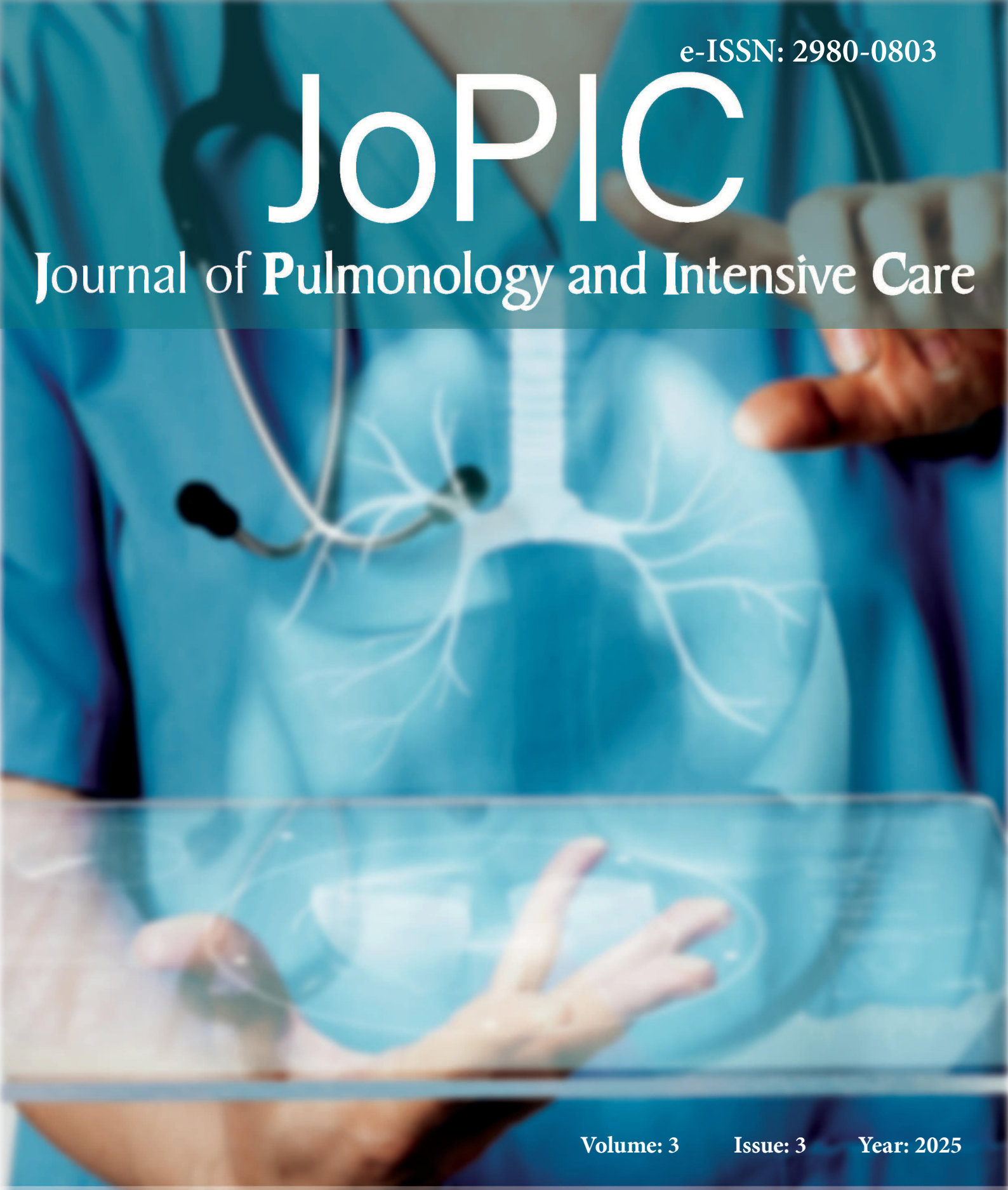

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Evaluation of tryptase levels in anaphylaxis

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ABSTRACT

Aims: Tryptase is a serine protease released from mast cells during an acute allergic reaction. Levels of serum tryptase vary among healthy individuals, and there has been a growing debate about the normal and abnormal ranges of tryptase depending on the numbers of mast cells, basal secretion rate, and renal function. To address this point, serum tryptase levels were analyzed in subjects with a prediagnosis or absolute diagnosis of anaphylaxis.

Methods: This was one-centered study performed in a Tertiary Hospital in Turkiye. Patients whose serum tryptase levels were measured between 2020 and 2023 were retrospectively included in this single-center study. Serum tryptase levels that is moment at reaction (RT) and as basal (BT) were analyzed with the same method with ImmunoCAP (Pharmacia, Uppsala, Sweden). The age, gender and reasons for admission of the patients were examined one by one.

Results: Out of approximately 400 test entries, there were valid results of 300. A ratio of 62% of the patients were female (n: 186) and 38% were male (n: 114). The mean age was 18-89 (41.5±14.7)/year. Serum levels of tryptase were measured at the time of reaction in 12.7% of the patients, 4.3% had both reaction and baseline tryptase levels, and the rest had only baseline tryptase analyses. A statistically significant difference was found between the tryptase levels during the reaction in males and females (p: 0.02, female/male: 7.26±4.91/16.93±11.11 µg/L). We found that approximately 90.3% of the patients had serum tryptase levels lower than 11.5 µg/L. There was a statistically significant difference between reaction time (RT) and baseline tryptase (BT) in drug-induced hypersensitivity reactions (p: 0.02), but no difference was found in venom hypersensitivity reactions (p:0.47). There was no correlation between age and tryptase during reaction, but a positive correlation was found between baseline tryptase (p:0.01 r:0.162).

Conclusion: There may be many reasons for high serum tryptase levels. For doctors, it is important to quickly recognize anaphylaxis and manage the treatment process quickly. In this study, we reviewed all tryptase results retrospectively and addressed the etiology of the cases we encountered in our center. We showed that age is a baseline variable in determining tryptase levels. Tryptase can be used as a useful biomarker in diagnosis.

Keywords: Tryptase, anaphylaxis, urticaria, venom, drug

INTRODUCTION

Tryptase is an abundant granule-derived serine protease that is mainly produced by mast cells (MC) and to a much lesser extent by basophils.[1-4] In humans, there are five isoforms as α-, β-, γ-, δ-, and ε-tryptase,[5-7] and precursor forms of α- and β-tryptase are spontaneously secreted by MC during allergic reactions such as anaphylaxis. Mature β-tryptase is retained in secretory granules until its released by activated cells,[9] whereas α-tryptase appears to be processed only to the proform by human MC.[5] Resting MC constitutively secrete monomeric (inactive) pro-tryptase whereas in the case of MC degranulation (e.g. during anaphylaxis), MC release mature tetrameric (active) tryptase.[8,9]

Serum tryptase levels can be measured during the first hours of anaphylaxis, and immunoCAP (Pharmacia, Uppsala, Sweden) measures monomeric and tetrameric forms together (i.e., total serum tryptase) with no subtype specification.[10] Tryptase has proven to be a very useful and specific biomarker to demonstrate MC activation and degranulation during an acute anaphylactic reaction (i.e., within 4 h after the event). Afterwards, a second test after at least 24 h of the allergic reaction to measure baseline value is recommended to make a comparison of tryptase levels. An increase of 20% of basal tryptase levels plus two during the reaction is considered as anaphylaxis.[11-14]

Diagnosis of anaphylaxis is based on suggestive clinical symptoms after exposure to a potential triggering agent which may be supported by in vitro tests.[15] Currently, plasma histamine (or its metabolite, methylhistamine in urine) and total serum tryptase are the only biomarkers available for routine use. The rationale for the use of these mediators for diagnosis is based on the fact that tryptase and histamine contained in MC granules are released upon activation of

the cell. Nowadays, serum tryptase concentration is the most used laboratory test to confirm anaphylaxis. According to current knowledge, tryptase is the best biomarker to assess MC activation. Levels are increased from 15 min to 3 h after anaphylaxis onset.[16,17]

Anaphylaxis is an acute, systemic type 1 hypersensitivity reaction that occurs after re-exposure to an antigen. Anaphylactic reaction is caused by cross-linkage of antigen-specific IgE molecules bound to the surfaces of tissue MC and peripheral blood basophiles, which then undergo degranulation and release a variety of potent mediators including histamine and tryptase. The clinical manifestations of anaphylaxis vary in expression based on immunologic and nonimmunologic factors, which makes a difference in tryptase elevations.[18,19]

A study of postmortem tryptase including 10 anaphylactic deaths found sensitivity of 0.86 and specificity of 0.88 using a 10 µg/L cut-off.[20] Another found tryptase to be elevated in 14/16 anaphylactic deaths (sensitivity 0.88).[21]

A study showed cutoff of tryptase levels at 8.23 ng/ml with a 94.12% sensitivity and 92.31% specificity by using fluoroimmunoassay (UniCAP Tryptase, Pharmacia & Upjohn) in patients with anaphylaxis, whereas the 13.5 ng/ml cutoff recommended by the manufacturers showed 35.29% sensitivity and 92.31% specificity.[22]

Role of Tryptase in Mastocytosis

Mastocytosis results from a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal MC that accumulate in one or more organ systems. If basal serum tryptase is more than 20 ng/ml, a minor criterion for the diagnosis of systemic mastocytosis is met.[23] MC develop from their uncommitted and MC-committed hematopoietic stem and progenitor cells in the bone marrow and other organs under the influence of stem cell factor, the ligand of the tyrosine kinase receptor KIT.[24]

Recently, elevated tryptase levels in several family members with atypical symptoms of MC activation have been shown to relate to the duplication or triplication of tryptase alpha and beta genes, and it is estimated that 4% to 6% of the general population have increased tryptase gene copy numbers with unclear clinical significance.[25] These patients present baseline and/or acute elevations of MC mediators including tryptase, urinary histamine, and/or prostaglandins.[26]

MC disorders are associated with a greater risk of anaphylaxis. These patients have generally elevated tryptase levels not only during the allergic reaction, but also at baseline. In cases of recurrent unexplained anaphylaxis, elevated basal serum tryptase levels are key to diagnose mastocytosis.[27] Recently, serum tryptase was introduced as an additional diagnostic marker of the disease.[28]

The most common cause of high tryptase value is hereditary alpha tryptasemia (91%), followed by chronic renal failure (7%) and hematological malignancies and mastocytosis (1%).[29] Moreover, obesity can be a cause of elevated tryptase,[30] as well as helminthic infections, hematological malignancies, cardiovascular disease, (nummular) eczema, or rare genetic mutations (e.g., GATA2 or PLAID).[29-31] Even alcohol consumption[32] or tobacco smoking[33] can decrease or elevate serum tryptase, respectively. Also, a case of a patient with Gaucher disease type 1, a lysosomal storage disorder, was reported to have an elevated tryptase level (up to 80 ng/ml) that improved upon initiation of enzyme replacement therapy.[34] Finally, interference with the immunoassay may lead to a false positive result (e.g., by heterophilic antibodies).[35] Tryptase also tends to rise with age.

In Turkiye, the most common causes of anaphylaxis in children are foods, bee venom and drugs;[18] drugs and bee venom in adults.[36] All drugs may potentially cause anaphylaxis. However, nonsteroidal anti-inflammatory agents and betalactam antibiotics are frequently seen.[37,38] When the cause cannot be determined despite all investigations such as measurement of specific IgE levels against potential allergens, skin tests, and detailed clinical evaluation, this is called idiopathic anaphylaxis. Symptoms are the same as those that occur during anaphylaxis with known triggers and may include angioedema, urticaria, tachycardia, pruritus, flushing, dyspnea, wheezing, tachypnea, stridor, dysphagia, hoarseness, nausea, vomiting, diarrhea, syncope, hypotension, and abdominal discomfort. Clinical diagnostic criteria are used for the diagnosis. The World Allergy Organization (WAO) criteria were used for diagnosis. Hypotension/bronchospasm/larynx involvement or acute onset of skin and/or mucosal involvement with respiratory failure or evidence of end-organ damage or severe gastrointestinal symptoms after known or probable allergen exposure.[39]

In a study conducted in our country, the most common culprit drugs were nonsteroidal anti-inflammatory drugs (NSAIDs) (56.9%) and β-lactams (34.7%). The culprit drugs were used parenterally in 13.2% of the patients. Serum basal tryptase value was 3.5 µg/L.[40]

Rationale of this study was that there wasn't many studies about the usefulness of tryptase in phenotyping allergic reactions as anaphylaxis or other immediate type hypersensitivity reactions. Because of this study was to assess the usefulness of tryptase to diagnose anaphylaxis in patients attending the allergic clinic and/or emergency room with clinical symptoms of allergic reaction. Our hypothesis was that tryptase is a useful biomarker in the diagnosis of immediate type hypersensitivity reactions.

METHODS

The study was carried out with the permission of the Kırıkkale University Scientific Researches Evaluation and Ethics Committee (Date: 26.02.2025, Decision No: 2005.02.27). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.This was a retrospective, one-centered study performed. Patient recruitment criteria was that files of patients with tryptase levels between 2020 and 2023 were evaluated in detail. Serum tryptase levels that is moment at reaction (RT) and as basal (BT) were analyzed with the same method with ImmunoCAP (Pharmacia, Uppsala, Sweden).

The age, gender and reasons for admission of the patients were examined one by one. Patients were classified into anaphylaxis, urticaria and control groups according to history and clinic. The diagnosis of "anaphylaxis" was confirmed according to the WAO diagnostic criteria by checking the medical history of patients diagnosed with anaphylaxis. The urticaria group included patients diagnosed with urticaria limited to skin involvement without any other symptoms or organ involvement. The control group included patients with no disease. When the causes of anaphylaxis were examined, they wererecorded in detail as drug, food, bee venom, idiopathic, cold and mastocytosis.

Statistical Analysis

The data was analyzed using SPSS Statistics software (IBM Corp., Armonk, NY, USA). Descriptive statistics, such as numbers and percentages, were used to summarize the demographic and clinical characteristics of the participants. To determine the factors influencing the decision to use tryptase multivariate regression analysis was performed. For the comparison of two groups, the Independent Samples t-test was applied for normally distributed variables, while the Mann-Whitney U test was used for variables that did not show normal distribution. The normality of the data distribution was assessed using the Shapiro-Wilk test. A p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

A total of 300 patients were scanned, whose tryptase levels were checked when they applied to the hospital (**Table 1**). A ratio of 62% of the patients were female (n:186) and 38% were male (n:114). The mean age was 18-89 (41.5±14.7)/year. Serum levels of tryptase was measured at the time of reaction in 12.7% of the patients, 4.3% had both reaction and baseline tryptase levels, and the rest had only baseline tryptase analyses. The baseline tryptase levels in women was 3.66±1.95 µg/L, and the baseline tryptase level in men was 3.83±1.19 µg/L (p: 0.053). A statistically significant difference was found between the tryptase levels during the reaction in males and females (p:0.02, female/male: 7.26±4.91/16.93±11.11 µg/L).

Table 1. Demographics of the study group were given

%	All	Anaphylaxis	Urticaria-angioedema	Control
n	300	153	93	54
Age * (min-max)	41.58±14.77 (18-89)	43.70±15.19 (18-89)	40.08±13.87 (19-72)	38.19±14.41 (18-75)
Female, n (%)	186 (62)	86 (56.2)	64 (68.8)	36 (66.7)
Etiology	246			
Drug allergy	91 (36.9)	65 (42.4)	26 (28)	-
Food allergy	15 (6.1)	8 (5.2)	7 (7.5)	-
Venom allergy	64 (26)	49 (32)	15 (16)	-
Idiopathic	65 (26.5)	22 (14.3)	43 (46.2)	-
Cold	5 (2)	4 (2.6)	1 (1.1)	-
Mastocytosis	6 (2.5)	5 (3.2)	1 (1.1)	-

Min: Minimum, Max: Maximum, *:Mean±standard deviation

The ratio of 51% of the applicants were diagnosed with anaphylaxis and 31% with urticaria. In 51 patients presenting with anaphylaxis, tryptase was measured at the time of the reaction with an average of 15.7±14.4 (2.3-75.5) µg/L. There were six patients diagnosed with mastocytosis. The values of baseline tryptase in 262 patients were 4±2.6 (1-183) µg/L. In general, it is seen that the first active agent causing complaints is drugs, followed by venom (**Figure**). The most common drug group was NSAID (n:43, 14.3%). In patients presenting with anaphylaxis, the most common cause was found to be drugs in 42% (n:65). The baseline tryptase levels of those with food allergy (n:15) were 3.20±1.38 (1-6) µg/L. Only one patient had their tryptase measured at the time of the reaction, and the value was found to be 30.6 µg/L.

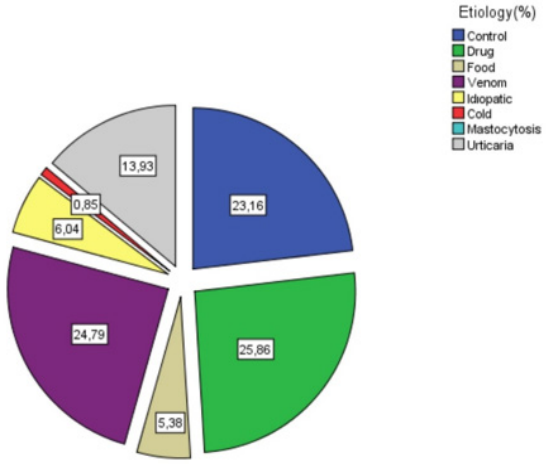

Figure. Rates of reasons in tryptase use during anaphylaxis

We found that approximately 90.3% of the patients had serum tryptase levels lower than 11.5 µg/L. There was a statistically significant difference between RT and BT in drug-induced hypersensitivity reactions (p: 0.02), but no difference was found in venom hypersensitivity reactions (p:0.47) (**Table 2, 3**).

Table 2. Basal and reaction time levels of serum tryptase

Mean±standard deviation (µg/L)	Anaphylaxis (n:153)	Urticaria-angioedema (n:93)	Control (n:54)	p
Basal tryptase	3.06±2.51	3.42±1.79	3.90±2.07	0.27
Reaction time tryptase	14.27±7.12	14.56±5.83	-	0.93

Table 3. Comparison of basal and reaction time tryptase among etiology

Mean±standard deviation (µg/L)	Basal (BT)*	During reaction (RT)*	p
Drug	3.61±1.96	11.92±9.79	0.02
Venom	3.89±2.19	10.74±2.78	0.47

There was no correlation between age and tryptase during reaction, but a positive correlation was found between baseline tryptase (p:0.01 r:0.162). When linear regression analysis was examined between age and reaction, p:0.009 odds ratio [OR]=0.023, confidence interval [CI] 0.06-0.040.

DISCUSSION

The relationship between basal tryptase and age was investigated. It was observed to be approximately 3.3 µg/L between the ages of 10 and 29, followed by a constant increase with age, and the median was found to be 5.4 µg/L after the

age of 70.[41] In our study, the mean basal tryptase was 4±2.6 (1-183) µg/L, and the basal tryptase value increased with increasing age.

Many centers consider the normal range of basal serum tryptase as being <11.4 ng/ml. We found similar baseline tryptase values. However, the use of upper limits of normal ranges as wide-ranging as 8.23 µg/L[22] and 14 µg/L[42] have also been reported. In our research data, RT were <8 µg/L, which may be due to early blood collection.

Recent publications suggest that the global incidence of anaphylaxis ranges from 50 to 112 episodes per 100.000 person-years, with an estimated lifetime prevalence of 0.3–5.1%.[39] A study evaluating 102 anaphylactic adult cases of food allergy or drug allergy concluded that tryptase levels were not increased and that more sensitive markers for anaphylaxis are needed.[43] In our study, when the increase rates in patients were compared from BT to RT, there was an increase of at least 20%+2 µg/L. According to our data, tryptase is a good marker for the diagnosis of anaphylaxis.

Drug-induced anaphylaxis is most commonly triggered by antibiotics and NSAIDs, with age and geographic variation worldwide. Drugs in general are cited as the leading cause of anaphylaxis deaths in adults.[44] NSAI drugs were the primary cause of both presentation and anaphylaxis. In our study, an increase in between BT and RT was found with the drugs, but not with venom. Another study found no association between the severity of NSAID hypersensitivity and elevated baseline serum tryptase levels. The same study also found an association between venom allergy and elevated baseline tryptase levels.[45] The higher baseline tryptase levels in the patients in this study may be due to factors such as different geographic regions and age.

Venom allergy is a typical IgE-mediated reaction because of sensitization to one or more allergens of the venom, and accounts for 1.5-34% of all cases of anaphylaxis.[46] Similarly, in our sample group, there was a 32% rate of venom-induced anaphylaxis applications.

They reported that tryptase levels are rarely elevated in food-induced anaphylaxis.[47,48] This is likely due to localized degranulation rather than general mast cell degranulation. It is thought that the small amount of tryptase entering the circulation is not sufficient to elevate serum levels.[48,49] In our study, we lacked RT data on patients who experienced food-induced anaphylaxis, and the value found in a single patient was elevated. This data contradicts the literature and may be due to the severity of the reaction.

Limitations

To validate our findings, future studies should be conducted with larger sample sizes and populations that have greater diversity in terms of occupation and other relevant factors. One of the limitations of our study is the chronic diseases of the patients and the lack of information on the time of reaction when tryptase was measured.

CONCLUSION

There may be many reasons for high serum tryptase levels. For doctors, it is important to quickly recognize anaphylaxis and manage the treatment process quickly. In this study, we reviewed all tryptase results retrospectively and addressed the etiology of the cases we encountered in our center. We showed that age is a baseline variable in determining tryptase levels. Tryptase can be used as a useful biomarker in diagnosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kırıkkale University Scientific Researches Evaluation and Ethics Committee (Date: 26.02.2025, Decision No: 2005.02.27).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The relationship between elevated blood metal levels and pneumoconiosis profusion scores and opacity size: a study on foundry workers

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ABSTRACT

Aims: This study aims to describe the demographic, clinical, and radiological characteristics of foundry workers diagnosed with pneumoconiosis and to investigate the association between blood metal levels and disease severity, with particular emphasis on radiological grading based on the International Labour Organization (ILO) classification, including profusion scores and small opacity types.

Methods: A total of 45 foundry workers with radiologically confirmed pneumoconiosis were included. Data on age, smoking history, pulmonary function tests, occupational duration, working units, and blood metal concentrations were collected. Radiological assessment was conducted using the ILO classification. Workers were categorized into two groups based on whole blood metal concentrations (normal vs. elevated). Additionally, radiological severity was compared across work units. Comparative and correlation analyses were performed.

Results: The cohort consisted predominantly of males (97.8%) with a mean age of 50.1±7.8 years and a mean work duration of 18.3±8.9 years. Profusion scores were categorized as 1 in 55.6% and >1 in 44.4% of the workers. The most common opacity pattern was small, rounded type p (75.6%). A statistically significant inverse correlation was observed between blood metal levels and profusion scores (r=−0.348, p=0.019), while profusion and opacity size were positively correlated (r=0.335, p=0.025). Neither work duration nor smoking history showed a significant association with radiologic severity. Notably, workers in grinding and sandblasting units exhibited more advanced radiological findings despite having blood metal levels within the normal range.

Conclusion: The severity of pneumoconiosis may not directly correlate with measured blood metal levels but appears to be influenced by exposure characteristics, specific work units, and possibly the effectiveness of protective measures. These findings underscore the importance of comprehensive occupational risk assessments beyond conventional blood metal biomonitoring.

Keywords: Pneumoconiosis, foundry workers, ILO radiologic classification, blood metal levels

INTRODUCTION

Pneumoconiosis remains a significant occupational health concern worldwide, particularly in industries with exposure to mineral and metal dusts such as foundries and welding environments. Although traditionally associated with mining or silica-rich industries, pneumoconiosis related to welding fumes and metal particles is increasingly recognized, especially in developing countries where industrial hygiene measures may be inconsistent.[1] Welder's siderosis, once considered benign and reversible, is now understood to be potentially progressive and capable of causing clinically significant respiratory impairment in certain cases.[2,3]

The International Labour Organization (ILO) classification provides a standardized radiographic method for identifying and grading pneumoconiosis severity, focusing on profusion and opacity characteristics.[4] Despite its widespread use, limited data exist on how these radiologic parameters correlate with specific occupational exposures, such as heavy metal fumes, particularly among foundry workers.

Furthermore, the relationship between whole blood metal levels and the clinical or radiologic severity of pneumoconiosis remains unclear. While higher exposure is intuitively expected to result in more severe radiologic findings, recent observations suggest that factors such as particle size, composition, individual susceptibility, and workplace protections may confound this relationship.[5,6]

Recent studies also emphasize the inadequacy of using only systemic biomarkers to estimate lung burden in workers exposed to complex dust environments.[7,8]

This study aimed to describe the clinical, functional, and radiologic characteristics of foundry workers diagnosed with pneumoconiosis and to evaluate whether those with elevated whole blood metal levels exhibited more severe radiologic findings compared to those with normal levels. This study also explored the influence of work unit and duration on disease severity.

METHODS

Ethics

This study has been approved by the Scientific Researches Ethics Committee of Eskişehir City Hospital (Date: 25.06.2025, Decision No: ESH/BAEK 2025/201). All procedures complied with the Declaration of Helsinki and relevant institutional ethical guidelines. Written informed consent was waived due to the retrospective nature of the study and the use of anonymized data.

Study Design and Participants

This cross-sectional descriptive study included 45 foundry workers diagnosed with pneumoconiosis between January 2021 and May 2025 at tertiary Eskişehir City Hospital occupational diseases clinic in Turkiye. All cases met radiologic diagnostic criteria for pneumoconiosis based on the ILO classification system.[4]

Data Collection

Data were extracted from hospital records and included demographic variables such as age and sex, as well as occupational details including the specific job unit and total duration of work in years. Smoking status was categorized as current smoker, ex-smoker, or never smoker, and pack-years were calculated accordingly. Pulmonary function test results, including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and the FEV1/FVC ratio, were recorded from spirometry assessments. Radiological evaluations were performed according to the ILO classification system, documenting profusion scores, opacity type and size, and the presence of large opacities.

Definition of Metal Exposure Groups Based on Whole Blood Metal Levels

Participants were classified into two groups according to their whole blood metal concentrations, measured by atomic absorption spectroscopy and compared to established reference values:

Normal blood metal level group: Workers whose blood metal levels were within the normal reference range.

Elevated blood metal level group: Workers with blood metal concentrations exceeding the upper limits of the normal reference range.

Definition of metal exposure: The classification of metal exposure was based on occupational hygiene assessments and previous institutional observations regarding the expected levels of airborne metal dust and fumes within different foundry work units. This classification relies solely on the work unit and does not incorporate any biological measurements.

Low exposure group: Workers assigned to units such as grinding, sandblasting, and finishing, where high-temperature processes are generally absent, resulting in low levels of metal fume exposure. However, other particulate risks such as respirable dust (e.g., silica) may still be present.

High exposure group: Workers in units involving high-temperature and molten metal processes, including melting, casting, molding, and hot pressing. These operations are associated with intense generation of metal fumes and vapors, leading to higher exposure risk.

The purpose of this classification is to differentiate exposure profiles based on specific job functions within the foundry environment and to complement individual-level measurements with a work organization-based approach for a more comprehensive occupational risk assessment.

Inclusion and Exclusion Criteria

Inclusion criteria were: being a foundry worker with at least one year of occupational exposure, having a diagnosis of pneumoconiosis based on the ILO radiologic classification, and availability of both blood metal levels and chest radiographs. Exclusion criteria included the presence or history of other interstitial lung diseases (such as idiopathic pulmonary fibrosis), active or previous pulmonary tuberculosis, a diagnosis or suspicion of lung cancer, and missing data related to occupational exposure or radiologic evaluation.

Statistical Analysis

Descriptive statistics were calculated for all variables. Participants were grouped by blood metal level (normal vs. elevated). Group comparisons used chi-square tests for categorical variables and Mann–Whitney U tests for continuous variables (due to non-normal distribution). Spearman correlation assessed relationships between profusion scores, opacity size, work duration, and pack-years. A p-value <0.05 was considered statistically significant. Analyses were performed using SPSS version 20.0 (IBM Corp, Armonk, NY).

RESULTS

Demographic and Clinical Characteristics

Among the 45 workers (97.8% male), the mean age was 50.1±7.8 years, and the mean work duration was 18.3±8.9 years. Smoking prevalence was high (66.7% current smokers). Mean FVC was 88.0±14.0% predicted; mean FEV1 was 83.9±14.9% predicted (**Table 1a, 1b, 1c**).

Radiological Findings

According to the ILO classification, 55.6% of workers were in profusion category 1 and 44.4% in >1. The dominant opacity type was small rounded (type p, 75.6%), with 11.1% showing large opacities (primarily category A) (**Table 2**).

Table 1a. Demographic characteristics

Variable	n	Mean±SD or n (%)	Range or %
Age (years)	45	50.07±7.81	35-64
Sex	45	Male: 44 (97.8%)	Female: 1 (2.2%)
Smoking status	45	Current: 30 (66.7%)	Ex-smoker: 12 (26.7%), non-smoker: 3 (6.7%)
Pack-years category	45	<10: 5 (11.1%)	10–20: 14 (31.1%), >20: 23 (51.1%), non-smoker: 3 (6.7%)
Work duration (years)	45	18.29±8.93	2-40
Work units	45	Melting/casting/pot: 14 (31.1%)	Grinding: 10 (22.2%), shot blasting/deburring/others: 21 (46.7%)

Table 1b. Pulmonary function tests

Variable	n	Mean±SD	Range
FVC (% predicted)	45	87.98±13.98	56-117
FEV1 (% predicted)	45	83.87±14.94	53-121
FEV1/FVC (%)	45	78.08±6.59	66-96

SD: Standard deviation, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second

Table 1c. Radiological characteristics

Variable	n	n (%) or category
ILO profusion category	45	Category 1: 25 (55.6%) Category >1: 20 (44.4%)
Opacity type	45	p: 34 (75.6%) q/r: 10 (22.2%) Irregular: 1 (2.2%)
Large opacity (A-C)	45	No: 40 (88.9%) A: 3 (6.7%) B: 1 (2.2%) C: 1 (2.2%)
Metal exposure level	45	Normal: 30 (66.7%) Elevated: 15 (33.3%)

ILO: International Labour Organization

Table 2. Comparison of clinical and radiologic parameters according to blood metal levels (normal vs. elevated)

Variable	Normal metal level (n=30)	Elevated metal level (n=15)	p-value
Age (years)	49.5±7.9	51.0±7.5	0.53
Male sex, n (%)	29 (96.7%)	15 (100%)	0.55
Current smoker, n (%)	20 (66.7%)	10 (66.7%)	1.00
Work duration (years)	19.5±9.3	16.2±7.2	0.18
FVC (% predicted)	85.7±14.1	92.0±12.3	0.11
FEV1 (% predicted)	82.0±15.4	87.8±13.1	0.20
FEV1/FVC (%)	77.6±6.7	79.0±6.1	0.41
ILO profusion category >1, n (%)	19 (63.3%)	1 (6.7%)	0.001
Large opacity present (A–C), n (%)	4 (13.3%)	1 (6.7%)	0.58

FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second, ILO: International Labour Organization

Metal Level, Units and Radiological Severity

Elevated blood metal levels were identified in 33.3% of participants, while 66.7% had levels within normal range. An inverse correlation between blood metal levels and profusion score was observed (r=–0.348, p=0.019), indicating that workers with elevated metals tended to have less severe radiologic findings.

Profusion score was positively correlated with opacity size (r=0.335, p=0.025). No significant correlation was found between profusion and either smoking pack-years or work duration.

Interestingly, most workers in high-metal exposure units (e.g., smelting) had lower profusion categories despite higher systemic metal levels. Conversely, workers from low-metal exposure units (e.g., sandblasting) often presented with more severe radiographic findings (**Table 3a, 3b**).

Table 3a. Distribution of blood metal levels (normal vs. elevated) by work unit

Work unit	Normal metal level n (%)	Elevated metal level n (%)
Melting/casting/pot	6 (42.9%)	8 (57.1%)
Grinding	10 (100%)	0 (0%)
Shot blasting/deburring	14 (66.7%)	7 (33.3%)
Welding	1 (100%)	0 (0%)
Powder coating/paint shop	1 (50.0%)	1 (50.0%)
Assembly	2 (100%)	0 (0%)
Mold preparation	0 (0%)	1 (100%)

Table 3b. Distribution of ILO profusion categories by work unit

Work unit	Profusion category 1 n (%)	Profusion category >1 n (%)
Melting/casting/pot	10 (71.4%)	4 (28.6%)
Grinding	3 (30.0%)	7 (70.0%)
Shot blasting/deburring	12 (57.1%)	9 (42.9%)
Welding	1 (100%)	0 (0%)
Powder coating/paint shop	2 (100%)	0 (0%)
Assembly	1 (50.0%)	1 (50.0%)
Mold preparation	0 (0%)	1 (100%)

ILO: International Labour Organization

DISCUSSION

This study characterized the clinical and radiologic features of foundry workers diagnosed with pneumoconiosis and examined the relationship between whole blood metal levels and radiologic severity using the ILO classification system. Contrary to initial expectations, an inverse correlation was observed between blood metal concentrations and radiological profusion scores (r=–0.348, p=0.019), suggesting that workers with higher systemic metal levels exhibited milder radiographic findings.

The capacity of blood metal levels to reflect disease severity is complex and may not serve as a standalone indicator of exposure or disease progression. While systemic metal concentrations reflect exposure in the workplace environment, they may not directly determine particle deposition and resulting lung injury. Moreover, individual metabolic variations, particle type, and effectiveness of protective measures are important factors influencing the relationship between blood metal levels and pulmonary pathology.

There are significant differences between metal fume exposure occurring in high-temperature processes such as

melting, casting, molding, and hot pressing, and silica dust exposure commonly seen in mechanical operations like grinding and sandblasting. Metal fumes consist of ultrafine metal oxide particles capable of systemic absorption, whereas silica dust comprises crystalline particles known to induce fibrotic changes in lung tissue.[5,6]

In our study, workers in units with expected high metal fume exposure generally exhibited milder radiological profusion scores despite the potential for systemic metal absorption. This may be explained by effective engineering controls and ventilation systems that reduce pulmonary deposition of harmful particles.[7] Moreover, metal fume exposure is more commonly associated with centrilobular ground-glass opacities on thoracic computed tomography, findings that are often less apparent on chest radiographs.[8]

Conversely, workers in units with high silica and mineral dust exposure, such as sandblasting and grinding, showed more severe radiological abnormalities. Although these mechanical processes do not generate metal fumes, they produce respirable crystalline silica and ultrafine particles, which may not be reflected in biological marker measurements but possess high fibrogenic potential, leading to significant lung damage.[9,10]

Furthermore, reliance on blood metal levels as sole biomarkers of exposure is increasingly questioned. Individual metabolic differences, physicochemical characteristics of particles, and sampling timing can all distort the correlation between systemic metal burden and pulmonary pathology.[11]

The observed positive correlation between profusion score and opacity size (r=0.335, p=0.025) aligns with previous studies indicating that radiologic progression accompanies increasing disease severity.[12]

Notably, no significant associations were found between disease severity and either cumulative work duration or smoking pack-years. This may reflect homogeneity of occupational tasks within the cohort or the predominance of acute or intermittent exposures over cumulative exposure metrics in disease progression.[13,14]

Overall, these findings emphasize that pneumoconiosis is a multifactorial disease influenced by dust type, particle behavior, exposure environment, protective measures, and genetic susceptibility.[15,16] Therefore, exclusive reliance on blood metal monitoring may fail to adequately capture risk, particularly in settings with mixed or non-metallic dust exposures.

CONCLUSION

Among foundry workers diagnosed with pneumoconiosis, whole blood metal levels exhibited a paradoxical inverse relationship with radiological disease severity. Workers in high-metal exposure units generally presented with milder radiologic findings, which may be due to the less conspicuous radiological manifestation of metal oxide particles in the lungs. In contrast, workers in units with presumed lower metal exposure frequently demonstrated more advanced disease, potentially linked to exposure to non-metallic particulates such as crystalline silica.

These findings underscore the critical need for a comprehensive occupational health surveillance approach that goes beyond conventional biomonitoring. Accurate risk identification and prevention require integrating detailed, task-specific exposure assessments and regular radiological evaluations, especially in work environments characterized by complex or mixed dust exposures.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Scientific Researches Ethics Committee of Eskişehir City Hospital (Date: 25.06.2025, Decision No: ESH/BAEK 2025/201).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

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

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The relationship between serum C-reactive protein to albumin ratio and the severity and prognosis of COVID-19

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ABSTRACT

Aims: During the coronavirus disease 2019 (COVID-19) pandemic, early identification of especially severe and critical cases may improve prognosis. In this context, laboratory parameters play an important role. This study investigated the relationship between the serum C-reactive protein (CRP)/albumin ratio (CAR) and disease prognosis in patients with COVID-19.

Methods: This study included patients who were hospitalized with a possible or confirmed diagnosis of COVID-19 at the Chest Diseases Clinic of the University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital Health Practice and Research Center between March 1, 2020, and March 31, 2021. Data on the patients were retrospectively reviewed using the hospital's record system. A total of 444 patients were included in the study and divided into two groups: those with a diagnosis of severe disease (n=141) and those without (n=303). The serum CAR was compared between the two groups. In addition, the relationship between CAR and demographic, clinical, and laboratory findings was evaluated.

Results: The mean CAR in the group with severe disease was found to be 36.1, while it was 17.1 in the group without severe disease, and the difference was statistically significant ($p<0.001$). ROC analyses showed that CAR had higher area under the curve (AUC) values compared to CRP alone in predicting severe disease, the development of complications, need for respiratory support or intensive care, and mortality. The optimal threshold values identified for CAR were as follows: 26.06 for predicting severe disease (sensitivity 66%, specificity 64%), 26.04 for complications (sensitivity 61%, specificity 62%), 26.06 for intensive care need (sensitivity 63%, specificity 62%), 25.21 for need for respiratory support (sensitivity 60%, specificity 60%), and 27.2 for mortality (sensitivity 62%, specificity 59%). These findings demonstrate that an increased CAR level is significantly associated with poor prognosis in COVID-19 patients. The relationship between serum CAR and the severity of COVID-19.

Conclusion: The data obtained indicate that the CAR is a potential biomarker for predicting severe disease and poor prognosis in COVID-19 patients. Therefore, integrating CAR into the clinical evaluation process may contribute to the early identification of high-risk patients and the timely implementation of appropriate treatment approaches.

Keywords: SARS-CoV-2, CAR, C-reactive protein, albumin

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China in December 2019, rapidly spread globally and led to the Coronavirus Disease 2019 (COVID-19) pandemic. The World Health Organization (WHO) declared it an international public health emergency, and the number of cases and deaths increased rapidly. While the disease can present with mild symptoms, severe and critical conditions develop in some cases, increasing the risk of mortality. Early identification of individuals with severe illness can enable timely treatment planning and potentially improve clinical outcomes. Therefore, reliable biomarkers that can predict disease severity are needed.

The hyperinflammatory response observed in COVID-19 can be evaluated using certain serum biomarkers. Among these, the C-reactive protein (CRP) to albumin ratio (CAR), which reflects both inflammation and nutritional status, has drawn attention. Previous studies have demonstrated that elevated CAR is associated with poor prognosis and increased mortality in various clinical conditions, including infections and malignancies. For instance, in patients with sepsis, CAR has been reported to be an effective predictor of mortality.[1] Similarly, a study investigating the role of CAR in predicting mortality among patients with acute pancreatitis demonstrated that it could serve as a prognostic

factor.[2] Furthermore, elevated CAR levels have been associated with higher mortality in malignancies such as small-cell lung cancer, non-small-cell lung cancer, and lung adenocarcinoma.[3-5] In a study conducted by Kim et al.,[6] CAR was found to be a more sensitive prognostic indicator than CRP or albumin alone. Moreover, an investigation carried out in an intensive care unit (ICU) reported that CAR was a clinically relevant prognostic marker for predicting 28-day mortality.[7] In conclusion, these findings support the potential utility of CAR as a prognostic indicator in critically ill patients. This study aims to evaluate the relationship between CAR at the time of admission and the development of severe disease and poor prognosis in patients hospitalized with a diagnosis of COVID-19.

METHODS

Ethics

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences (UHS) Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 21.09.2020, Decision No: 96/11). The research process was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

This retrospective study includes 444 patients who were hospitalized with a diagnosis of COVID-19 between March 1, 2020, and March 31, 2021, at the Department of Pulmonary Diseases, University of Health Sciences (UHS) Dışkapı Yıldırım Beyazıt Training and Research Hospital Health Practice and Research Center. Demographic, clinical, radiological, and laboratory data of the patients; treatment approaches used; complications that developed; need for respiratory support and intensive care; and hospital outcomes (discharge/death) were retrospectively evaluated using the hospital information management system.

Measurement of Biochemical Parameters

CRP levels were measured using the immunoturbidimetric method with the Siemens ADVIA Chemistry XPT automated biochemistry analyzer (Siemens Healthineers, Germany) from venous blood samples taken at the time of admission. The results were recorded in milligrams per liter (mg/L).

Serum albumin levels were determined from the same samples using the bromocresol green (BCG) method, with the same analyzer. Measurements were recorded in grams per deciliter (g/dl). The CAR was calculated for each patient using their CRP and albumin values.

Determination of Disease Severity

Patients were grouped according to the WHO classification of COVID-19 disease severity. Critical illness was defined by the presence of life-supporting conditions such as acute respiratory distress syndrome (ARDS), sepsis, septic shock, the need for invasive or non-invasive mechanical ventilation (NIMV), or vasopressor therapy. Severe disease was characterized by oxygen saturation (SpO_2) below 90%, a respiratory rate greater than 30 breaths per minute, or signs of significant respiratory distress (use of accessory respiratory muscles, inability to complete sentences while speaking). Patients who did not meet any of these criteria were considered to have non-severe disease. Those who met the criteria for critical illness were included in the severe group, while those who did not were classified in the non-severe group.

Inclusion Criteria

Patients with the following characteristics were included in the study:

- Patients aged 18 years and older
- Those who met the definition of a "suspected case" according to the guideline published by the Turkish Ministry of Health, General Directorate of Public Health during the pandemic period
- Patients who tested positive for SARS-CoV-2 by molecular diagnostic method (reverse transcription-polymerase chain reaction)
- Patients who had findings consistent with COVID-19 pneumonia on chest computed tomography (e.g., bilateral ground-glass opacities, subpleural consolidation) and were started on treatment according to the national guideline

Exclusion Criteria

Before inclusion in the study, patients with the following characteristics were excluded from evaluation:

- Pregnant individuals
- Those with another active infectious focus unrelated to COVID-19 (e.g., urinary tract infection, bacterial pneumonia, etc.)
- Patients with a diagnosis of rheumatologic or autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, vasculitis)
- Patients with a diagnosis of malignancy (cancer) that could affect serum albumin levels
- Individuals with chronic liver disease (e.g., cirrhosis, chronic hepatitis)
- Patients assessed to have clinical or biochemical malnutrition
- Individuals with a body-mass index ≥40 kg/m^2, consistent with morbid obesity

Statistical Analysis

The data analysis was performed using SPSS version 21.0 (IBM®, Chicago, USA). The normality of distribution of variables was assessed using visual methods (histogram and probability plots) and analytical methods (Shapiro-Wilk test). Descriptive statistics were presented as mean±standard deviation for normally distributed numerical data, median and minimum–maximum range for non-normally distributed numerical data, and as number and percentage for nominal variables. Normally distributed numerical variables were analyzed between two groups using the Independent Samples T-test, while non-normally distributed numerical variables were analyzed using the Mann-Whitney U test. Nominal data

were evaluated between two groups using the Pearson Chi-square test or Fisher's Exact test. To determine the factors affecting COVID-19 severity, complication development, need for ICU and respiratory support, and mortality, the area under the curve (AUC) in receiver operating characteristic (ROC) analysis was evaluated, and the data were expressed with a 95% confidence interval. In the statistical analyses of this study, a p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 444 patients were included in the study. According to the WHO classification of COVID-19 disease severity, 141 patients (31.8%) were classified in the severe disease group, while 303 patients (68.2%) were in the non-severe disease group. Individuals in the severe disease group were significantly older compared to those in the non-severe group (p=0.001), and symptoms such as dyspnea (p=0.044) and loss of appetite (p=0.014) were observed more frequently in this group. Additionally, in patients with severe COVID-19, body temperature was higher (p<0.001), diastolic blood pressure was lower (p=0.006), SpO_2 was lower (p<0.001), and respiratory rate was higher (p<0.001). All these findings indicate significant associations between severe disease and certain clinical and symptomatic characteristics, as shown in **Table 1**.

Table 1. Comparison of clinical and demographic characteristics between severe and non-severe COVID-19 patients

Characteristics	Non-severe COVID-19 (n=303)	Severe COVID-19 (n=141)	p value
Age (median, years)	64	70	0.001
Female sex, n (%)	144 (47.5)	64 (45.4)	0.675
Symptoms			
Dyspnea, n (%)	218 (71.9)	114 (80.9)	0.044
Loss of appetite, n (%)	105 (34.7)	66 (46.8)	0.014
Comorbidities			
Hipertension, n (%)	158 (52.1)	82 (58.2)	0.237
Diabetes mellitus, n (%)	101 (33.3)	55 (39.0)	0.244
Clinical findings			
Body temperature (°C, median)	36.7	37.0	<0.001
Diastolic blood pressure (mmHg, median)	75	70	0.006
Oxygen saturation (% median)	88	75	<0.001
Respiratory rate (median/minute)	22	26	<0.001

COVID 19: Coronavirus disease 2019

The vast majority of the 444 patients included in the study (84.5%) received oxygen therapy during hospitalization. ICU support was required in 31.1% of the patients. Among those who needed respiratory support, 27.5% received NIMV, 13.3% received invasive mechanical ventilation (IMV), and 28% were treated with high-flow nasal oxygen (HFNO). The overall mortality rate was found to be 11.8% (n=52). These findings indicate that the need for advanced respiratory support and the risk of mortality are considerable in COVID-19 patients.

It was determined that many laboratory parameters significantly differed between severe and non-severe COVID-19 patients (**Table 2**). In the severe group, leukocyte, neutrophil, CRP, ferritin, D-dimer, and pro-B natriuretic peptide (Pro-BNP) levels were significantly higher (p<0.001), while lymphocyte and albumin levels were significantly lower (p<0.001). Additionally, the CAR was significantly higher in the severe disease group (p<0.001). The neutrophil-to-lymphocyte ratio (NLR) was also markedly elevated in severe cases (p<0.001). These findings indicate that systemic inflammation and tissue damage are more pronounced in severe COVID-19 cases.

Table 2. Selected laboratory parameters in severe and non-severe COVID-19 patients

Parameter	Non severe COVID-19 (n=303)	Severe COVID-19 (n=141)	p value
Leukocyte (x10^9/L)	5.9	7.7	<0.001
Lymphocyte (x10^9/L)	0.8	0.5	<0.001
Neutrophil (x10^9/L)	4.6	6.3	<0.001
NLR	5.3	10.5	<0.001
CRP (mg/L)	62	116	<0.001
Albumin (g/dl)	3.5	3.2	<0.001
CAR	17.1	36.1	<0.001
Ferritin (ng/ml)	390.5	835.5	<0.001
D-dimer (µg/ml)	1.0	2.7	<0.001
Pro-BNP (pg/ml)	379.5	1297	<0.001

COVID 19: Coronavirus disease 2019, NLR: Neutrophil/lymphocyte ratio, CRP: C-reactive protein, CAR: CRP/albumin ratio, Pro-BNP: Pro-B-type natriuretic peptide

Based on the ROC analysis, D-dimer level showed the highest diagnostic accuracy in predicting severe COVID-19, with an AUC value of 0.759. The CAR was also considered a significant marker for predicting disease severity, with an AUC of 0.694. Ferritin and CRP levels similarly stood out with high AUC values (AUC: 0.688 and 0.681, respectively). On the other hand, lymphocyte count showed a significant inverse association, with an AUC of 0.316, indicating that lower lymphocyte levels may be associated with severe disease (**Table 3**).

Table 3. AUC values of predictive parameters for severe COVID-19 disease

Parameter	AUC	%95 GA	p value
D-dimer (µg/ml)	0.759	0.714–0.805	<0.001
CRP/albumin ratio (CAR)	0.694	0.642–0.746	<0.001
Ferritin (ng/ml)	0.688	0.634–0.741	<0.001
C-reactive protein (CRP) (mg/L)	0.681	0.629–0.733	<0.001
Lymphocyte (x10^9/L)	0.316	0.263–0.368	<0.001

AUC: Area under the curve, COVID 19: Coronavirus disease 2019

The ROC analysis for the biomarkers effective in predicting severe disease is presented in **Figure**.

In the prediction of disease severity in COVID-19, the optimal cut-off value of the CAR was determined to be 26.06 (with 66% sensitivity and 64% specificity); for the prediction

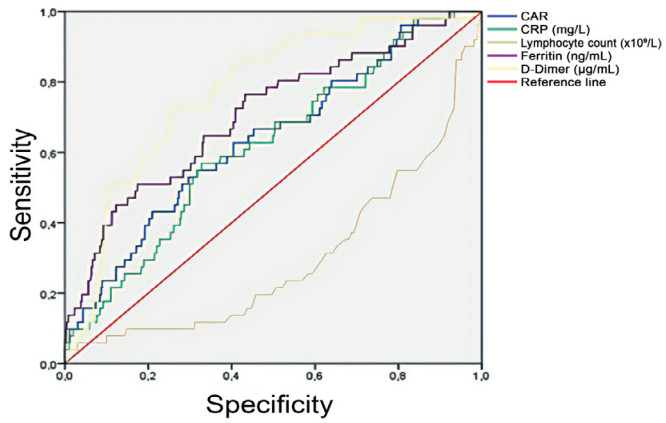

Figure. The role of predictive markers in estimating severe disease in COVID-19
COVID 19: Coronavirus disease 2019, CRP: C-reactive protein

of complications, 26.04 (61% sensitivity, 62% specificity); for the prediction of ICU requirement, 26.06 (63% sensitivity, 62% specificity); for the prediction of the need for respiratory support, 25.21 (60% sensitivity, 60% specificity); and for the prediction of mortality, 27.2 (62% sensitivity, 59% specificity).

In non-severe COVID-19 patients, CAR showed a statistically significant positive correlation with age, body temperature, respiratory rate, leukocyte and neutrophil counts, neutrophil/lymphocyte ratio (NLR), ferritin, D-dimer, interleukin-6 (IL-6), and CRP levels; and a negative correlation with SpO_2, lymphocyte count, and albumin levels ($p<0.05$).

The correlation results are presented in **Table 4**.

DISCUSSION

In this study, the relationship between the CAR and disease severity was evaluated in patients with COVID-19. The findings revealed that CAR levels were significantly higher in individuals in the severe disease group. Severe disease was also characterized by more advanced clinical features, such as older age, increased inflammatory response, and pronounced respiratory impairment. In this group, biomarkers reflecting inflammation and tissue damage—such as CRP, ferritin, D-dimer, and Pro-BNP—were significantly elevated, while lymphocyte and albumin levels were notably decreased. This indicates that systemic inflammation increases with disease severity and that the immune response may be suppressed. CAR, in particular, may serve as a more comprehensive biomarker for predicting disease severity, as it reflects both elevated CRP and decreased albumin levels. The ROC analysis demonstrated that CAR has significant diagnostic value in predicting severe COVID-19 disease. Furthermore, correlation analyses showed that CAR was significantly associated with many clinical and laboratory parameters, especially in the non-severe patient group. In this group, CAR had a positive correlation with age, respiratory rate, body temperature, leukocyte and neutrophil counts, ferritin, and D-dimer levels, and a negative correlation with lymphocyte and albumin levels, as well as SpO_2. These findings suggest that CAR may be a sensitive indicator of inflammatory activity, particularly in the early stages of the disease. In the severe patient group, however, these correlations weakened or lost statistical significance. This may indicate that the inflammatory response becomes more complex in the later stages of the disease and that CAR plays a more prominent prognostic role in the early phase. In conclusion, CAR is a biomarker that may contribute to clinical decision-making by reflecting both systemic inflammation and disease severity. However, to increase the generalizability of these findings and to clearly define its clinical applications, multicenter, prospective studies with larger sample sizes are needed.

The clinical course of COVID-19 infection varies depending on individual factors and the intensity of the immune response. Advanced age is a significant risk factor associated with more severe forms of the disease. This relationship is reflected in higher hospitalization rates, increased need for intensive care, and elevated mortality.[8-10] In more severe forms of the infection, in addition to prominent respiratory symptoms such as fever, hypoxia, and tachypnea, clinical manifestations like hemodynamic instability are more frequently observed. In our current study, individuals diagnosed with severe disease were shown to be significantly

Table 4. Correlation of CRP/albumin ratio with clinical and laboratory parameters

Parameter	Non-severe COVID-19 (n=303)	p value	Severe COVID-19 (n=141)	p value
Age	ρ=0.210	<0.001	ρ=–0.082	0.337
Body temperature (°C)	ρ=0.139	0.015	ρ=0.039	0.649
Oxygen saturation (%)	ρ=–0.459	<0.001	ρ=–0.112	0.186
Respiratory rate (/min)	ρ=0.306	<0.001	ρ=0.026	0.761
Diastolic blood pressure (mmHg)	ρ=0.144	0.012	ρ=–0.019	0.823
Leukocyte (×10⁹/L)	ρ=0.265	<0.001	ρ=0.200	0.017
Neutrophil (×10⁹/L)	ρ=0.377	<0.001	ρ=0.181	0.032
Lymphocyte (×10⁹/L)	ρ=–0.292	<0.001	ρ=–0.019	0.827
Neutrophil/lymphocyte ratio (NLR)	ρ=0.478	<0.001	ρ=0.182	0.030
Albumin (g/dl)	ρ=–0.480	<0.001	ρ=–0.392	<0.001
Ferritin (ng/ml)	ρ=0.416	<0.001	ρ=0.143	0.092
D-Dimer (µg/ml)	ρ=0.376	<0.001	ρ=0.152	0.072
C-reactive protein (CRP, mg/L)	ρ=0.986	<0.001	ρ=0.973	<0.001

COVID 19: Coronavirus disease 2019

older. In this patient group, symptoms and findings such as dyspnea, loss of appetite, elevated body temperature, hypoxia, tachypnea, and decreased diastolic blood pressure were more frequently observed. In line with other studies, severe COVID-19 patients also showed multiple laboratory abnormalities, including low albumin and lymphocyte levels, and elevated leukocyte, neutrophil, D-dimer, CRP, and ferritin levels.[11,12] In this study as well, the laboratory findings of patients with severe disease were consistent with previous reports. Moreover, the ROC analysis results demonstrated that these parameters are statistically significant markers for predicting disease prognosis and mortality.

CRP and albumin are laboratory parameters that are commonly used in clinical practice due to their high accessibility, low cost, and rapid turnaround time. CRP, an acute-phase reactant, reflects the intensity of the inflammatory process, while albumin levels provide insight into a patient's nutritional status and overall systemic response. Elevated CRP levels are associated with poor prognosis in conditions such as infection, sepsis, tissue damage, and malignancies, whereas low albumin levels are considered an independent predictor of mortality. The combination of these two parameters—CAR—offers the advantage of simultaneously assessing both the level of inflammation and the patient's metabolic state, potentially making it a stronger prognostic marker than using either biomarker alone.[6] The CAR has been evaluated as a prognostic indicator not only in infectious diseases but also in a wide range of clinical conditions. Particularly in conditions involving systemic inflammatory responses—such as sepsis, acute pancreatitis, and malignancy—CAR has been shown to be associated with mortality.[1-6] In a study by Fairclough et al.[13] on acute medical admissions, patients with CAR>2 had a significantly higher mortality rate. Similarly, in a study of intensive care patients, CAR was found to predict 28-day mortality with 64.2% sensitivity and 52.7% specificity, with a calculated cut-off value of 34.3.[7] Another study in septic patients found that CAR measured at admission and discharge was effective in predicting 90-day mortality, with an AUC of 0.612 for admission CAR and 0.619 for discharge CAR.[1]

Additionally, Kim et al.[6] reported that CAR was superior to CRP in predicting mortality among patients with sepsis and septic shock, and that CAR values above 5.09 were significantly associated with 180-day mortality. The prognostic value of CAR has also been emphasized in cancer patients. For example, Zhou et al.[3] found that individuals with small cell lung cancer who had a pre-treatment CAR >0.441 had worse survival outcomes. In stage 4 non-small cell lung cancer patients receiving palliative chemotherapy, CAR was found to be a prognostic factor for overall survival, and in the adenocarcinoma subgroup, a cut-off value of 0.195 was determined to be significant.[4] Another study in patients undergoing surgery for stage 3A lung adenocarcinoma reported that CAR, with a cut-off value of 0.6, was a significant prognostic factor for recurrence-free survival.[5]

Among the biomarkers used to evaluate systemic inflammation in COVID-19 patients, CRP and albumin levels measured at hospital admission offer practical advantages due to their rapid turnaround, low cost, and widespread availability. Accumulating evidence supporting the prognostic value of these parameters in various clinical conditions has also been extended to the context of COVID-19, where similar associations are being explored. In COVID-19, CRP levels are known to rise in response to an excessive cytokine release and inflammatory reaction, and this increase has been shown to correlate with disease severity, mortality, radiological severity, and respiratory failure.[14-19] On the other hand, low serum albumin levels have also been reported to be associated with poor clinical outcomes.[20,21]

Recent studies have proposed that the CAR may serve as an effective biomarker for predicting disease severity and mortality in COVID-19 patients.[22-24] In the literature, studies examining the prognostic value of CAR in COVID-19 patients have reported varying threshold values and predictive strengths. For example, a retrospective study involving 90 patients identified a positive correlation between CAR and disease severity, and determined a cut-off value of 0.296 with 76.7% sensitivity and 80.4% specificity for distinguishing severe disease.[22] In another study evaluating 197 patients, the AUC value of CAR measured at admission for predicting severe disease was calculated as 0.718, with a cut-off of 0.9 yielding 69.1% sensitivity and 70.8% specificity.[23] In a study conducted by Güney et al.,[24] patients were divided into three groups based on CAR levels, and in-hospital mortality was found to be 8.2 times higher in the group with the highest CAR levels compared to the lowest group. The findings in our study are consistent with this literature. CAR levels were found to be statistically significantly higher in the severe disease group. ROC analysis demonstrated the diagnostic power of CAR in predicting adverse outcomes such as severe disease, development of complications, intensive care requirement, need for respiratory support, and mortality, with cut-off values of 26.06; 26.04; 26.06; 25.21; and 27.2, respectively. The sensitivity for these threshold values ranged between 60–66%, and specificity between 59–64%. Additionally, the AUC value for CAR was higher than that of CRP alone, supporting the prognostic performance of the ratio. In correlation analyses, in the severe disease group, CAR showed a significant positive correlation with leukocyte count, neutrophil count, NLR, AST, ALT, CRP, ESR, and procalcitonin levels, while a negative correlation was observed with albumin levels. No significant correlations were found with other parameters. These findings suggest that CAR is a highly applicable biomarker with the potential to reflect systemic inflammation and disease severity in COVID-19 patients.

Limitations and Future Directions

This study has several limitations. Firstly, due to its retrospective design, data were obtained from existing records, which carries the risk of potential data omissions and information bias. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings. Furthermore, only certain comorbidities and clinical conditions could be excluded from the study, and it was not possible to fully control for all potential confounding diseases or conditions that could affect CRP and albumin levels. This may introduce some uncertainty in the interpretation of measured CAR levels. Moreover, given the dynamic nature of the inflammatory response, the evaluation of biochemical parameters at a single time point (i.e., at admission) may be

insufficient to reflect changes over time. These limitations suggest that the results should be interpreted with caution, and highlight the need for prospective, multicenter studies with larger sample sizes.

CONCLUSION

The findings of this study demonstrate that the CAR is significantly associated with disease severity and adverse clinical outcomes in COVID-19 patients. Given that CAR reflects both the inflammatory response and nutritional status, particularly in the early stages of illness, it may serve as a valuable biomarker for prognostic assessment. Routine evaluation of CAR in clinical practice may aid in the early identification of high-risk patients and facilitate timely implementation of appropriate treatment strategies. However, to validate these findings and clearly define the role of CAR in clinical practice, further large-scale, multicenter, and prospectively designed studies are warranted.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences (UHS) Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 21.09.2020, Decision No: 96/11).

Informed Consent

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

Referee Evaluation Process

Externally peer reviewed

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

Financial Disclosure

The authors declare that this study did not receive any financial support.

Author Contributions

All authors declare that they contributed to the design, execution, and analysis of the study and have approved the final version of the manuscript.

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The effect of medication adherence on symptom control, airway inflammation and exacerbations in asthmatics*

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ABSTRACT

Aims: In asthma patients with good compliance to treatment, symptoms, functional and inflammatory parameters are expected to be at normal levels. In our study, the effect of treatment compliance on asthma symptom control, airway inflammation, and attacks within 6 months in asthmatic patients was investigated.

Methods: 113 patients who have been diagnosed with asthma for at least 6 months and were under inhaler treatment were included in the study. Respiratory function tests, asthma control test (ACT) and Morisky 8 items medication adherence scale (MMAS-8) were performed and exhaled nitric oxide (FENO) levels were measured. After 6 months, patients were questioned about any asthma exacerbations in this 6 months period.

Results: According to ACT, 57.5% of patients were not under control. 49.6% of patients had poor medication adherence according to MMAS-8. 24.1% of patients had high FENO levels. There was no association between MMAS-8 scores and FENO levels (p=0.34 r=-0.091). There was positive correlation between ACT and MMAS-8 scores (r=0.371 p=0.001). ACT scores were higher in patients with low FENO levels (p=0.01). 11 asthmatics experienced asthma exacerbation during 6 months follow-up period. Medication adherence was not found to be a significant factor for exacerbations, however baseline ACT scores and FEV1 values were lower in patients who experienced asthma attacks (r=-0.107, p=0.002).

Conclusion: As a result, our study demonstrated that medication adherence determined by MMAS-8 is an important factor of asthma symptom control.

Keywords: Asthma control, adherence, airway inflammation, exacerbations

*This study was presented as a summary presentation at the 13th World Asthma Congress (Madrid, Spain, 12–15 March, 2016), as a poster at the Turkish Thoracic Society 18th Annual Congress (Antalya, 01–05 April, 2015), and received a poster presentation award in the field of asthma and allergy.

INTRODUCTION

Asthma is a chronic respiratory disease characterized by airway inflammation and bronchoconstriction. Achieving optimal asthma control is vital in reducing symptoms, preventing exacerbations, and improving the quality of life of patients.

The primary goal of current asthma treatment is to achieve disease control. Asthma control includes patient symptom control and assessment of future risks.[1,2] Achieving and maintaining optimal asthma control requires a combination of pharmacologic therapy and patient compliance with prescribed medications.[3,4] Noncompliance with medications negatively impacts the course of the disease in asthmatic patients and leads to increased airway inflammation, functional limitations, healthcare costs, decreased quality of life, emergency hospitalizations, and even increased mortality.[1,5]

In recent years, researchers have investigated the role of exhaled nitric oxide (FeNO) as a biomarker for asthma control and its potential association with patient adherence to treatment.[6] This study aimed to determine the effect of treatment adherence on asthma control and airway inflammation in patients with asthma, and to investigate the role of FeNO and treatment adherence in predicting future risk of asthma within the following 6 months. FeNO reflects

eosinophilic airway inflammation through the measurement of nitric oxide produced by airway epithelial cells. Its levels are influenced by various factors such as smoking status, presence of respiratory infections, and asthma phenotype (e.g., eosinophilic vs. non-eosinophilic). According to GINA guidelines, FeNO measurement can support the diagnosis and monitoring of asthma in specific patient subgroups, particularly those with suspected type 2 inflammation or uncertain response to inhaled corticosteroids. Previous studies have also explored the relationship between medication adherence and FeNO, suggesting potential but inconsistent associations.

METHODS

Ethics

The protocol has been approved by the Gazi University Clinical Researches Ethics Committee (Date: 06.01.2014, Decision No: 09). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Data was collected from patients who consulted the chest diseases outpatient clinic and were diagnosed with asthma and used inhaler treatment. These cases were followed up prospectively for 6 months. Written informed consent was obtained from all patients who participated in the study.

The patient's age, gender, smoking history, educational status, employment status, length of time diagnosed with asthma, skin-prick test, asthma medications, comorbidities, non-asthma drugs used for comorbidity, and pulmonary function tests at admission were recorded. At the beginning of our study, FeNO measurement was performed for all patients with asthma who applied to our outpatient clinic. Patients were asked to complete the asthma control test (ACT) and the 8-item Morisky medication adherence scale (MMAS-8). 6 months after their admission, all patients were contacted by telephone or by scanning their file information, and they were questioned if they had an asthma attack that required systemic steroid use for at least 3 days within these 6 months. Smoking status was included as a covariate in statistical analysis to account for its known impact on FeNO levels.

Method of Data Collection

Cases: Patients who applied to the pulmonology outpatient clinic of our hospital for control purposes between 01/01/2014 and 01/07/2014 who were diagnosed with asthma at least 6 months before according to the guidelines of GINA (Global Initiative for Asthma) and the Turkish Thoracic Society and were treated with inhalers for at least 6 months were included. Patients who had an attack the previous month or had an acute lower respiratory tract infection were not included in the study because it would affect the FeNO value. Patients with asthma who had agreed to give informed written consent and who were able to read and fill out written questionnaires were prospectively included in the study.

Examined Parameters

Pulmonary function test (PFT): PFT measurement was performed using a Vmax 20 (Sensor Medics/VIASYS, Conshohocken, Pennsylvania, USA) device. The measurement was taken at least three times while the patients were at rest and the best result was included in the evaluation. Values were expressed as a percentage considering the absolute value and expected value.

Asthma control test (ACT): A printed ACT was given to the patients who were asked to read and fill in for themselves. The answers to the five questions were scored separately, and the patient's total score was determined. According to the total score, the cases were categorized into two groups: controlled (ACT>19) and uncontrolled (ACT≤19).[2,7,8]

Fractionated expiratory air nitric oxide measurement (FeNO): FeNO measurement was performed with a portable nitric oxide analyzer (NIOX MINO; Aerocrine, Solna, Sweden) that uses an electrochemical method in accordance with the ATS/ERS recommendations as previously described.[6,9,10] The FeNO measurement was taken before PFT in the patients. The unit of measurement was expressed as particles per billion (ppb) at an exhalation flow rate of 0.05 L/s during a single exhalation. The patients were asked to exhale in a comfortable sitting position, against the pressure of 5 cm H_2O created by the mouth particle with a flow rate of 0.05 L/sec, from the mouthpiece for 2–3 seconds until total lung capacity after inhalation through the mouthpiece that purifies the nitric oxide in the inspiratory air, without holding their breath. The duration of exhalation was kept above 6 seconds to reach the plateau concentration. The measured FeNO value was classified as: low=<5 ppb, normal=5–25 ppb, moderate=25–50 ppb, and high=>50 ppb.[9,10] In this study, a FENO value of >25 ppb was taken as the threshold value.

8-item Morisky medication adherence scale (MMAS-8): The validated Turkish translation of the MMAS-8 questionnaire was given to the patients to assess treatment compliance where 8 points was high, 6–7 points was moderate, and <6 points was low adherence.[11,12] Copyright owner (Morisky Medication Adherence Research, LLC) provided written permission to use the MMAS-8 questionnaire in this research.

Statistical Analysis

The research data were uploaded and evaluated using the SPSS 15.0 software. Descriptive statistics were presented as mean±standard deviation (mean±SD), median (minimum and maximum), frequency distribution, and percentage. In addition to descriptive statistics, Chi-square, Yates corrected Chi-square, and Fisher's exact tests were used. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests). When the variables were found not to fit a normal distribution, the Mann–Whitney U test, Kruskal–Wallis test, and Spearman's test were used for statistical significance and relationships. A binary logistic regression test also evaluated the relationship between drug adherence and asthma control. The statistical significance level was accepted as $p<0.05$. Additionally, a post-hoc power analysis for the primary outcome (association between MMAS-8 and ACT) indicated a statistical power greater than 80%, supporting adequacy of the sample size for this analysis.

RESULTS

The study included 113 patients diagnosed with asthma and who met the inclusion criteria. The demographic data of the patients are presented in **Table 1**. The asthma-related characteristics of the patients are presented in **Table 2**. Most patients (65.5%) had forced expiratory volume (FEV1)≥80%. 63 (55.8%) of patients were using a combination therapy that included inhaled corticosteroids, and most (77%) were non-atopic. Notably, only 8% of patients had severe asthma, which we acknowledge may limit the robustness of analyses related to exacerbations.

Table 1. Demographic characteristics of the patients

	n=113
Gender; n (%)	
Female	80 (70.8)
Male	33 (29.2)
Age, years, (mean±SD)	51.39±13.01
Smoking habit, n (%)	
Smokers	24 (21.2)
Non-smokers	70(61.9)
Ex-smokers	19 (16.8)
Asthma duration, yrs, (mean±SD)	7.87±8.09
Educational level, n (%)	
Primary school	46 (40.7)
High school	33 (29.2)
University	34 (30.1)
Presence of comorbidities* n (%)	
No	40 (35.4)
Yes	73 (64.6)
Number of comorbidities (mean±SD)	1.24±1.2

SD: Standard deviation, *Osteoporosis, heart failure, arrhythmia, diabetes mellitus, chronic liver disease, gastro esophageal reflux, sinusitis, rhinitis, malignancy

Table 2. Asthma-related characteristics of the patients

	n=113
FEV1; % predicted (mean±SD)	86.9±19.52
Cases according to FEV1 %, n (%)	
FEV1≥80%	74 (65.5)
FEV1 79-60%	30 (26.5)
FEV1<60%	9 (8)
Asthma treatment used; n (%)	
ICS*	50 (44.2)
Combination (include ICS) **	63 (55.8)
Asthma control status based on ACT	
Controlled	65 (57.5)
Uncontrolled	48 (42.5)
Level of medication adherence (MMAS-8 score); n (%)	
Low (MMAS-8<6 point)	56 (49.6)
Medium (MMAS-8=6-7 point)	42 (37.2)
High (MMAS-8 =8 point)	15 (13.2)
FENO levels (ppb); n: 108 (%)	
Low (FENO<25 ppb)	82 (75.9)
High (FENO≥25 ppb)	26 (24.1)
Asthma severity n (%)	
Intermittent	74 (65.4)
Mild	30 (26.5)
Severe	9 (7.9)
Use of drugs for comorbidity; n (%)	
Yes	60 (53.1)
No	53 (46.9)
Number of drugs used for comorbidity (mean±SD)	1.17±1.47

FEV1: Forced expiratory volume, SD: Standard deviation, ICS: Inhaled corticosteroids, ACT: Asthma control test, MMAS-8: 8-item Morisky medication adherence scale, FENO: Fractionated expiratory air nitric oxide measurement, * Low dose ICS, ** Low dose ICS-LABA, medium dose ICS-LABA, medium/high dose ICS and LTRA/LAMA

Regarding asthma symptom control, 57.5% (n=65) of patients had asthma that was under control (ACT≥20), while 42.5% (n=48) were not under control (ACT<20). Only 15 (13.3%) patients had high, and 42 (37.2%) had moderate adherence to asthma medications measured by the MMAS-8 questionnaire (**Table 2**).

FeNO measurement could not be performed in five of 113 patients as they could not perform the measurement maneuver. The mean FENO level of 108 patients was 19.9±15.37 ppb. Eighty-two patients (75.9%) had low, and 26 (24.1%) patients had high FENO levels (low: ≤25 ppb and high: >25 ppb) (**Table 2**).

The effect of medication adherence on asthma control was evaluated by comparing MMAS-8 with ACT. The mean ACT was significantly lower in the low adherent group (ACT was 19.5±3.45 for low, 21.7±3.8 for moderate, and 22.8±2.6 for high adherent groups, p=0.02). 41.1% (n=23) of the patients in the group with low medication adherence had well-controlled asthma with a ratio of 71.4% (n=30) in the group with moderate adherence and 80.0% (n=12) in the group with high adherence (p=0.02). It was shown that asthma symptom control improved as adherence rates increased (**Figure 1**). The odds of uncontrolled asthma were 5.74 (95% CI 1.45–22.6, p=0.013) in patients with low medication adherence compared with the high adherent group. A moderate positive correlation was observed between ACT and MMAS-8 values (r=0.371, p=0.001).

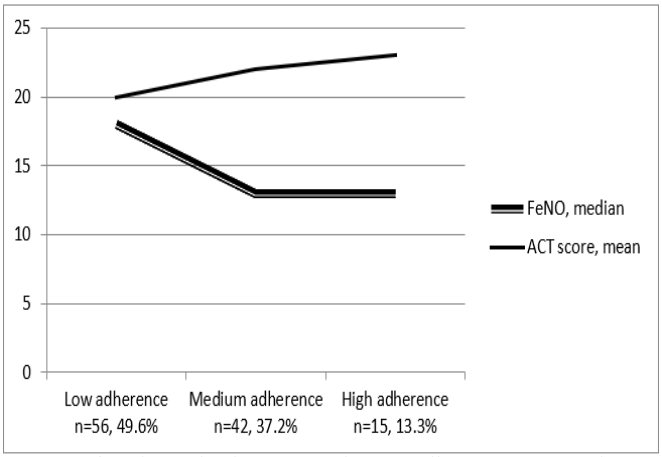

Figure 1. The relationship between medication adherence, FeNO and ACT
FENO: Fractionated expiratory air nitric oxide measurement, ACT: Asthma control test

The effect of medication adherence on airway inflammation was evaluated by comparing MMAS-8 with FeNO. The ratio of patients with asthma having high FeNO levels was non-significantly high in the low adherent group (FeNO levels >25 was measured in 33.3% for low, 15% for medium, and 14%

for high adherent groups, p=0.07). Median FeNO levels in different adherence groups are shown in **Figure 1**.

There was no statistically significant difference in adherence and asthma symptom control between the groups of different education levels (p=0.32). Furthermore, the asthma symptom control status (p=0.31), medication adherence (p=0.98), and FeNO levels (p=0.21) were not different between smokers and non-smokers. The median FeNO level of smokers (10.5 ppb) was significantly lower than non-smokers (15 ppb) and ex-smokers (19 ppb) as expected (p=0.002). There was no significant difference in medication adherence and gender (p=0.052). The relationship between the type of asthma medication used and ACT level, medication adherence, and FeNO levels could not be identified.

Asthma symptom control was worse in patients with high airway inflammation. The mean ACT of the patients in the low FeNO group (≤25 ppb) was 21±3.6 and 18.8±3.5 in the high (>25 ppb) FeNO group (p=0.01).

The presence of comorbidities was not different between adherent and non-adherent patient groups. Medication adherence was low in almost half of both groups with and without comorbidity. Asthma symptom control was not significantly different between patients with and without comorbidity. A poor but significant negative correlation was found between the number of existing comorbidities and FEV1 (r=–0.107, p=0.002). We recognize that adherence was assessed solely via the MMAS-8 questionnaire, without objective measures such as dose counters or pharmacy refill records. This is acknowledged as a limitation in the discussion.

Follow-up Evaluations After 6 Months

Four patients could not be contacted after 6 months, and follow-up data could not be obtained. Among the 109 patients who could be reached, 11 (10.1%) had at least one asthma exacerbation. One (0.9%) patient had three, and ten (9.2%) patients had one asthma exacerbation. At the 6-month follow-up, 72.7% of patients with an asthma exacerbation had uncontrolled asthma at initial evaluation. In comparison, the rate was 39.8% patients who did not have an asthma exacerbation—the initial mean ACT in patients who had an exacerbation was 17.5±3.7 and 20.8±3.5 for patients who did not (p=0.02). When comparing asthma medication use with exacerbation rates over a 6-month period, it was observed that 2.1% of patients using only inhaled corticosteroids (ICS) experienced exacerbations, whereas 16.4% of patients on combination therapy including ICS experienced exacerbations (p=0.03). The initial median FeNO levels of patients who had an exacerbation was 19±2.6 ppb and for those who did not was 15±1.3 (p=0.23; **Figure 2**).

The probability of having an exacerbation within 6 months was not associated with medication adherence, the presence of comorbidities, educational level, or the use of non-asthma drugs. However, the ratio of patients experiencing an exacerbation within 6 months was higher in the group using a combination therapy that included inhaled corticosteroids than the group using only inhaled corticosteroids medication (16.4% vs 2.1%, p=0.02). Patients who had an exacerbation had lower initial FEV1 than those who did not (65% vs 89.5%, p=0.007).

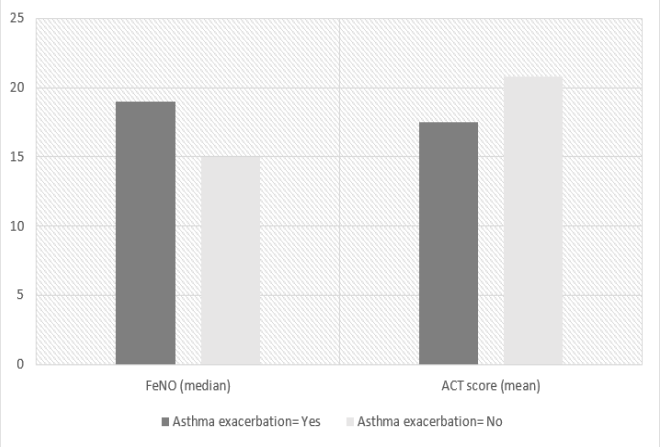

Figure 2. Comparison of the initial FeNO levels and initial ACT in patients who experienced or not an exacerbation during the 6 months period
FENO: Fractionated expiratory air nitric oxide measurement, ACT: Asthma control test

DISCUSSION

This study shows that asthma symptom control was worse in patients with asthma who are medication non-adherent and that FeNO values were higher in patients with uncontrolled asthma. In this patient group, ACT score and low FEV1 value are significant parameters in predicting asthma attacks at 6-month follow-up.

Adherence to treatment is crucial for achieving asthma control and managing inflammation effectively. In determining adherence, methods such as checking the last prescription date, identifying the number of medications obtained from reimbursement systems, use of dose counters, electronic inhaler monitors, and using specifically developed questionnaires can be beneficial.[13-15] Bårnes and Ulrik[16] investigated adherence levels to inhaler therapy among patients with asthma. From their extensive literature review, they identified an average adherence rate ranging from 22% to 63%. In this study, adherence was calculated as the total number of days of supplied medicine divided by the number of days of observation by linking the electronic prescriptions with the prescription fill information. Factors such as young age, being African American, having a low level of education, and having mild asthma were found to be associated with low adherence levels. Oguzülgen et al.[11] evaluated the criterion validity of the MMAS-8 adherence scale among patients with asthma in Turkiye. The findings revealed that 34.8% of patients exhibited high adherence to medication. In our study, the low and moderate treatment adherence rate was 86.8% and that factors such as education level, gender, medication used in asthma maintenance therapy, and the presence of additional comorbidities did not affect medication adherence.

Asthma control is expected to improve as medication adherence increases. In our study, as medication adherence assessed with MMAS-8 increased, the rate of asthma under control as measured by ACT increased. Woehrle et al.[17] investigated the relationship between medication adherence and symptom control in adults with asthma over a 90-day period using digital companion paired inhaler devices. At

baseline, 33% of patients had well-controlled asthma, which increased to 53.6% at the second ACT. It was concluded that improvement in medication adherence led to better asthma control, which corroborates our findings.

FeNO, a marker of eosinophilic airway inflammation, decreases with inhaler steroid treatment in patients with asthma and increases during an asthma attack.[18,19] In addition to asthma, FeNO can also increase because of eosinophilic bronchitis, bronchiectasis, and lower respiratory tract infections, but is low for smokers and those using steroid inhalers.[6] McNichol et al.[20] showed a greater reduction in FeNO in patients with poor treatment adherence in patients receiving directly observed inhaled corticosteroid therapy. In another study of 250 cases, low FeNO level in patients using inhaled corticosteroids correlated to high medication adherence.[21] In our study, although all patients were receiving inhaler corticosteroid treatment, FeNO was high in 24.1% of the cases and there was no association between MMAS-8 scores and FeNO levels (p=0.34 r=−0.091). This result can be explained by the fact that some of our patients were smokers or use inhaled corticosteroids. The lack of a statistically significant association between adherence and FeNO may relate to heterogeneous FeNO distribution, smoking habits, variations in inhaler technique, and treatment intensity differences.

Inflammation monitoring is also helpful in evaluating asthma control.[1,22] In the study by Gemicioğlu et al.[23] in which the FeNO level was investigated in different types of asthma, a negative correlation was found between the ACT score and FeNO (p<0.002, r=−0.31). Studies have reported no correlation between FeNO levels and FEV1 percentage, but there was a positive correlation between ACT score and basal FEV1 percentage (p=0.001, r=0.22).[24] As shown in other studies, it was emphasized that it would be more accurate to evaluate ACT together with respiratory function tests and FeNO measurements.[25] In our study, the mean ACT score in the group with high (>25 ppb) FeNO level was 18.8±3.5 and in the low (≤25 ppb) group 21±3.6 (p=0.01), and in 34% of patients with uncontrolled asthma, FeNO was above 25 ppb. Additionally, when patients with asthma were grouped as under control (ACT≥20) and uncontrolled (ACT<20), the median level of FeNO was same for both groups, which was considered to be related to the heterogeneous distribution of FeNO (minimum–maximum 5–90 ppb) and individual patient factors. However, it was thought that since all patients were receiving inhaled corticosteroids and other asthma maintenance treatments, some of them being active smokers and some having smoked in the past might be a factor.

In this study investigating the effect of patients' medication adherence on future risks and attacks, the attack rate of 113 patients during the 6-month follow-up was 10%. Contrary to what was expected, there was no statistically significant relationship between medication adherence and attack status, possibly because only 8% of the participants had severe asthma or 58% had their asthma symptoms under control. However, the number of patients with attacks in all three groups (low, medium, and high adherence) was low, which made it difficult to interpret the statistical results.

In a cohort study investigating factors that could predict an asthma attack, 43 of 154 asthma patients with a baseline FEV1 value of 72.62±17.96% had an attack within 4 months. In this study, the median FEV1 in those who had an asthma attack was 68% (55–79%), the median ACT score was 12 (10–16), and these rates were lower than in patients who did not have an asthma attack (p=0.013, p=0.003). However, the FeNO level of patients who had attacks was lower than those who did not have attacks (p=0.7).[26] In our study, the median FeNO level in patients who experienced attacks was 19±2.6 ppb (p=0.23), with a mean FEV1 of 65% (p=0.007), and a mean ACT score of 17.5±3.7 (p=0.02). However, FeNO levels were not different in patients who had or did not have an attack in this study. In patients using combination therapy that includes inhaled corticosteroids (ICS), a higher incidence of exacerbations was observed compared to those using only ICS. This finding could be attributed to the fact that these patients may have more severe asthma, with disease severity being a known risk factor for exacerbations.[27] Baseline ACT scores, FEV1 values, and comorbidity prevalence were compared between patients on combination therapy and those on ICS monotherapy, to better contextualize the higher exacerbation rate.

Limitations

A limitation of this study could be that the smoking status was not included among the patient selection criteria. Also, the very small number of patients who had an asthma attack might have played a role in some of the expected parameters not being statistically significant. If the number of patients were larger, the number of patients experiencing attacks might have increased further. Furthermore, the small number of exacerbation events reduced statistical power to detect associations with FeNO, adherence, and exacerbation risk, limiting generalizability.

CONCLUSION

This study showed that asthma symptom control was worse in patients with asthma who were medication non-adherent and FeNO values were higher in patients whose asthma was not under control. It was concluded that medication adherence, which can be easily evaluated with the MMAS-8 questionnaire, could contribute to the improvement of asthma control at patient follow-up. Our data also demonstrate the value of interpreting ACT, FEV1, and FeNO together when assessing asthma control in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The protocol has been approved by the Gazi University Clinical Researches Ethics Committee (Date: 06.01.2014, Decision No: 09).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Investigation of systemic inflammation levels in patients followed up with a diagnosis of pneumonia

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ABSTRACT

Aims: Although pneumonia is typically considered a localized infection, it can trigger a systemic inflammatory response. Systemic inflammation is characterized by cytokine release throughout the body, increased acute phase reactants, and immune cell imbalance, which can elevate disease severity and the risk of complications. Recently, hematological parameters such as the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) have gained prominence in assessing this inflammatory response. This study aimed to evaluate systemic inflammation levels in patients diagnosed with pneumonia using SII and SIRI, and to analyze their correlation with classical inflammatory biomarkers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Methods: Between January 1, 2023, and June 1, 2025, a total of 50 patients hospitalized and followed with a diagnosis of pneumonia in the Departments of Pulmonology and Internal Medicine at Yozgat Bozok University Research and Training Hospital, along with 50 healthy individuals who presented to the same clinics during the same period, were included in the study. The study was designed retrospectively, with the pneumonia cases constituting the patient group and healthy volunteers serving as the control group. Demographic characteristics (age, sex), smoking status, clinical histories, laboratory findings, treatment processes, complete blood count (CBC), CRP levels, and ESR were recorded. Patients with active malignancy, hematological or autoimmune diseases, or those receiving immunosuppressive therapy were excluded from the study. For each participant, the SII and SIRI values were calculated.

Results: Of the participants, 66% were male and 34% female, with a mean age of 61.98±16.78 years in the pneumonia group and 59.20±16.10 years in the control group. SII was significantly higher in the pneumonia group (1301.28±886.78) compared to the control group (545.20±488.26), as was SIRI (5.66±6.58 vs. 0.91±1.21) ($p<0.001$ for both). Smokers exhibited significantly higher SII (1535.9±1094.1 vs. 977.2±560.3) and SIRI (7.51±8.13 vs. 3.10±3.72) values than non-smokers ($p=0.031$ and $p=0.014$, respectively).

Conclusion: This study demonstrated that new-generation inflammation indices such as SII and SIRI reflect the intensity of inflammatory response in pneumonia patients and show significant correlation with CRP levels. These findings suggest that integrating these indices into clinical practice may serve as effective tools in evaluating disease prognosis and monitoring treatment response.

Keywords: Pneumonia, systemic immune-inflammation index (SII), systemic inflammatory response index (SIRI)

INTRODUCTION

Community-acquired pneumonia (CAP) is an infectious disease that imposes a substantial global health burden, particularly among elderly individuals and those with comorbidities, often leading to severe clinical courses. The clinical management of CAP varies depending on the early diagnosis and the ability to predict disease severity. Consequently, there is a growing need for objective, rapid, and cost-effective diagnostic tools.[1,2]

Traditional inflammatory markers such as CRP and ESR are indicative of infection but are often insufficient in reflecting disease severity or distinguishing between different pathophysiological processes. Therefore, attention has shifted toward more comprehensive and dynamic indicators of inflammation. In this context, the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) have recently emerged as novel biomarkers for various infectious and inflammatory conditions.[3]

SII and SIRI are calculated using complex formulas that incorporate neutrophil (NEU), lymphocyte (LYM), monocyte (MONO), and platelet (PLT) levels, offering an integrated view of the immune and inflammatory burden within the body. Initially applied in oncology—for example, in gastric cancer[4] and hepatocellular carcinoma[5]—these indices have shown utility in prognostic assessments. More recently, their diagnostic and prognostic value in infectious diseases, including CAP, has gained recognition.

Tortum et al.[6] reported that SII was effective in predicting disease severity among pneumonia patients evaluated in emergency departments. Zeng et al.[7] identified SIRI as a significant predictor in post-ischemic stroke pneumonia. Similarly, Corica et al.[8] highlighted gender-specific differences in inflammatory responses in CAP, noting the potential for these biomarkers to have varying clinical implications across patient subgroups.

Environmental factors also influence the levels of these inflammatory indices. Smoking, in particular, is known to elevate inflammatory cytokines and cellular activity, thereby increasing index values. Lee et al.[9] demonstrated a markedly heightened inflammatory response in smokers. Moreover, a meta-analysis by Yang et al.[10] associated elevated SII with poor prognosis across various cancer types, reflecting the systemic impact of widespread inflammation.

The validity of these indices has also been confirmed in chronic inflammatory diseases. Wu et al.[11] showed that SII correlated with disease activity in ankylosing spondylitis, while Shao et al.[12] demonstrated their diagnostic and prognostic utility in pediatric *Mycoplasma pneumoniae* infections. Elmeazawy et al.[13] reported that SII and SIRI could predict necrotizing pneumonia development in children. Miao et al.[14] found that SII could estimate the risk of postoperative pneumonia in patients undergoing lung resection.

Furthermore, Suwadi et al.,[15] in a systematic review, reported that SII could potentially serve as a diagnostic tool even in other respiratory conditions such as acute pulmonary embolism. These findings suggest that beyond infectious diseases, these biomarkers have broad applicability in evaluating systemic inflammation.

METHODS

Ethics

Ethical approval for the study was obtained from the Non-interventional Clinical Researches Ethics Committee of Yozgat Bozok University Faculty of Medicine (Date: 04.06.2025, Decision No: 2025-GOKAEK-2511_2025.06.04_524). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

Between January 1, 2023, and June 1, 2025, data were collected from 50 patients who were hospitalized and followed with a diagnosis of pneumonia in the Departments of Pulmonology and Internal Medicine at Yozgat Bozok University Research and Training Hospital. Patients with active malignancy, hematological disease, autoimmune disease, or a history of immunosuppressive therapy were excluded from the study. During the same period, individuals who presented to the same clinics and were found to have no pathological findings on clinical evaluation and diagnostic work-up were accepted as the healthy control group. The study was conducted retrospectively. Demographic data (age, sex), smoking status, clinical histories, laboratory results, treatment processes, complete blood count (CBC), CRP levels, and ESR were recorded.

Data Collection

Data were retrieved from the hospital information management system. Comprehensive clinical data, including participants' demographic information (age, sex), smoking status, disease history, hemogram, and biochemical parameters, were recorded. Among the laboratory data, hemogram parameters (PLT, NEU, LYM, MONO values) formed the primary variables of the study. To determine the level of systemic inflammation, the SII and SIRI were calculated using the following formulas:

SII: (PLT×NEU)/LYM

SIRI: (NEU×MONO)/LYM

SII and SIRI are composite indicators reflecting the degree of systemic inflammation based on peripheral blood cell counts. SII reflects the inflammatory burden by accounting for increased NEUs and PLTs along with decreased LYMs, while SIRI assesses the cellular immune response by comparing NEU and MONO levels with LYMs. These indices, calculated from routinely performed CBC tests, are cost-effective, rapid, and accessible, and offer valuable clinical insight into infection severity and prognosis.

No diagnostic or therapeutic intervention was performed in this study; data were obtained solely from existing medical records. Accordingly, the study was conducted as a retrospective observational study in line with ethics committee approval.

Statistical Analysis

The data analyses were performed using SPSS version 22.0. Continuous variables were expressed as mean±standard deviation (SD). The distribution of variables was evaluated using the Kolmogorov-Smirnov test. Independent samples t-test was used for comparing normally distributed variables, while the Mann–Whitney U test was applied for non-normally distributed variables. Categorical variables were analyzed using the Chi-square test. The correlation between SII and SIRI indices and CRP and ESR levels was assessed using the Spearman correlation test. A p-value of <0.05 was considered statistically significant in all tests.

RESULTS

Among the 100 individuals included in the study, 66 were male and 34 were female. No statistically significant difference was observed between the groups in terms of gender (p=1.00). The participants' ages ranged from a minimum of 19 to a maximum of 84 years. The mean age was calculated as

61.98±16.78 years in the pneumonia group and 59.20±16.10 years in the control group, with no statistically significant difference between the two groups in terms of age (p=0.106).

When evaluating comorbidities in the patients, chronic obstructive pulmonary disease (COPD), hypertension, and diabetes mellitus were the most common conditions. Additionally, in some cases, coronary artery disease, asthma, hyperthyroidism, heart failure, valvular heart diseases, benign prostatic hyperplasia, vertebrobasilar insufficiency, a history of tuberculosis, and chronic kidney disease were also observed.

In the pneumonia group, the mean NEU value was 9.15±8.24×10^9/L, compared to 3.95±1.62 ×10^9/L in the control group. The mean LYM value was 1.93±1.77×10^9/L in the pneumonia group and 2.04±0.62×10^9/L in the control group. The MONO value was 0.94±0.43×10^9/L in the pneumonia group and 0.37±0.11×10^9/L in the control group. The hemoglobin (Hb) level was 13.83±2.12 g/dl in the pneumonia group and 13.89±2.62 g/dl in the control group. The PLT count was 265.34±103.29×10^9/L in the pneumonia group and 239.02±47.83×10^9/L in the control group (**Table 1**).

Table 1. Comparative parameter table between pneumonia and control groups

Parameter	Pneumonia mean	Pneumonia SD	Control mean	Control SD
NEU (10^3/µL)	9.15	8.24	3.95	1.62
LYM (10^3/µL)	1.93	1.77	2.04	0.62
MONO (10^3/µL)	0.94	0.43	0.37	0.11
Hb (g/dl)	13.83	2.12	13.89	2.62
PLT (10^3/µL)	265.34	103.29	239.02	47.83
ESR (mm/h)	42.00	31.81	6.95	4.76
CRP (mg/L)	93.84	71.84	2.07	2.67

SD: Standard deviation, NEU: Neutrophil, LYM: Lymphocyte, MONO: Monocyte, Hb: Hemoglobin, PLT: Platelet, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

The mean SII was calculated as 1301.28±886.78 in the pneumonia group and 545.20±488.26 in the control group, with this difference being statistically significant (p=0.000). Similarly, the mean SIRI was 5.66±6.58 in the pneumonia group and 0.91±1.21 in the control group, and the difference between the groups was also statistically significant (p=0.000) (**Figure 1, 2**).

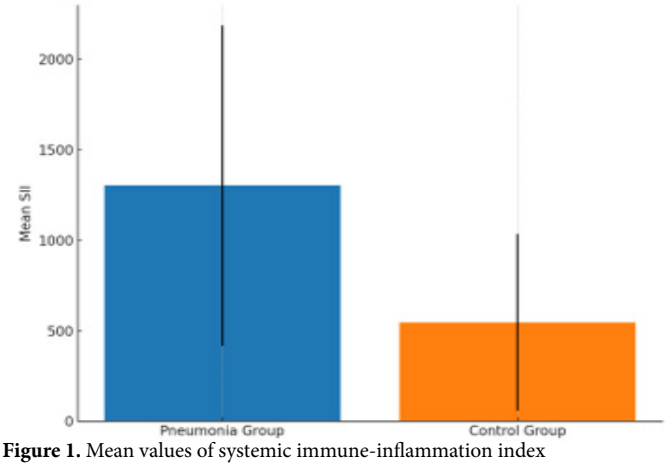

Figure 1. Mean values of systemic immune-inflammation index

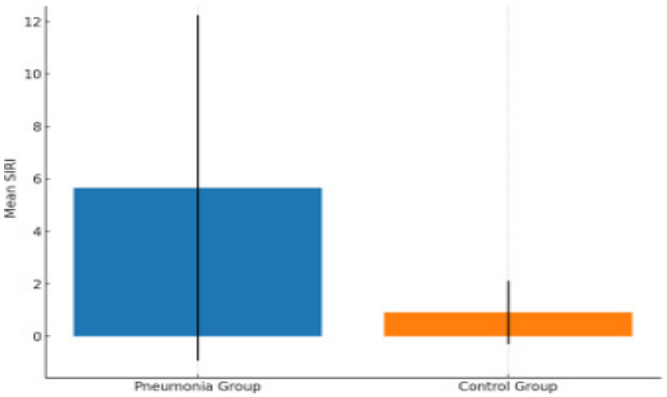

Figure 2. Mean values of systemic inflammatory response index

Among the biochemical markers of inflammation, the CRP level was found to be 93.84±71.84 mg/L in pneumonia patients, whereas it was 3.46±2.78 mg/L in the control group; this difference was also considered statistically significant (p=0.000). Furthermore, the ESR was 42.00±31.81 mm/h in the pneumonia group and 7.03±4.83 mm/h in the control group, which was also found to be statistically significant (p=0.000) (**Table 1, 2**).

Table 2. Comparative table of inflammatory markers

Parameter	Pneumonia mean	Pneumonia SD	Control mean	Control SD
SII	1301.28	886.78	545.20	488.26
SIRI	5.66	6.58	0.91	1.21
CRP (mg/L)	93.84	71.84	3.46	2.78
ESR (mm/h)	42.00	31.81	7.03	4.83

SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

When evaluating the relationship between smoking status and systemic inflammation indices, the mean SII value in smokers was 1535.9±1094.1 and the SIRI value was 7.51±8.13. In non-smokers, these values were calculated as 977.2±560.3 for SII and 3.10±3.72 for SIRI. Statistical analysis revealed significant differences between the groups in terms of both SII (p=0.031) and SIRI (p=0.014). These findings indicate that smoking increases the systemic inflammatory response (**Table 3, Figure 3**).

Table 3. Comparison of SII and SIRI values according to smoking status in pneumonia patients

Parameter	Smokers (mean±SD)	Non-smokers (mean±SD)	p-value
SII	1535.9±1094.1	977.2±560.3	0.031
SIRI	7.51±8.13	3.10±3.72	0.014

SD: Standard deviation, SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index

The relationship between the SII and SIRI indices and the levels of CRP and erythrocyte sedimentation in pneumonia patients was evaluated using the Spearman correlation coefficient. A correlation coefficient (r) between 0.1–0.3 was interpreted as weak, 0.3–0.5 as moderate, and ≥0.5 as strong. Spearman correlation analysis revealed a moderate positive correlation between SII and CRP (r=0.41, p=0.003), and a stronger positive correlation between SIRI and CRP (r=0.48,

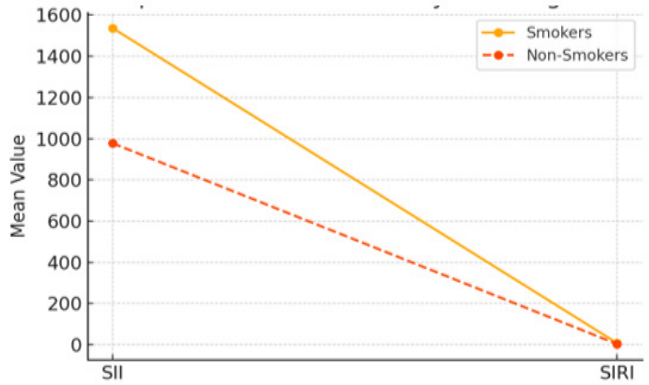

Figure 3. Comparison of SII and SIRI according to smoking status
SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index

p<0.001). In contrast, no statistically significant relationship was found between SII and sedimentation (r=0.21, p=0.149) or between SIRI and sedimentation (r=0.10, p=0.505) (**Table 4, Figure 4**).

Table 4. Correlation analysis between SII and SIRI with CRP and sedimentation

Correlation pair	Correlation (r)	p-value
SII–CRP	0.41	0.003
SII–ESR	0.21	0.149
SIRI–CRP	0.48	<0.001
SIRI–ESR	0.10	0.505

SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

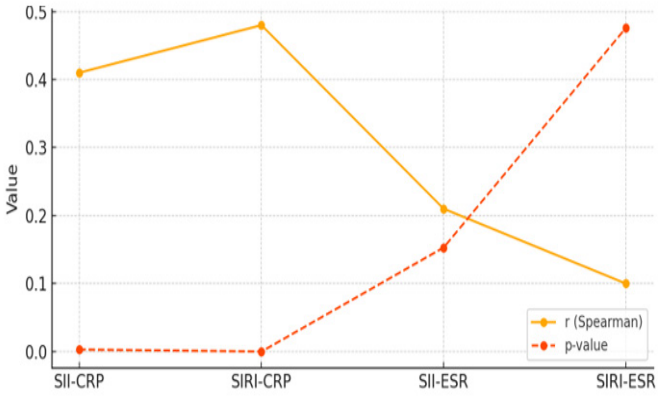

Figure 4. Relationship between SII/SIRI and CRP and sedimentation in the pneumonia group
SII: Systemic immune-inflammation index, SIRI: Systemic inflammatory response index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

DISCUSSION

In this study, systemic inflammation parameters in pneumonia patients were comprehensively examined, revealing significant differences compared to the control group. Of the 100 participants, 66% were male and 34% were female, with no statistically significant difference between sexes (p=1.00). While this finding suggests that gender may not be a determining factor in the development of pneumonia, the literature indicates that in CAP, males often present with higher hospitalization rates, more frequent comorbidities such as COPD, and a more pronounced pro-inflammatory response (Cillóniz et al.[2]). In contrast, female patients may display differences in clinical presentation and treatment response.[8]

The mean age of participants was 61.98±16.78 years (range: 19–84), indicating that pneumonia can occur not only in the elderly but also in younger adults. However, with increasing age, the incidence and risk of complications rise, and in elderly patients, immune senescence, the presence of comorbidities, reduced functional capacity, and atypical presentations complicate diagnosis and management (Cillóniz et al.[2]).

The most common comorbidities were COPD, hypertension, and diabetes mellitus. COPD, through its effects on both lung parenchyma and systemic inflammatory balance, represents a major risk factor for pneumonia. Additionally, the use of inhaled corticosteroids (ICS) may increase infection risk. Lee et al.[18] reported that ICS use significantly increased the risk of pneumonia and tuberculosis in a dose-dependent manner.

Laboratory analysis revealed a significantly higher NEU count in the pneumonia group (9.15±8.24×10^9/L) compared to controls (3.95±1.62×10^9/L), reflecting an acute immune response and systemic inflammation. Elevated NEUs directly influence composite inflammatory indices such as SII and SIRI, which correlate with disease severity (Yang et al.[3]).

The pneumonia group also exhibited a lower lymphocyte count (1.93±1.77×10^9/L) compared to controls (2.04±0.62×10^9/L), suggesting possible immunosuppression during infection. Lymphocytopenia is associated with infection extent and immune insufficiency. Tortum et al.[6] demonstrated that low lymphocyte counts, in combination with elevated SII, were associated with increased intensive care requirements and mortality in pneumonia patients. Our findings support the view that pneumonia patients exhibit weakened immune function, with lymphocyte counts serving as an important biomarker in this context.

In the pneumonia group, the mean MONO count was 0.94±0.43×10^9/L, compared to 0.37±0.11×10^9/L in the control group, representing a significant increase indicative of a systemic inflammatory response to infection. MONOs, as key cells of innate immunity, migrate to infected tissues, perform phagocytosis, and regulate the release of inflammatory mediators. Elmeazawy et al.[13] reported that elevated MONO counts are critical in predicting necrotizing pneumonia in pediatric patients, correlate with increases in SII and SIRI, and reflect disease severity. Our findings similarly suggest that MONO elevation in pneumonia may serve not only as a diagnostic biomarker but also as an indicator of clinical progression and complication risk.

Hb levels averaged 13.83±2.12 g/dl in the pneumonia group and 13.89±2.62 g/dl in the control group, with no significant difference regarding anemia. In acute infections, Hb typically remains stable in the early phase. Hu et al.[5] demonstrated that in hepatocellular carcinoma, Hb was not directly associated with systemic inflammation, whereas composite indices such as SII provided more sensitive markers. This may explain the preserved Hb levels observed in our study cohort.

PLT counts were 265.34±103.29×10^9/L in the pneumonia group and 239.02±47.83×10^9/L in the control group. Beyond their hemostatic function, PLTs are active participants in immune responses. Prina et al.[26] found that thrombocytosis in CAP was associated with poor prognosis, higher mortality,

and complications. In our study, the elevated PLT counts may similarly represent part of the inflammatory response.

SII, SIRI, CRP, and ESR values were significantly higher in the pneumonia group than in controls (p=0.000). Among pneumonia patients who smoked, SII (1535.9±1094.1 vs. 977.2±560.3; p=0.031) and SIRI (7.51±8.13 vs. 3.10±3.72; p=0.014) were notably elevated. The mean SII was 1301.28±886.78 in the pneumonia group compared to 545.20±488.26 in controls (p=0.000), indicating a markedly stronger systemic inflammatory response. This aligns with Tortum et al.,[6] who reported that higher SII values in pneumonia patients presenting to the emergency department predicted greater disease severity, intensive care requirements, and increased complication risk.

In our study, the SIRI value was found to be significantly higher in the pneumonia group compared to the control group (5.66±6.58 vs. 0.91±1.21; p=0.000). Calculated as the ratio of NEU and MONO counts to lymphocyte counts, SIRI reflects both the extent of infection and the magnitude of the immune response. In the literature, Zeng et al.[7] reported that SIRI is an effective biomarker for predicting the development of pneumonia following ischemic stroke, whereas Zheng et al.[16] demonstrated that elevated SIRI in patients undergoing thrombectomy for acute ischemic stroke was an independent risk factor for pneumonia, with each unit increase raising the risk by 17% (OR=1.169, p=0.014) and showing significant associations with intensive care requirement, complications, and mortality. Our findings indicate that the elevated SIRI levels observed in the pneumonia group reflect the severity of infection and systemic inflammatory burden, aligning closely with the existing literature.

Among classical inflammatory markers, CRP levels averaged 93.84±71.84 mg/L in the pneumonia group and 3.46±2.78 mg/L in the control group, while ESR values were 42.00±31.81 mm/h and 7.03±4.83 mm/h, respectively (both p=0.000). Marrie[1] and Cillóniz et al.[2] have emphasized the diagnostic and therapeutic follow-up value of these markers in CAP, while Wang et al.[4] noted their role in calculating systemic inflammation indices.

A significant association was also found between smoking status and inflammatory parameters. Both SII and SIRI values were markedly higher in smokers (SII: 1535.9±1094.1 vs. 977.2±560.3; p=0.031 / SIRI: 7.51±8.13 vs. 3.10±3.72; p=0.014). Lee et al.[9] demonstrated that toxic components in cigarette smoke activate alveolar macrophages, epithelial cells, and dendritic cells, thereby enhancing the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which in turn augment peripheral NEU activation, suppress lymphocyte function, and increase MONO activation. Similarly, Tabakoğlu et al.[19] reported that a smoking history of at least 20 pack-years significantly increased SII values (B=180.053, p=0.034), attributing this to chronic inflammatory stimulation, oxidative stress, and immune cell activation. Our findings are consistent with these mechanisms, further highlighting the amplifying effect of smoking on systemic inflammatory responses.

Correlation analysis revealed significant positive associations between SII and CRP (r=0.41, p=0.003) and between SIRI and CRP (r=0.48, p<0.001). These results demonstrate that both indices are closely related to biochemical inflammatory markers. Wu et al.[11] and Miao et al.[14] similarly reported that these indices correlate with CRP and reflect the severity of inflammation. Shao et al.[12] emphasized the utility of SII and SIRI in the diagnosis and follow-up of pediatric *Mycoplasma pneumoniae* infections.

Taken together, these findings suggest that SII and SIRI are robust diagnostic and prognostic biomarkers in pneumonia, and that evaluating them alongside classical markers such as CRP and ESR may significantly enhance clinical decision-making. Furthermore, integrating these indices into established clinical risk stratification models, such as those by Fine et al.[20] and Chalmers et al.,[21] may allow earlier and more accurate prediction of mortality and complication risk.

Limitations

However, our study has certain limitations. First, its single-center design may restrict the generalizability of the findings. Second, the relatively small sample size could reduce statistical power, particularly in subgroup analyses. Lastly, the retrospective design limits the ability to establish causal relationships. Therefore, to validate our results and obtain stronger evidence, larger-scale, multicenter, prospective studies are warranted.

CONCLUSION

This study demonstrates that the systemic inflammation indices SII and SIRI may serve as valuable diagnostic and prognostic biomarkers in patients with pneumonia. The findings reveal that classical inflammatory parameters—such as NEUs, MONOs, CRP, and ESR—are significantly elevated in the pneumonia group. Moreover, the positive correlation between SII and SIRI with CRP supports the role of these indices in reflecting the systemic impact of infection. The observation that SII and SIRI levels are higher among smokers underscores the pro-inflammatory effect of tobacco use on the immune response.

In light of these results, the routine use of systemic inflammation indices such as SII and SIRI in infectious diseases like pneumonia may offer substantial benefits in early diagnosis, severity assessment, and monitoring of treatment response. Future prospective studies with larger sample sizes are warranted to provide stronger evidence for the integration of these parameters into routine clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study was obtained from the Non-interventional Clinical Researches Ethics Committee of Yozgat Bozok University Faculty of Medicine (Date: 04.06.2025, Decision No: 2025-GOKAEK-2511_2025.06.04_524).

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

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

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Approach to the adult patient with non-traumatic chest pain in the emergency department

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ABSTRACT

Chest pain is one of the most common reasons for presentation to the emergency department and may be attributable to a wide spectrum of cardiac and non-cardiac etiologies. Given that this clinical manifestation may indicate life-threatening conditions—such as acute coronary syndrome, aortic dissection, pulmonary embolism, pneumothorax, pericardial tamponade, and mediastinitis—a prompt and structured diagnostic approach is essential. Clinical data including history, physical examination findings, vital signs, and prior test results play a pivotal role in risk stratification and guiding the diagnostic algorithm. Electrocardiography, cardiac biomarkers, D-dimer testing, chest radiography, and—when indicated—advanced imaging modalities such as computed tomography, magnetic resonance imaging, and echocardiography, contribute significantly to diagnostic accuracy. This review discusses a systematic approach to adult patients presenting with non-traumatic chest pain in the emergency setting, and summarizes key clinical scenarios and therapeutic strategies in differential diagnosis based on current literature.

Keywords: Emergency department, non-traumatic chest pain, diagnostic approach

INTRODUCTION

Chest pain is among the most frequent presenting complaints in the emergency department and is associated with a broad range of clinical conditions. Patients may exhibit symptoms related to the cardiovascular, pulmonary, gastrointestinal, or musculoskeletal systems. The primary responsibility of emergency physicians is the early identification and exclusion of potentially life-threatening causes of chest pain. Notably, patients with serious underlying etiologies may present with normal vital signs and non-specific physical examination findings, thereby creating a misleading impression of clinical stability. This review aims to provide a systematic approach to the evaluation of adult patients presenting to the emergency department with non-traumatic chest pain, with a focus on both life-threatening and commonly encountered causes. Topics related to the outpatient evaluation of clinically stable patients are beyond the scope of this review.

EPIDEMIOLOGY

Chest pain ranks as the second most common reason for adult visits to emergency departments in the United States, accounting for approximately 6–7% of all annual emergency presentations.[1] This corresponds to an estimated 7 to 8 million visits per year. Among all chest pain presentations, a life-threatening underlying pathology is identified in approximately 6% of cases, with the vast majority (over 90%) of these attributable to acute coronary syndrome.[2] Moreover, the likelihood of diagnosing a life-threatening condition increases significantly with advancing age.

INITIAL ASSESSMENT AND STABILIZATION

In patients presenting to the emergency department with chest pain, the initial priority is the rapid assessment of hemodynamic status and prompt identification of life-threatening conditions to facilitate immediate intervention. This process begins with a focused history and physical examination. In cases of non-traumatic chest pain, critical diagnoses that must be promptly excluded include acute coronary syndrome, aortic dissection, pulmonary embolism (PE), tension pneumothorax, cardiac tamponade, mediastinitis, myocarditis, Takotsubo cardiomyopathy, and perforated peptic ulcer. These conditions may present with symptoms that mimic those of more benign etiologies. Importantly, patients with severe underlying pathology may exhibit normal vital signs, whereas those with less serious causes may present with marked physiological disturbances. Therefore, findings such as abnormal vital signs, respiratory or circulatory distress, signs of hypoperfusion, sudden and severe thoracic or abdominal pain, or pulse discrepancies between extremities should be considered indicators of a potentially serious condition, and treatment should not be delayed while awaiting definitive diagnosis.

INITIAL MANAGEMENT STRATEGIES IN HEMODYNAMIC INSTABILITY

In patients presenting with hemodynamic instability or severe chest pain, rapid resuscitation measures should be implemented as follows:

Airway and ventilatory support: The need for invasive or non-invasive ventilation should be promptly assessed based on clinical findings.

Oxygen therapy: Supplemental oxygen should be administered only when indicated, with a target oxygen saturation typically between 90–92%. However, in patients with acute coronary syndrome who have normal oxygen saturation, routine oxygen supplementation is not recommended.

Intravenous access and laboratory sampling: Rapid establishment of intravenous access is essential to initiate diagnostic work-up without delay, and blood samples should be obtained for necessary laboratory investigations. In cases of suspected acute coronary syndrome, cardiac biomarkers—particularly high-sensitivity troponin—should be evaluated. If PE is suspected, D-dimer testing should be incorporated into the diagnostic algorithm in conjunction with appropriate clinical scoring systems.

Cardiac monitoring and ECG: Continuous cardiac monitoring should be initiated, and a 12-lead electrocardiogram (ECG) should be obtained at the earliest opportunity.[3]

Arrhythmia management: For life-threatening arrhythmias, advanced cardiac life support (ACLS) protocols should be followed.

Circulatory support: In cases of shock, immediate treatment of the underlying cause is paramount (e.g., emergency thoracostomy for tension pneumothorax, pericardiocentesis for tamponade).

Aspirin administration: In the absence of suspected aortic dissection or gastrointestinal perforation, 162–325 mg of non-enteric coated aspirin should be administered by chewing.

Chest radiography: A portable chest X-ray should be obtained in all patients presenting with chest pain. However, it should be noted that certain critical diagnoses may not present with classic radiographic findings.

Bedside ultrasonography: Point-of-care ultrasound is valuable in rapidly identifying life-threatening conditions in hemodynamically unstable patients. It aids in detecting pericardial effusion, right ventricular (RV) dilation, myocardial dysfunction, pneumothorax, and aortic enlargement.

ELECTROCARDIOGRAPHY AND ITS ROLE IN INITIAL ASSESSMENT

In all patients presenting to the emergency department with chest pain, early evaluation for potential cardiac etiologies is of paramount importance. In this context, the standard 12-lead ECG serves as the primary diagnostic tool, particularly in individuals at risk for acute coronary syndrome (ACS). According to the guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA), an ECG should be obtained and interpreted within the first 10 minutes of emergency department presentation. While there is no universally defined age threshold for ECG acquisition in younger adults, some studies advocate for routine ECG assessment in individuals over the age of 30.[4] Given its low cost, ease of use, and non-invasive nature, ECG is considered a prudent diagnostic measure even in patients with a low pre-test probability of cardiac disease. In such cases, performing an ECG is often preferable to risk missing an early diagnosis.

Although ECG is a readily available and rapid diagnostic tool for the evaluation of ACS, its sensitivity for detecting acute myocardial infarction (AMI) is limited. A single ECG recording may identify less than half of myocardial infarction (MI) cases. Among patients with normal or non-specific ECG findings, the incidence of AMI ranges from 1% to 5%, while unstable angina may occur in approximately 4% to 23% of cases.[5,6] Serial ECG assessments can enhance diagnostic accuracy, particularly when early signs such as hyperacute T waves are present. If the initial ECG is non-diagnostic but symptoms persist and clinical suspicion remains high, repeat ECGs should be performed. Management decisions should be guided by a combination of ECG findings and symptom assessment. When prior ECG records are available, current findings must be compared to determine whether changes are new.

ECG FINDINGS ASSOCIATED WITH LIFE-THREATENING DIAGNOSES

In patients presenting to the emergency department with chest pain, exclusion of cardiac causes is of critical importance. A 12-lead ECG should be obtained and interpreted within the first 10 minutes of arrival, serving as an essential tool for early diagnosis, particularly in individuals at risk for ACS. Due to its low cost, rapid availability, and non-invasive nature, ECG is generally recommended even in patients with a low likelihood of cardiac etiology.

However, the sensitivity of ECG for diagnosing AMI is limited; a single recording may detect fewer than half of all AMI cases. Early changes such as hyperacute T waves can be subtle and easily overlooked, underscoring the importance of serial ECG assessments to improve diagnostic sensitivity. A normal ECG does not definitively rule out AMI or unstable angina. Therefore, current findings should be interpreted in conjunction with clinical features and compared to previous ECGs when available.

Key ECG findings suggestive of life-threatening conditions include ST-segment elevations consistent with ST-elevation myocardial infarction (STEMI), new-onset left bundle branch block, signs of posterior AMI (ST depression and tall R waves in leads V1–V4, ST elevation in leads V7–V9), and the "de Winter" pattern. Diffuse ST-segment depression and T wave abnormalities may also reflect underlying myocardial ischemia.

In association with other critical diagnoses, certain characteristic ECG patterns may be observed. In pericarditis, diffuse ST-segment elevations accompanied by PR-segment depression are typical findings. PE may present with the $S_1Q_3T_3$ pattern, right bundle branch block, or right axis deviation.[7] In cases of pericardial tamponade, low voltage QRS complexes and electrical alternans can be noted. Ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, as well as conduction blocks, may occur following STEMI. Sinus tachycardia, while non-specific, may be a common manifestation in several life-threatening conditions including PE, cardiac tamponade, and aortic dissection. Therefore, a normal ECG should not be interpreted as definitive exclusion of serious underlying pathology.

CHEST RADIOGRAPHY AND ITS ROLE IN INITIAL ASSESSMENT

Chest radiography is a frequently utilized, rapid, and widely accessible imaging modality in the initial evaluation of patients presenting to the emergency department with chest pain. Although it can aid in the identification of certain life-threatening conditions, it is often insufficient as a standalone diagnostic tool; thus, radiographic findings should always be interpreted in conjunction with the clinical context.

Pneumothorax is typically recognized on upright chest radiographs by the presence of a visible pleural line and a radiolucent space between the pleura and the chest wall. In cases of large air leaks, lung collapse, mediastinal shift, and tracheal deviation may indicate tension pneumothorax. Pleural effusion is generally observed as blunting of the costophrenic angles or hemithorax opacification; in large effusions, mediastinal structures may be displaced toward the contralateral side.

PE often presents with a normal chest radiograph. However, in certain cases, rare and nonspecific findings such as Hampton's hump or the Westermark sign may be observed. Pulmonary congestion or acute heart failure of cardiac origin may manifest as cardiomegaly, pulmonary venous engorgement, Kerley B lines, and alveolar edema patterns on imaging.[8]

Aortic dissection or aneurysm may be suggested on chest radiography by findings such as mediastinal widening, irregularity of the aortic contour, tracheal deviation, and inferior displacement of the left main bronchus; however, computed tomography (CT) angiography is required for definitive diagnosis.[9] In cases of pericardial tamponade or large effusions, the cardiac silhouette may appear enlarged and globular, often described as a "flask-shaped" configuration, though echocardiography is essential for confirmation. Stress cardiomyopathy typically presents with a normal chest radiograph, although cardiomegaly and signs of interstitial pulmonary edema may be present if heart failure coexists. In esophageal rupture and mediastinitis, radiographic clues may include mediastinal free air, subcutaneous emphysema, and air tracking around the trachea; a left-sided pleural effusion may also be observed.

In conclusion, while chest radiography may offer important clues for certain critical diagnoses, its limited sensitivity often renders it insufficient as a standalone tool. Therefore, it should always be interpreted in conjunction with clinical findings and, when necessary, supplemented by advanced imaging modalities.

SUBSEQUENT EVALUATION

In patients presenting to the emergency department with chest pain, a definitive diagnosis is often not established during the initial evaluation, which includes triage, history taking, and physical examination. Therefore, the diagnostic process must continue in parallel with simultaneous therapeutic interventions. A detailed clinical history—including comorbid conditions and the specific characteristics of the presenting symptoms—provides critical information for narrowing the differential diagnosis and identifying potentially life-threatening causes. Physical examination findings, with a focus on vital signs and cardiac or pulmonary indicators, can further guide diagnostic reasoning. Unless a clearly non-cardiac or non-pulmonary etiology (such as herpes zoster) is identified, both electrocardiography and chest radiography should be routinely included in the assessment.

HISTORY OF PRESENT ILLNESS

In patients with chest pain, distinguishing the affected organ system based solely on symptom history can be challenging. The overlapping afferent neural pathways of intrathoracic structures often result in similar or non-specific symptom presentations. Thus, while symptom characteristics may provide diagnostic clues, they are rarely sufficient for establishing an early diagnosis in isolation. Atypical presentations are common and may be misinterpreted, potentially leading to diagnostic delays and adverse outcomes.[10,11] Key aspects to be addressed during history taking include the following:

Onset and character of pain: Sudden and severe chest pain is characteristic of critical conditions such as aortic dissection, pneumothorax, and PE. Most patients with aortic dissection report abrupt onset of symptoms.[12] Pneumothorax often occurs spontaneously at rest, without a clear precipitating event.

Duration and episodic nature: Whether the pain is continuous or episodic, along with its duration and frequency, holds diagnostic value. Additionally, determining the precise onset of symptoms is essential for the appropriate interpretation of cardiac biomarkers.

Precipitating events: A history of recent trauma, surgery, endoscopic procedures, or prolonged immobilization may raise suspicion for conditions such as PE or esophageal rupture. However, a classic predisposing event is not always present.

Relation to exertion: Pain triggered or worsened by physical exertion is commonly associated with ACS. While stable

angina tends to occur predictably with exertion, unstable angina may arise at rest or with minimal physical activity.

Quality and radiation of pain: Cardiac chest pain is typically described as a sensation of pressure, tightness, or heaviness and may radiate to the shoulders, arms, neck, jaw, back, or epigastric region. Radiation to the shoulders or exertion-induced pain should raise concern for ACS.

Non-ischemic causes: Sharp, stabbing, pleuritic, or position-dependent pain is more often associated with non-cardiac etiologies. Pericardial pain typically worsens in the supine position and improves when leaning forward. Pneumothorax may initially present with sharp pain that becomes dull over time. Gastrointestinal causes, on the other hand, frequently produce a burning sensation.

ASSOCIATED SYMPTOMS

Symptoms accompanying chest pain can offer valuable clues to guide the diagnostic process. Although diaphoresis, nausea, and vomiting are commonly associated with ACS, they may also be present in aortic dissection, PE, or esophageal spasm.[13] Dyspnea is a prominent feature in conditions such as PE, pneumothorax, and pneumonia. Hemoptysis may suggest PE or valvular heart disease, whereas cough and fever are more indicative of infectious causes such as bronchitis. Unilateral extremity pain and swelling raise concern for deep vein thrombosis, which may lead to PE. Fever may also accompany pericarditis, myocarditis, and, less commonly, MI.

RISK FACTORS

Major risk factors for ACS include advanced age, male sex, family history of cardiovascular disease, hypertension, dyslipidemia, diabetes mellitus, cigarette smoking, and a history of coronary artery disease.[14] However, the absence of these factors does not entirely exclude the possibility of serious cardiac pathology. Stimulant substances such as cocaine and amphetamines may provoke severe cardiovascular complications, particularly in younger individuals.

Key risk factors for aortic dissection include hypertension, connective tissue disorders such as Marfan syndrome, bicuspid aortic valve, pregnancy, and prior aortic surgery. In younger patients, underlying genetic or structural predispositions are more commonly implicated.

PE risk is elevated in the presence of recent surgical procedures, prolonged immobilization, central venous catheterization, malignancy, thrombophilia, pregnancy, and hormonal therapies.[15] In younger individuals, an obvious risk factor may be absent; however, further evaluation may reveal underlying genetic or hematologic predispositions, such as Factor V Leiden mutation.

Tobacco use is a significant risk factor for both cardiovascular and pulmonary diseases and is also an independent risk factor for spontaneous pneumothorax. The risk of pneumothorax is increased in individuals with HIV infection and in those with *Pneumocystis jirovecii* pneumonia. In women with endometriosis, catamenial pneumothorax—typically occurring during menstruation—should be considered.[16] Thoracic pressure changes associated with activities such as SCUBA diving, as well as a prior history of pneumothorax, are known to increase the risk of recurrence; similarly, air travel may also contribute to recurrence risk.[17]

PREVIOUS DIAGNOSES AND INTERVENTIONS

Obtaining information about prior diagnostic evaluations for similar symptoms can significantly guide current clinical decision-making. A recent coronary CT angiography (CCTA) or invasive cardiac catheterization demonstrating normal or minimally stenotic coronary arteries substantially reduces the likelihood of ACS. For instance, patients found to have minimal or no coronary artery disease have been shown to have a 98% event-free survival rate over a 10-year follow-up period with respect to MI.[18] However, a recent negative stress test alone is not sufficient to rule out ACS in patients presenting with ongoing chest pain.

PHYSICAL EXAMINATION

In patients presenting with chest pain, physical examination is essential for both the assessment of vital signs and the early recognition of life-threatening conditions. Individuals with serious underlying etiologies often appear anxious, restless, and distressed, and may exhibit accompanying signs such as diaphoresis, tachypnea, or dyspnea. Any significant abnormalities in vital parameters should be addressed without delay, and appropriate emergency management protocols should be promptly initiated.

PHYSICAL EXAMINATION FINDINGS IN SPECIFIC DIAGNOSES

Acute aortic dissection may not always present with specific findings on physical examination. However, when the dissection involves major aortic branches, signs of end-organ ischemia may emerge, including MI, ischemic stroke, mesenteric ischemia, or limb ischemia. Although uncommon, the presence of pulse deficits or significant blood pressure discrepancies between the upper extremities can be diagnostically meaningful. According to data from the International Registry of Acute Aortic Dissection, aortic regurgitation murmur is present in 32% of cases, pulse deficits in 15%, signs of shock or cardiac tamponade in 8%, acute heart failure in 7%, and cerebrovascular events in 5%. Additionally, up to 30% of patients may exhibit neurological manifestations such as Horner's syndrome, paraparesis, or paraplegia.[12]

In ACS, physical examination is often non-diagnostic, with patients typically presenting with minimal physical findings. However, the presence of pulmonary rales—either in conjunction with or independent of an S3 gallop—may suggest left ventricular dysfunction and associated congestive heart failure. Signs of right-sided heart failure, such as jugular venous distention, hepatojugular reflux, and peripheral edema, may be observed and can be associated with either ACS or PE. A new systolic murmur may indicate mechanical complications such as papillary muscle dysfunction or a ventricular septal defect. In pericarditis, the presence of a

characteristic pericardial friction rub on auscultation can provide a valuable diagnostic clue.

In patients with suspected PE, physical findings such as unilateral lower extremity swelling or localized wheezing may heighten clinical suspicion. However, it is important to note that extremity examinations are often unremarkable. In pneumothorax, diminished or absent breath sounds on the affected side represent the most frequently observed physical finding. Subcutaneous emphysema may be present but is relatively uncommon.

In certain cases, physical examination can support non-cardiac etiologies. For example, epigastric tenderness combined with positive fecal occult blood may indicate a gastrointestinal source of chest pain. Additionally, in patients with mediastinal emphysema, the presence of Hamman's sign—a crackling sound heard over the precordium with a stethoscope—may provide a diagnostic clue suggestive of esophageal rupture or pneumomediastinum.

TARGETED LABORATORY TESTING BASED ON CLINICAL SUSPICION

In patients presenting with chest pain, laboratory investigations should be guided by clinical suspicion and utilized to support the diagnostic process. Particularly in life-threatening cardiac and thromboembolic conditions, accurate interpretation of biomarkers is essential for prompt clinical decision-making.

Cardiac Biomarkers

Cardiac troponins are the most sensitive and specific indicators for the diagnosis of AMI. High-sensitivity troponin I or T assays typically begin to rise within 2–3 hours of symptom onset and peak around 12 hours. A single normal troponin level does not exclude early-stage AMI; however, a low initial value combined with a downward trend on serial testing may support early discharge in low-risk patients.[19-21] Elevated troponin levels may also be observed in non-ischemic cardiac conditions such as myocarditis, heart failure, or PE.

D-Dimer

In patients with suspected PE who are categorized as low-to-intermediate risk, D-dimer serves as a useful rule-out test due to its high sensitivity. However, D-dimer levels may be physiologically elevated in the presence of factors such as advanced age, malignancy, infection, recent surgery, and pregnancy. It may also aid in excluding aortic dissection, particularly when used in conjunction with the Aortic Dissection Detection Risk Score.[22]

Complete Blood Count

Leukocytosis may suggest infectious or inflammatory etiologies, including pneumonia, pericarditis, or mediastinitis. Anemia may be associated with serious conditions such as myocardial ischemia or aortic rupture.

BNP/NT-proBNP

These biomarkers are useful in suggesting acute heart failure. Low levels are valuable in ruling out the diagnosis. However, they must be interpreted within the clinical context, as values may be affected by age, renal impairment, or sepsis.

Coagulation Studies

In patients receiving anticoagulation therapy or at risk for bleeding, tests such as PT, aPTT, and INR should be obtained to assess coagulation status.

Basic Biochemical Tests

Electrolytes, renal function parameters, and serum creatinine levels are essential, particularly prior to procedures involving contrast media such as CT angiography or coronary angiography.

Liver Enzymes and Lipase

In patients presenting with epigastric or right upper quadrant pain, liver function tests and lipase levels are helpful in excluding hepatobiliary pathology or pancreatitis.

Arterial Blood Gas (ABG)

Although sometimes used in the evaluation of suspected PE, ABG has limited diagnostic utility. Assessment of the alveolar-arterial oxygen gradient offers only marginal diagnostic sensitivity and is not routinely recommended.

IMAGING MODALITIES

In patients with chest pain in whom initial ECG and laboratory tests are non-diagnostic, advanced imaging plays a pivotal role in the diagnostic pathway. CT is particularly valuable in the evaluation of non-ACS etiologies due to its broad diagnostic capabilities. CT can assess aortic dissection, PE, pneumothorax, pneumonia, and mediastinal or chest wall pathologies, and may also reveal alternative diagnoses when performed for suspected PE or dissection.

Aortic Dissection

CT angiography is the first-line imaging modality due to its rapid acquisition and widespread availability. Magnetic resonance imaging (MRI) offers superior structural assessment of the aorta but is limited in emergent settings. Transesophageal echocardiography (TEE) may provide reliable diagnostic information, especially in hemodynamically unstable patients when performed by experienced operators. The choice of imaging should be guided by clinical status, contrast tolerance, and institutional resources.

Pulmonary Embolism

Contrast-enhanced CT pulmonary angiography (CTPA) is considered the gold standard for diagnosing PE. While subsegmental emboli can be visualized, their clinical relevance remains controversial. In cases with poor image quality or contraindications to contrast, ventilation/perfusion (V/Q) scintigraphy may be employed. Lower extremity Doppler ultrasonography is also helpful in cases with suspected deep vein thrombosis.

Acute Coronary Syndrome (ACS)

In low-to-intermediate risk and clinically stable patients, CCTA is effective for ruling out ACS.[23] With high-resolution CT scanners, obstructive lesions can be accurately identified.

Additionally, CCTA can be utilized within the "triple rule-out protocol" to simultaneously exclude PE and aortic dissection; however, increased radiation exposure must be considered.[24]

Echocardiography and Cardiac Inflammation

Transthoracic echocardiography (TTE) is the primary modality for diagnosing pericarditis, myocarditis, and pericardial effusion. Myocarditis may present with global ventricular dysfunction, whereas apical ballooning is typical in Takotsubo cardiomyopathy. TTE is also useful in detecting signs of tamponade and regional wall motion abnormalities.

Gastrointestinal and Mediastinal Pathologies

For rare but serious causes such as esophageal rupture, mediastinitis, or perforated peptic ulcer, thoracic and/or abdominal CT can support the diagnosis by demonstrating free air, fluid collections, or signs of inflammation. These entities represent critical clinical emergencies requiring thorough and prompt evaluation.

LIFE-THREATENING CONDITIONS AND MANAGEMENT APPROACHES

Certain conditions in patients presenting to the emergency department with chest pain require prompt diagnosis and immediate intervention to prevent potentially fatal outcomes. Early recognition and management are therefore critical in these scenarios.

Acute Coronary Syndrome (ACS)

ACS is one of the most critical cardiac causes of chest pain. It may present with atypical symptoms, particularly in the elderly, women, or patients with diabetes, and should not be excluded based solely on a single ECG or troponin measurement. Diagnosis should be supported by high-sensitivity troponin assays and serial ECGs. Treatment includes antiplatelet and anticoagulant therapy, beta-blockers, and reperfusion strategies when indicated—such as primary percutaneous coronary intervention or coronary artery bypass grafting.

Aortic Dissection and Aneurysm

These conditions are typically seen in hypertensive patients or younger individuals with connective tissue disorders. Aortic dissection should be suspected in the presence of sudden, tearing chest pain accompanied by pulse or blood pressure discrepancies. CT angiography is the primary imaging modality for diagnosis, while TEE may be preferred in unstable patients. Management begins with anti-impulse therapy aimed at reducing heart rate and blood pressure. If surgical indications are present, urgent operative intervention is required.

Pulmonary Embolism (PE)

PE, a consequence of venous thromboembolism, presents with a wide clinical spectrum. Patients may exhibit nonspecific findings such as dyspnea, tachycardia, and hypoxia. In cases with suspected PE, clinical risk stratification should be performed using validated algorithms such as the Wells score and PERC criteria; diagnosis should then be confirmed with D-dimer testing and CTPA when appropriate.

Bedside ultrasonography and particularly echocardiography can provide valuable diagnostic insights in hemodynamically unstable patients. In appropriate clinical scenarios, the presence of RV dilation or dysfunction demonstrates approximately 50% sensitivity and 83% specificity for PE.[25] Notably, McConnell's sign—characterized by akinesia or hypokinesia of the RV free wall with preserved apical motion—is considered more specific for PE compared to general RV dysfunction.[26]

While thrombolytic therapy or embolectomy may be considered in hemodynamically unstable patients, anticoagulation remains the mainstay of treatment in hemodynamically stable individuals.

Pneumothorax

Spontaneous or secondary pneumothorax can also be life-threatening in patients presenting with chest pain and dyspnea. In the absence of trauma, spontaneous pneumothorax is commonly seen in tall, thin young males or individuals with underlying lung disease. In cases of tension pneumothorax, diagnosis is clinical, and immediate needle thoracostomy should be performed without delay for imaging. In stable patients, management options include chest tube placement, needle aspiration, or observation depending on clinical status and pneumothorax size.

Mediastinitis

Mediastinitis, particularly when secondary to esophageal perforation, surgical interventions, or odontogenic infections, carries a high risk of mortality. Diagnosis is typically established via CT, and delays in identification significantly increase the risk of adverse outcomes. Early initiation of broad-spectrum intravenous antibiotics is essential, and timely consultation with cardiothoracic surgery is strongly recommended.[27,28]

Pericardial Tamponade

Tamponade results from the accumulation of fluid in the pericardial sac, which impairs cardiac filling and may lead to obstructive shock. Bedside echocardiography allows for rapid diagnosis. Emergent pericardiocentesis is a life-saving intervention that can restore hemodynamic stability.

Myocarditis and Stress Cardiomyopathy

Myocarditis may result from a variety of causes, most commonly viral infections, and can lead to heart failure or arrhythmias. Diagnosis is supported by echocardiography, cardiac biomarkers, and, when needed, cardiac MRI. Takotsubo cardiomyopathy, typically triggered by emotional or physical stress, mimics MI but is characterized by the absence of obstructive coronary artery disease. Management is generally supportive.

Perforated Peptic Ulcer

Although uncommon, perforated peptic ulcers may present with epigastric pain radiating to the chest, mimicking other thoracic emergencies. Diagnosis is typically established by CT. Prompt initiation of intravenous antibiotics and early surgical consultation are essential components of management.

CONCLUSION

In adult patients presenting to the emergency department with non-traumatic chest pain, a rapid, systematic, and targeted evaluation is crucial for the early recognition and management of life-threatening conditions. Diagnostic tests guided by clinical history and physical examination findings can significantly reduce unnecessary interventions while improving outcomes by lowering morbidity and mortality. Therefore, a multidisciplinary approach and adherence to structured clinical algorithms are fundamental to the effective evaluation of chest pain in the emergency setting.

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.

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Review

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Behçet's disease and pulmonary involvement

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ABSTRACT

Behçet's disease (BD) is a systemic vasculitis involving arteries and veins of all sizes and is characterized by a heterogeneous spectrum of clinical manifestations, including mucocutaneous, ocular, vascular, and neurological involvement, typically following a relapsing-remitting course. Although thoracic involvement is infrequent, it can affect various anatomical structures within the chest and present with a wide range of clinical symptoms. Pulmonary artery involvement may lead to life-threatening complications such as pulmonary artery aneurysms (PAAs) and pulmonary artery thrombosis (PAT), which are significant causes of mortality in BD. Timeyl diagnosis, appropriate radiological assessment, prompt initiation of immunosuppressive therapy are critical to reducing morbidity and mortality. This review provides an overview of the pulmonary manifestations of BD.

Keywords: Vasculitis, Behçet's disease, pulmonary artery aneurysm, pulmonary artery thrombosis

INTRODUCTION

Behçet's disease (BD) is a chronic multisystemic vasculitis of unknown etiology. It was first described in 1937 by Hulusi Behçet in three patients with oral and genital ulcerations, uveitis, and erythema nodosum.[1,2] BD is an autoinflammatory vasculitis that can affect arteries and veins of all sizes, with the most common characteristic findings including venular involvement and pulmonary artery aneurysms (PAAs). Although BD is a form of vasculitis, the vasculitis lesions in BD lack necrotizing vasculitis or giant cell formation. Autoantibodies are not positive. Leukocytoclastic vasculitis and fibrinoid necrosis of the vessel wall are observed.[2]

Although its etiology remains unclear, environmental factors are considered to trigger BD in individuals with a genetic predisposition. BD is not genetically transmitted through Mendelian inheritance, while its high incidence along the Silk Road implicates the role of genetic factors in the development of the disease. The disease has been found to be more prevalent in carriers of HLA-B51/HLAB5. HLA B51 is a common genetic factor in Japanese, Middle Eastern, and Turkish populations.[3] In a review evaluating studies from 12 countries in Latin America, HLA-B51 positivity was found to be 38% in Argentina, 30% in Brazil, and 9% in Mexico.[4] Several factors including tumor necrosis factor (TNF), heat shock proteins, and major histocompatibility complex class I have been identified in the etiology. Genetic differences in MHC-1 opathies are controversial. Mitochondrial DNA is considered to play a role in the new inflammatory pathway.[2,5] Epidemiologically, BD has been identified in both sexes between the ages of 20 and 40. It is more severe in young populations and in males. Geographical differences in incidence between males and females and in terms of organ involvement have been reported.[2]

Clinical symptoms of BD are often heterogeneous and there are no pathognomonic laboratory findings. Diagnosis is made based on clinical criteria as well as international diagnostic criteria. The disease has been shown to be characterized by a decrease in the number of attacks and remissions with advanced age.[6,8] As a systemic vasculitis, it commonly manifests with mucocutaneous lesions and may also present with musculoskeletal, vascular, ocular, neurological, and gastrointestinal involvement.[2,6] Venous involvement is far more common than arterial involvement. Most common pulmonary manifestation is PAA or pulmonary artery thrombosis (PAT). Pulmonary involvement was commonly reported in studies published in the 1960s. Varying incidence rates ranging from 1% to 10-16% have been reported. Generally, screening for pulmonary involvement is not preferred unless clinical findings are suggestive.[9,10] The aim of this review was to summarize pulmonary involvement in BD in light of current literature.

PULMONARY INVOLVEMENT

In BD, elevated levels of free oxygen radicals have been observed, resulting from neutrophile hyperfunction. In turn, increased release of free oxygen radicals from neutrophils can cause acute inflammatory tissue damage, leading to superoxide-mediated injury in the respiratory pathways,

which subsequently contributes to pulmonary involvement.[8] It has been reported that pulmonary involvement occurs within 3 to 4 years after diagnosis.[11]

Clinical manifestations vary depending on immunological variations.[8] Most common clinical findings reported in studies include dyspnea, cough, chest pain, pleural pain, fever, excessive sweating, and hemoptysis. Nonspecific bronchial hyperreactivity is also observed due to increased inflammation.[8,11]

Radiographic examination with posterior anterior chest radiography or computed tomography (CT) often presents with aneurysms of the thoracic aorta, pulmonary artery, or mediastinal veins with hilar and mediastinal widening, and rarely, nonspecific focal opacities due to parenchymal involvement.[10] Studies have reported that chest radiography is normal in 31.2% of cases of isolated PAT and other involvement. CT is recommended for patients with suspected pulmonary involvement. Cavitary lesions, subpleural nodules, and consolidations can be detected on CT. Common acute phase symptoms include subpleural nodules and infarctions in the presence of hemoptysis, while cavitation is the hallmark symptom in the chronic phase. This is due to the infarction and necrosis in the nodules.[8] Arterial and venous manifestations are mainstay features of BD, both of which are valuable in the differential diagnosis of other forms of vasculitis.[8] Ultrasonography (USG) is recommended for imaging venous and arterial systems, which is particularly used to demonstrate inflammation and thrombosis in venous vessels. Magnetic resonance angiography (MRA) is an alternative imaging modality for assessing the venous vessel wall.[12]

There are two main pulmonary artery manifestations in BD: PAA and PAT. It has been shown that the right ventricle is involved in 30% and deep vein thrombosis (DVT) occurs in 80% of BD patients. DVT can be present in both the lower and upper extremities and is a finding detected in pulmonary embolism. Vascular involvement has been shown to be more common in males approximately within the one-year period after disease onset. In one-third of those affected, venous involvement manifests as superior vena cava syndrome, pulmonary thromboembolism, or cerebral venous thrombosis.[13,14] Aneurysms are frequently observed in the main pulmonary artery and its branches.[13] BD is a cause of mortality and morbidity, with a reported mortality rate of 26%.[15] Although Hughes-Stovin syndrome, particularly in PAAs, resembles BD both radiologically and histopathologically, it lacks the characteristic oral and genital ulcerations seen in BD. Bronchiectasis resulting from vascular compression by PAAs has been identified in BD.[8,10] Aneurysms have been reported as saccular-or fusiform-shaped. They may contain partial thrombus. In PAT, occlusion, stenosis, and mural thrombus are observed in the vascular lumen. Studies on aneurysms and thrombus have found that they are more common bilaterally and in the inferior lobe artery. Recurrence rate after treatment has been reported as 40%.[8,14,17]

The incidence of parenchymal and pleural involvement has been reported as 1-10%. Pulmonary infarction, atelectasis, and hemorrhage occur secondary to pulmonary artery occlusion or PAT. Focal and subpleural consolidation on CT are signs of pulmonary infarction. Nodules can be detected in diffuse airways obstruction caused by hemorrhage. Small vessel disease, bronchitis, fibrosis, emphysema, eosinophilic pneumonia, and cryptogenic organizing pneumonia are other types of manifestations. Parenchymal involvement is nonspecific.[10,17,18] Cases of multiple parenchymal cystic lesions, parenchymal infarctions, and air trapping due to peribronchial cuffing, stenosis, or occlusion have been reported.[8,19] Case reports have documented multiple parenchymal cystic lesions attributed to air trapping secondary to parenchymal infarctions or stenosis/occlusion resulting from peribronchial inflammation.

Mediastinal involvement can be seen in the diffuse form of fibrosing mediastinitis and collateral obstruction of superior vena cava.[10]

TREATMENT

The primary goal is to suppress inflammation, with the ultimate aim of reducing relapses and damage in major organ involvement. A multidisciplinary approach is essential in induction and maintenance therapy.[12]

Corticosteroids, cyclophosphamide, azathioprine, and cyclosporine are recommended for immunosuppressive therapy. The choice of these medications varies depending on age, gender, organ type involved, disease severity, and disease duration. Initial treatment with pulse corticosteroids is recommended for severe pulmonary involvement. The use of anticoagulants in vascular manifestations is controversial. Anti-TNF-alpha (anti-TNFα) is recommended for recurrent thrombosis. One of the leading problems in these cases is post-thrombotic syndrome. High-dose corticosteroids and cyclophosphamide are recommended for both PAA and PAT. Azathioprine may be considered as an alternative. There are also case reports documenting the use of cyclophosphamide and infliximab in relapses and recurrences. Alternatively, tocilizumab is recommended for vascular involvement. In some cases, endovascular treatment may be required for PAAs.[12,15,20-23]

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

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

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Case Report

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A case of desquamative interstitial pneumonia with unidentified etiology

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ABSTRACT

Desquamative interstitial pneumonia (DIP) is a rare form of interstitial lung disease, most commonly associated with cigarette smoking. However, in certain cases, environmental, occupational, or immunological factors may play a predominant role. Histopathologically, DIP is characterized by a diffuse and uniform inflammatory process involving the alveolar lumen and interstitium, with the presence of numerous large, mononuclear macrophages in the alveolar spaces and septa. It typically exhibits minimal or moderate septal thickening due to limited collagen deposition and contains few inflammatory cells. Compared to other interstitial pneumonias, DIP generally has a more favorable prognosis. Smoking cessation and corticosteroid therapy have been reported to yield excellent outcomes. Herein, we present a rare case of DIP in a young adult patient with no history of smoking or identifiable environmental exposure, who demonstrated resistance to standard therapy.

Keywords: Desquamative interstitial pneumonia, idiopathic interstitial pneumonias, nonsmoking

INTRODUCTION

Desquamative interstitial pneumonia (DIP) is a rare subtype of idiopathic interstitial pneumonia (IIP), typically associated with cigarette smoking. First described by Liebow[1] in 1965, DIP is pathologically defined by the accumulation of pigment-laden macrophages in the alveolar spaces, mild chronic inflammation in the interalveolar septa, and varying degrees of fibrosis. According to the American Thoracic Society (ATS) and the European Respiratory Society (ERS), DIP is classified under the category of "smoking-related interstitial lung diseases", along with respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).[2] While both conditions are linked to smoking, DIP is distinguished by more extensive alveolar involvement and a more severe clinical course.

The exact prevalence of DIP remains unknown. Owing to its rarity, most epidemiological data are derived from studies of idiopathic pulmonary fibrosis (IPF), where the estimated prevalence ranges from 3 to 6 per 100.000.[3] Although historically associated with tobacco use, up to 40% of DIP cases have been reported in lifelong non-smokers, suggesting alternative etiological factors. Environmental exposures and autoimmune disorders have also been implicated.[4] In this report, we present a rare case of biopsy-proven DIP in a young, non-smoking adult with no apparent environmental exposure or occupational risk, who failed to respond to corticosteroid therapy.

CASE

A 35-year-old male police officer presented to our clinic with a one-week history of dry cough and progressive shortness of breath. Initial chest radiography revealed bilateral basal non-homogeneous opacities, suggestive of pneumonia. Thoracic computed tomography (TCT) showed bilateral basal consolidations, and empirical antibiotic therapy was initiated.

His medical history included rheumatic fever at age 12, and a family history of Behçet's disease in two older sisters. He denied smoking, alcohol use, recreational drug use, or any known environmental/occupational exposures. Physical examination revealed diffuse bilateral inspiratory crackles; no clubbing or systemic signs were observed.

High-resolution computed tomography (HRCT) demonstrated fibrotic changes in the apical regions and diffuse ground-glass opacities predominantly in the basal segments of both lower lobes, as well as the medial segment of the middle lobe and the inferior lingular segment (**Figure**). Quantiferon-TB Gold test was negative. Bronchoalveolar lavage (BAL) revealed active inflammation but no malignant cells or acid-fast bacilli.

Pulmonary function tests (PFTs) showed: Forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC): 105%, FEV1: 98%, FVC: 96%, carbon monoxide diffusing

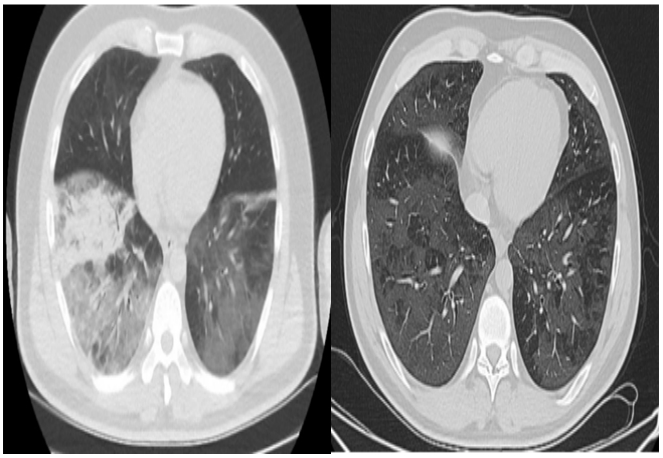

Figure. Diffuse ground-glass opacities predominantly in the basal segments of both lower lobes

capacity (DLCO): 66%. Immunologic screening including antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and extractable nuclear antigens (ENA) panels were negative. Due to lack of clinical and radiological improvement, oral prednisolone was initiated. However, no significant radiological regression was observed at 3-and 6-month follow-up HRCTs. Subsequently, video-assisted thoracoscopic surgery (VATS) was performed.

Histopathological analysis revealed extensive intra-alveolar and focal intrabronchial accumulation of macrophages, some of which contained intracytoplasmic pigment. Mild interstitial inflammation and small lymphoid aggregates in bronchovascular areas were noted, consistent with a diagnosis of DIP.

Due to further decline in DLCO and PFT values, the patient was considered steroid-resistant, and azathioprine therapy was added. Given the patient's young age and progressive course, he was referred for lung transplantation evaluation.

DISCUSSION

IIPs encompass a heterogeneous group of diffuse parenchymal lung diseases characterized by variable degrees of inflammation and fibrosis with no known cause. DIP predominantly affects males between 30 and 50 years of age, with over 90% of reported cases occurring in smokers. However, non-smoking-related cases have increasingly been documented in association with environmental exposures (e.g. textile dust, metal fumes, paint sprays), certain medications (e.g., nitrofurantoin, sirolimus), autoimmune diseases (especially connective tissue disorders), and genetic mutations such as those involving surfactant proteins.[5]

Histologically, DIP is characterized by the accumulation of pigmented macrophages in the alveolar spaces, minimal interstitial fibrosis, and mild chronic inflammation.[6] Our patient's biopsy demonstrated these features, despite the absence of common risk factors such as smoking or occupational exposure.

Clinically, patients present with non-specific symptoms such as subacute onset of dyspnea and persistent dry cough. Fever and systemic symptoms are typically absent. Hemoptysis is extremely rare. On auscultation, fine bilateral crackles may be heard, while clubbing is uncommon.[7]

Radiologically, HRCT typically shows bilateral, lower-lobe predominant ground-glass opacities in a diffuse and homogeneous pattern, without honeycombing—helping to differentiate DIP from usual interstitial pneumonia (UIP) or IPF. In progressive stages, cyst formation and traction bronchiectasis may appear. Compared to NSIP or UIP, fibrosis is less pronounced in DIP.[8] In our patient, bilateral basal ground-glass opacities were present, without radiological signs of fibrosis.

The diagnosis of DIP is established based on clinical suspicion, radiologic findings, BAL analysis, and histopathology. BAL fluid often demonstrates macrophage predominance. In recent years, transbronchial cryobiopsy has emerged as a promising alternative diagnostic method, offering larger sample size with a less invasive approach.[9] However, when transbronchial biopsy is inconclusive, surgical lung biopsy remains the gold standard.[10] In our case, due to the lack of clinical response and the atypical radiologic appearance, definitive diagnosis was achieved via VATS biopsy.

DIP is generally a treatable condition. Smoking cessation remains the cornerstone of management. In mild cases, remission may occur with cessation alone. Systemic corticosteroids are recommended for symptomatic or progressive cases. In refractory cases, immunosuppressive agents such as azathioprine or mycophenolate mofetil may be required. Macrolide therapy has also been proposed as an adjunct in certain cases. Lung transplantation should be considered for patients with progressive disease despite optimal medical therapy.[5] In our case, azathioprine was initiated due to steroid unresponsiveness, and the patient was referred for transplantation.

CONCLUSION

This case highlights the diagnosis of DIP in a young adult male without a history of smoking or known environmental exposure, who presented with progressive symptoms and was unresponsive to corticosteroid therapy. The case underscores the heterogeneity of DIP and the importance of considering non-smoking-related etiologies in the differential diagnosis of interstitial lung diseases. Histopathological confirmation remains crucial in atypical presentations to ensure accurate diagnosis and appropriate management.

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

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Author Contributions

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

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