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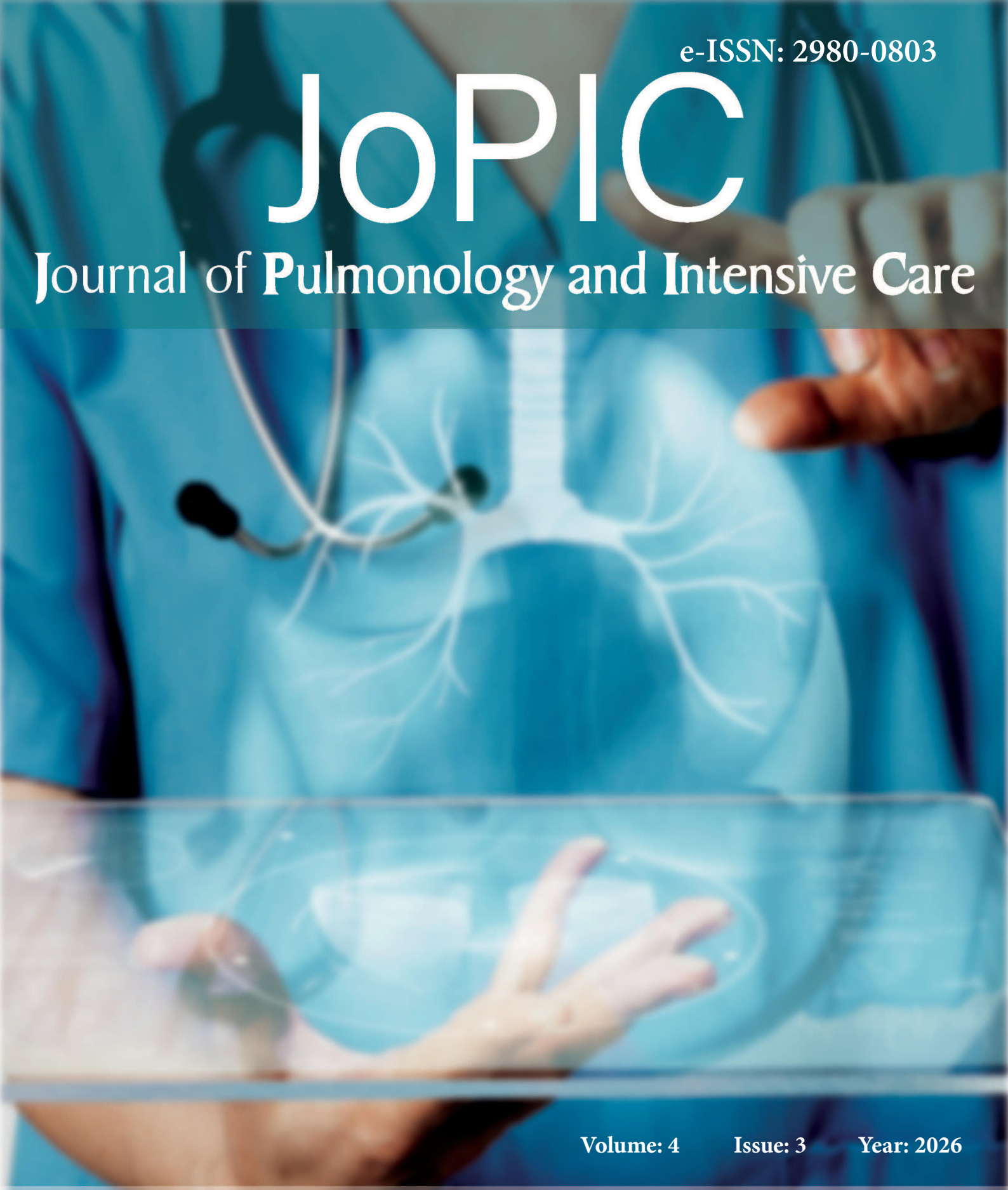

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Original Article

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Phenotypic assessment of COPD using clinical, radiological, and functional parameters

Duygu Acar Karagül*, Sevgi Behiye Saryal

Department of Chest Diseases, Faculty of Medicine, Ankara University, Ankara, Turkiye

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***Corresponding Author:** Duygu Acar Karagül, dyguacar@yahoo.com

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition with variable clinical presentation and disease progression. This study aimed to investigate the distribution of patients across defined COPD phenotypes and to compare their clinical, radiological, and functional characteristics.

Methods: This cross-sectional descriptive study included 96 patients diagnosed with COPD. Patients were classified into four phenotype groups: asthma-COPD overlap (ACO; previously termed ACOS), non-exacerbator (NE), frequent exacerbator with emphysema (FEE), and frequent exacerbator with chronic bronchitis (FECB). Demographic, clinical, and pulmonary function parameters were analyzed and compared among groups. Forced expiratory volume in one second (FEV1), body-mass index (BMI), COPD Assessment Test (CAT), diffusing capacity for carbon monoxide (DLCO), and inspiratory capacity/total lung capacity (IC/TLC) ratio were evaluated.

Results: Of the patients, 83 (86.5%) were male and 13 (13.5%) were female, with a mean age of 65.22±7.85 years. The distribution of phenotypes was as follows: ACO (9%), NE (53%), FEE (19%), and FECB (19%). The mean annual exacerbation rate was 1.27±1.2, and the mean FEV1 was 50.21±16.56%. The ACO phenotype was characterized by a higher proportion of female patients, younger age, history of asthma and atopy, better clinical status, and relatively preserved lung function. In contrast, the FEE phenotype demonstrated a higher exacerbation frequency, poorer quality of life, and more severe airflow limitation. Patients in the FEE group had lower FEV1 and BMI, higher CAT scores, increased lung volumes and airway resistance, lower DLCO and partial pressure of oxygen (pO_2), and an IC/TLC ratio below 25%.

Conclusion: Distinct COPD phenotypes, particularly ACO and FEE, exhibit significant differences in clinical and functional characteristics. Recognition of these phenotypes may help guide individualized management strategies, including pulmonary rehabilitation, nutritional support, and optimization of pharmacological and interventional treatments.

Keywords: Asthma-COPD overlap, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, frequent exacerbation, phenotype

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a multifactorial and heterogeneous disorder characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible, usually due to significant exposure to noxious particles or gases.[1] Despite being historically defined by spirometric parameters, especially the forced expiratory volume in one second (FEV_1), it has become increasingly clear that COPD encompasses a spectrum of clinical, functional, and radiological presentations that cannot be fully explained by airflow limitation alone.[2] Patients with similar degrees of obstruction may exhibit strikingly different symptom burdens, exacerbation risks, and prognoses.[3]

Recent GOLD 2024 reports emphasize that COPD should be viewed as a syndrome with multiple phenotypes and underlying endotypes, reflecting diverse pathobiological mechanisms such as chronic inflammation, tissue remodeling, and systemic effects.[4,5] Traditional classification based solely on spirometry fails to capture this complexity and provides limited insight into prognosis, comorbidities, and treatment response.[6] Accordingly, contemporary research has shifted toward phenotypic and endotypic characterization, integrating clinical features, biomarkers, and imaging-based parameters to achieve a more personalized management approach.[7,8]

Phenotyping allows identification of subgroups that share clinical or biological traits, such as frequent exacerbators, chronic bronchitic, emphysematous, or asthma-COPD overlap (ACO) phenotypes. This approach enables more precise therapeutic strategies, improved prediction of outcomes, and better design of clinical trials.[9,10] Beyond

clinical observation, recent advances in high-resolution computed tomography (HRCT) and quantitative imaging have provided objective markers for structural airway and parenchymal abnormalities, enhancing the ability to distinguish emphysema-predominant from airway-predominant disease.[11,12]

In parallel, studies employing multi-omics analyses-including genomics, transcriptomics, proteomics, and metabolomics-have identified molecular signatures associated with distinct COPD phenotypes and therapeutic responses.[13-15] For example, genetic studies have identified multiple susceptibility loci associated with COPD and COPD-related phenotypes, while distinct inflammatory profiles, including eosinophilic inflammation, have been linked to clinically relevant disease characteristics and exacerbation risk.[16-18] Similarly, inflammatory biomarkers, particularly blood eosinophil counts, may help identify clinically relevant treatable traits, while systemic inflammatory markers such as C-reactive protein and fibrinogen may provide additional information regarding disease activity and prognosis.[18,19]

Overall, phenotyping provides a framework to better understand the dynamic course of COPD-punctuated by exacerbations and variable clinical progression-and to identify targets for more effective, individualized interventions.[19]

Therefore, the present study aimed to evaluate the applicability of the phenotypic classification in COPD patients presenting to our clinic and to identify distinctive clinical, functional, radiological, and laboratory characteristics among these phenotype groups.

METHODS

Ethics

This study was conducted with the approval of the Ankara University Faculty of Medicine Ethics Committee (Date: 25.07.2014, Decision No: 38615). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants prior to their inclusion in the study.

Patients and Study Design

This cross-sectional descriptive study included 96 stable COPD patients without recent exacerbations who attended the COPD outpatient clinic of Ankara University Faculty of Medicine, Department of Chest Diseases, between September 2014 and March 2016.

Patient Selection and Evaluation

Eligible patients were aged 40 years or older and had a confirmed diagnosis of COPD according to the 2015 GOLD criteria (post-bronchodilator $FEV_1/FVC<0.70$).[3] At the time of study design, the terminology ACOS was used in the prevailing GesEPOC and GOLD frameworks; however, the updated term ACO is used throughout this manuscript for consistency with current literature.

Demographic and clinical data-including symptoms, comorbidities, exacerbation frequency, atopy, occupational and family history, smoking exposure (pack-years), and body-mass index (BMI)-were recorded. Pulmonary function was assessed using spirometry, whole-body plethysmography, and single-breath carbon monoxide diffusion capacity (DLCO) measurement.

An early bronchodilator reversibility test was performed to support the diagnosis of asthma-COPD overlap syndrome (ACOS). A ≥15% and ≥400 ml increase in FEV_1 from baseline was accepted as a major criterion, while a ≥12% and ≥200 ml increase was considered a minor criterion (**Table 1**).

Table 1. Asthma-COPD overlap (ACO) phenotype diagnostic criteria

Major criteria
High positivity in the reversibility test:
->15% and >400 ml increase in FEV1
Sputum eosinophilia
Asthma history
Minor criteria
Elevated total IgE
History of atopy
Positivity in the reversibility test:
->12% and >200 ml increase in FEV1

COPD: Chronic obstructive pulmonary disease, ACO: Asthma-COPD overlap, FEV1: Forced expiratory volume in one second, IgE: Immunoglobulin E

Symptom burden and quality of life were evaluated using the six-minute walk test (6MWT), arterial blood gas analysis, the COPD Assessment Test (CAT), and the St. George's Respiratory Questionnaire (SGRQ). Serum total immunoglobulin E (IgE) levels and sputum eosinophil counts were obtained for ACO differentiation (**Table 1**).

Radiological evaluation included chest radiographs and thoracic computed tomography (CT) scans, which were reviewed for emphysema, bronchial wall thickening, bronchovascular branching, and bronchiectasis.

Thoracic CT scans were visually evaluated by two experienced radiologists who were blinded to the clinical phenotype classification. Assessments were based on qualitative radiological findings including emphysema, bronchial wall thickening, hyperlucency, bronchovascular branching, and bronchiectasis. Quantitative software-based CT analysis was not performed.

Phenotype Classification

Phenotypic categorization was based on the Spanish COPD Guidelines (GesEPOC), identifying four distinct clinical phenotypes (Figure 1):

- Non-exacerbator COPD (NE)
- Asthma-COPD overlap syndrome (ACOS)
- Frequent exacerbator with emphysema (FEE)
- Frequent exacerbator with chronic bronchitis (FECB)

Diagnostic criteria for ACO were determined according to the coexistence of major and minor criteria (**Table 1**).[4]

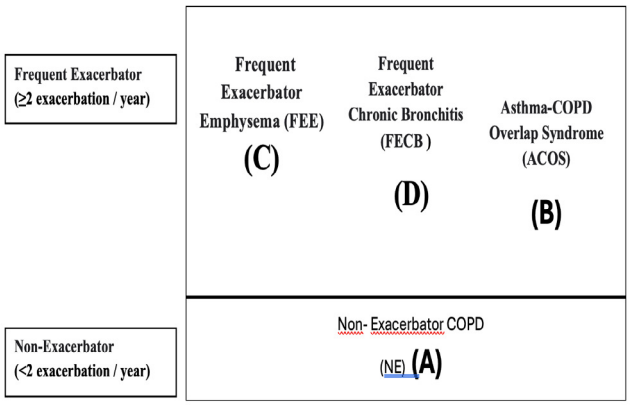

Figure 1. Phenotyping according to Spanish COPD guideline GesEPOC

FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis, COPD: Chronic obstructive pulmonary disease, ACOS: Asthma-COPD overlap syndrome, NE: Non-exacerbator, EPOC: Enfermedad pulmonar obstructiva crónica

Statistical Analysis

Data distribution was tested using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Group comparisons for continuous variables were performed using one-way analysis of variance (ANOVA) with post hoc tests, while categorical variables were analyzed using the Chi-square or Fisher's exact test, as appropriate. Correlations between variables were evaluated using Pearson's correlation coefficient. Results are presented as mean±standard deviation (SD) for normally distributed variables, median (minimum-maximum) for nonparametric data, and as counts or percentages for categorical variables. Post hoc pairwise comparisons following ANOVA were performed using the Tukey HSD test. Statistical significance was defined as $p<0.05$. Analyses were conducted using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 96 patients were included in the study (**Table 2**). The distribution of phenotypes according to the GesEPOC criteria is shown in **Figure 2**. Of all patients, 83 (86.5%) were male and 13 (13.5%) were female. The proportion of females was significantly higher in the ACO group (55.6%) compared with the other phenotypes (p=0.007; **Figure 3**). Patients with ACO were younger and had fewer smoking pack-years, although the differences were not statistically significant. The ACO group had the highest mean BMI, whereas the FEE group had the lowest. Disease duration was significantly longer in ACO patients ($p<0.001$), while the FEE group had the highest number of hospitalizations (**Table 3**).

All patients with ACO (100%) reported a prior history of asthma, a finding that differed significantly from other groups ($p<0.001$). Likewise, atopy was more prevalent among ACO patients (66.7%) than in the NE, FEE, and FECB groups (p=0.003). Active smoking rates did not differ between groups (p=0.788). Cough and sputum production were significantly more frequent in the FECB group ($p<0.001$), whereas other symptoms showed no group differences.

Symptom severity and quality-of-life scores varied among phenotypes. mMRC dyspnea and CAT scores were highest in the FEE group, whereas SGRQ total, symptom, and impact scores were lowest in the NE group ($p<0.001$). Six-minute walk distance (6MWD) differed significantly among groups

Table 2. General characteristics of all patients (n: 96)

Parameters	Mean±SD	Median (min-max)
Age	65.22±7.85	65 (48-84)
Smoking (package-year)	49.84±29.58	40 (1-150)
Body-mass index (kg/m²)	26.67±5.18	25.65 (15.8-42.9)
Number of exacerbations per year	1.27±1.2	1 (0-6)
Number of hospitalizations per year	0.63±0.9	0 (0-6)
CAT score	11.9±7.1	10 (0-32)
St George total score	32.77±22.4	28.7 (1.05-82)
6-Minute Walk Test (m)	442±91	460 (220-640)
FEV1%	50.21±16.56	50 (17-84)
Reversibility ΔFEV1%	10.63±9.62	8 (-7-41)
Reversibility ΔFEV1 (ml)	142.83±134.82	120 (-50-670)
DLCO %	67.8±24.3	66 (21-116)

SD: Standard deviation, min: Minimum, max: Maximum, CAT: COPD Assessment Test, FEV1%: Forced expiratory volume in 1 second, percent predicted, DLCO%: Diffusing capacity of the lungs for carbon monoxide, percent predicted

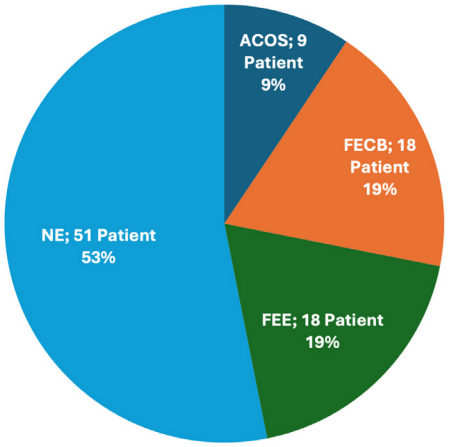

Figure 2. Distribution of patients across groups

ACOS: Asthma-COPD overlap syndrome, FECB: Frequent exacerbator chronic bronchitis, FEE: Frequent exacerbator emphysema, COPD: Chronic obstructive pulmonary disease, NE: Non-exacerbator

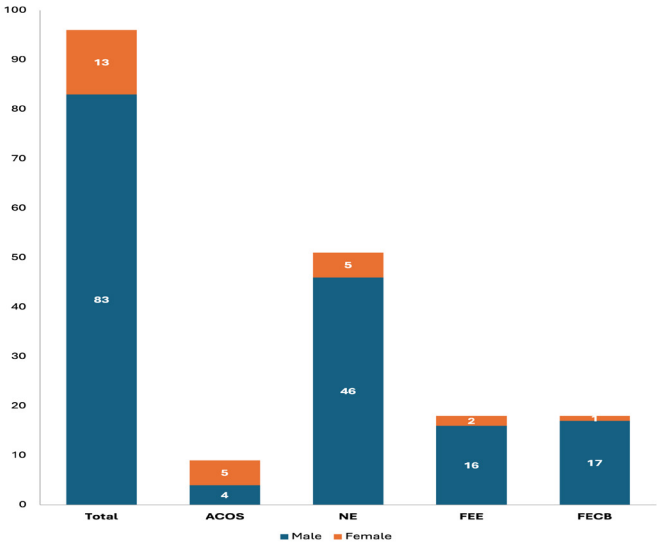

Figure 3. Gender distribution of patients across groups

ACOS: Asthma–COPD overlap syndrome, NE: Non-exacerbator, FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis

(p=0.010), although no significant difference was found between the two frequent-exacerbator phenotypes (p=0.297) (**Table 4**).

Table 3. General characteristics of phenotype groups

Parameters	ACO	NE	FEE	FECB	p-value
Age	57.88±7.76[a] 55 (48-68)	65.31±7.65[b] 64 (49-84)	66.11±8.05[b] 66 (49-78)	67.77±6.56[b] 68 (55-76)	0.016
Smoking (package-year)	35.50±39.98 17.50 (4-100)	50.04±28.95 40 (1-150)	53.11±29.30 50 (3-110)	51.05±29.11 45 (3-100)	0.656
Body-mass index kg/m^2	32.98±5.87 [a] 33.05 (25.2-42.9)	26.29±4.76 [bc] 25.5 (17-36)	23.07±4.25 [c] 22.6 (15.8-29.5)	27.05±3.13 [b] 25.75 (22.8-33.3)	<0.001
Duration of disease	23.44±8.45 [a] 21 (15-40)	9.62±5.73 [b] 10 (1-21)	10.44±6.02 [b] 10 (2-25)	13.5±6.51 [b] 13.5 (1-25)	<0.001
Number of exacerbations per year	1.0±0.70 [a] 1 (0-2)	0.43±0.50 [b] 0 (0-1)	2.61±1.14 [c] 2 (2-6)	2.52±1.06 [c] 2 (2-6)	<0.001
Number of hospitalizations per year	0.44±0.52 [a] 0 (0-1)	0.17±0.38 [a] 0 (0-1)	1.05±0.87 [b] 1 (0-6)	0.63±0.97 [c] 0 (0-6)	<0.001

ACO: Asthma-COPD overlap, NE: Non-exacerbator, FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis

Table 4. Quality of life scores, dyspnea scores, 6-Minute Walking Tests

Parameters	ACO	NE	FEE	FECB	p-value
mMRC	1.22±0.83 [a] 1 (0-3)	1.23±0.90 [a] 1 (0-4)	4.92±2.32 [b] 4 (1-8)	4.5±1.9 [ab] 4 (1-8)	0.001
CAT score	10.75±5.49 [ab] 10.5 (2-21)	9.16±5.41 [a] 8 (0-25)	17.73±8.58 [c] 18 (4-32)	14.6±6.74 [bc] 12 (8-29)	<0.001
6MWT m	464.44±81.25 [a] 480 (360-640)	466.29±82.28 [a] 468 (260-580)	401.8±90.77 [ab] 405 (220-520)	363.75±90.38 [b] 345 (220-520)	0.010
St George symptom score	52.42±21.77 [a] 53.4 (15.15-86.66)	32.76±21.67 [b] 28.18 (6.32-86.23)	58.78±21.82 [a] 65.01 (15.56-88.12)	58.89±16.15 [a] 63.25 (28.87-84.03)	<0.001
St George activity score	50.16±37.11 [a] 49 (0-92.51)	30.79±28.63 [ab] 29.49 (0-92.45)	66.01±27.9 [b] 72.44 (0-100)	56.2±28.93 [ab] 59.46 (5.96-92.51)	0.001
St George impact score	26.78±18.36 [a] 21.7 (3.62-57.07)	11.46±12.09 [b] 7.77 (0-61.09)	35.63±23.29 [a] 33.7 (8.92-77.31)	31.81±24.37 [a] 28.61 (0-81.09)	<0.001
St George total score	37.95±22.8 [a] 31.36 (7.40-67.20)	20.78±16.19 [b] 20.27 (1.05-65.88)	48.8±20.71 [a] 47.24 (7.14-82)	43.20±22.65 [a] 43.28 (10.98-80.99)	<0.001

ACO: Asthma–COPD overlap, NE: Non-exacerbator, FEE: Frequent exacerbator with emphysema, FECB: Frequent exacerbator with chronic bronchitis, mMRC: Modified medical research council, CAT: COPD assessment test, 6MWT: Six-Minute Walk Test

Spirometric and plethysmographic parameters also varied. The FEV_1/FVC ratio ranged from 35% to 69% across groups, with significantly lower FEV_1% predicted and absolute values in the FEE group ($p<0.001$). Reversibility was detected only in three ACO patients. Residual volume (RV) was elevated in all phenotypes but significantly higher in FEE, accompanied by increased functional residual capacity (FRC) and reduced inspiratory capacity to total lung capacity ratio (IC/TLC) ($p=0.008$), consistent with marked hyperinflation. Airway conductance (Gaw) was significantly lower in frequent exacerbator groups ($p=0.044$). The FEE group also demonstrated reduced diffusion capacity (DLCO) and lower pO_2 values, while hypercapnia was observed in all groups except ACO (**Table 5**).

Total serum IgE levels did not differ significantly among groups but were higher in the ACO group overall.

Radiological findings supported phenotypic differentiation. On chest radiography, hyperlucency was noted in 55.6% of ACO, 81.2% of NE, 88.9% of FEE, and 50% of FECB patients. On thoracic CT, hyperlucency was most frequent in the FEE phenotype (93%). Bronchial wall thickening was most common in FECB (68.7%), whereas bronchiectasis occurred in over half of the FEE (56%) and FECB (50%) groups, consistent with the higher frequency of exacerbations in these phenotypes.

DISCUSSION

COPD is increasingly recognized as a heterogeneous condition encompassing a spectrum of clinical, functional, and biological profiles rather than a single disease entity. Phenotyping aims to identify patient subgroups with shared pathophysiologic mechanisms, clinical presentations, and therapeutic responses. In the present study, COPD patients classified according to the GesEPOC framework demonstrated distinct demographic, functional, and radiological characteristics, particularly within the ACO and FEE phenotypes.

The ACO group was characterized by a higher proportion of females, younger age, longer disease duration, and higher BMI. These findings are consistent with previous reports indicating that ACO patients often exhibit eosinophilic inflammation, greater reversibility, and relatively preserved lung function compared with other COPD phenotypes.[9,18] The higher prevalence of atopy and prior asthma diagnosis further supports the concept that ACO represents a distinct inflammatory phenotype. Although serum IgE levels did not differ significantly between groups, they tended to be higher in ACO patients, in line with previous studies suggesting that eosinophilic and allergic markers may aid phenotype identification.[7,20]

In contrast, the FEE phenotype demonstrated the poorest clinical and functional status. Lower FEV_1%, reduced DLCO, increased lung volumes, and a lower IC/TLC ratio

Table 5. Pulmonary function tests results of phenotype groups

Parameters	ACO	NE	FEE	FECB	p-value
FVC%	84.66±13.26 [a]	80.07±15.88 [a]	63.94±16.34 [b]	68.22±15.83 [b]	<0.001
FVC lt	2.66 ±0.9[ab]	2.89 ±0.7 [a]	2.23±0.4 [b]	2.40±0.4[ab]	0.006
FEV1%	57.55±14.29 [a]	55.66±14.52 [ab]	35.77±15.2 [c]	45.55±14.97 [bc]	<0.001
FEV1 lt	1.45±0.5 [a]	1.56±0.5 [a]	0.97±0.3 [b]	1.24±0.3[ab]	<0.001
FEV1/FVC%	56±12.12 [a]	54.18±9.11 [a]	42.63±8.19 [b]	51.51±9.62 [a]	<0.001
FEF 25-75%	21.44±7.6	22.8±11.08	16.5±10.47	18.66±8	0.122
FEF 25-75 lt	0.68±0.3 [a]	0.68±0.3 [a]	0.40±0.1 [b]	0.56±0.2 [ab]	0.003
Reversibility ΔFEV1%	14.12±8.95	10.57±9.34	6.2±10.43	12.5±9.98	0.320
Reversibility ΔFEV1 lt	0.177±0.116	0.163±0.148	0.058±0.096	0.131±0.106	0.149
TLC%	115.66±16.35	114.40±21.10	130.42±20.92	110.36±22.33	0.243
TLC lt	5.97±1.75	7.050±1.64	8.16±1.10	6.71±1.22	0.079
IC lt	2.86±1.62	2.94±1.06	2.03±4.61	2.67±1.08	0.274
RV%	166±31[a]	168±52 [a]	242±79 [b]	167±44 [a]	0.014
RV lt	3.20±0.80 [a]	3.96±1.22 [a]	5.61±1.58 [b]	3.96±0.95 [a]	0.004
FRC%	110.66±22.51 [a]	124.03±36.06[a]	181.14±38.86 [b]	122.9±35.11 [a]	0.001
FRC lt	3.10±0.68 [a]	4.16±1.14 [b]	6.12±1.21 [c]	4.03±0.80 [ab]	<0.001
VC%	92.25±9.17	77.9±14.3	70.2±25.51	78.33±17.10	0.281
VC lt	2.65±1.38	2.80±0.75	2.75±0.92	2.66±0.56	0.973
IC/TLC%	45.33±11.18 [a]	40.64±12.01 [a]	24.85±6.86 [b]	38.27±11.61 [a]	0.008
RV/TLC%	54.33±7.31	56.34±14.04	68±12.24	67.09±27.91	0.148
Raw%	128.5±33.8	147.77±96.81	238.66±150.07	194±78.14	0.125
sRaw%	331±135.69	399.84±424.1	841±568.21	471.81±231.39	0.075
Gaw%	55.28±18.47 [a]	49.5±18.06 [ab]	35.5±23.2 [b]	35.54±11.53 [b]	0.044
sGaw lt/s/cmH2O	0.77±0.31	0.68±0.025	0.041±0.038	0.055±0.025	0.087
DLCO%	83.80±20.06	70.10±25.90	48.37±18.44	68.87±16.10	0.052
DLCO ml/mmHg/min	18650±12010.41	17630±7002.27	11862.50±4778.8	16475±4565.63	0.207
DLCO/VA%	97.60±23.02	81.57±27	74±29.94	97±14.18	0.192
DLCO/VA ml/mmHg/min/lt	4582±1216.78 [a]	3238.45±1123.07 [b]	2853.75±1156.75 [b]	3738.75±625.03 [ab]	0.033

ACO: Asthma-COPD overlap, NE: Non-exacerbator, FEE: Frequent exacerbator emphysema, FECB: Frequent exacerbator chronic bronchitis, m: Meter, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in one second, FEF: Forced expiratory flow, TLC: Total lung capacity, IC: Inspiratory capacity, RV: Residual volume, FRC: Functional residual capacity, VC: Vital capacity, IC/TLC: Inspiratory capacity/total lung capacity ratio, RV/TLC: Residual volume/total lung capacity ratio, Raw: Airway resistance, sRaw: Specific airway resistance, Gaw: Airway conductance, sGaw: Specific airway conductance, DLCO: Diffusing capacity of the lung for carbon monoxide, %: Percentage of predicted value, lt: Litre, lt/s/cmH_2O: Litre per second per centimetre of water

indicated marked hyperinflation and impaired gas exchange. Similar findings have previously been associated with increased mortality and hospital readmission risk.[21,22] These observations suggest that patients with the FEE phenotype may require closer clinical follow-up and more comprehensive management approaches.

The FECB phenotype exhibited a high symptom burden characterized by cough and sputum production, consistent with previous studies linking chronic bronchitis to increased exacerbation frequency and airway inflammation.[23,24] Although lung function impairment was less severe than in FEE patients, bronchial wall thickening and bronchiectasis were prominent CT findings, supporting the role of persistent airway inflammation in this phenotype.

Patients with the NE phenotype demonstrated the most stable clinical profile, with lower CAT and SGRQ scores and fewer exacerbations. These findings are compatible with previous studies indicating that NE patients generally have milder symptom burden and slower disease progression.[9]

The significantly higher mMRC scores and lower 6MWD observed particularly in the FEE and FECB phenotypes reflect the substantial symptomatic and functional burden associated with frequent exacerbations. Reduced exercise capacity in these phenotypes may be related to severe airflow limitation, dynamic hyperinflation, impaired gas exchange, and systemic deconditioning. Similar associations between dyspnea severity, exercise intolerance, and exacerbation frequency have been reported previously in COPD populations.

Recent advances in COPD research further support the concept that COPD represents a biologically heterogeneous syndrome rather than a uniform airflow-limitation disorder. Emerging evidence from genetic and multi-omics studies suggests that COPD encompasses biologically distinct molecular patterns that may contribute to clinically relevant phenotypic heterogeneity.[13-17] In particular, quantitative CT analysis and artificial intelligence-based imaging approaches may improve future identification of clinically meaningful COPD subgroups.[11,12,26] These developments are consistent with our findings demonstrating marked radiological and functional differences between ACO, FEE, FECB, and NE phenotypes.

The growing emphasis on inflammatory endotypes and "treatable traits" has also expanded the understanding of

COPD pathobiology. Recent studies have highlighted the clinical importance of eosinophilic inflammation, mucus plugging, and immune dysregulation in determining exacerbation risk and disease severity.[25,27,28] These concepts align with our observations regarding ACO and exacerbator phenotypes and support the transition toward multidimensional COPD assessment integrating clinical, radiological, and inflammatory parameters.

Our findings reinforce that phenotyping provides clinically meaningful insights into COPD heterogeneity and may contribute to more individualized management strategies. Identifying high-risk subgroups such as the FEE phenotype may be particularly valuable for optimizing follow-up and supportive interventions, whereas recognition of the ACO phenotype may support consideration of anti-inflammatory approaches in selected patients.

Limitations

Limitations of this study include its single-center, cross-sectional design and the relatively small sample size of some phenotypic subgroups, particularly ACO. Future multicenter and longitudinal studies integrating imaging, molecular, and clinical parameters are needed to validate these findings and explore their implications for prognosis and therapeutic response. Another limitation is that patient recruitment was performed between 2014 and 2016. Since COPD phenotyping concepts, imaging approaches, and GOLD recommendations have evolved substantially over the last decade, some phenotype definitions and therapeutic perspectives may differ from current clinical frameworks.

CONCLUSION

This study highlights the clinical importance of COPD phenotyping using the GesEPOC framework. Distinct differences among phenotypes-particularly the favorable clinical profile of the ACO group and the severe functional impairment observed in the FEE group-further emphasize the heterogeneity of COPD beyond spirometric classification alone. Integrating clinical, radiological, and functional parameters may provide a more comprehensive understanding of disease characteristics and contribute to more individualized patient management. Future multicenter and longitudinal studies are needed to further validate phenotype-specific findings and explore their prognostic and therapeutic implications.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Ankara University Faculty of Medicine Ethics Committee (Date: 25.07.2014, Decision No: 38615).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: DAK, SBS; Design: DAK, SBS; Control: SBS; Data Collection and/or Processing: DAK; Analysis and/or Interpretation: DAK, SBS; Literature Review: DAK; Article Writing: DAK; Critical Review: SBS. All Authors Read and Approved the Final Version of the Manuscript.

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Evaluation of the clinical course of acute phase reactants and associated factors in geriatric patients followed up in icu due to community- and hospital-acquired pneumonia

Derya Hoşgün*, Emine Banu Çakıroğlu, Saadettin Sevim, Melek Doğancı, Güler Eraslan Doğanay, Hilal Sazak

Department of Intensive Care Unit, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye

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***Corresponding Author:** Derya Hoşgün, deryahosgun@gmail.com

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ABSTRACT

Aims: Advancing age leads to numerous physiopathological changes, particularly in the respiratory system. Moreover, biomarkers and acute phase reactants are affected by age-related inflammation and cellular and humoral immunity changes. Our aim in this study was to evaluate the age-related course of acute phase reactants in community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) patients and to assess its relationship with independent intra-intensive unit (ICU) mortality.

Methods: Patients followed up in ICU due to CAP and HAP were evaluated retrospectively. Patients were divided into four groups in terms of age: (I) 18-64 years, (II) 65-75 years, (III) 76-90 years, and (IV) 91+ years. Acute phase reactants were measured at ICU admission and at 72 hours after admission.

Results: A total of 549 patients comprising 389 CAP and 160 HAP patients were included in the study. Mean age was 73 (range, 22-99) years and 33% of the participants were female. Age and gender were similar between the two groups. On laboratory examination, neutrophil count (NE), C-reactive protein (CRP), procalcitonin (PCT), CRP and PCT were significantly higher in the HAP group than in the CAP group. The rate of intra-ICU independent mortality was significantly higher in HAP patients than in CAP patients (24.4% vs 11.6, p<0.001). All laboratory parameters except for lymphocyte count (LY) on admission were similar between the groups.

Conclusion: The response of LY to advancing age was greater than the response of other inflammatory acute phase reactants. In patients with severe pneumonia, serial measurement of WBC, CRP, PCT, and NE may be useful in predicting short-term intra-ICU mortality.

Keywords: Age, community-acquired pneumonia, course of acute phase reactants, hospital-acquired pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) occurs at any time of life, while hospital-acquired pneumonia (HAP) develops 48 hours after hospital admission or within 48 hours of discharge. Both CAP and HAP are serious infectious diseases associated with significant mortality and morbidity. In both conditions, the risk of mortality and morbidity increases particularly in intensive care unit (ICU) patients due to the implementation of respiratory support therapies such as high-flow nasal oxygen (HFNO), noninvasive mechanical ventilation (NIMV), and invasive mechanical ventilation (IMV). In CAP and HAP patients, numerous scoring systems are used for the diagnosis, treatment, and mortality prediction.[1,2]

Acute phase reactants and biomarkers are inflammatory markers whose serum levels increase and decrease in response to several clinical conditions such as chronic diseases, fever, anorexia, sepsis, septic shock, and bacteremia. These markers are commonly used in CAP and HAP patients, particularly for the diagnosis and as markers of clinical variability and pneumonia severity. Procalcitonin (PCT), C-reactive protein (CRP), white blood cell count (WBC), neutrophil count (NE), and lymphocyte count (LY) are acute phase reactants frequently used in clinical practice. Of these, WBC, NE, and LY are simple parameters that are easily and routinely measured in complete blood count (CBC). In a previous study using CURB-65 (confusion, serum urea nitrogen level, respiratory rate, blood pressure and age ≥65 years), CRP levels were found to correlate with CURB-65 scores in patients with non-Coronavirus Disease 2019 (COVID-19) pneumonia. In CAP patients, the sensitivity and specificity of CRP are reported to be 40-90% as opposed to 38-91% for PCT.[3-5] In pneumonia patients, clinical improvement and change occur within 48 to 72 hours, while clinical stabilization begins

within 48 hours. The diagnosis and treatment planning are guided by serial and sequential measurements. There are several studies on the use of acute phase reactants such as CRP and PCT in predicting mortality and prognosis.[6,7]

With advancing age, numerous physiopathological changes occur in the respiratory system, particularly in elastic recoil pressure, lung compliance, and respiratory muscle strength. Due to these changes, the frequency of pneumonia is typically higher in the geriatric age group compared to the younger population. Moreover, in the advanced age group, pneumonia may have an atypical clinical course due to the increased incidence of comorbidities and age-related changes, resulting in higher mortality and morbidity. On the other hand, biomarkers and acute phase reactants are known to be affected by the inflammation and cellular and humoral immunity changes occurring with advanced age. The age-related variation and cut-off values of acute phase reactants in patients over 65 years old with CAP and HAP requiring intensive care due to severe pneumonia have not been clearly defined in the literature. Compared with studies in patients under 65, few studies have focused on the geriatric age group. The association of acute phase reactants with intensive care-specific independent mortality in elderly patients with pneumonia, in relation to disease severity, has been evaluated in only a limited number of studies.[8-11] In clinical practice, it is essential to define the age-related trajectory of acute phase reactants and their role in predicting clinical prognosis in geriatric patients with severe community- and hospital-acquired pneumonia. Therefore, our aim in this study was to evaluate the age-related course of acute phase reactants in CAP and HAP patients and to assess its relationship with independent intra-ICU mortality.

METHODS

This study was conducted with the approval of the Scientific Researches Ethics Committee of the Ankara Atatürk Sanatorium Training and Research Hospital (Date: 14.02.2024, Decision No: 2024 BÇEK/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This retrospective study included patients with CAP and HAP who were admitted to our intensive care unit between 2021 and 2023. CAP was defined as pneumonia occurring in the community setting, whereas HAP was defined as pneumonia developing at least 48 hours after hospital admission or following discharge. All the patients met the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) ICU admission criteria. Major criteria were defined as the need for mechanical ventilation and septic shock requiring vasopressor support. Minor criteria were specified as radiologically confirmed multilobar infiltrates, confusion, hypothermia and hypotension requiring fluid resuscitation, thrombocytopenia, leukopenia, uremia, a respiratory rate ≥30 breaths per minute, and an arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤250 on arterial blood gas analysis. According to the ATS and IDSA criteria, patients with one major criterion or at least three minor criteria were included in the study. Patients presenting with relevant respiratory symptoms and undergoing clinical, radiological, and microbiological evaluations for diagnostic purposes were included in the study. Moreover, all the patients included in the study received an appropriate diagnosis of CAP or HAP, underwent clinical treatment, and were followed up according to national and international guidelines.[12-14] All the patients were evaluated for independent intra-ICU mortality and prognosis using the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system and the Sequential Organ Failure Assessment (SOFA) within the first 72 hours after ICU admission.[15] Patients included in the study were divided into four groups in terms of age: (I) 18-64 years, (II) 65-75 years, (III) 76-90 years, and (IV) 91+ years. CURB-65 was used to assess the severity of CAP and the Clinical Pulmonary Infection Score (CPIS) was calculated retrospectively for HAP.[12-14] Patients aged under 18 years, pregnant women, patients hospitalized due to diagnoses other than pneumonia or due to malignancy, collagen tissue diseases, and hematological diseases were excluded from the study.

WBC, NE, LY, CRP, and PCT values were recorded in all patients during ICU admission and at 72 hours after admission. Hemoglobin (Hgb) level measured at ICU admission was evaluated for each patient. Normal ranges of WBC, Hgb, NE, and LY (photometric method) were accepted as 4.6-10.2 $\times10^3/\mu L$, 12-16 g/dl, 2-7 $\times10^3/\mu L$, and 0.8-4 $\times10^3/\mu L$, respectively. Normal ranges of CRP, and PCT were accepted as 0-5 mg/L, and <0.25 ng/ml, respectively. CRP was measured using the turbidimetric assay and PCT was measured using the immunoassay method.

Statistical Analysis

Data were analyzed using SPSS for Windows version 21.0 (Armonk, NY: IBM Corp.). Categorical variables were expressed as frequencies (n) and percentages (%). Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test and histograms. Normally distributed continuous parameters were compared using Student's t-test or One-Way Analysis of Variance (ANOVA), while parameters with nonnormal distribution were analyzed by Mann-Whitney U test or Kruskal-Wallis test. Categorical variables were compared by Chi-square or Fisher's Exact test as appropriate. The accuracy of different laboratory parameters to predict 72-h mortality was evaluated by receiver operating characteristic (ROC) analysis. The accuracy of the tests was measured by the area under the ROC curve (AUC), in which an AUC close to 1 represents a perfect diagnostic test and an AUC of 0.5 represents a worthless test. A p value of <0.05 was considered significant.

RESULTS

A total of 549 patients comprising 389 (70.85%) CAP patients and 160 (29.15%) HAP patients were included in the study. Mean age was 73 years in CAP patients and 72 years in HAP patients (p=0.693). Comorbidities were present in 68.4% of CAP patients and in 70.6% of HAP patients (p=0.605). The rate of independent intra-ICU mortality was 11.6% in CAP patients and 24.4% in HAP patients and a significant difference was observed between the two groups (p<0.001). Both APACHE II and SOFA scores were significantly different between the two groups (p<0.001 for both). **Table 1** presents the demographic and clinical characteristics of the patients.

Table 1. Demographic and clinical characteristics

Variables	CAP (n=389)		HAP (n=160)		p
Gender					
Female, n (%)	129 (33.2)		52 (32.5)		
Male, n (%)	260 (66.8)		108 (67.5)		0.881
Variables	**CAP (n=389) median (min-max)**		**HAP (n=160) median (min-max)**		**p**
Age (years)	73 (22-99)		72 (25-93)		0.693
CURB-65 score	3 (3-5)				
CPIS			9.1±1.3		
APACHE II score	15 (10-30)		24 (10-30)		<0.001
SOFA score	5 (2-20)		10 (3-20)		<0.001
Variables	**CAP (n=389)**		**HAP (n=160)**		**p**
	No, n (%)	**Yes, n (%)**	**No, n (%)**	**Yes, n (%)**	
Intra-ICU mortality	344 (88.4)	45 (11.6)	121 (75.6)	39 (24.4)	< 0.001
Chronic illness	123 (31.6)	266 (68.4)	47 (29.4)	113 (70.6)	0.605
COPD	223 (57.3)	166 (42.7)	100 (62.5)	60 (37.5)	0.263
Neurological disorder	353 (90.7)	36 (9.3)	141 (88.1)	19 (11.9)	0.353
DM	318 (81.7)	71 (18.3)	130 (81.3)	30 (18.7)	0.891
Hypertension	305 (78.4)	84 (21.6)	102 (63.7)	58 (36.3)	< 0.001
CAD	344 (88.4)	45 (11.6)	128 (80)	32 (20)	0.010
Heart failure	362 (93.1)	27 (6.9)	137 (85.6)	23 (14.4)	0.006
AF	373 (95.9)	16 (4.1)	149 (93.1)	11 (6.9)	0.174

CAP: Community-acquired pneumonia, HAP: Hospital-acquired pneumonia, CURB-65: (Confusion, uremia, elevated respiratory rate, hypotension, and age ≥65), CPIS: Clinical pulmonary infection score, APACHE II: Acute Physiology and Chronic Health Evaluation II, SOFA: The Sequential Organ Failure Assessment, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CAD: Coronary artery disease, AF: Atrial fibrillation

Table 2 presents mean serum levels of laboratory parameters (acute phase reactants and biomarkers) measured in the study. Of these, serum levels of NE at admission, CRP at admission and at 72 hours, and PCT at admission and 72 hours were significantly different between the two groups (p=0.034, p=0.001, p=0.001, p<0.001, p<0.001, respectively).

Table 2. Laboratory parameters

Variables	CAP (n=389) median (min-max)	HAP (n=160) median (min-max)	p
WBC (µL) on admission	11000 (500-72550)	12500 (1900-38000)	0.074
WBC (µL) on 72nd hour	9900 (600-70000)	9850 (2400-45900)	0.255
LY (µL) on admission	850 (100-29010)	830 (120-6990)	0.627
LY (µL) on 72th hour	920 (80-45640)	840 (140-9300)	0.180
NE (µL) on admission	9290 (10-54410)	10760 (830-36300)	0.034
NE (µL) on 72th hour	8120 (30-50000)	8080 (2080-43790)	0.158
CRP (mg/L) on admission	69.20 (1.41-524)	98.56 (2.3-520)	0.001
CRP (mg/L) on 72th hour	66 (0.09-717)	90.18 (0.57-425)	0.001
PCT (ng/ml) on admission	0.16 (0.1-100)	0.345 (0.02-100)	<0.001
PCT (ng/ml) on 72th hour	0.11 (0.01-100)	0.38 (0.016-84.32)	<0.001

CAP: Community-acquired pneumonia, HAP: Hospital-acquired pneumonia, Min: Minimum, Max: Maximum, WBC: White blood cell count, LY: Lymphocyte count, NE: Neutrophil count, CRP: C-reactive protein, PCT: Procalcitonin

Independent predictors of intra-ICU mortality were found to be statistically significant in the overall patient population, including age, type of pneumonia (CAP and HAP), APACHE II and SOFA scores, CURB-65 score in CAP and CPIS in HAP, comorbidities such as COPD, neurological disorders, and DM (p=0.044, p<0.001, p<0.001, p<0.001, p<0.001, p=0.011 p=0.003, and p=0.021, respectively). WBC, NE, CRP, and PCT levels measured at admission and at 72 hours were statistically significant for predicting mortality (p<0.05). **Table 3** presents the association between laboratory parameters and mortality status in patients with and without mortality. Of note, WBC, CRP, NE, and PCT were statistically significant for predicting mortality at a cut-off value of >15.1, >93.72, >10.73, and >0.66, respectively (**Figure**). Serum levels of 72-h LY were significantly different among the four age

Table 3. Association between laboratory parameters and intra-ICU mortality

Variables	Without mortality (n=465) median (min-max)	With mortality (n=84) median (min-max)	p
WBC (µL) on admission	10800 (500-72550)	15250 (1000-38000)	<0.001
WBC (µL) on 72th hour	9500 (600-70000)	10700 (3600-51500)	0.017
LY (µL) on admission	860 (100-19500)	810 (140-29010)	0.587
LY (µL) on 72th hour	880 (100-15000)	820 (80-45640)	0.230
NE (µL) on admission	9260 (10-54410)	12130 (720-36300)	0.003
NE (µL) on 72th hour	7900 (30-50000)	9500 (3000-33990)	0.007
CRP (mg/L) on admission	74.01 (1.41-520)	124.35 (3.14-524)	<0.001
CRP (mg/L) on 72th hour	69.30 (0.09-717)	127.34 (7.3-463)	<0.001
PCT (ng/ml)on admission	0.16 (0.01-100)	0.95 (0.03-100)	<0.001
PCT (ng/ml) on 72th hour	0.12 (0.01-75)	1.52 (0.016-100)	<0.001

ICU: Intensive care unit, Min: Minimum, Max: Maximum, WBC: White blood cell count, LY: Lymphocyte count, NE: Neutrophil count, CRP: C-reactive protein, PCT: Procalcitonin

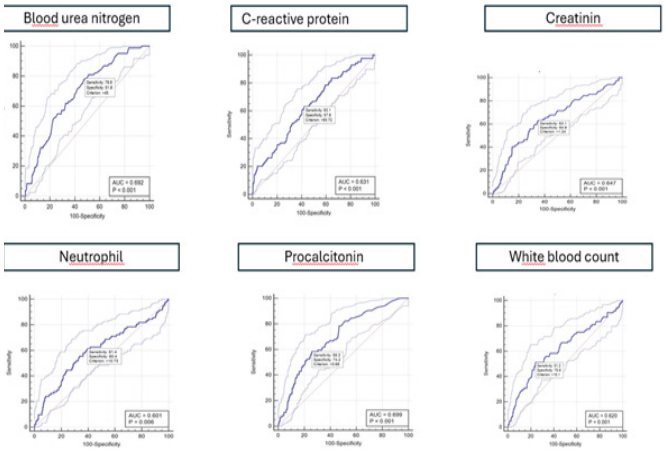

Figure. Receiver operating characteristic curve for blood urea nitrogen, C-reactive protein, creatinine, neutrophil, procalcitonin, white blood cell count to predict intra-ICU independent mortality
AUC: Area under the curve, ICU: Intensive care unit

groups (p=0.014). **Table 4** presents the laboratory parameters for age groups.

DISCUSSION

The present retrospective study evaluated geriatric patients with severe CAP and HAP and found that the rate of independent intra-ICU mortality was significantly higher in HAP patients. Similarly, both baseline and 72-h WBC, CRP, PCT, and NE levels were significantly higher in HAP patients with mortality. It was also found that the decrease in 72-h LY levels became more prominent with advanced agewith advancing age.

In the literature, geriatric patients are defined as those aged 65 years and older. Individuals aged 65-74 are considered young-old, those 75-84 as middle-old, and those 85 years and above as oldest-old. In the literature, elderly patients with acute respiratory failure in intensive care have been evaluated across different age groups. It has been demonstrated in the literature that intensive care unit admissions have increased among patients over the age of 85.[16-18] Therefore, in our study, patients were categorized into age-based groups of 18-64, 65-75, 76-90, and ≥91 years.

In individuals aged over 65, a number of changes occur in individual cells and in whole organs, leading to functional losses and physiopathological changes. Especially in the lungs, changes occur in compliance, resistance, respiratory muscle strength, gas exchange, ventilation/perfusion ratio, mucociliary transport, and cough reflex. In geriatric patients, pneumonia is the most common reason for ICU and hospital admission. In such patients, both the incidence of comorbidities and the rate of pneumonia-related mortality increase with advancing age.[8-10] Moreover, such patients have an increased need for ICU admission particularly due to acute respiratory failure. It has also been reported that the need for mechanical ventilation increases by 10 times in individuals aged over 85 compared to individuals aged 55.[19] Studies evaluating patients with severe CAP have reported in-hospital and 28-day independent mortality rates as 9.3% and 14-21%, respectively.[20,21] In a study evaluating patients with CAP, it was found that the in-hospital mortality rate in patients aged over 90 years was significantly higher than in patients aged 65-69 years.[22,23] In a study evaluating geriatric patients, the in-hospital mortality rate was 43.5% in HAP patients and 19.6% in CAP patients.[24] Studies conducted in HAP patients have reported that the mortality rate in HAP patients is higher than in CAP patients due to disease severity. Additionally, the statistically significant difference in cardiovascular comorbidities among the pneumonia groups observed in our study was considered to be associated with an increased mortality rate. In our study, the rate of independent intra-ICU mortality was 11.2% in CAP patients and 24.4% in HAP patients. As suggested in the literature, this difference could be attributed to the greater disease severity in HAP. On the other hand, previous studies have reported a relatively higher mortality rate in HAP due to higher patient age and the greater disease severity.[22-24] Likewise, mean age of our patients with mortality was higher in the HAP group than in the CAP group.

In lower respiratory tract infections such as HAP and CAP, changes occur in inflammatory acute phase reactants due to a number of factors including immune response, inflammatory cytokines, and inflammatory processes.[1] Moreover, with advancing age, changes occur in cellular and humoral immunity. To date, no reference values have been defined for serum levels of acute phase reactants in the elderly compared to the young population. Therefore, it is difficult to establish reference values due to comorbidities, physiopathological alterations, and functional losses.[25] CRP, PCT, WBC, NE, and LY are acute phase reactants frequently used in clinical practice.

Table 4. Laboratory parameters in different age groups

Variables	Group I (n=163) median (min-max)	Group II (n=170) median (min-max)	Group III (n=199) median (min-max)	Group IV (n=17) median (min-max)	p
WBC (µL) on admission	10880 (1000-36600)	12050 (1400-72550)	11400 (1900-37700)	8200 (500-30900)	0.249
WBC (µL) on 72nd hour	9400 (1600-45900)	9700 (600-70000)	10150 (2400-51500)	8700 (700-24500)	0.639
LY (µL) on admission,	900 (100-7420)	850 (110-16520)	800 (120-29010)	520 (400-6990)	0.136
LY (µL) on 72th hour,)	1000 (150-9300)	790 (190-21870)	860 (80-45640)	750 (230-6680)	0.014
NE (µL) on admission,	9430 (720-33790)	9960 (830-54410)	9500 (1450-35680)	6450 (10-29510)	0.407
NE (µL) on 72th hour,	7770 (1180-43790)	8000 (1970-50000)	8370 (1080-34970)	7330 (30-22720)	0.703
CRP (mg/L) on admission	71.51 (2-524)	69.12 (3-480)	96.90 (1.41-520)	66.08 (5.46-290)	0.090
CRP (mg/L) on 72th hour	63 (1.43-425)	66.38 (1-330)	82.29 (0.09-717)	84.94 (7.12-251)	0.105
PCT (ng/ml) on admission	0.2 (0.01-100)	0.215 (0.01-98.330)	0.26 (0.01-100)	0.16 (0.02-11.58)	0.765
PCT (ng/ml) on 72th hour	0.11 (0.01-100)	0.2 (0.01-54)	0.13 (0.016-100)	0.24 (0.04-10.72)	0.500

Group I: 18-64 years, Group II: 65-75 years, Group III: 76-90 years, Group IV: 91+ years, Min: Minimum, Max: Maximum, WBC: White blood cell count, LY: Lymphocyte count, NE: Neutrophil count, CRP: C-reactive protein, PCT: Procalcitonin

A study conducted in CAP patients aged over 65 who were followed up in ICU reported that the roles of leukocytosis, CRP, and PCT in early diagnosis and prognosis prediction were limited.[18] Another study evaluated a geriatric group with CAP and showed that WBC and PCT were higher and LY levels were lower in the group with in-hospital mortality than in other groups.[26] Studies conducted in pneumonia patients aged over 65 have suggested that the severity of leukocytosis or leukopenia is consistent with the severity of the disease. Another study evaluated geriatric patients with severe CAP and showed that both WBC and NE were higher and LY was lower in the group with poor prognosis. In the same study, the lower LY value was associated with immunosuppression and impaired regulation of the immune system, whereas the higher WBC and NE values were attributed to multiple organ dysfunction and injury to organ parenchymal cells due to severe infection.[27,28] In studies evaluating CAP patients aged over 80 and 90 years, CRP, PCT, WBC, and NE were higher and LY was lower in patients with mortality.[29] Literature suggests that serial measurement of serum CRP and PCT levels is essential for monitoring the prognosis in CAP patients followed up in ICU. It is also proposed that clinical and laboratory evaluation of pneumonia patients should be performed within 48-72 hours, except in cases with clinical worsening and resistant infection.[2,12,13] In our study, inflammatory acute phase reactants were measured both at ICU admission and at 72 hours. Our findings indicated that WBC, CRP, PCT, and NE were significant predictors of independent intra-ICU mortality, which was consistent with the findings of numerous studies in the literature. In the literature, there are varying cut-off values reported for WBC, CRP, PCT, and NE.[18,26-30] The cut-off values in our study were determined based on the values obtained at ICU admission and we did not find any significant difference among the age groups with regard to WBC, CRP, PCT, and NE. A number of studies have proposed that it is difficult to establish a reference range for most of the inflammatory acute phase reactants due to the aging process.[25] Similarly, our findings indicated that appropriate reference values should be established to determine age-specific cut-off values for the inflammatory acute phase reactants to be used in predicting independent mortality in severe pneumonia patients followed up in ICU. Unlike many studies in the literature, our study showed that LY was statistically insignificant in predicting independent intra-ICU mortality. It was also revealed that the decrease in the 72-h LY with advancing age was statistically more significant than the decrease in other acute phase reactants. These findings suggest that the response of LY to advancing age in patients followed up in ICU, regardless of the type of pneumonia, is greater than the response of WBC, PCT,CRP, and NE.

Limitations

Our study had several limitations. First, it was a retrospective and single-center study and evaluated severe and critical pneumonia patients only. Second, it only evaluated independent, and hence non-specific, intra-ICU mortality. Third, acute phase reactants were only measured at admission and at 72 hours. Finally, medical treatments that could affect serum levels of inflammatory acute phase reactants could not be evaluated due to the retrospective nature of our study.

CONCLUSION

Overall, our findings indicated that serum levels of LY, one of the inflammatory acute phase reactants, decreased with advancing age on the third day after admission in patients with severe pneumonia. Additionally, the response of LY to advancing age was greater than the response of other inflammatory acute phase reactants. Further multicenter, prospective studies with a larger number of cases are needed to determine the benefits of LY in clinical practice in elderly patients with severe pneumonia. Our findings also suggested that in patients with severe pneumonia, serial measurement of WBC, CRP, PCT, and NE may be useful in predicting short-term mortality. Multicenter and prospective studies are required to determine age-specific reference and cut-off values for the acute phase reactants to be used in predicting mortality in geriatric patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Scientific Researches Ethics Committee of the Ankara Atatürk Sanatorium Training and Research Hospital (Date: 14.02.2024, Decision No: 2024 BÇEK/8).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Designing the Study: DH; Analyzing the Data: DH; Writing the Manuscript: DH; Literature search: DH, EBÇ, MD, SS, HS; Conceptualization of Study Design: DH, EBÇ, MD, SS, HS; Data Collection: SS, MD, EBÇ, SS, GED, DH; Interpretation: SS, MD, EBÇ, SS, GED, DH.

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The relationship between the severity of COVID-19 pneumonia and ABO blood groups

Ümran Toru Erbay*[1], Şebnem Emine Parspur[1], Feride Marım[1], İlknur Kaya[1], Deniz Uysal[2], Zeynep Yaren Yılmaz Tan[1], Furkan Tan[1], Ömer Faruk Tekin[3]

[1]Department of Chest Diseases, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkiye
[2]Department of Pulmonology, Yalova State Hospital, Yalova, Turkiye
[3]Department of Public Health, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkiye

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***Corresponding Author:** Ümran Toru Erbay, umran.erbay@ksbu.edu.tr

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ABSTRACT

Aims: It is known that the distribution of ABO blood groups creates significant differences in viral infections and that blood group type can also be used as a biomarker to predict the risk of SARS-CoV-2 infection. In this study, we aimed to investigate the relationship between disease severity and blood groups in patients diagnosed with COVID-19 pneumonia.

Methods: Designed as a retrospective cohort study, our study included patients who were admitted to the Pulmonology Department of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital for inpatient treatment with a diagnosis of COVID-19 pneumonia between 31.03.2020 and 30.09.2020 and sociodemographic characteristics, blood group, Rh status, admission information, and CT findings were recorded from electronic patient records. Blood group characteristics were examined in the categorization based on the radiologically defined severity classification of COVID-19 pneumonia.

Results: The study group consisted of 93 males (47.2%) and 104 females (52.8%). Regarding blood type distribution, 50 (25.4%) patients had type O, 105 (53.3%) had type A, 26 (13.2%) had type B, and 16 (8.1%) had type AB. The blood group distribution according to the Rh factor was 25 (12.7%) Rh (-) and 172 (87.3%) Rh (+). No statistically significant difference was found in the distribution of COVID-19 pneumonia severity on chest computed tomography (CT) based on blood groups (p=0.200). No statistically significant difference was found in the relationship between COVID-19 pneumonia severity on chest CT and the Rh factor (p=0.283). On the other hand, when the relationship between the Rh factor and COVID-19 severity was examined, it was found that patients in the Rh (-) group had a higher rate of intensive care unit (ICU) admission (p=0.001), a higher rate of high-flow oxygen requirement during follow-up (p=0.030), and a higher mortality rate (p=0.02) compared to the Rh (+) group.

Conclusion: We have determined that there is no association between ABO blood group distribution characteristics and the severity of COVID-19 pneumonia, but there may be a prognostic association between the Rh factor and the severity of COVID-19.

Keywords: COVID-19, pneumonia, ABO blood group, Rh, SARS-CoV-2

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began in December 2019 as a cluster of patients with pneumonia of unknown origin linked to a seafood market in Wuhan, China, and spread throughout the Wuhan region.[1] Despite strict measures taken to control the viral outbreak, the disease continued to spread across China, straining hospital resources and healthcare workers.[2] SARS-CoV-2 continued to spread through human-to-human transmission and rapidly evolved into a global emergency.[3,4]

The gold standard for COVID-19 diagnosis is reverse transcription polymerase chain reaction (RT-PCR) using nasopharyngeal and oropharyngeal swabs.[5] However, while RT-PCR is highly specific, it is a test with varying levels of sensitivity.[6] Low sensitivity and false-negative rates highlight the importance of medical imaging; while chest X-rays are more practical, computed tomography (CT) has been shown to be superior in the diagnostic evaluation of COVID-19.[7]

To date, numerous factors have been identified that may be associated with poor prognosis and outcomes following COVID-19 infection, including gender, race, ethnicity, age, obesity, and pre-existing medical conditions.[8] In addition to these studies, blood type has also been investigated as a risk factor for COVID-19.

Although several studies have investigated the association between ABO blood groups and chest CT severity in COVID-19 patients, data from Turkish cohorts specifically evaluating radiologically defined pneumonia severity classifications-as categorized by Turkish Ministry of Health adult treatment guidelines-remain limited. The aim of

the present study is to contribute to this body of evidence by examining blood type characteristics in relation to radiologically and clinically defined COVID-19 severity in a Turkish tertiary care setting.

METHODS

Ethics

This study was conducted with the approval of the Ethics Committee for Non-interventional Clinical Researches at Kütahya University of Health Sciences (Date: 17.09.2020, Decision No: 2020/14). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

Our study, designed as a retrospective cohort study, included patients who were radiologically suspected of having COVID-19 between 31.03.2020 and 30.09.2020 and were diagnosed with COVID-19 pneumonia following a positive RT-PCR result, and who were hospitalized for treatment at Pulmonology Department of KSBÜ Evliya Çelebi Training and Research Hospital. The patients' electronic records were reviewed to document sociodemographic characteristics, blood type, Rh status, clinical information, and chest CT findings. Patients radiologically suspected of having COVID-19 and/or those with positive RT-PCR results were classified as COVID, while patients without findings consistent with COVID-19 on chest CT and/or with negative RT-PCR results were classified as Non-COVID. These patients were further divided into three groups based on chest CT findings: mild-moderate and severe-very severe. Radiological criteria: CT findings were classified according to the severity criteria defined in the Turkish Ministry of Health COVID-19 Adult Treatment Guidelines (2020). Cases without radiological evidence of severe pneumonia on CT were classified as 'mild pneumonia'; cases with bilateral diffuse pulmonary involvement were classified as 'severe pneumonia'; and patients who subsequently met intensive care criteria during ward follow-up were reclassified as 'very severe pneumonia. Chest CT images were evaluated by two experienced pulmonologists working in the clinic, both with direct clinical experience in COVID-19 management during the study period. In cases of discordant radiological classification between the two evaluating physicians, consensus was reached through discussion. Blood group characteristics were examined in the categorization based on the severity classification of radiologically defined COVID-19 pneumonia.

Inclusion Criteria

Patients aged 18 years or older with radiological findings consistent with COVID-19 pneumonia and a confirmed COVID-19 diagnosis based on PCR test, Total Antibody Test, Anti-SARS-CoV-2 IgM and/or IgG, and who were hospitalized for treatment at the Pulmonology Department of KSBÜ Evliya Çelebi Training and Research Hospital with a diagnosis of COVID-19 pneumonia between 31.03.2020 and 30.09.2020 were included in our study.

Exclusion Criteria

Individuals under 18 years of age who were admitted to the Pulmonology Department of KSBÜ Evliya Çelebi Training and Research Hospital between 31.03.2020 and 30.09.2020 with a confirmed diagnosis of COVID-19 pneumonia but without pulmonary involvement, as well as patients who were diagnosed with COVID-19 pneumonia after consultation but treated as outpatients and/or sent to quarantine without hospitalization, were excluded from our study.

Data Collection

Certain data from electronic patient records reviewed by the researchers were transferred to a prepared data form without identifying information. The flowchart is shown in **Figure**. The data form included patients' sociodemographic characteristics, blood type and Rh status, and laboratory parameters such as CRP, D-dimer, ferritin, fibrinogen, and lymphocyte counts. Chest CT findings were evaluated by pulmonologists working in the clinic, and patients were divided into 3 groups. Based on the adult treatment guidelines prepared by the Ministry of Health, patients were classified according to the severity of involvement on their admission CT scans: cases without radiological findings of severe pneumonia were classified as 'mild pneumonia,' and patients with bilateral diffuse pneumonia on CT were classified as 'severe pneumonia,' and patients admitted with a diagnosis of severe COVID-19 pneumonia whose treatment was managed on the ward but who later met intensive care criteria and required intensive care monitoring were classified as 'very severe pneumonia.' Blood group characteristics were examined in this categorization based on the classification.

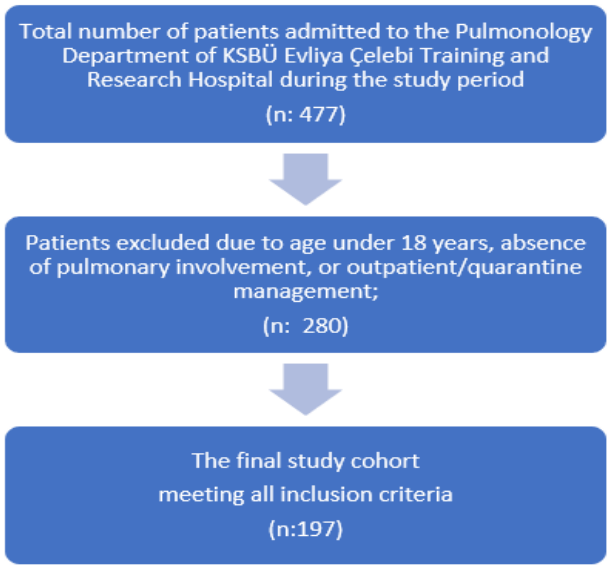

Figure. Flowchart of patient selection. Of 477 patients admitted during the study period, 280 were excluded according to the predefined exclusion criteria. The final study cohort consisted of 197 patients who met all inclusion criteria

Statistical Analysis

The data from the study were analyzed using the SPSS 25.0 software package. Descriptive statistics were presented as counts and percentages for categorical variables, and as means and standard deviations for numerical variables. The Chi-square test was used to compare categorical variables. Since the data did not follow a normal distribution, the Mann-Whitney U test and the Kruskal-Wallis test were applied to compare measured values between groups. Statistical significance was set at $p<0.05$.

RESULTS

Our study included 93 male (47.2%) and 104 female (52.8%) patients. No significant differences were observed between the genders in the study group. The mean age of the patients was 57.8±16.4 years (mean±SD). The mean length of hospital stay was 17.9±21.3 days.

In the blood group analysis, A Rh-positive A (+) was the most common blood group (91 patients, 46.2%), followed by O Rh-positive O (+) (43 patients, 21.8%). 23 patients (11.7%) were AB (+); 15 patients (7.6%) were B (+); 14 patients (7.1%) were A (–); 7 patients (3.6%) were O (–); 3 patients (1.5%) were AB (–); and only 1 patient (0.5%) was in the B (–) group. A total of 25 patients (12.7%) were Rh (–), while 172 patients (87.3%) were Rh (+). Some characteristics of the patients are shown in **Table 1**.

Table 1. Selected patient characteristics

Characteristics	Number (n)	Percent (%)
Gender		
Male	93	47.2
Female	104	52.8
Blood group		
O	50	25.4
A	105	53.3
B	26	13.2
AB	16	8.1
Rh factor		
Rh-	25	12.7
Rh+	172	87.3
COVID severity at CT (n=190)		
Non-COVID	21	11.1
Mild and moderate	87	45.7
Severe and very severe	82	43.2
Need for HFNO during inpatient follow-up (n=145)*		
No	139	95.9
Yes	6	4.1
ICU admission during follow-up (n=156)		
No	132	84.6
Yes	24	15.4
IMV (n=129)		
No	118	91.5
Yes	11	8.5
NIMV (n=135)		
No	112	83.0
Yes	23	17.0
Elevation of liver function tests during follow-up		
No	158	80.2
Yes	39	19.8

CT: Computed tomography, *HFNO: High flow nasal oxygen, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation

Based on the severity of COVID-19, no findings suggestive of COVID-19 were detected on the chest CT scans of 21 patients (11.1%). Mild and moderate COVID-19 findings were detected in 87 patients (45.7%), and severe and very severe COVID-19 findings were detected in 82 patients (43.2%). No significant differences were found between blood groups and chest CT findings or COVID-19 severity. When patients were divided into two groups based on Rh status Rh (+) and Rh (–), no significant differences were found in chest CT severity. The relationship between patients' blood groups and certain case characteristics is shown in **Table 2**, and the relationship between Rh groups and certain case characteristics is shown in **Table 3**.

During the hospital stay, the need for high-flow oxygen therapy developed in 6 patients (4.1%). Although no significant difference was observed in the analysis conducted for blood groups A, B, O, and AB, when patients were divided into 2 groups according to Rh status Rh (-) and Rh (+). The rate of high-flow oxygen requirement during inpatient follow-up was found to be statistically significantly higher in the Rh (-) group compared to the Rh+ group (p=0.030).

During inpatient follow-up, 24 patients (15.4%) were transferred to the intensive care unit. Although no significant difference was observed in the analysis conducted for blood groups A, B, O, and AB, when patients were grouped by Rh status (Rh- and Rh+), the rate of transfer to the intensive care unit (ICU) during inpatient follow-up was found to be statistically significantly higher in the Rh- group compared to the Rh+ group (p=0.001).

During follow-up in the ward, 14 patients died (7.1%), while 183 patients were discharged. In the analysis conducted according to blood groups A, B, O, and AB, no significant difference was found in mortality rates among the groups. However, when grouped as Rh (-) and Rh (+), a higher mortality rate was observed in the Rh (-) group (p=0.020).

DISCUSSION

COVID-19 first emerged in December 2019 in Wuhan, China, with cases of pneumonia of unknown origin; this disease, caused by SARS-CoV-2, quickly spread from person to person and evolved into a global pandemic.[1-4] COVID-19, declared as a pandemic by the World Health Organization, can present with a wide clinical spectrum ranging from mild upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ failure.[8]

The gold standard for COVID-19 diagnosis is RT-PCR testing using nasopharyngeal and oropharyngeal swabs; however, due to the variable sensitivity of this test and rates of false negative results, the diagnostic value of imaging methods has come to the fore.[5,6] In this context, chest CT is recognized as a superior method compared to chest X-rays for the diagnosis and severity assessment of COVID-19 pneumonia.[7] While factors such as advanced age, male gender, obesity, and comorbid chronic diseases have been identified as factors negatively affecting the clinical course of the disease,[8] research has begun to investigate the effects of genetic markers, such as blood type, on disease severity in order to fully explain inter-individual differences in prognosis.[9,10]

Our study examined the relationship between the severity of pneumonia and blood groups in patients diagnosed with

Table 2. The relationship between blood groups and certain characteristics of the cases

Characteristics	Group O n (%)	Group A n (%)	Group B n (%)	Group AB n (%)	p-value*
Gender					
Male	25 (50)	46 (43.8)	13 (50)	9 (56.3)	0.741
Female	25 (50)	59 (56.2)	13 (50)	7 (43.8)	
Follow-up result					
Discharge	48 (96)	97 (92.4)	23 (88.5)	15 (93.8)	0.688
Death	2 (4)	8 (7.6)	3 (11.5)	1 (6.3)	
COVID severity at CT (n=190)					
Non-COVID	8 (17)	7 (6.7)	2 (8.3)	4 (26.7)	0.200
Mild and moderate	19 (40.4)	53 (51)	10 (41.7)	5 (33.3)	
Severe and very severe	20 (42.6)	44 (42.3)	12 (50)	6 (40)	
Need for HFNO during inpatient follow-up (n=145)					
No	36 (97.3)	71 (95.9)	21 (95.5)	11 (91.7)	0.865
Yes	1 (2.7)	3 (4.1)	1 (4.5)	1 (8.3)	
ICU admission during follow-up (n=156)					
No	33 (86.8)	70 (86.4)	18 (81.8)	11 (73.3)	0.584
Yes	5 (13.2)	11 (13.6)	4 (18.2)	4 (26.7)	
IMV (n=129)					
No	34 (100)	57 (90.5)	18 (85.7)	9 (81.8)	0.141
Yes	0 (0)	6 (9.5)	3 (14.3)	2 (18.2)	
NIMV (n=135)					
No	32 (91.4)	54 (80.6)	18 (85.7)	8 (66.7)	0.221
Yes	3 (8.6)	13 (19.4)	3 (14.3)	4 (33.3)	
Elevation of liver function tests during follow-up					
No	42 (84)	87 (82.9)	16 (61.5)	13 (81.3)	0.084
Yes	8 (16)	18 (17.1)	10 (38.5)	3 (18.8)	

*p-values were calculated using the appropriate statistical tests. A p-value <0.05 was considered statistically significant. CT: Computed tomography, HFNO: High flow nasal oxygen, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation

COVID-19. No association was found between radiological severity on chest CT and blood groups or the Rh factor. ICU transfer, need for high-flow oxygen therapy and death during follow-up were significantly more common in the Rh (-) group.

In a study conducted in Turkiye, blood group A was the most common, followed by blood group O, among patients diagnosed with COVID-19.[11] Consistent with the literature, our study demonstrated that the most common blood group among individuals diagnosed with COVID-19 was A Rh(+), followed by O Rh(+).

A study examining the relationship between ABO blood groups and COVID-19 infection reported that individuals with blood group A are more susceptible to the infection, while blood group O may offer protection against it.[9] In a study investigating whether the ABO and Rh blood group systems contribute to susceptibility to COVID-19, no significant differences were observed with respect to ABO blood group.[10] In our study as well, in line with the literature, the highest number of patients was found in the A blood group. Although it has been found that individuals with blood type A are more susceptible to COVID-19 compared to those with blood type O, a study revealed that individuals with blood type A have a lower risk of intubation and death compared to those with blood type O.[12] In a different study, it was reported that individuals with blood type O have a lower risk of severe illness and death compared to other blood groups.[13] In another study by Arent and colleagues,[14] the risk of COVID-19 was found to be higher in individuals with blood type A; additionally, blood type A was found to be more protective against moderate/severe symptoms. Studies in the literature regarding the relationship between COVID-19 and blood type show variability. In our study, however, when the relationship between ABO blood groups and the risk of intubation and death was examined, no significant differences were found among the groups.

In a study examining the Rh factor, it was shown that Rh (-) individuals have a lower risk of infection compared to Rh (+) individuals.[12] This finding was also observed in a study reporting that Rh (+) individuals are more likely to test positive for SARS-CoV-2.[13] The same study reported that being Rh (+) is associated with a higher likelihood of a positive PCR test, as well as higher risks of intubation and death.[13] In another study by Zietz and colleagues,[12] it was shown that COVID-19 patients with the Rh (-) blood type had lower risks of infection, intubation, and death. Similarly, another study demonstrated that individuals with the Rh (-) blood group, particularly those with the O (-) blood group, are less susceptible to SARS-CoV-2 infection.[15] In a different study, no intensive care admissions or mortality were observed in patients with the Rh (-) blood group, while admission rates to the ICU were found to be significantly higher in the Rh (+) group, and no significant association was reported between

Table 3. Relationship between Rh groups and certain characteristics of the cases

Characteristics	Rh (-) group n (%)	Rh (+) group n (%)	p-value*	OR (95% CI)
Gender				
Male	12 (48)	81 (47.1)	1.000	0.96 (0.42-2.23)
Female	13 (52)	91 (52.9)		
Follow-up result				
Discharge	20 (80)	163 (94.8)	0.020*	4.53 (1.38-14.86)
Death	5 (20)	9 (5.2)		
COVID severity at CT (n=190)				
Non-COVID	3 (13)	18 (10.8)	0.273	
Mild and moderate	7 (30.4)	80 (47.9)	0.382	0.53 (0.12-2.23)
Severe and very severe	13 (56.5)	69 (41.3)	0.860	1.13 (0.29-4.40)
Need for HFNO during inpatient follow-up (n=145)				
No	16 (84.2)	123 (97.6)	0.030*	7.69 (1.43-41.4)
Yes	3 (15.8)	3 (2.4)		
ICU admission during follow-up (n=156)				
No	12 (57.1)	120 (88.9)	0.001*	6.00 (2.17-16.60)
Yes	9 (42.9)	15 (11.1)		
IMV (n=129)				
No	12 (80)	106 (93)	0.119	3.31 (0.77-14.19)
Yes	3 (20)	8 (7)		
NIMV (n=135)				
No	13 (81.3)	99 (83.2)	0.736	1.14 (0.30-4.38)
Yes	3 (18.8)	20 (16.8)		
Elevation of liver function tests during follow-up				
No	21 (84)	137 (79.7)	0.790	0.96 (0.42-2.23)
Yes	4 (16)	35 (20.3)		

*Chi-square test, OR: Odds ratio, CT: Computed tomography, CI: Confidence interval, HFNO: High flow nasal oxygen, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation

mortality and Rh antigens.[11] Similar results were obtained in another study, which demonstrated that the Rh (-) blood group is protective, while the Rh (+) blood group is significantly more susceptible to COVID-19.[10] Ray and colleagues[15] reported that the Rh (-) blood group is associated with a lower risk of developing severe COVID-19 infection, suggesting that the Rh (-) blood group may have a protective effect against severe SARS-CoV-2 disease. A separate study by Zietz and colleagues[12] reported similar findings, concluding that COVID-19 patients with a negative Rh factor had a lower likelihood of developing infection, requiring intubation, or dying. In another study examining the relationship between the ABO and Rh blood group systems and COVID-19, it was determined that the Rh factor plays a role in the severity of COVID-19 infection, and it was reported that Rh (+) individuals are more prone to severe infection and complications.[16]

In our study, blood groups and Rh factor were not significantly associated with radiological or clinical severity of COVID-19 pneumonia. To the best of our knowledge, this is the first study to evaluate this relationship. However, the need for high-flow oxygen therapy and ICU transfer was significantly higher in the Rh (-) group.

However, the proportion of patients requiring high-flow oxygen therapy during their hospital stay and the rates of transfer to the ICU during follow-up were found to be significantly higher in the Rh (-) group. In the evaluation based on clinical follow-up results, while no significant difference was observed in mortality rates between the two groups according to blood groups, we found that mortality rates were higher in the Rh (-) group.

Limitations

The main limitation of our study is its retrospective design and the small study population. One of the limitation was that formally validated CT severity scoring system (e.g., CT-SS, CO-RADS, or the RSNA expert consensus classification) was not applied, as the study was designed and conducted during the early pandemic period (2020), when these standardized tools were either newly introduced or not yet widely adopted in our center. Given the retrospective nature of the study and the reliance on electronic patient records, formal blinding of radiological readers to clinical data was not feasible.

A key limitation of this study is that, due to the small sample size, it was not possible to perform a fully adjusted multivariate logistic regression analysis; therefore, the association between the Rh factor and clinical outcomes should not be interpreted independently of potential confounding variables. Although the differences observed between the Rh(-) and Rh(+) groups in terms of HFNO requirements, ICU admissions and mortality rates were statistically significant, these findings must be interpreted with caution given the limited sample size. This is one of the limitations of the study.

Another drawback of our study is that only inpatients were included. Prospective studies with larger populations would be more valuable.

CONCLUSION

This study found no statistically significant association between ABO blood group distribution and the radiological severity of COVID-19 pneumonia on chest CT. However, Rh(-) blood type was associated with significantly higher rates of high-flow nasal oxygen requirement, ICU admission, and in-hospital mortality compared to Rh(+) blood type. These findings suggest a potential prognostic role for the Rh factor in COVID-19 clinical outcomes, though the small Rh(-) subgroup size necessitates cautious interpretation. These results are in contrast to the majority of published studies that report a protective effect of Rh(-) blood type, underscoring the importance of larger, prospective, multicenter studies-ideally with multivariable adjustment-to definitively characterize the relationship between blood group systems and COVID-19 severity.

Our study is the first in the literature examining the relationship between blood type and the severity of COVID-19 pneumonia radiologically and clinically. However, we believe that further studies in larger populations are needed in this regard. There is a need for recent studies examining blood group associations in the context of current variants and post-vaccination populations.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Ethics Committee for Non-interventional Clinical Researches at Kütahya University of Health Sciences (Date: 17.09.2020, Decision No: 2020/14).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: ÜE, ŞEP, FM, DU; Design: ÜE, ŞEP; Control: ÜE, İK; Data Collection and/or Processing: İK, ŞEP, FM, ÖFT; Analysis and/or Interpretation: ÜE, İK, ÖFT; Literature Review: İK, FT, ZYYT; Article Writing: ÜE, İK; Critical Review: All Authors.

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The prognostic value of PET/CT-derived volumetric parameters for postoperative recurrence in resected non-small cell lung cancer

Ezgi Erdem Türe*[1,2], Özlem Özmen[3,4], Pınar Akın Kabalak[1], Şevki Mustafa Demiröz[5,6]

[1]Department of Chest Diseases, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye
[2]Department of Chest Diseases, Ankara Etlik City Hospital, Ankara, Turkiye
[3]Department of Nuclear Medicine, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye
[4]Department of Nuclear Medicine, Ankara Etlik City Hospital, Ankara, Turkiye
[5]Department of Thoracic Surgery, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye
[6]Department of Thoracic Surgery, Faculty of Medicine, Gazi University, Ankara, Turkiye

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***Corresponding Author:** Ezgi Erdem Türe, eezgierdem@gmail.com

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ABSTRACT

Aims: Non-small-cell lung cancer (NSCLC) recurrence is high even after complete surgical resection. This study aimed to investigate the relationship between recurrence and 18F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and to determine prognostic factors.

Methods: Patients with pathologically confirmed stage I-II NSCLC who underwent surgical resection were retrospectively analyzed. Before surgery, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were derived by applying SUV_{max}-based thresholds of 2.5 and 42%. Data regarding demographics, clinicopathological features, and tumor characteristics were gathered. Kaplan-Meier method was used for disease-free survival (DFS) and overall survival rates. Factors associated with recurrence were evaluated using univariate and multivariate Cox regression analysis.

Results: The mean age of the 179 patients included in the study was 61.24 years. The median follow up duration was 50 months. Recurrence occurred in 38.5% of the patients. Prognostic factors for recurrence were larger tumor size, visceral pleural invasion, and PL2 involvement. When stratified by histology, MTV measured using SUV_{max} thresholds of 2.5 and 42% was significantly higher in patients with recurrence in the squamous cell carcinoma subgroup. In univariate analysis, high $MTV_{42\%}$ was associated with shorter DFS. In multivariate analysis, $MTV_{2.5}$ remained independently associated with DFS. SUV_{max} and TLG were not independently associated with DFS.

Conclusion: Larger tumor size and pleural invasion were associated with shorter DFS. $MTV_{2.5}$ was independently associated with DFS; however, its low discriminatory performance limits its current clinical utility, and the finding requires external validation.

Keywords: Disease-free survival, NSCLC, recurrence, SUV_{max}, total lesion glycolysis, metabolic tumor volume

INTRODUCTION

Lung cancer has a high incidence and mortality. Non-small cell lung cancer (NSCLC) is observed in 80-85% of cases, and the most common subtype is adenocarcinoma.[1,2] NSCLC is usually diagnosed at an advanced or metastatic stage, and the 5-year survival rates are low.[3] Even for patients who receive surgical intervention with complete resection (R0), the estimated 5-year survival rate is approximately 73%.[4] Therefore, identifying additional poor prognostic factors remains critically important. The TNM staging system is widely recognized as a critical prognostic factor and the primary guide for treatment decisions.[5] However, it does not always accurately represent the tumor's biological behavior, indicating a need for supplementary prognostic biomarkers.

18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) is a widely used imaging technique for differential diagnosis, staging, monitoring therapeutic responses, detecting recurrent disease, and assisting in radiotherapy planning. In clinical practice, the most commonly used 18F-FDG PET/CT parameter for measuring the metabolic activity of a lesion is the maximum standardized uptake value (SUV_{max}).

In 18F-FDG PET/CT scans, the most commonly used parameter for evaluating lesions is SUV_{max}. This parameter provides a semi-quantitative measurement of the radioactivity concentration within a lesion. SUV_{max} is calculated as the highest standardized uptake value obtained

from the voxel demonstrating the highest activity within the region of interest drawn around the lesion.[6] Several studies have demonstrated an association between elevated SUV_{max} values and poor prognosis in malignancies;[7,8] however, this relation was not confirmed in some studies.[9] In addition to SUV based metrics, total lesion glycolysis (TLG) and metabolic tumor volume (MTV) can be derived from PET/CT and have been suggested to be more reliable parameters for predicting prognosis than SUV.[10-12]

Despite numerous studies evaluating PET/CT-derived metabolic parameters in NSCLC, their prognostic value in patients with completely resected early-stage disease remains controversial. Previous studies have reported inconsistent findings regarding SUV_{max}, MTV, and TLG because of differences in patient populations, tumor stages, histopathological composition, and thresholding methods used for volumetric analysis. Moreover, studies comparing different MTV/TLG thresholding approaches and evaluating these parameters according to histopathological subtype remain limited. The primary aim of this study was to evaluate the prognostic value of PET/CT-derived metabolic parameters for predicting recurrence in early-stage NSCLC. To address these gaps, we evaluated metabolic parameters using two commonly applied thresholding methods and performed histopathological subtype-specific analyses in a homogeneous cohort of completely resected stage I-II NSCLC patients. The secondary aim of this study was to evaluate the relationship between PET/CT-derived parameters across histopathological subtypes and recurrence, as well as to identify other prognostic factors associated with recurrence.

METHODS

Ethics

This study was conducted with the approval of the Ethics Committee for Clinical Researches of the Ankara Keçiören Training and Research Hospital (Date: 12.06.2019, Decision No: 2012-KAEK-15/1915). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Evaluation

We screened patients diagnosed with NSCLC who underwent surgical resection from January 2012 to December 2016. Follow-up was performed at the same institution, and survival and recurrence data were obtained from hospital records.

Only patients with histologically proven stage I-II NSCLC who underwent complete tumor resection (R0) were included in the study. Surgical procedures consisted of lobectomy or pneumonectomy with systematic lymph node dissection. The study included patients with pathologically confirmed N0 status based on postoperative histopathological evaluation following surgical resection. The 7th edition of the TNM classification system was used to determine pathological staging, because it was in routine clinical use during the study period. Histopathological subtypes of adenocarcinoma, squamous cell carcinoma (SCC), and adenosquamous carcinoma were included. Exclusion criteria included non-R0 resection, limited resection (segmentectomy or wedge resection), surgery performed at another center, stage III-IV NSCLC, oligometastatic disease, second primary malignancy, multiple primary lung cancers, thoracic radiotherapy, unavailable preoperative PET/CT images, and incomplete postoperative follow-up data.

Patient demographic characteristics (age, gender, and presence of comorbidities), histological subtype (adenocarcinoma, SCC, and adenosquamous carcinoma), pathological tumor size and stage, visceral pleural invasion (VPI) and PL2 involvement were recorded. In the modified Hammar system, PL0 is defined as tumor growth restricted to the subpleural lung parenchyma, without invasion beyond the elastic layer of the visceral pleura. Tumor invasion beyond the elastic layer is defined as PL1, invasion reaching the pleural surface is defined as PL2, and invasion into the parietal pleura is defined as PL3. VPI is defined as the presence of PL1 or PL2 invasion.[13]

Locoregional recurrence was defined as recurrence in the ipsilateral lung lobe and/or metastasis to the ipsilateral mediastinal or hilar lymph nodes following lobectomy or pneumonectomy. Distant metastasis was defined as recurrence occurring in sites other than the ipsilateral lung. Recurrence was defined based on clinical evaluation, imaging findings, and histopathological assessment. Patients with clear radiological progression on thoracic CT or 18F-FDG PET/CT were considered to have recurrence based on imaging findings. In cases with suspicious findings, histopathological confirmation was obtained by biopsy.

18F-FDG PET/CT Imaging Protocol

Only preoperative 18F-FDG PET/CT scans performed before initiation of oncologic management were included, with image data sourced from the institutional picture archiving and communication system (PACS). All examinations were performed within a mean of 33±2.5 days before surgery. Primary tumor SUVmax, mean SUV (SUV_{mean}), MTV and TLG were calculated.

An integrated PET-CT scanner (Siemens Biograph-6 Hi-Rez; Siemens Medical Solutions, Knoxville, TN, USA) was used for imaging. According to the standard imaging protocol, all patients restricted food and water intake for at least 6 hours prior to imaging. Patients with peripheral blood glucose values under 180 mg/dl received intravenous 18F-FDG at doses of 370-555 MBq (10-15 mCi). After a standardized uptake period of 60 minutes at rest, imaging was performed. Initially, a low-dose computed tomography (CT) scan was acquired from the vertex to the proximal femur with patients positioned supine and arms raised, using the CareDose protocol (Siemens). PET imaging was performed using 6-8 bed positions, with a scanning duration of 3 minutes for each position. CT-derived data were applied for attenuation correction, and PET datasets were reconstructed via an iterative reconstruction method employing 4 iterations and 8 subsets, with additional Gaussian filtering.

18F-FDG PET/CT Image Analysis

18F-FDG PET/CT images were analyzed using dedicated software by one experienced nuclear medicine physician who was blinded to the clinical data.

SUV_{max} was calculated as follows:

SUV_{max}=tissue concentration (MBq/ml)/injected FDG activity (MBq)/body weight (g). SUV_{mean} within the same region was recorded.

Various methods for calculating MTV and TLG have been described in the literature. In the absence of a universally accepted standard for volumetric PET analysis, two thresholding methods were selected because they represent the most commonly used approaches in NSCLC. Accordingly, MTV was calculated using two different approaches. First, metabolically active tumor volume was defined as the volume of voxels demonstrating an uptake greater than 42% of the primary tumor SUV_{max}.[14] Second, MTV was calculated using a fixed absolute SUV threshold of 2.5, including all voxels with an SUV ≥2.5.8 TLG was derived by multiplying MTV and SUV_{mean}. Parameters calculated using the fixed SUV threshold were termed $MTV_{2.5}$ and $TLG_{2.5}$, whereas those calculated using the 42% SUV_{max} threshold were termed $MTV_{42\%}$ and $TLG_{42\%}$. SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$ values were calculated separately for adenocarcinoma and SCC, and their associations with recurrence were evaluated.

Statistical Analysis

Categorical variables were presented as frequencies and percentages, while continuous variables were reported as mean±standard deviation or median (minimum-maximum). The Shapiro-Wilk test was used to assess normality. Comparisons between groups were performed using the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the Chi-square test or Fisher's exact test.

The prognostic performance of SUV_{max}, MTV, and TLG for recurrence was examined through receiver operating characteristic curve analysis. Threshold values yielding the highest discriminatory power were determined using the Youden criterion, and diagnostic performance metrics including sensitivity, specificity, positive predictive value, and negative predictive value were subsequently calculated. Based on these thresholds, patients were categorized into high and low risk groups according to SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$. Disease-free survival (DFS) and 5 years survival were estimated using the Kaplan-Meier approach, with between-group differences evaluated by the log-rank test. Variables associated with DFS were further explored using univariate and multivariate Cox proportional hazards models. Because the volumetric parameters derived using the fixed and relative thresholding methods were potentially correlated, two separate multivariable models were constructed. Model 1 included SUV_{max}, $MTV_{2.5}$, and $TLG_{2.5,}$ whereas model 2 included SUV_{max}, $MTV_{42\%}$, and $TLG_{42\%}$, together with the selected clinicopathological covariates. Statistical significance was defined as a two-sided p value below 0.05. All analyses were conducted using IBM SPSS Statistics (version 26.0; IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 503 individuals with histologically proven non-small cell lung cancer who underwent curative N0, R0 surgical resection between 2012 and 2016 were initially evaluated. After applying the predefined inclusion criteria, 179 patients were ultimately included in the analysis. The majority of patients were male (n=160, 89.4%). The mean age was 61.24±7.63 years. At least one comorbid condition was identified in 108 patients (60.3%). The median duration of follow-up was 50 (6-94) months. Pathological stage I disease was identified in 131 patients (73.2%), while 48 patients (26.8%) had stage II disease. Histopathologically, 86 patients (48%) had adenocarcinoma, 86 patients (48%) had SCC. During the follow-up period, disease recurrence was observed in 69 (38.5%) patients. The median interval from surgery to recurrence was 19 (4-80) months. Patient and tumor characteristics are summarized in **Table 1**.

Table 1. Patient and tumor characteristics

Patient characteristics	**n (%)**
Gender	
Male	160 (89.4%)
Female	19 (10.6%)
Age (years)*	61.24±7.63
The presence of comorbidities	108 (60.3%)
Follow-up time (months)**	50 (6-94)
Recurrence	69 (38.5%)
Recurrence time (months)**	19 (4 - 80)
Tumor characteristics	
TNM staging	
Stage I	131 (73.2%)
Stage II	48 (26.8%)
Histopathology	
Adenocarcinoma	86 (48%)
Squamous cell carcinoma	86 (48%)
Adenosquamous carcinoma	7 (4%)

*Mean±standard deviation **Median (min-max) TNM: Tumor, node, metastasis, Min: Minimum, Max: Maximum

Association of Demographic Findings and Tumor Characteristics with Recurrence

No statistically significant associations were found between recurrence status and age, gender, or the presence of comorbidities, pathological stages and histopathological subtype. Tumor size was larger in the recurrence group, and this difference was statistically significant (p=0.046). The presence of VPI and PL2 involvement was significantly higher in patients with recurrence than in those without recurrence (p=0.029 and p=0.018, respectively). The association of demographic and tumor characteristics with recurrence is presented in **Table 2**.

18F-FDG PET/CT-Derived Parameters and Association with Recurrence

The overall and histopathological subgroup analyses of SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$ are summarized in **Table 3**. In the overall analysis, SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, $MTV_{42\%}$, and $TLG_{42\%}$ values were not significantly different between the recurrence and non-recurrence groups. When stratified by histopathological subtype, no significant differences were observed in the adenocarcinoma subgroup for any of the evaluated parameters. In contrast, in the

Table 2. Association of demographic findings and tumor characteristics with recurrence

	Without recurrence n (%)	Recurrence n (%)	p
Age*	61.24±7.57	61.25±7.81	
Gender			0.247
Male	96 (60%)	64 (40%)	
Female	14 (73.7%)	5 (26.3%)	
Comorbidity			
Absent	49 (69%)	22 (31%)	0.092
Present	61 (56.5%)	47 (43.5%)	
TNM staging			
Stage I	85 (64.9%)	46 (35.1%)	0.119
Stage II	25 (52.1%)	23 (47.9%)	
Histopathology			
Adenocarcinoma	50 (58.1%)	36 (41.9 %)	0.332
Squamous cell carcinoma	54 (62.8%)	32 (37.2%)	
Adenosquamous carcinoma	6 (85.7%)	1 (14.3%)	
Tumor size (cm)*	3.45±1.53	3.94±1.68	0.046
Visceral pleural invasion (PL1-PL2)			
Absent	81 (66.9%)	40 (33.1%)	0.029
Present	29 (50%)	29 (50%)	
PL2 involvement			
Absent	63 (70%)	27 (30%)	0.018
Present	47 (52.8%)	42 (47.2%)	

p<0.05 statistically significant; * Mean±standard deviation TNM: Tumor, node, metastasis, PL1: Tumor invasion beyond the elastic layer of the visceral pleura, PL2: Tumor invasion to the surface of the visceral pleura

SCC subgroup, $MTV_{2.5}$ and $MTV_{42\%}$ were significantly higher in patients with recurrence compared to those without recurrence (p=0.026 and p=0.016, respectively). No statistically significant differences were found for SUV_{max}, $TLG_{2.5}$ and $TLG_{42\%}$ parameters in either subgroup.

To evaluate the sensitivity and specificity of metabolic parameters in predicting recurrence, ROC curve analysis was performed and optimal cut-off values were determined. The determined cut-off values, sensitivity, specificity, AUC and p value are presented in **Table 4**, and the ROC curve in **Figure 1**. According to the cut-off values, the metabolic parameters were categorized into two different groups as high and low.

Univariate and Multivariate Cox Regression Analysis

Univariate and multivariate Cox regression analysis results are presented in **Table 5**. In univariate analysis, VPI, PL2 involvement, and tumor size were identified as significant predictors of DFS (p=0.009, p=0.011, and p=0.035; respectively). VPI was associated with shorter DFS (HR, 1.902; 95% CI, 1.176-3.077; p=0.009), while PL2 involvement was also associated with shorter DFS (HR, 1.874; 95% CI, 1.154-3.043; p=0.011). $MTV_{42\%}$ was significantly associated with DFS, with lower values (≤30.66) indicating reduced recurrence risk (p=0.036).

In multivariate analysis, $MTV_{2.5}$ remained independently associated with DFS in model 1 (p=0.038), whereas SUV_{max} and $TLG_{2.5}$ were not significant. In model 2, none of the parameters derived using the 42% threshold (SUV_{max}, $MTV_{42\%}$, and $TLG_{42\%}$) were identified as independent prognostic factors.

Survival Analysis

The 5-year survival rate was 87.2%, and the 5-year DFS rate was 63.7%. The 5-year DFS rate was 66.5% at low $MTV_{42\%}$ and

Table 3. 18F-FDG PET/CT metabolic parameters according to recurrence status and histopathology

Parameter	Total median (min-max)	Recurrence median (min-max)	No recurrence median (min-max)	p
SUV_{max}				
Overall	12.22 (2.48-42.92)	12.64 (8.62-16.58)	12.22 (7.75-19.12)	0.458
Adenocarcinoma	10.20 (2.79-26.93)	9.74 (6.80-14.43)	11.00 (5.76-18.60)	0.662
SCC	14.45 (2.48-42.92)	14.45 (11.23-17.60)	14.32 (10.66-21.00)	0.855
$MTV_{2.5}$ (cm^3)				
Overall	21.85 (0.05-347.41)	26.71 (8.45-49.47)	19.28 (5.91-46.64)	0.300
Adenocarcinoma	18.01 (0.05-347.41)	17.06 (4.63-32.33)	18.51 (5.18-47.72)	0.830
SCC	24.28 (0.05-136.57)	35.67(14.44-71.66)	20.98 (8.78-74.10)	0.026
$TLG_{2.5}$				
Overall	113.92(0.12-2504.82)	124.70(35.87-280.11)	108.74(30.20-282.19)	0.512
Adenocarcinoma	94.17 (0.13-2504.82)	86.97 (19.58-245.69)	94.71 (21.02-267.56)	0.707
SCC	143.75 (0.12-923.21)	202.29(79.23-589.26)	115.65(47.98-296.93)	0.068
$MTV_{42\%}$ (cm^3)				
Overall	10.22 (1.03-154.12)	12.38 (3.85-24.03)	9.39 (4.24-19.54)	0.271
Adenocarcinoma	10.83 (1.03-154.12)	9.75 (3.34-19.07)	11.95 (3.30-24.28)	0.612
SCC	10.29 (1.25-54.25)	14.89 (7.70-29.45)	8.42 (4.35-16.51)	0.016
$TLG_{42\%}$				
Overall	73.35 (4.35-1622.88)	76.82 (27.31-195.16)	72.06 (26.96-175.72)	0.461
Adenocarcinoma	68.34 (4.35-1622.88)	67.28 (15.45-171.90)	70.13 (19.40-193.14)	0.720
SCC	88.27 (6.08-596.01)	125.73(66.32-281.11)	74.18 (30.84-175.72)	0.064

Values are presented as median (min-max). p<0.05 was statistically significant. Min: Minimum, Max: Maximum, 18F-FDG: Fluorine-18 fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standardized uptake value, SCC: Squamous cell carcinoma, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

Table 4. Diagnostic performance of SUV_{max}, MTV, and TLG cutoff values for recurrence

Parameter	Cut-off	AUC	p-value	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SUV_{max}	6.56	0.533	0.458	0.449-0.617	88.4	22.7	41.5	75.0
$MTV_{2.5}$ (cm^3)	25.31	0.546	0.300	0.459-0.633	52.17	62.73	46.8	67.6
$TLG_{2.5}$	200.48	0.529	0.512	0.443-0.616	40.60	66.4	44.4	64.7
$MTV_{42\%}$ (cm^3)	30.66	0.549	0.271	0.461-0.637	20.29	90.91	58.3	64.5
$TLG_{42\%}$	139.77	0.533	0.461	0.445-0.620	37.68	72.73	46.4	65.0

SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

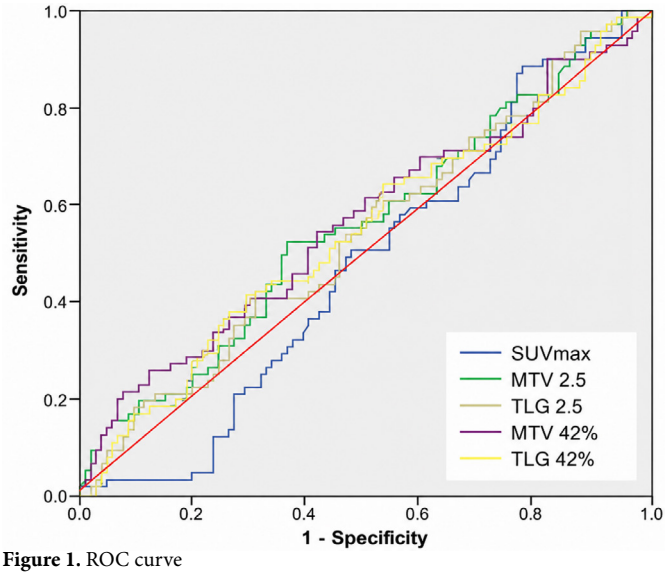

Figure 1. ROC curve
SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, ROC: Receiver operating characteristic

45.8% at high $MTV_{42\%}$ (p=0.038). The 5-year DFS according to $MTV_{42\%}$ is shown in **Figure 2**. While $MTV_{42\%}$ $MTV_{42\%}$ was associated with 5-year DFS but not with 5-year survival, it was not associated with 5-year survival. SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, and $TLG_{42\%}$ were not found to be associated with either 5-year survival or 5-year DFS (**Table 6**).

DISCUSSION

In this study, we evaluated the association between PET/CT-derived parameters and recurrence. Histopathological subgroup analyses were conducted to further explore their relationship with recurrence and to identify additional clinicopathological prognostic factors. In this study, larger tumor size and the presence of VPI, particularly PL2 involvement, were significantly associated with recurrence. In the SCC subgroup, $MTV_{2.5}$ and $MTV_{42\%}$ were significantly higher in patients with recurrence, whereas these parameters were not significant in adenocarcinoma. In multivariate

Table 5. Univariate and multivariate Cox regression analysis for disease-free survival

	Univariate Cox regression		Multivariate Cox regression (model 1)		Multivariate Cox regression (model 2)	
Parameter	**Hazard ratio***	**p**	**Hazard ratio***	**p**	**Hazard ratio***	**p**
Gender	0.584 (0.265-1.451)	0.246				
The presence of comorbidity	1.587 (0.956-2.637)	0.074				
Histopathology	0.696 (0.456-1.062)	0.093	0.767 (0.491-1.198)	0.243	0.721 (0.455-1.140)	0.162
Tumor size	1.169 (1.011-1.351)	0.035				
TNM staging	1.555 (0.942-2.567)	0.084	0.954 (0.644-2.271)	0.554	1.071 (0.551-2.083)	0.839
Visceral pleural invasion	1.902 (1.176-3.077)	0.009				
PL2 involvement	1.874 (1.154-3.043)	0.011	1.655 (0.954-2.271)	0.073	1.547 (0.880-2.720)	0.129
SUV_{max}						
Low (≤6.56)	1.854	0.101	1.769	0.165	1.874	0.118
High (<6.56)	(0.887-3.875)		(0.790-3.962)		(0.853-4.119)	
$MTV_{2.5}$ (cm^3)						
Low (≤25.31)	1.534	0.076	2.288	0.038		
High (25.31<)	(0.956-2.460)		(1.046-5.006)			
$TLG_{2.5}$						
Low (≤200.48)	1.208	0.441	0.448	0.051		
High (200.48<)	(0.747-1.955)		(0.201-1.025)			
$MTV_{42\%}$ (cm^3)						
High (30.66<)	1.874	0.036			1.319	0.510
Low (≤30.66)	(1.041-3.373)				(0.579-3.001)	
$TLG_{42\%}$						
Low (≤139.77)	1.428	0.152			0.977	0.948
High (139.77<)	(0.877-2.325)				(0.495-1.930)	

* Values in parentheses indicate the 95% confidence interval. p<0.05 was statistically significant. TNM: Tumor, node, metastasis, PL2: Tumor invasion to the surface of the visceral pleura, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

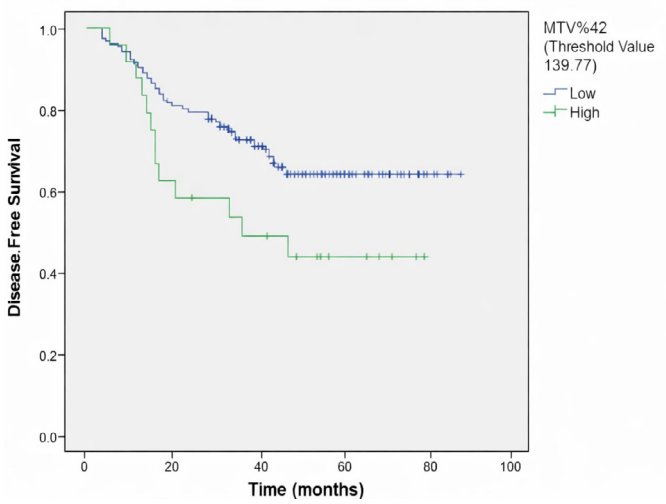

Figure 2. 5-year disease-free survival for $MTV_{42\%}$
MTV: Metabolic tumor volume

Table 6. The relationship between 5-year survival and 5-year disease-free survival with SUV_{max}, MTV, and TLG

	5-year survival		5-year disease-free survival	
	%	p	%	p
SUV_{max}				
Low (≤6.56)	75.8	0.456	75.8	0.147
High (6.56<)	68.5		61.0	
$MTV_{2.5}$ (cm^3)				
Low (≤25.31)	74.5	0.150	69.6	0.073
High (25.31<)	63.6		55.8	
$TLG_{2.5}$				
Low (≤200.48)	71.9	0.488	66.7	0.322
High (200.48<)	66.2		58.5	
$MTV_{42\%}$ (cm^3)				
Low (≤30.66)	72.3	0.058	66.5	0.038*
High (30.66<)	54.2		45.8	
$TLG_{42\%}$				
Low (≤139.77)	73.2	0.154	67.5	0.116
High (139.77<)	62.5		55.4	

*p<0.05 was statistically significant. SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

analysis, $MTV_{2.5}$ remained independently associated with DFS, while $MTV_{42\%}$ was associated only with 5-year DFS.

Demographic Findings and Tumor Characteristics

In studies evaluating postoperative recurrence rates have been reported to range from 25% to 37%. The associations between age, gender, comorbidities, and recurrence were variable across studies.[15-19] Taylor et al.[20] reported a significant association between tumor size, pathological stage, and recurrence in 1.143 patients with NSCLC. Tumors larger than 3 cm had a higher risk of recurrence. Other studies have similarly demonstrated an association between increased recurrence risk and both tumor size and pathological stage.[16,18,21] In our study, the recurrence rate was 38.5%. Age, gender, comorbidities were not significantly associated with recurrence. No significant association was found between pathological stage and recurrence. An unexpected finding of this study was the higher proportion of recurrence observed among patients with pathological stage I disease. This result should be interpreted with caution and is most likely attributable to selection bias inherent to the retrospective study design. However, a significant relationship was observed between tumor size and recurrence. The recurrence group had a larger tumor size. The lack of a significant association with pathological stage, despite the significance of tumor size, may be explained by limitations of the 7th TNM staging system in fully reflecting the prognostic impact of the T factor, which led to modifications of the T descriptor in the 8th TNM staging system.

Hung et al.[22] reported recurrence rates of 29.0% for PL1 and 48.1% for PL2 in 355 N0 patients with non-small cell lung cancer. PL2 involvement was associated with a significantly higher recurrence rate than PL1 involvement. Patients with VPI have significantly higher rates of postoperative recurrence than those without VPI.[19,23,24] In our study, consistent with the literature, the PL2 group showed a higher recurrence rate compared with patients without PL2 involvement. Additionally, the presence of VPI and PL2 involvement was associated with a higher recurrence rate.

18F-FDG PET/CT Findings of Tumor

Previous studies have reported considerable variability in the median values of metabolic parameters among stage I-II NSCLC patients undergoing curative surgery. Hyun et al.[11] reported median values of SUV_{max} 10.9, MTV 15.4 cm^3, and TLG 71.6, whereas Melloni et al.[25] found lower median values (SUV_{max} 6.5, MTV 2.95 cm^3, TLG 9.61). Agarwal et al.[9] reported a median SUV_{max} of 5.9, and Park et al.[12] reported mean values of SUV_{max} 4.55, MTV 5.92, and TLG 14.42 in stage I NSCLC. Previous studies have shown that primary tumor SUV_{max}, MTV, and TLG are significantly higher in patients with recurrence.[18,19,26] In our study, the median values of SUV_{max}, MTV and TLG differed from those reported in previous studies. In the overall analysis, no significant association was observed between PET derived metabolic parameters and recurrence. Several factors may explain this finding.

First, variability in SUV threshold values used to define MTV and TLG may influence the results. MTV can also be calculated independently of SUV threshold values. The most accurate method for determining MTV is manual delineation of tumor boundaries, in which lesion contours are drawn slice by slice to obtain the true tumor volume and achieve highly accurate results, potentially reducing tumor heterogeneity. However, this approach is time-consuming and not practical for routine clinical use. Another possible explanation is the influence of histopathological differences. Previous studies have shown that SCC is metabolically more active and has significantly higher SUV_{max}, MTV, and TLG values.[11,27,28] Based on this, we performed subgroup analyses in our study and observed that PET/CT-derived metabolic parameters differed between adenocarcinoma and SCC groups.

Interestingly, contrary to our expectations, $SUV_{max,}$ MTV, and TLG values were higher in the non-recurrence group among patients with adenocarcinoma, whereas these parameters were higher in the recurrence group in SCC. These differences can be explained by the histopathological characteristics of the tumors. FDG uptake is associated

with overexpression of glucose transporter-1 (GLUT-1), which is higher in SCC than in adenocarcinoma.[29,30] In addition, intratumoral heterogeneity and variations in tumor vascularity may contribute to these differences,[31] as angiogenesis is more pronounced in SCC.[32] Furthermore, heterogeneity within adenocarcinoma subtypes may explain the variability in our findings, as different histological patterns exhibit distinct metabolic behaviors and prognostic profiles.[33] Previous studies have reported that MTV and TLG derived from FDG PET/CT are independent prognostic factors in lung adenocarcinoma patients undergoing curative surgery.[34] In addition, higher SUV_{max}, MTV, and TLG values have been associated with an increased risk of recurrence in pathologically N0 lung adenocarcinoma patients.[18] However, in our study, no significant association was observed between these parameters and recurrence in the adenocarcinoma subgroup. In contrast, in our subgroup analyses, $MTV_{2.5}$ and $MTV_{42\%}$ were significantly higher in patients with recurrence in the SCC subgroup. These findings suggest that histopathological subtype may be relevant when interpreting PET/CT-derived metabolic parameters.

Univariate and Multivariate Cox Regression Analysis

Previous studies have shown that age, stage, tumor size, SUV_{max}, MTV, and TLG are significant prognostic factors for DFS in univariate analyses.[11,35] In univariate analyses, MTV and TLG have superior predictive performance for recurrence risk compared with SUV_{max}.[25,28] In our study, gender, presence of comorbidities, histological type, and pathological stage were not identified as prognostic factors for DFS. In contrast, tumor size, VPI, and PL2 involvement were significant prognostic markers, with recurrence risk increasing with larger tumor size and the presence of pleural invasion. Among the metabolic parameters, only $MTV_{42\%}$ was identified as a prognostic factor for recurrence in univariate analysis, with higher values (>30.66) associated with increased recurrence risk. In contrast to previous reports, SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$, and $TLG_{42\%}$ were not significant predictors.

In multivariate analyses, prognostic factors vary across studies. Some studies reported SUV_{max} as an independent prognostic factor,[36] whereas others found MTV or TLG as an independent prognostic factor of recurrence.[25,26,28,35] In our study, only $MTV_{2.5}$ remained independently associated with DFS. SUV_{max}, $MTV_{42\%}$, $TLG_{42\%}$, and $TLG_{2.5}$ were not associated with recurrence.

These findings may be explained by the limited discriminative performance of these parameters in our cohort. The AUC values for SUV_{max}, MTV, and TLG ranged between 0.53 and 0.55, indicating relatively low discriminative ability. These findings suggest that the selected cutoff values may have limited sensitivity and specificity when used alone for predicting recurrence.

Survival

High SUV_{max}, MTV, and TLG patients with high SUV_{max}, MTV, and TLG values had worse overall and 5-year survival rates, as well as recurrence rates.[11,13,21,25-27,34-38] In our study, the 5-year survival and 5-year DFS rates similar to those reported in the literature. However, the cutoff values used for the metabolic parameters varied among studies. In our study, only high MTV42% was associated with worse 5-year DFS. SUV_{max}, $MTV_{2.5}$, $TLG_{2.5}$ and $TLG_{42\%}$ were not associated with either 5-year survival or 5-year DFS.

Limitations

First, the retrospective, single-center design may have introduced selection bias. In addition, the absence of mortality in the non-recurrence group may further support the presence of selection bias in the study cohort. Second, standardized uptake values are influenced by various technical and biological factors, including partial volume effects, image resolution, reconstruction algorithms, image noise, the time interval between radiopharmaceutical injection and image acquisition, attenuation correction, normalization procedures, and plasma glucose levels. Third, the lack of standardized methods for calculating MTV and TLG is another limitation. Fourth, heterogeneity in histopathology subtypes may have affected the determination of prognostic factors. Fifth, tumor staging in this study was based on the 7th edition of the TNM classification system, which was the standard in routine clinical practice during the study period. The cohort consisted of patients treated between 2012 and 2016, allowing for adequate long-term follow-up to assess recurrence and survival outcomes. Although newer editions of the TNM classification and evolving treatment strategies have since been introduced, all patients in this study were staged uniformly according to a single system, ensuring internal consistency. Re-staging according to subsequent TNM editions was not feasible due to the retrospective design and limited availability of detailed data required for accurate reclassification. Therefore, the potential impact of temporal changes in staging and management should be considered when interpreting the generalizability of the findings. Finally, several established prognostic factors, including smoking history, lymphovascular invasion, spread through air spaces, molecular alterations (e.g., EGFR and ALK), and adjuvant treatment information, were not consistently available in the medical records and therefore could not be included in the analyses. The absence of these variables may have resulted in residual confounding and should be considered when interpreting the study findings.

CONCLUSION

In this cohort of patients with completely resected stage I-II NSCLC, larger tumor size, VPI, and PL2 involvement were associated with recurrence. $MTV_{2.5}$ was independently associated with DFS in one multivariable model, whereas its discriminatory performance for recurrence was limited. Therefore, these findings should be considered exploratory and require validation in larger, multicenter prospective cohorts before PET/CT-derived volumetric parameters can be incorporated into routine prognostic assessment.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Ethics Committee for Clinical Researches of the Ankara Keçiören Training and Research Hospital (Date: 12.06.2019, Decision No: 2012-KAEK-15/1915).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: EET, ÖÖ; Design: EET, ÖÖ; Control: EET; Data Collection and/or Processing: EET, ÖÖ; Analysis and/or Interpretation: EET; Literature Review: EET, ÖÖ, PAK, ŞMD; Article Writing: EET, ÖÖ, PAK, ŞMD; Critical Review: All Authors.

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Case Report

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Stepwise LMA-fiberoptic bronchoscopy-double-lumen tube airway management for one-lung ventilation in a young patient with pulmonary hydatid cyst: a case report

Mesher Ensarioğlu*[1], Ali Alagöz[2]

[1]*Department of Anesthesiology and Reanimation, Ankara Gülhane Training and Research Hospital, University of Health Sciences, Ankara, Turkiye*
[2]*Department of Anesthesiology and Reanimation, Ankara Atatürk Sanatorium Training and Research Hospital, University of Health Sciences, Ankara, Turkiye*

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***Corresponding Author:** Mesher Ensarioğlu, meshercapras@gmail.com

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ABSTRACT

Airway management in thoracic surgery becomes challenging when the underlying pathology affects the airway, with additional complexity introduced when one-lung ventilation is required for surgical access. This report describes a 19-year-old male with no prior health issues, in whom a routine pre-employment chest radiograph identified a mass in the right upper zone. Further imaging with thoracic computed tomography revealed a 15×7 cm lesion in the right upper lobe's posterior segment, leading to compression of the trachea. The patient was referred for video-assisted thoracoscopic evaluation with an initial diagnosis of cystic lung disease. An airway management plan was prepared preoperatively, including a laryngeal mask airway (LMA), fiberoptic bronchoscope (FOB), bronchial blocker, and double-lumen tube (DLT). After standard monitoring, preoxygenation, and induction with midazolam, fentanyl, and propofol, an LMA was placed, and FOB examination showed near-complete extraluminal obstruction of the right main bronchus, with the left main bronchus remaining patent. The patient underwent video-assisted thoracoscopic surgery (VATS) for cyst resection, and postoperative analgesia was provided via ultrasound-guided erector spinae plane block (ESPB). Histopathological examination of the resected material confirmed the diagnosis of pulmonary hydatid cyst. This step-by-step approach, utilizing LMA, FOB, and DLT sequentially, can effectively maintain airway security in cases where mass-related airway compression complicates lung isolation during thoracic procedures.

Keywords: Airway management, one-lung ventilation, bronchoscopy, pulmonary hydatid cyst, echinococcosis

INTRODUCTION

Airway management in thoracic surgery plays a paramount role in overall patient care, especially in cases requiring one-lung ventilation; proper airway control is required before an intervention can be performed.[1,2] While it is possible for cases operated on for parenchymal pathologies to be managed relatively similarly to each other, when a patient is to be operated on for an airway pathology, the airway management itself may be difficult.[3] This issue becomes more prominent when one-lung ventilation is required for the procedure itself, further complicating the already difficult approach. In this case report, airway management of with a bronchopleural mass will be presented.

CASE

A 19-year-old male patient with no known diseases was evaluated for an initial workplace health check-up at 175 cm height and 56 kg weight. In the requested routine chest x-ray, a mass was present on the right upper zone and the patient was referred to a hospital for further evaluation. At the investigation performed at the referred hospital, a computed thorax tomography was performed, in which a 15×7 cm mass in the right upper lobe posterior segment was reported, causing mass compression on the trachea and near-complete narrowing of the right main bronchus (**Figure 1**, **2**). The patient was then referred to our centre for diagnostic and therapeutic evaluation, with an initial video-assisted thoracoscopy (VATS) plan.

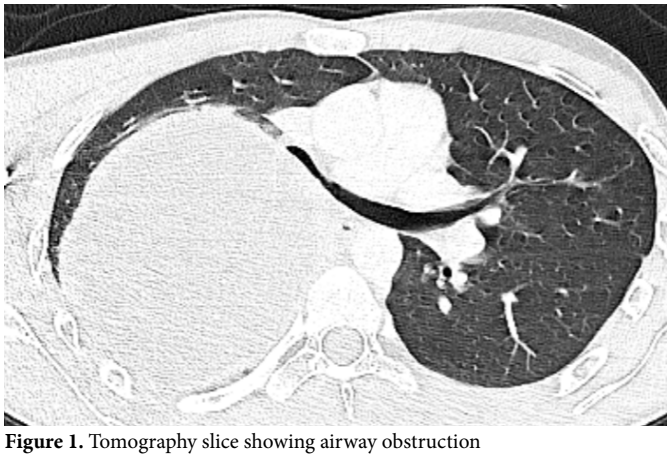

Figure 1. Tomography slice showing airway obstruction
The tomography slide presents an evident obstruction in the right main bronchus

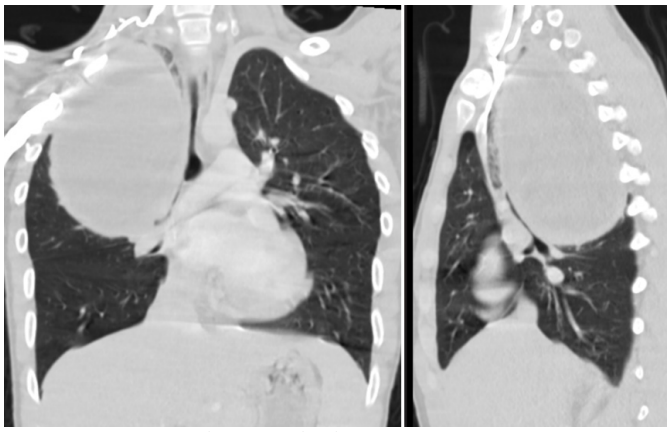

Figure 2. Reconstructed tomography slices

Reconstructed tomography slides show obstruction at the tracheal level, which also limits access to right lung structures. The mass occupies most of the right upper lobe

The patient was preoperatively evaluated at the anesthesia outpatient clinic. He was asymptomatic, with no dyspnoea, stridor, cough or positional symptoms and unrestricted exercise tolerance. Peripheral oxygen saturation on room air was 96%, and complete blood count, biochemistry and coagulation parameters were all within normal limits. Airway examination revealed a Mallampati class 2 oropharyngeal view, an upper lip bite test of class 1 and unrestricted head and neck movement, with no predictors of difficult facemask ventilation. Pulmonary function testing and preoperative arterial blood gas analysis were not obtained: the patient was young, asymptomatic and functionally stable.

A preoperative pulmonary risk score was calculated: the ARISCAT index yielded 47 points, comprising 24 points for the intrathoracic approach and 23 points for an operative duration exceeding three hours, with age ≤50 years, absence of respiratory infection in the preceding month, absence of anemia, a preoperative room-air SpO_2 of 96%, and non-emergency surgery each contributing no points. Hydatid disease was not the leading preoperative consideration; thus, serological testing (indirect haemagglutination or ELISA) was consequently not performed before surgery. After planning with senior anesthesiology consultants, the patient was given an ASA score of II and airway equipment additional to the double lumen tube (DLT) was considered for detailed investigation of the airway and lung separation, including laryngeal mask airway (LMA), fiberoptic bronchoscopy (FOB) and bronchial blocker, was prepared.

After standard ASA monitorization and preoxygenation, IV 2 mg midazolam, 1 mcg/kg fentanyl, and 2 mg/kg propofol were given intravenously for induction. LMA was then introduced for airway preservation and FOB was utilized through it to investigate the nature of the mass and if the airway would be adequate for double-lumen tube (DLT) lung separation. If the airway later was to be determined insufficient for DLT, a bronchial blocker would have been used. FOB revealed that the right main bronchus was mostly obstructed by extra-luminal compression, while the left main bronchus was spared with adequate lumen preservation. The LMA was then removed, facemask ventilation was performed successfully, and after rocuronium 0.6 mg/kg and an additional 100 mg propofol intravenously, a 39 Fr left-sided DLT was inserted. The tube size was chosen to minimize airway trauma. DLT placement was confirmed by FOB, and lung separation was confirmed by deflation of the right lung.

During one-lung ventilation, volume-controlled ventilation was delivered according to lung-protective principles, with a tidal volume of 4-6 ml/kg ideal body weight, 5 cmH_2O of positive end-expiratory pressure, and plateau inspiratory pressure maintained below 30 cmH_2O. The inspired oxygen fraction was titrated to the lowest value that maintained peripheral oxygen saturation above 92%. At the conclusion of surgery, a manual recruitment maneuver was performed, sustaining an inspiratory pressure of 30 cmH_2O for 10 seconds.

VATS was then performed to preserve the cyst's location. On thoracoscopic inspection, the lesion appeared as a smooth, white cyst with a tense surface, an appearance characteristic of hydatid disease. This led to a preliminary diagnosis of pulmonary hydatid cyst and prompted the surgical team to isolate the operative field before any manipulation of the lesion. Methylprednisolone 1 mg/kg and pheniramine hydrogen maleate 45.5 mg were then administered intravenously as prophylaxis against an anaphylactic reaction, and adrenaline, vasopressors and intravenous fluids were prepared and immediately available.

Thoracotomy under VATS imaging was then performed for cyst localization and resection. Following field isolation, the cyst contents were aspirated in a controlled manner, and the germinative membrane was removed intact (**Figure 3**). There was no uncontrolled spillage and no allergic, respiratory, or hemodynamic disturbance at any point. The total operative duration was four hours. After completion of the surgical intervention, an ultrasonography-guided erector spinae plane block (ESPB) was used for analgesia. Sugammadex was used to reverse neuromuscular blockade. The patient was extubated after confirmation of spontaneous respiration with sufficient tidal volume and spontaneous eye opening. The patient was then admitted to the thoracic surgery intensive care unit as part of routine follow-up. Histopathological examination of the resected material confirmed the diagnosis of pulmonary hydatid cyst. The postoperative course was uneventful, with no respiratory complications.

Figure 3. Intraoperative appearance of the excised hydatid membrane

The germinative (laminated) membrane of the pulmonary hydatid cyst, removed after controlled aspiration of the cyst contents and shown in a surgical dish. The smooth, avascular, pearly-white membrane is characteristic of Echinococcus granulosus and supported the intraoperative diagnosis, which was subsequently confirmed by histopathological examination

DISCUSSION

Proper airway management plays a crucial role in patients undergoing surgical interventions, especially so in the cases of hydatid cysts and similar infectious causes that require not only one-lung ventilation but also local control of the disease during the procedure to prevent complications.[4] The need for one-lung ventilation itself brings some possible complications to the table, among which some may be caused by the utilized double-lumen intubation tube and possible airway trauma caused by it.[2,3] However, the advantages given by one-lung ventilation, which not only allows one thoracic side to be operated on but also, in the case of hydatid cyst, keeps the other lung safe from possible ruptures, often outweighs the disadvantages.

The justification of resection in hydatid cyst is mainly the control of the disease and to provide a curative approach. However, due to the disease's symptoms being non-specific, the initial approach would be same to any cystic disease of the lung.[5] In case of hydatic diseases, the local control of the disease is essential, and like reported in our case, further imaging even intraoperative may be required for a differential diagnosis.[4,6] In the present case, hydatid disease was not the leading preoperative consideration; the patient was referred with a working diagnosis of cystic lung disease, and serological testing was therefore not obtained before surgery. Suspicion in our patient was first raised by the thoracoscopic appearance of the lesion and the diagnosis was ultimately established by histopathological examination of the resected material.

Supraglottic airway devices have been routinely used in anaesthesiology for ease of maintaining the airway during short-lasting procedures. The approach to a possibly occluded airway requires further expertise in airway management and often demands multiple combinations of methods.[7] Awake intubation or utilization of LMA and other supraglottic devices before intubation have been successfully used, with the combination of fiberoptic intubation and LMA being defined as a handy technique for anticipated complex cases, as was our case.[8]

Operations on pulmonary hydatid cysts have routinely been performed with double-lumen endotracheal tubes, as reported in the literature, and with an emphasis on possible anaphylaxis. In a study by Tercan et al.,[9] six patients out of 393 had an allergic reaction, including anaphylaxis, in the peri-operative period. One of the six patients was lost despite antihistaminic corticosteroid and vasopressor treatment.[9] An additional benefit of DLT intubation was reported in a case report: the isolation of the operated lung prevented the spill-over of an intraoperative cyst rupture, in which the patient also had pneumothorax of the contralateral lung. As stated by the authors, the management of this case would not have been possible under single-tube lumen intubation.[10] Gupta et al.[11] also reported a similar case and suggested that, mainly due to positive pressure ventilation, small fragments of a ruptured cyst could have lodged in the contralateral lung without the protective effect of DLT. Given this risk, prophylaxis with methylprednisolone and pheniramine was administered before surgical manipulation in our patient, and vasoactive drugs and intravenous fluids were prepared in advance. This proved a reasonable precaution, since definitive treatment required deliberate puncture and aspiration of the cyst.

One-lung ventilation in this setting was conducted according to lung-protective principles, with a reduced tidal volume, applied positive end-expiratory pressure and the lowest inspired oxygen fraction compatible with adequate saturation. Tidal volumes of 4-5 ml/kg predicted body weight with 5-10 cmH_2O of PEEP and routine recruitment are currently recommended to limit ventilator-induced lung injury.[12]

CONCLUSION

A combined approach using appropriate airway equipment and a clear sequence is required to control any possible complications arising from difficult anatomical positioning and mass-related issues. In this case, the airway of a patient with a mass of unknown origin was properly managed, with the airway adequately secured without interfering with the mass. A step-by-step approach using an LMA, FOB, and a left-sided DLT was carefully implemented. Overall, airway management remains a vital component of the approach for patients with a mass of unknown origin.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

This case report did not receive any financial support.

Author Contributions

Concept: ME, AA; Design: ME, AA; Control/Supervision: AA; Data Collection and/or Processing: ME; Analysis and/or Interpretation: ME, AA; Literature Review: ME; Article Writing: ME; Critical Review: All Authors.

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Letter to the Editor

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Comment on: The relationship between troponin levels in pneumonia and the severity of pneumonia and the oxidant-antioxidant balance

Fatih Alper Ayyıldız

Department of Emergency Medicine, Eskişehir City Hospital, Eskişehir, Turkiye

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Corresponding Author: Fatih Alper Ayyıldız, dralperayyildiz@gmail.com

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Keywords: Troponin, pneumonia, oxidative stress

Dear Editor,

I read with great interest the recent article by Öner and Karalezli[1] evaluating the relationship between troponin levels, oxidative stress markers, and pneumonia severity. The authors should be commended for addressing an important and relatively underexplored aspect of pneumonia pathophysiology, particularly the integration of cardiac biomarkers and redox balance into clinical assessment.

From the perspective of an emergency physician, the identification of readily available biomarkers that may aid in early risk stratification is of substantial clinical value. The observed association between elevated troponin levels and increasing Pneumonia Severity Index (PSI) stages is consistent with prior evidence suggesting that myocardial injury frequently accompanies severe infection and systemic inflammatory states, including sepsis.[2] In this context, troponin elevation may reflect not only primary cardiac pathology but also secondary myocardial stress related to hypoxia, inflammation, and hemodynamic instability.

However, an important consideration in emergency department practice is the limited specificity of troponin elevation. As highlighted in previous literature, cardiac troponins may be elevated in a wide range of non-coronary conditions, including pulmonary and systemic diseases, which can complicate clinical interpretation and decision-making.[3] Therefore, while the findings of the present study are clinically intriguing, the routine use of troponin as a standalone marker for pneumonia severity should be approached with caution, particularly in heterogeneous emergency populations.

The inclusion of oxidative stress parameters, such as thiol–disulfide balance and ischemia-modified albumin, represents a novel and valuable aspect of the study. Increasing evidence suggests that oxidative stress plays a significant role in the pathophysiology and progression of community-acquired pneumonia.[4] The demonstration of altered redox homeostasis in parallel with disease severity provides additional insight into the underlying biological processes and may contribute to a more comprehensive assessment framework.

From a practical standpoint, however, the applicability of these biomarkers in the emergency setting remains uncertain. Unlike troponin, measurements such as thiol–disulfide balance and ischemia-modified albumin are not routinely available in most emergency departments, which may limit their immediate clinical utility. In time-critical environments where rapid decision-making is essential, biomarkers must not only be informative but also accessible and cost-effective.

In addition, established clinical prediction tools such as PSI and CURB-65, although imperfect, remain the cornerstone of risk stratification in pneumonia. Prior studies have demonstrated that the addition of novel biomarkers may improve prognostic accuracy, but this incremental benefit must be weighed against practicality and clinical impact.[5]

In conclusion, this study provides valuable insight into the interplay between myocardial injury, oxidative stress, and pneumonia severity. While the findings are promising, further large-scale, prospective studies are needed to clarify the clinical role and added value of these biomarkers in emergency care settings. I thank the authors for their contribution to this evolving field.

ETHICAL DECLARATIONS

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The author declares no conflicts of interest.

Financial Disclosure

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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Journal of
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Author reply to "The relationship between troponin levels in pneumonia and the severity of pneumonia and the oxidant-antioxidant balance"

Sevil Öner*[1], Ayşegül Karalezli[2]

[1]*Department of Pulmonary Diseases, Yenimahalle Training and Research Hospital, Ankara, Turkiye*
[2]*Department of Pulmonary Diseases, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Turkiye*

Dear Editor,

We would like to thank the author for their thoughtful and constructive comments on our study entitled "The relationship between troponin levels in pneumonia and the severity of pneumonia and the oxidant-antioxidant balance." We are pleased that the clinical relevance of integrating cardiac biomarkers and oxidative stress parameters in pneumonia has been recognized.

We fully agree with the comment regarding the limited specificity of cardiac troponins. As emphasized both in our discussion and in previous literature, troponin elevation is not specific to acute coronary syndromes and may occur in a variety of conditions, including systemic infections and pulmonary diseases. In our study, we aimed to minimize this limitation by excluding patients with acute coronary syndrome, renal failure, and other major confounding conditions. Moreover, our primary objective was not to propose troponin as a standalone diagnostic marker, but rather to evaluate its association with disease severity in the context of pneumonia. In this regard, we believe that the observed correlation between troponin levels and PSI stages supports its potential role as an adjunctive biomarker reflecting systemic disease burden and possible myocardial involvement.

We also appreciate the emphasis on the challenges of clinical interpretation in emergency settings. We agree that, due to its limited specificity, troponin should be interpreted cautiously and always in conjunction with clinical findings, imaging, and other laboratory parameters. Our findings should therefore be considered as hypothesis-generating rather than practice-changing.

Regarding oxidative stress markers, we agree that parameters such as thiol–disulfide balance and ischemia-modified albumin are not yet routinely available in most emergency departments. The primary aim of including these markers was to provide a more comprehensive pathophysiological perspective by demonstrating the relationship between oxidative stress and disease severity. While their immediate clinical applicability may be limited, we believe that these findings may contribute to future research exploring more accessible or standardized oxidative stress markers.

We also concur that established clinical scoring systems such as PSI and CURB-65 remain the cornerstone of pneumonia risk stratification. Our intention was not to replace these tools but to explore whether additional biomarkers could complement existing systems. As noted, the incremental clinical value of such biomarkers should be validated in larger, prospective, and multicenter studies.

Finally, we agree that further large-scale studies are needed to clarify the clinical utility, cost-effectiveness, and practical integration of these biomarkers into routine care. Our study should be viewed as an initial step toward better understanding the complex interaction between myocardial injury, oxidative stress, and pneumonia severity.

We thank the author again for their valuable comments and for contributing to the scientific discussion in this evolving field.

Sincerely,