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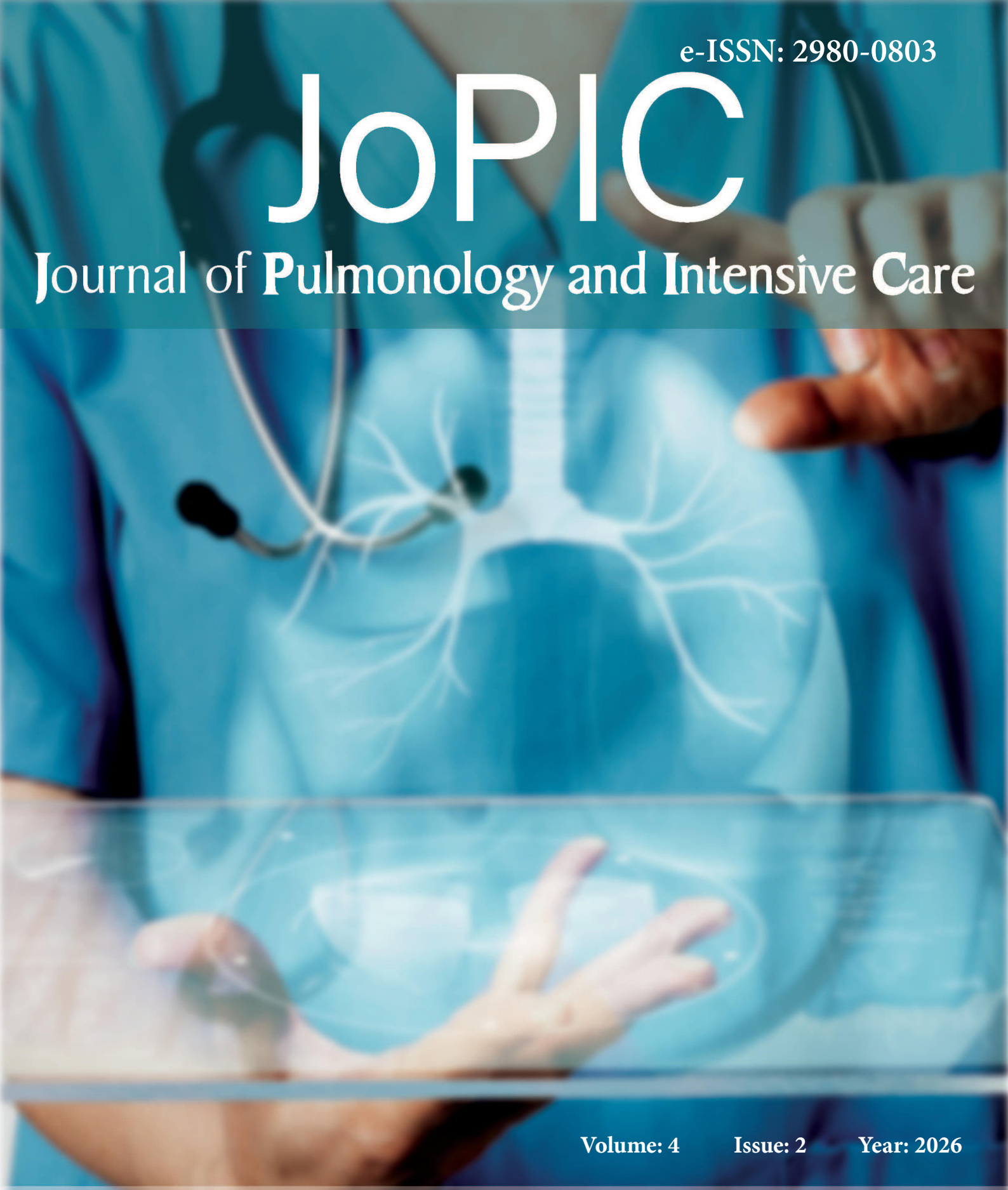

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## ORIGINAL ARTICLES



## CASE REPORT

Journal of
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Original Article

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# Incidence and prognostic value of COVID-19-associated coagulopathy in intensive care unit patients: a retrospective cohort study

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## ABSTRACT

**Aims:** COVID-19-associated coagulopathy (CAC) is a critical complication contributing to mortality in critically ill patients. The prognostic utility of established scoring systems like Sepsis-Induced Coagulopathy (SIC) and Disseminated Intravascular Coagulation (DIC) in this specific context requires further elucidation. This study aimed to determine the incidence, associated risk factors, and mortality impact of CAC in intensive care unit (ICU) patients, and to evaluate the predictive performance of SIC and DIC scores.

**Methods:** A single-center, retrospective cohort study was conducted on 320 consecutive COVID-19 patients admitted to the ICU between March 2020 and December 2021. Coagulopathy was defined as a DIC score ≥5 or SIC score ≥4 at any point during ICU stay. Demographic, clinical, and laboratory data were analyzed. Predictive values for mortality were assessed using receiver operating characteristic (ROC) curve analysis.

**Results:** The incidence of CAC was 39.1% (n=125). Patients with coagulopathy had significantly lower platelet counts and elevated PT, APTT, INR, D-dimer, ferritin, CRP, creatinine, LDH, and IL-6 levels on admission (all $p<0.05$). Mortality was markedly higher in the coagulopathy group (79.8% vs. 42.4%, $p<0.001$). A strong positive correlation was found between DIC and SIC scores at all time points (Day 1: $r=0.434$; Day 7: $r=0.524$; Day 14: $r=0.686$; all $p<0.001$). Both scores were significant predictors of mortality; the DIC score demonstrated a superior predictive ability with an area under the curve (AUC) of 0.85 (95% CI: 0.79-0.90), compared to an AUC of 0.81 (95% CI: 0.75-0.87) for the SIC score.

**Conclusion:** CAC is prevalent in critically ill COVID-19 patients and is independently associated with a near-doubling of mortality risk. The DIC and SIC scores are valuable, correlated tools for risk stratification, with the DIC score showing a stronger predictive value for mortality. These findings underscore the necessity of early identification and aggressive, individualized management of coagulopathy in this patient population.

**Keywords**: COVID-19, coagulopathy, disseminated intravascular coagulation, sepsis-induced coagulopathy, intensive care, predictive scoring

## INTRODUCTION

COVID-19 is recognized not only as a respiratory tract infection but also as a systemic disease with multisystemic effects. One of its most significant complications, COVID-19-associated coagulopathy (CAC), substantially increases mortality.[1] Studies indicate that thrombocytopenia, elevated D-dimer, and fibrinolytic imbalances serve as key biomarkers of CAC.[2] The Sepsis-Induced Coagulopathy (SIC) and Disseminated Intravascular Coagulation (DIC) scores are considered important tools for determining the severity of CAC and patient prognosis.[3] The cytokine storm triggered by COVID-19 induces endothelial damage and microvascular thrombosis, thereby activating the coagulation cascade.[4] This study aimed to investigate the incidence, risk factors, and prognostic value of CAC, specifically evaluating the utility of SIC and DIC scores, in a cohort of critically ill COVID-19 patients.

## METHODS

### Ethics

This study was conducted with the approval of the Ethics Committee of the Ankara Training and Research Hospital, University of Health Sciences (Date: 22.12.2021, Decision No: E-93471371-514.01.99). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Study Design
This study was conducted as a single-center, retrospective cohort study. The study included COVID-19 patients who were monitored and treated at the Intensive Care Unit (ICU) of the Ankara Training and Research Hospital, University of Health Sciences between March 2020 and December 2021.

### Patient Selection
Patients aged over 18 years who were followed in the intensive care unit, with a COVID-19 diagnosis confirmed by polymerase chain reaction (PCR) test and with no known history of coagulopathy, were included in the study.

### Data Collection and Evaluation
The demographic data of the included patients (age, sex, body mass index [BMI], history of comorbidities, smoking/alcohol use, COVID-19 vaccination status, time from diagnosis to ICU admission) were retrospectively reviewed. Clinical scoring (APACHE-II and SOFA) at the time of ICU admission and on the 7$^{th}$ and 14$^{th}$ days of hospitalization was retrospectively evaluated.

### Definition of Coagulopathy and Scoring
The DIC Score and the SIC Score were calculated at ICU admission and on days 7 and 14, in accordance with the criteria established by the International Society on Thrombosis and Haemostasis (ISTH).[5,6] Consistent with the ISTH's diagnostic guidance for overt DIC and the recent consensus definitions for SIC, a DIC Score of ≥5 and/or an SIC Score of ≥4 at any point during the ICU stay was considered indicative of COVID-19-CAC.[5,7] These thresholds were chosen as they represent the validated cut-off values for defining overt coagulopathy in critically ill patient populations and have been widely adopted in COVID-19 research to identify patients at highest risk of thrombotic complications and mortality.[8,9] The assessment at "any point during ICU stay" was employed to capture the dynamic nature of CAC, which may develop or resolve over the course of the critical illness, as recommended in longitudinal studies of critically ill patients.[10] The incidence of coagulopathy, mortality rates, and the factors influencing them were retrospectively analyzed.

### Statistical Analysis
The dataset was complete for all primary outcome variables and key laboratory parameters used in the analysis (including D-dimer, platelet count, PT, aPTT, INR, fibrinogen, and inflammatory markers). Therefore, no imputation methods were required, and all 320 patients were included in the final analyses without exclusions due to missing data.

All data were analyzed using SPSS 22.0 statistical software (IBM Corp., Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation and median (minimum-maximum). Categorical variables were presented as numbers (%). The normality of continuous variables was assessed using the Shapiro-Wilk test. For continuous variables not following a normal distribution, the Mann-Whitney U test was used. For comparison of categorical variables, the Chi-square test or Fisher's Exact Test was applied. Receiver Operating Characteristic (ROC) analysis was used to determine the predictive value of the scores for mortality. Correlation between continuous variables was analyzed using Spearman's correlation test. A p-value<0.05 was considered statistically significant.

To identify independent risk factors associated with mortality, univariate and multivariate logistic regression analyses were performed. Variables with a p-value<0.10 in univariate analysis were included in the multivariate model. Backward stepwise elimination method was used to select the final model. The goodness-of-fit of the logistic regression model was assessed using the Hosmer-Lemeshow test. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Due to the high correlation between DIC and SIC scores (r=0.686, p<0.001), separate multivariate models were constructed for each score to avoid multicollinearity. The discriminative performance of the models was evaluated using ROC analysis, and the area under the curve (AUC) was calculated. In the final model, p<0.05 was considered statistically significant.

## RESULTS
The mean age of the patients included in the study (**Table 1**) was 68.02±16.29 years, with an equal gender distribution (female 50.0%; male 50.0%). Hypertension (55.6%) and diabetes mellitus (37.2%) were the most frequently observed comorbidities. It was determined that

**Table 1.** Demographic data

| Variable | Value (n=320) |
|---|---|
| Age (years) | 68.02±16.29 |
| Gender | |
| Female | 160 (50.0%) |
| Male | 160 (50.0%) |
| BMI (kg/m²) | 28.03±6.79 |
| Obesity | |
| Yes | 49 (15.3%) |
| No | 271 (84.7%) |
| Comorbidities | |
| Hypertension | 178 (55.6%) |
| Diabetes mellitus | 119 (37.2%) |
| Pulmonary disease | 70 (21.9%) |
| Coronary artery disease | 64 (20.0%) |
| Chronic kidney disease | 36 (11.3%) |
| Cancer/immunological disease | 20 (5.8%) |
| Smoking | 7 (2.2%) |
| Alcohol use | 3 (0.9%) |
| COVID-19 vaccination status | |
| Unknown | 12 (3.7%) |
| None | 124 (38.8%) |
| 1 dose | 15 (4.7%) |
| ≥2 Doses | 169 (52.8%) |
| Time from diagnosis to ICU admission (days) | 1 (1-23) |
| SOFA score (admission) | 2 (1-10) |
| APACHE II score (admission) | 11 (2-30) |

BMI: Body-mass index, ICU: Intensive care unit, SOFA: Sequential Organ Failure Assessment, APACHE II: Acute Physiology and Chronic Health Evaluation II, Data are presented as mean±standard deviation, median (min-max), or number (%)

52.8% of the patients had received at least two doses of the COVID-19 vaccine.

In patients who developed coagulopathy (Table 2), platelet count was significantly lower (p=0.031), while prothrombin time (PT) (p<0.001), activated partial thromboplastin time (APTT) (p=0.007), international normalized ratio (INR) (p<0.001), D-dimer (p<0.001), ferritin (p<0.001), C-reactive protein (CRP) (p=0.005), creatinine (p<0.001), lactate dehydrogenase (LDH) (p<0.001), and interleukin-6 (IL-6) (p=0.008) levels were significantly higher.

**Table 2.** Comparison of laboratory results at intensive care unit admission between patients who developed coagulopathy (n=125) and those who did not (n=195)

| Parameter | No coagulopathy (n: 195) median (min-max) | | Coagulopathy (n: 125) median (min-max) | | p-value |
|---|---|---|---|---|---|
| Leukocyte (×10³/μL) | 8.7 | 1.5-26.0 | 9.9 | 1.3-39.0 | 0.102 |
| Lymphocyte (×10³/μL) | 0.66 | 0.10-18.0 | 0.61 | 0.10-6.9 | 0.192 |
| Neutrophil (×10³/μL) | 7.2 | 1.1-24.0 | 8.3 | 0.15-37.0 | 0.069 |
| Hemoglobin (g/dl) | 12.7 | 6.3-44.8 | 12.0 | 5.8-44.7 | 0.174 |
| Hematocrit (%) | 39 | 19-59 | 38 | 15-68 | 0.208 |
| Platelet (×10³/μL) | 218 | 47-692 | 189 | 12-598 | 0.031 |
| PT (s) | 14.0 | 11.0-44.4 | 16.0 | 12.0-44.4 | <0.001 |
| APTT (s) | 32.0 | 21.0-62.0 | 33.0 | 21.6-73.0 | 0.007 |
| INR | 1.02 | 0.80-4.4 | 1.20 | 0.90-4.4 | <0.001 |
| D-dimer (μg/L) | 690 | 70-43.810 | 1.400 | 110-81.990 | <0.001 |
| Fibrinogen (mg/dl) | 550 | 222-1.131 | 550 | 76-942 | 0.199 |
| Ferritin (ng/ml) | 512 | 14-12.367 | 832 | 16-16.900 | <0.001 |
| CRP (mg/L) | 79 | 1-390 | 98 | 0.1-412 | 0.005 |
| Procalcitonin (ng/ml) | 0.4 | 0.1-45.0 | 0.29 | 0.1-100.0 | 0.207 |
| ESR (mm/h) | 41 | 2-148 | 43 | 1-140 | 0.838 |
| Creatinine (mg/dl) | 0.9 | 0.8-8.0 | 1.1 | 0.2-7.7 | <0.001 |
| Albumin (g/L) | 34.0 | 17.0-46.0 | 31.0 | 18.0-46.0 | <0.001 |
| AST (U/L) | 30.0 | 6.0-300.0 | 34.0 | 2.0-15.400.0 | 0.343 |
| ALT (U/L) | 22.0 | 1.0-263.0 | 23.0 | 2.0-1.452.0 | 0.691 |
| LDH (U/L) | 400 | 60-1.56 | 482 | 163-5.398 | <0.001 |
| IL-6 (pg/ml) | 33 | 2-5.000 | 62 | 4-5.000 | 0.008 |
| Lactate (mmol/L) | 1.6 | 0-24.0 | 1.7 | 0-24.0 | 0.018 |

PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, IL-6: Interleukin-6. Statistical test: Mann Whitney U test. Bold values indicate statistical significance (p<0.05)

The changes in the coagulopathy scores of the patients on days 1, 7, and 14 are shown in Figures 1 and 2. It was observed that the DIC and SIC scores decreased over time. The distribution of coagulopathy incidence by day is presented in Figure 3.

Table 3 presents a significant correlation found between the DIC and SIC scores (Day 1: r=0.434, p<0.001; Day 7: r=0.524, p<0.001; Day 14: r=0.686, p<0.001). This finding indicates that both scoring systems can support each other in the assessment of coagulopathy.

Out of a total of 320 patients, 125 (39.1%) developed coagulopathy. The mortality rate was significantly higher in the coagulopathy group (79.8% [100/125]) compared to the non-coagulopathy group (42.4% [83/195]) (p<0.001) (Table 4).

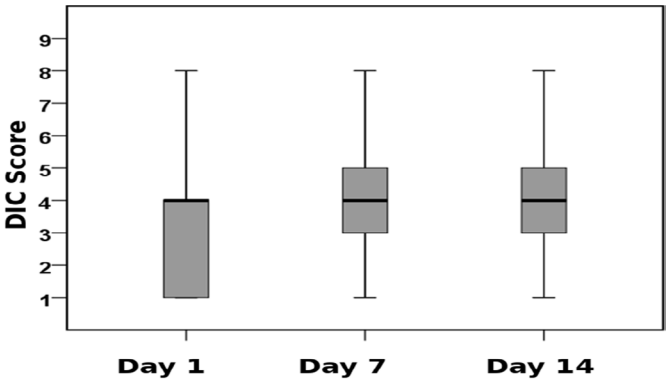


**Figure 1.** Disseminated Intravascular Coagulopathy (DIC) score on days 1, 7, and 14

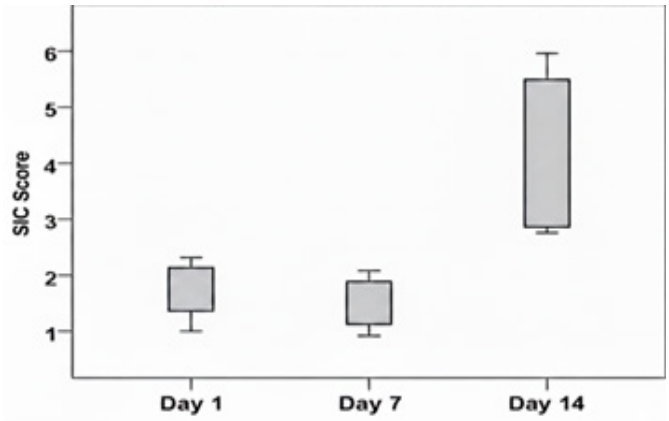


**Figure 2.** Time course of the Sepsis-Induced Coagulopathy (SIC) score on days 1, 7, and 14 in intensive care unit patients with COVID-19

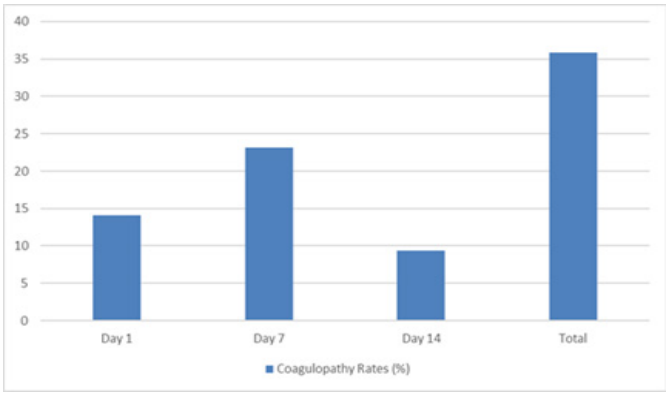


**Figure 3.** Incidence of COVID-19-associated coagulopathy among intensive care unit patients on days 1, 7, and 14 of hospitalization

**Table 3.** Correlation between DIC and SIC scores

| Time point | Correlation coefficient (r) | p-value |
|---|---|---|
| Day 1 | 0.434 | <0.001 |
| Day 7 | 0.524 | <0.001 |
| Day 14 | 0.686 | <0.001 |

DIC: Disseminated Intravascular Coagulation, SIC: Sepsis-Induced Coagulopathy. Statistical test: Spearman's rank correlation test

**Table 4.** Mortality rates according to coagulopathy status

| Coagulopathy status | Number of patients (n) | Mortality, n (%) | p-value |
|---|---|---|---|
| Present | 125 | 100 (79.8%) | <0.001 |
| Absent | 195 | 83 (42.4%) | |
| Total | 320 | 183 (57.2%) | |

This finding demonstrates that COVID-19-CAC substantially increases the risk of mortality in ICU patients.

The AUC value of the SIC score (**Figure 4**) for predicting mortality was calculated as 0.81 (95% CI: 0.75-0.87, p<0.001). This result indicates that the SIC score has good predictive value for mortality estimation.

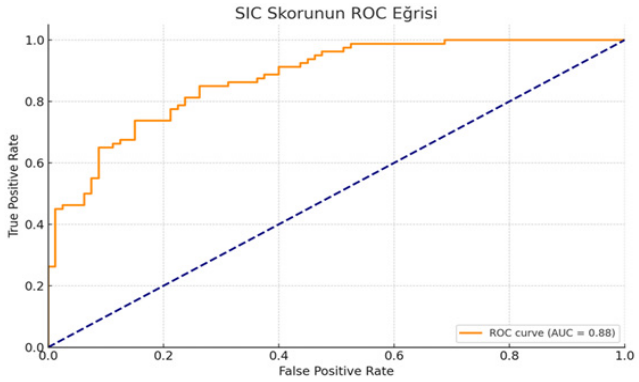


**Figure 4.** Receiver operating characteristic (ROC) curve for the predictive value of the Sepsis-Induced Coagulopathy (SIC) score in forecasting mortality

For the DIC score (**Figure 5**), the AUC value was found to be 0.85 (95% CI: 0.79-0.90, p<0.001). This result indicates that the DIC score has a stronger ability to predict mortality compared to the SIC score.

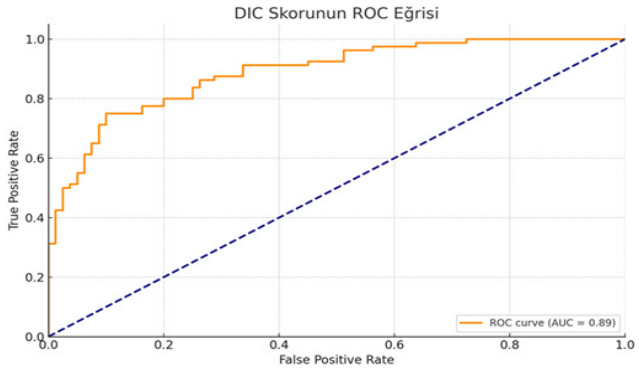


**Figure 5.** Receiver operating characteristic (ROC) curve for the predictive value of the Disseminated Intravascular Coagulation (DIC) score in forecasting mortality

In patients who died (**Table 5**), both DIC and SIC scores on days 1, 7, and 14 were significantly higher (p<0.001 for all).

**Table 5.** Distribution of DIC and SIC scores on days 1, 7, and 14 according to mortality status

| Score | Survivors (n:137) (mean±SD) | Non-survivors (n:183) (mean±SD) | p-value |
|---|---|---|---|
| Day 1 DIC score | 2.77±1.48 | 3.47±1.54 | <0.001 |
| Day 7 DIC score | 3.46±1.40 | 4.65±1.58 | <0.001 |
| Day 14 DIC score | 3.25±1.53 | 4.74±1.39 | <0.001 |
| Day 1 SIC score | 2.03±0.89 | 2.71±1.13 | <0.001 |
| Day 7 SIC score | 1.47±0.76 | 2.69±0.95 | <0.001 |
| Day 14 SIC score | 2.29±1.17 | 3.26±1.31 | <0.001 |

SD: Standard deviation, DIC: Disseminated Intravascular Coagulation, SIC: Sepsis-Induced Coagulopathy

## Multivariate Analysis of Mortality Risk Factors

Univariate logistic regression analysis was performed to identify potential risk factors associated with mortality. The analysis revealed that age (OR: 1.05, 95% CI: 1.03-1.07, p<0.001), hypertension (OR: 1.62, 95% CI: 1.08-2.43, p=0.020), diabetes mellitus (OR: 1.53, 95% CI: 1.01-2.32, p=0.045), chronic kidney disease (OR: 1.92, 95% CI: 1.02-3.61, p=0.043), DIC score (OR: 1.92, 95% CI: 1.58-2.33, p<0.001), SIC score (OR: 2.28, 95% CI: 1.82-2.86, p<0.001), APACHE II score (OR: 1.14, 95% CI: 1.09-1.19, p<0.001), SOFA score (OR: 1.32, 95% CI: 1.19-1.46, p<0.001), D-dimer >2000 µg/L (OR: 3.24, 95% CI: 2.08-5.05, p<0.001), platelet count <150,000/mm³ (OR: 2.58, 95% CI: 1.63-4.08, p<0.001), PT >14 sec (OR: 2.34, 95% CI: 1.53-3.58, p<0.001), CRP >100 mg/L (OR: 1.84, 95% CI: 1.22-2.77, p=0.003), LDH >500 U/L (OR: 2.06, 95% CI: 1.36-3.12, p=0.001), IL-6 >50 pg/ml (OR: 2.42, 95% CI: 1.58-3.71, p<0.001), and ferritin >1000 ng/ml (OR: 1.98, 95% CI: 1.31-2.99, p=0.001) were significantly associated with mortality (**Table 6**).

**Table 6.** Univariate and multivariate logistic regression analysis for factors associated with mortality

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Age (per year) | 1.05 (1.03-1.07) | <0.001 | 1.04 (1.02-1.06) | <0.001 |
| Gender (male) | 1.28 (0.86-1.91) | 0.224 | - | - |
| Hypertension | 1.62 (1.08-2.43) | 0.020 | 1.48 (0.94-2.33) | 0.089 |
| Diabetes mellitus | 1.53 (1.01-2.32) | 0.045 | 1.39 (0.87-2.22) | 0.168 |
| COPD | 1.41 (0.86-2.31) | 0.175 | - | - |
| Coronary artery disease | 1.38 (0.84-2.27) | 0.203 | - | - |
| Chronic kidney disease | 1.92 (1.02-3.61) | 0.043 | 1.58 (0.79-3.16) | 0.197 |
| DIC score (day 1, per point) | 1.92 (1.58-2.33) | <0.001 | 1.68 (1.34-2.11) | <0.001 |
| SIC score (day 1, per point) | 2.28 (1.82-2.86) | <0.001 | 1.96 (1.51-2.54)* | <0.001* |
| APACHE II score (per point) | 1.14 (1.09-1.19) | <0.001 | 1.08 (1.03-1.14) | 0.002 |
| SOFA score (per point) | 1.32 (1.19-1.46) | <0.001 | - | - |
| D-dimer (>2000 µg/L) | 3.24 (2.08-5.05) | <0.001 | 2.18 (1.31-3.63) | 0.003 |
| Platelet (<150.000/mm³) | 2.58 (1.63-4.08) | <0.001 | 1.92 (1.15-3.21) | 0.013 |
| PT (>14 sec) | 2.34 (1.53-3.58) | <0.001 | 1.45 (0.88-2.39) | 0.145 |
| INR (>1.2) | 2.18 (1.43-3.32) | <0.001 | - | - |
| CRP (>100 mg/L) | 1.84 (1.22-2.77) | 0.003 | 1.38 (0.87-2.19) | 0.172 |
| LDH (>500 U/L) | 2.06 (1.36-3.12) | 0.001 | 1.52 (0.95-2.43) | 0.081 |
| IL-6 (>50 pg/ml) | 2.42 (1.58-3.71) | <0.001 | 1.61 (0.98-2.65) | 0.060 |
| Ferritin (>1000 ng/ml) | 1.98 (1.31-2.99) | 0.001 | 1.44 (0.90-2.30) | 0.128 |
| Creatinine (>1.2 mg/dl) | 1.88 (1.24-2.85) | 0.003 | 1.51 (0.94-2.42) | 0.088 |

*Separate model was constructed for SIC score (due to correlation with DIC score) DIC: Disseminated Intravascular Coagulation, SIC: Sepsis-Induced Coagulopathy, OR: Odds Ratio, CI: Confidence Interval, COPD: Chronic Obstructive Pulmonary Disease, Variables with p<0.10 in univariate analysis were included in the multivariate model. Backward stepwise elimination method was used

In Model 1 (including DIC score) multivariate analysis, independent predictors of mortality were DIC score (OR: 1.68, 95% CI: 1.34-2.11, p<0.001), age (OR: 1.04, 95% CI: 1.02-1.06, p<0.001), APACHE II score (OR: 1.08, 95% CI: 1.03-1.14, p=0.002), D-dimer >2000 µg/L (OR: 2.18, 95% CI: 1.31-3.63, p=0.003), and platelet count <150.000/mm³ (OR: 1.92, 95% CI: 1.15-3.21, p=0.013) . Hypertension, diabetes mellitus, chronic

kidney disease, and other laboratory parameters lost their significance as independent predictors in the multivariate model.

In Model 2 (including SIC score) analysis, SIC score (OR: 1.96, 95% CI: 1.51-2.54, p<0.001) along with age, APACHE II score, D-dimer >2000 µg/L, and thrombocytopenia were identified as independent predictors of mortality.

Both models demonstrated good fit according to the Hosmer-Lemeshow test (p=0.382 and p=0.415, respectively). The discriminative performance of the models was excellent; Model 1 had an AUC of 0.88 (95% CI: 0.84-0.92, p<0.001), and Model 2 had an AUC of 0.87 (95% CI: 0.83-0.91, p<0.001). Nagelkerke $R^2$ values were 0.512 for Model 1 and 0.498 for Model 2, indicating that the models explained approximately 50% of the variance in mortality.

## DISCUSSION

One of the most significant complications of COVID-19 is known as COVID-19-CAC.[11] CAC is characterized by DIC, SIC, thrombosis, and microvascular clot formation. This process leads to organ failure and increased mortality.[12]

COVID-19-CAC is linked to endothelial dysfunction, inflammation, hypercoagulability, and suppressed fibrinolysis.[13] SARS-CoV-2 binds to endothelial cells via ACE-2 receptors, triggering endothelial inflammation and disrupting vascular integrity. This process leads to increased von Willebrand factor (VWF) levels, elevating the risk of microthrombosis.[14] Furthermore, autopsy findings indicate that alveolar capillary microthrombi are widespread in COVID-19 patients and cause pulmonary vascular complications. Specifically, severe endothelial damage, alveolar capillary microthrombi, and increased neovascularization have been detected in the lungs.[15] These findings suggest that COVID-19 may lead to pulmonary vascular complications. The cytokine storm observed in the advanced stages of COVID-19 is associated with excessive production of proinflammatory cytokines such as IL-6, TNF-α, and IL-1β. The cytokine storm increases platelet activation, leading to hypercoagulability. Elevated IL-6 levels are directly correlated with disease severity and serve as a strong biomarker for predicting mortality.[16]

In COVID-19 patients, the SIC Score and the DIC Score play a significant role in predicting mortality. Studies show that mortality rates are markedly higher in patients with an SIC score ≥ 4 and a DIC score ≥ 5.[7]

Thrombotic complications of COVID-19 are commonly observed in patients. In particular, deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis are frequently seen in the advanced stages of the disease.[17] The incidence of COVID-19-related DVT in ICU patients ranges between 20-40%, while PE is one of the most important causes of sudden respiratory failure due to COVID-19.[18] The risk of arterial thrombosis associated with coagulopathy is increased by 15-20%. These findings demonstrate that COVID-19 creates a systemic hypercoagulable state, which is associated with organ damage.[19]

In COVID-19 patients, D-dimer levels ≥2000 µg/L have been found to show a strong correlation with disease severity and mortality. While initially high fibrinogen levels indicate hypercoagulability, a decrease in fibrinogen levels in the advanced stages of the disease is associated with the development of DIC.[20]

Heparin and low molecular weight heparin (LMWH) therapy play a crucial role in the management of COVID-19-associated coagulopathy. A D-dimer level above 2130 µg/L has been shown to be a strong predictor of mortality. The use of prophylactic LMWH in patients with D-dimer ≥ 2000 µg/L has been demonstrated to significantly reduce mortality.[21]

Different approaches exist for anticoagulant treatment. Prophylactic anticoagulant therapy should be initiated in patients with D-dimer ≥2000 µg/L. Patients with an SIC score ≥4 are candidates for therapeutic anticoagulant treatment. Heparin Resistance: In COVID-19, heparin resistance may develop in some patients; in such cases, alternative anticoagulants should be considered. Recent studies emphasize that high-dose heparin may be risky in certain patients and that individualized anticoagulant treatment protocols are necessary.[9]

### Limitations

This study has several limitations. First, the single-center, retrospective design may introduce bias in data collection and limit the generalizability of the findings. Second, our study included a relatively small patient cohort, which may affect statistical power. Third, anticoagulation treatment protocols were not standardized and were left to the discretion of individual clinicians, making it difficult to assess their impact on coagulopathy management and mortality outcomes. A fourth limitation is the lack of long-term follow-up data (e.g., post-discharge thrombotic events or survival). Finally, some advanced laboratory parameters that may play a role in coagulopathy pathophysiology (e.g., antiphospholipid antibodies, platelet function tests) were not routinely measured. Sixth, despite the use of multivariate analysis, the possibility of residual confounding from unmeasured variables cannot be completely excluded. Seventh, the analysis of day 7 and day 14 scores may have introduced survival bias, as patients who died or were discharged before these time points were excluded from the longitudinal score comparisons. Despite these limitations, our study clearly demonstrates the high incidence of coagulopathy, the value of prognostic scores, and its severe impact on mortality in ICU patients with COVID-19. Larger, prospective, multi-center studies are needed to validate our findings and clarify treatment guidelines.

## CONCLUSION

COVID-19-CAC is a critical condition requiring early diagnosis and aggressive management. The use of SIC and DIC scores can be an important tool in guiding patient risk stratification and treatment selection. Anticoagulant treatment strategies, especially in high-risk patients, should be meticulously applied and coagulation parameters closely monitored.[9] Preventing thrombotic events caused by COVID-19 is one of the most critical components of reducing mortality rates. Therefore, early-stage anticoagulant therapy

and individualized coagulopathy management can positively alter the course of the disease.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This study was conducted with the approval of the Ethics Committee of the Ankara Training and Research Hospital, University of Health Sciences (Date: 22.12.2021, Decision No: E-93471371-514.01.99).

### 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

Concept: GT, MN, MÇ, AÖ, ÇK, HB; Design: GT, MN, MÇ, AÖ, ÇK, HB; Control: GT, MN, MÇ, AÖ, ÇK, HB; Data Collection and/or Processing: GT, MN, MÇ, AÖ, ÇK, HB; Analysis and/or Interpretation: GT, MN, MÇ, AÖ, ÇK, HB; Literature Review: GT, SA, MN, MÇ, AÖ, ÇK, HB; Article Writing: GT, SA, MN, MÇ, AÖ, ÇK, HB; Critical Review: GT, SA, MN, MÇ, AÖ, ÇK, HB.

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# Ischemia-modified albumin as a marker of disease severity and hospitalization in community-acquired pneumonia: a prospective case-control study

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## ABSTRACT

**Aims:** Community-acquired pneumonia (CAP) is an important public health problem because of its high morbidity, mortality, and health care costs. Many biomarkers have been used to determine the severity and prognosis of pneumonia. Ischemia-modified albumin (IMA) is a marker of oxidative stress and has been found to increase in many inflammatory conditions. The aim of this study was to investigate the role of IMA levels in CAP and to evaluate their relationship with pneumonia severity.

**Methods:** A total of 150 patients with a diagnosis of CAP and 150 healthy individuals were included in the study. IMA levels were evaluated in both groups. The patients with CAP were divided into outpatient, inpatient and intensive care groups, and their IMA levels were compared.

**Results:** There was no significant difference between the two groups in terms of age or gender (p>0.05 for both). No significant difference was observed in the IMA levels of the patient and control groups (p>0.05). The lowest IMA level was observed in the outpatient group (p=0.001). When the patients in the outpatient and hospitalized (inpatient and intensive care together) groups were evaluated, the cut-off value of IMA was 77.60 ABSU, sensitivity was 64.9%, specificity was 75.0%, positive predictive value was 89.2%, and negative predictive value was 40.3%.

**Conclusion:** IMA does not appear to differentiate CAP patients from healthy individuals; however, it may be useful in reflecting disease severity and supporting hospitalization decisions.

**Keywords:** Oxidative stress, biomarker, hospitalization decision, inflammation, risk stratification

## INTRODUCTION

Pneumonia is responsible for a significant portion of doctor consultations, treatment costs, missed work and school days, and deaths worldwide.[1] It is the most common cause of infection-related deaths. The reported annual incidence of pneumonia in Europe is 0.5-1.1%, which increases with age.[2,3] While deaths due to infectious diseases have decreased with the widespread use of antibiotics and active immunization as a result of the great advances in medicine, community-acquired pneumonia (CAP) still leads to high rates of morbidity and mortality. In Turkey, lower respiratory tract infections constitute the fifth cause of death at a rate of 4.2%.[4]

Due to their localization, the lungs are exposed to many toxic, irritant and infectious agents. In case of infection caused by the entry of microorganisms into the body, there is a significant increase in the production of free radicals.[5] A change in the balance between oxidants and antioxidants is defined as oxidative stress, which has been associated with various respiratory tract diseases. Asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis have been shown to be associated with oxidative stress.[6,7]

In cases of pneumonia, there are several inflammatory biological markers used for the prediction of disease severity and treatment follow-up.[8] Moreover, various objective criteria have been defined to help the physician make treatment decisions in hospitalized patients. In such cases, the pneumonia severity index (PSI) is the most commonly used tool to select an appropriate empirical antibiotic and determine disease severity in patients with pneumonia.

Among all the recently studied cardiac markers, ischemia-modified albumin (IMA) is the test approved by the U.S. Food and Drug Administration.[9] The principle of this test is the reduction of cobalt-binding capacity of albumin by oxidative free radicals generated during hypoxic acidosis through chemical changes in albumin. This new albumin molecule is called IMA and measured spectrophotometrically using the albumin cobalt binding (ACB) test.[10,11] The formation of this new albumin molecule that has lost its ability to bind cobalt is one of the earliest markers of ischemia.[12] Recent studies have shown that IMA, which attract researchers' interest as a cardiac ischemia marker, can also increase in different

pathologies.[13-15] IMA is generated due to high oxidative stress not only in myocardial ischemia but also in different ischemia models affecting other organs.[16] Serum IMA levels increase in non-cardiac ischemic diseases, pulmonary embolism, cardiopulmonary resuscitation, end-stage renal diseases, cerebrovascular ischemia, acute mesenteric ischemia, systemic sclerosis, arthroscopic knee surgery, postexercise skeletal muscle ischemia, diabetes mellitus, liver diseases, various cancers, infection, and peripheral arterial diseases.[10,16]

In today's conditions where we are confronted with oxidative stress at any moment, there are not sufficient studies evaluating the relationship between pneumonia and oxidative stress. There is a study in the literature that was conducted in the emergency department, which reported that IMA was associated with pneumonia, but no comprehensive study has been undertaken to further investigate the relationship of this oxidative stress marker with pneumonia severity and etiopathogenesis. The aim of this study was to investigate the role of the IMA level in CAP and to evaluate its relationship with pneumonia severity.

## METHODS

### Ethics

This study was approved by the Clinical Researches Ethics Committee of Ankara Yıldırım Beyazıt University (Date: 02.04. 2018, Decision No: 73). 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.

This single-center, prospective, case-control study was conducted in the Department of Chest Diseases between April 2018-March 2019.

A total of 150 adult patients newly diagnosed with CAP and 150 healthy controls were included in the study. The controls were randomly selected from healthy individuals who attended routine controls in the outpatient clinic and had no known acute infection at the time of enrollment. However, detailed screening for chronic diseases and inflammatory conditions was not systematically performed. In the subgroup analysis, the patients with CAP were divided into three groups according to PSI: those that received outpatient treatment (outpatient group), those admitted to the hospital (inpatient group), and those admitted to the intensive care unit (intensive care group). The PSI classification was used to assess disease severity and to guide hospitalization decisions, with higher PSI classes indicating more severe disease and a greater likelihood of inpatient or intensive care admission. Patients were classified according to PSI risk classes (I-V), where higher classes indicate increased severity and a higher likelihood of hospitalization or intensive care admission. The demographic data, clinical and laboratory parameters of all the CAP groups and the healthy controls were recorded. The IMA and C-reactive protein (CRP) levels were also evaluated in the CAP and control groups and compared between the three CAP subgroups. In addition, the correlations between the IMA and (CRP) levels were assessed among the patients with CAP. Patients or controls aged below 18 years, those with mental disorders, and pregnant women were excluded from the study.

### Laboratory Tests

IMA measurement was performed using the reduced ACB capacity test with the rapid and colorimetric method developed by Bar-Or et al.[17] To summarize, 200 uL patient serum was transferred to glass tubes, to which 50 uL 0.1% $CoCl_2x6H_{20}$ (Sigma Aldrich Lot: S38901-248; Sigma Aldrich, St. Louis, MO, USA) was added. After shaking gently, the mixture was incubated for 10 minutes to ensure sufficient cobalt-albumin binding. Then, 50 uL 1.5 mg/ml dithiothreitol (DTT) (Sigma-Aldrich Lot: D5545-1G; Sigma-Aldrich) was added as the coloring agent. After 2 minutes, to stop the binding between cobalt and albumin, 1 mL 0.9% NaCl was added. A blank was prepared for each sample. At the DTT addition step, to obtain a blank, 50 µL distilled water was used instead of 50 µL 1.5 mg/ml DTT. Absorbance values at 470 nm were measured using a spectrophotometer and recorded. Color development in the samples with DTT was compared with the tubes containing the blank solution, and the results were presented as absorbance units (ABSU).

CRP levels were measured turbidimetrically using a BNII Nephelometer Analyzer (Siemens, Munich, Ger- many) with the CardioPhase hsCRP kit (Siemens Healthcare Diagnostics Products, Marburg, Germany).

### Statistical Analysis

The data was performed using IBM® SPSS® (ver. 20.0; SPSS Inc., Chicago, IL, USA) software package. The normality distribution of data was evaluated using the Kolmogorov-Smirnov test. Parametric tests were applied for variables with normal distribution. Mean±standard deviation were used in the descriptive statistics of continuous variables. Pearson's test was used for correlation analysis. In the intergroup comparisons of categorical variables, the chi-square and Fisher's exact tests were used. When comparing two groups in relation to continuous variables, Student's t-test was conducted. Analysis of variance was used. Tukey's test was employed as a post hoc method. Non-parametric tests were not applied as the data were found to be normally distributed. The results were considered significant at a 95% confidence level and a p value of $<0.05$. The receiver operating characteristic analysis was performed to determine the cut-off value of IMA. Multivariate analysis was not performed in this study.

## RESULTS

The study included a total of 300 cases, of which 150 were in the CAP group and 150 were in the control group. In the CAP group, 38% (n=57) of the patients were female and 62% (n=93) were male, while 47.3% (n=71) of the controls were female and 52.7% (n=79) were male. The mean age of the 150 patients diagnosed with CAP was 61.03±1.7 years, and that of the control group was 58.0±10.6 years (p=0.082). There was no significant difference in age and gender between the two groups (p=0.102 and p=0.082, respectively). The mean IMA levels were 77.97±6.17 in the CAP group and 77.01±7.51 in the control group. There were not significant differences between

the two groups in terms of the IMA levels (p=0.742). The demographic data and laboratory findings of the patients with CAP are shown in **Table** and their comorbidities in **Figure 1** according to the outpatient, inpatient and intensive care groups. The mean age of the outpatient group was statistically significantly lower than the other two groups (p=0.035). There were no significant differences in gender between the three groups (p=0.794). IMA was 74.77±5.57 ABSU in the outpatient patients, 78.58±6.01 ABSU in the inpatient patients and 80.60±5.97 ABSU in the intensive care patients. Accordingly, IMA was statistically significantly lower in the outpatient patients compared to the inpatient patients and those receiving intensive care (p=0.004 and p=0.001, respectively). The distribution of the mean IMA values between the groups is shown in **Figures 2** and **3**. The CRP value of the outpatient patients was statistically significantly lower than those of the inpatient and intensive care patients (p=0.001 and p=0.003, respectively).

**Table.** Comparison of the demographic data and laboratory findings between the three CAP groups

| | Ambulatory treatment n=36 (PSI I-III) | Hospitalized in ward n=92 (PSI IV-V) | Admitted to intensive care unit n=22 | p value |
|---|---|---|---|---|
| | Mean±SD | Mean±SD | Mean±SD | |
| **Gender, n (%)** | | | | |
| Female | 12 (33.3) | 36 (39.1) | 9 (40.9) | 0.794 |
| Male | 24 (66.7) | 56 (60.9) | 13(59.1) | |
| IMA (ABSU) | 74.77±5.57 | 78.58±6.01 | 80.60±5.97 | 0.001 |
| CRP (mg/L) | 63.64±69.05 | 156.42±105.49 | 153.26±107.92 | 0.001 |
| $SaO_2$(%) | 96.23±-1.79 | 88.08±9.08 | 84.68±9.68 | 0.001 |

SD: Standard deviaton, CAP: Community acquired pneumonia, PSI: Pneumonia Severity Index, IMA: Ischemia-modified albumin, CRP: C-reactive protein, $SaO_2$: Oksygen saturation

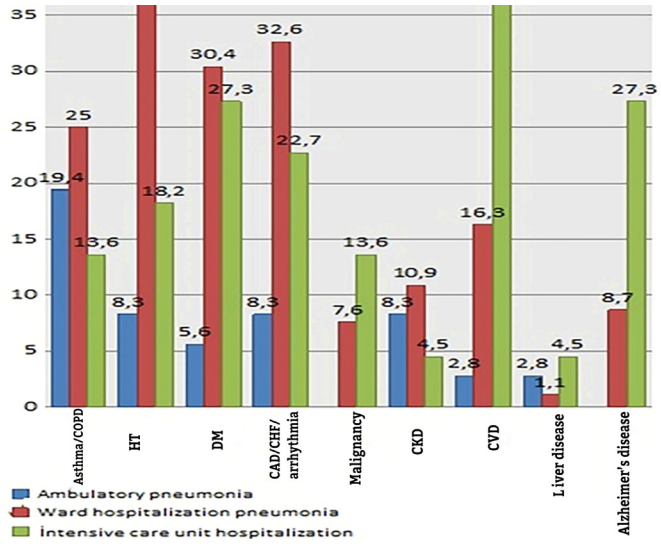


**Figure 1.** Distribution of comorbidities in the patient group with community-acquired pneumonia (%)
COPD: Chronic obstructive pulmonary disease, HT: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease, CVD: Cerebrovascular disease

When the relationship between IMA and CRP was analyzed within the CAP group, a statistically significant positive correlation was detected (r=0.343; p=0.001). The results of this analysis are shown in **Figure 4**.

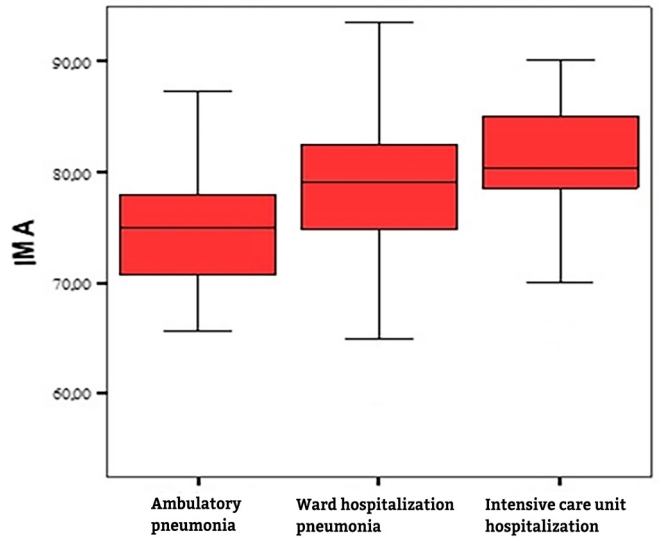


**Figure 2.** Distribution of IMA values among the community-acquired pneumonia cases
IMA: Ischemia modified albumin

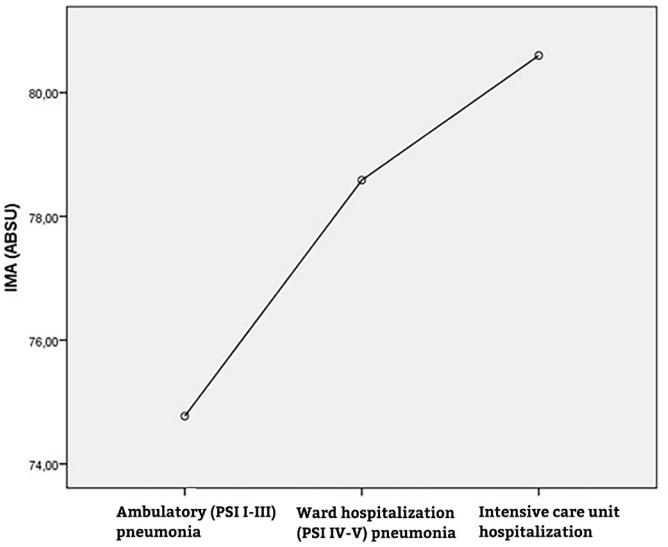


**Figure 3.** Distribution of ischemia modified albumin (IMA) levels between the study groups
IMA: Ischemia modified albumin, ABSU: Absorbance units

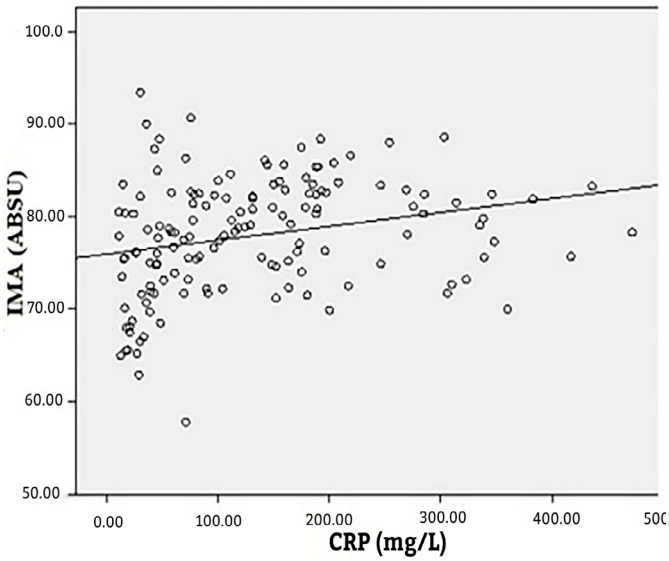


**Figure 4.** IMA-CRP correlation in the community-acquired pneumonia group
IMA: Ischemia modified albumin, ABSU: Absorbance units, CRP: C-reaktif protein

To determine whether an IMA cut-off value could be determined for patients hospitalized due to CAP, the patients were evaluated in two groups as outpatient patients and hospitalized patients (both inpatient and intensive care unit). The area under the curve for the serum IMA levels was 0.708±0.049 (95% confidence interval =0.612-0.804) p<0.001, cut-off value was 77.60 ABSU, sensitivity was 64.9%, specificity was 75.0%, positive predictive value was 89.2%, and negative predictive value was 40.3% (**Figure 5**).

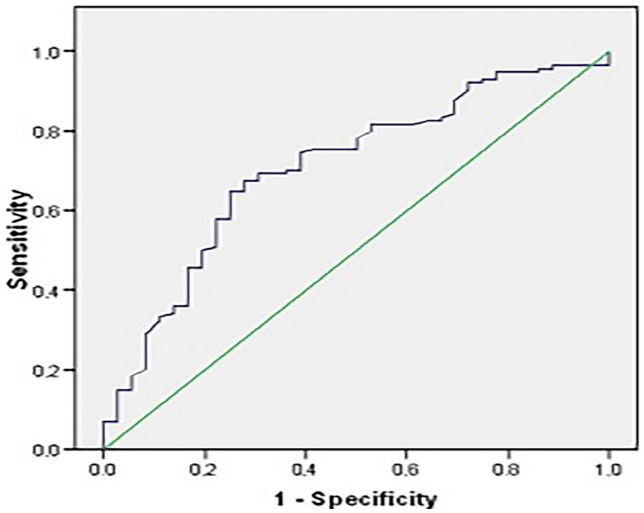


**Figure 5.** ROC curve demonstrating the correlation between community-acquired pneumonia and IMA
ROC: Receiver operating characteristic, IMA: Ischemia modified albumin

## DISCUSSION

In this study, although the serum IMA levels were found to be statistically similar between the CAP and control groups, they were significantly lower among the outpatient patients compared to the inpatient and intensive care groups. In addition, the IMA levels were positively correlated with the CRP levels in the CAP group. These results suggest that IMA levels may be useful in the evaluation of the severity of CAP cases. In addition, they may assist the physician in determining critically ill patients and making a decision for hospitalization.

While death due to infectious diseases continues to decrease with the widespread use of antibiotics and active immunization policies, CAP remains an important lower respiratory tract infection with a high risk of mortality and morbidity. In CAP, disease severity and prediction of clinical outcomes are prerequisites to manage health resources and provide sufficient treatment options. This involves decisions regarding hospitalization in the inpatient or intensive care unit, early discharge and antimicrobial therapy evaluation. To reduce the rate of unnecessary hospitalization, professional organizations have developed prediction rules (CURB-65, PSI) for classification based on the mortality risk of patients with CAP. Since the CURB-65 and PSI scoring systems are only moderately sensitive and specific in determining the risk in patients with CAP, there is still an emphasis on the need for additional risk factors and prognostic markers to improve the prognostic performance of risk scores.[18]

IMA is a new acute coronary syndrome marker found to be associated with oxidative stress. Recent studies have revealed that in addition to its role in acute coronary syndrome, IMA can also play a role in many pathological processes, including pneumonia that alter the balance between oxidant-antioxidant systems. The lung is one of the organs that is most affected by oxidants, and therefore pneumonia is expected to affect the level of IMA.

In the current study, when the CAP cases were compared with the control group, there was no statistically significant difference in terms of the serum IMA levels (p>0.05). In a prospective case-control study by Bolatkale et al.,[19] it was shown that the serum IMA levels significantly increased compared with the healthy controls. To our knowledge, that study was the first to analyze the serum IMA levels in adult patients admitted to the emergency department with CAP. The authors showed, for the first time, that IMA could be a new biomarker that was sensitive for and specific to CAP diagnosis in patients diagnosed in the emergency department. In our study, there was no statistically significant difference between the CAP cases and the control group in terms of the IMA levels. There were 150 subjects in our patient group and 150 subjects in our control group. Of the patients in the CAP group, 22 were admitted to the intensive care unit, 92 were hospitalized in the inpatient, and 36 received outpatient care. In a study by Bolatkale et al.,[19] the case group comprised 81 subjects and the control group comprised 81 subjects. In the case group, six patients required intensive care, 24 were hospitalized in inpatient, and 51 received outpatient treatment. The incompatibility between the results of our study and the findings of Bolatkale et al.[19] can be attributed to the differences in the number of individuals in the patient and control groups. Moreover, in the current study, the IMA value of the outpatient patients was found to be statistically significantly lower than the inpatient and intensive care patients. To our knowledge, there are no studies in the literature that evaluate pneumonia severity and IMA levels according to disease prognosis. In light of our findings, we concluded that serum IMA levels may be useful as a biomarker in the evaluation of severity of CAP cases, making a decision to admit the patient to the inpatient or intensive care unit, and patient follow-up.

We observed a statistically significant correlation between IMA and CRP in the pneumonia group. Similarly, in a study by Bolatkale et al.,[19] a positive correlation was detected between CRP and IMA. Acute inflammatory conditions such as CAP are characterized by the inflammation of pulmonary parenchyma as a response to an infectious event involving systemic and local cytokine secretion and neutrophil uptake. Excessive cytokine production triggers an inflammatory response that can cause organ failure and death. Severity of the infection is correlated with the degree of the inflammatory response of the immune system.[20] Specifically, CRP has superior diagnostic value in bacterial infections with a high plasma concentration. However, in majority of viral infections, CRP levels remain normal or increase only slightly.[21] A recent study reported a significant correlation between CRP and mortality and defined CRP as an independent risk factor for 30-day mortality.[22] Regarding inflammatory markers, recent studies have found that CRP has limited diagnostic value for pneumonia at the first step in cases where the probability of pneumonia is below 10%.[23]

According to our study, the serum IMA levels, which were correlated with CRP, may be useful as a biomarker reflecting disease severity rather than diagnosis and follow-up of infectious processes such as pneumonia.

PSI is an important index to determine the prognosis and mortality of patients.[24] In our study where we classified the patients with CAP according to PSI, we determined that the IMA level could be an important parameter in deciding whether a patient should be hospitalized and predicting the prognosis of CAP. In addition, IMA is similar to other biomarkers in terms of cost, which can be considered as another advantage of this parameter.

### Limitations

This study has several limitations that should be considered when interpreting the findings. First, it was conducted in a single center, which may limit the generalizability of the results to different populations and healthcare settings. Although the overall sample size was relatively adequate, the number of patients requiring intensive care was limited, which may have affected the strength of subgroup analyses related to severe disease. Serum IMA levels were measured only at the time of admission, and serial measurements during treatment and follow-up were not performed. Therefore, the potential value of dynamic changes in IMA levels for monitoring treatment response or predicting clinical outcomes could not be evaluated. In addition, the reference range and expected variation of IMA levels in pulmonary infections have not yet been clearly established, making it difficult to interpret the results within a standardized clinical framework. Smoking status was not recorded in either the patient or control groups. Given the known association between smoking, oxidative stress, and albumin modification, this may have influenced serum IMA levels and introduced a potential confounding factor. Another important limitation of this study is the lack of detailed comorbidity data in the control group. Since comorbid conditions may influence oxidative stress and IMA levels, this may have affected the comparability between groups and contributed to the observed findings. Another limitation of this study is that multivariate analysis was not performed to adjust for potential confounding factors such as age, comorbidities, and inflammatory markers.

## CONCLUSION

In this prospective case-control study, serum IMA levels were not significantly different between patients with CAP and healthy controls; however, IMA levels were significantly higher in hospitalized patients compared with outpatient cases. Moreover, a positive correlation was observed between IMA and CRP levels, suggesting that IMA may reflect inflammatory burden and disease severity rather than the presence of pneumonia itself. Although IMA does not differentiate CAP patients from healthy individuals, it may serve as an adjunctive biomarker for assessing disease severity and supporting hospitalization decisions. Its diagnostic value appears limited, but its association with clinical severity suggests a potential role in risk stratification.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of Ankara Yıldırım Beyazıt University (Date: 02.04. 2018, Decision No: 73).

### 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: MY, EŞP; Design: MY, EŞP; Supervision: EŞP, HCH; Materials: ÖE; Data Collection and/or Processing: MY; Analysis and/or Interpretation: MY, ÖE; Literature Review: MY; Writing the Article: MY; Critical Review: EŞP, HCH, ÖE.

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# Intensive care utilization in COPD and advanced-stage lung cancer

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## ABSTRACT

**Aims:** Patients with terminal lung cancer and chronic obstructive pulmonary disease (COPD) frequently require intensive care unit (ICU) care; however, survival benefit of ICU admission remains uncertain. This study aimed to evaluate ICU outcomes and the impact of palliative care service integration in a tertiary chest diseases hospital among patients with COPD and malignancy.

**Methods:** Between 2013-2019, 731 patients transferred to ICU were evaluated retrospectively. Outcomes were compared before and after the establishment of a palliative care unit in 2016.

**Results:** Lung cancer accounted for 33.5% of cases, while COPD represented 66.5%. ICU mortality was 91.7% in lung cancer patients and 82% in COPD patients. Overall ICU survival was only 10.5%. In addition, 4.1% of patients died shortly after ICU discharge. Mean ICU stay was 7.8 days for lung cancer and 11.6 days for COPD patients. The establishment of a palliative care unit did not significantly reduce ICU referral rates.

**Conclusion:** ICU treatment for end-stage COPD and lung cancer is associated with very poor survival outcomes. Strengthening palliative care services and establishing structured end-of-life decision-making policies supported by legal regulations may help optimize ICU utilization.

**Keywords**: COPD, intensive care unit, lung cancer

## INTRODUCTION

Advanced lung cancer and chronic obstructive pulmonary disease (COPD) constitute a major proportion of admissions to tertiary chest diseases hospitals. The global burden of both diseases continues to increase. The World Health Organization estimates that newly diagnosed cancer cases will reach 29.4 million by 2040.[1,2] COPD is also among the leading causes of mortality and healthcare costs worldwide, particularly in low- and middle-income countries.[3,4]

Recent advances in oncological treatment have prolonged survival in lung cancer patients. Targeted therapies, in particular, have demonstrated significant improvements in both survival outcomes and quality of life, even in malignancies associated with poor prognoses, such as ovarian cancer, gliomas, and small cell lung carcinoma. Hospital admissions among patients with malignancies occur not only during the terminal or end-of-life stages of disease but also other treatment or disease-related complications.[5,6] The clinical heterogeneity of cancer patients presenting to the ED poses significant challenges in accurately predicting survival outcomes during ICU stay. Despite improvements in supportive therapies, predicting prognosis in critically ill cancer patients remains difficult. ICU admission decisions are particularly challenging because of limited healthcare resources and the poor prognosis associated with advanced malignancy.[7-11]

Similarly, patients with advanced COPD experience frequent exacerbations, respiratory failure, pulmonary hypertension, recurrent infections, and repeated hospital admissions, all of which substantially reduce quality of life and increase healthcare utilization.[12-15] Prognostic estimation in severe COPD is also difficult, particularly during acute exacerbations requiring ventilatory support. Previous studies demonstrated discrepancies between predicted and actual survival outcomes in critically ill COPD patients. A study conducted in the UK showed a significant discrepancy between clinical estimates and actual outcomes: clinicians predicted a 180-day survival rate of only 3% for COPD patients admitted to the ICU, whereas the observed survival rate was 36%.[16,17]

Palliative care is recommended to be integrated early in the course of chronic diseases such as cancer and COPD.[18] Initiating palliative care in the early stages of illness influences the attitudes and decisions of both patients and their families throughout the disease course. Early palliative care may reduce unnecessary ICU admissions and prevent futile end-of-life interventions.

Due to limited palliative care resources and the absence of clear legal regulations regarding end-of-life decision-making and do-not-resuscitate practices, making ICU

decisions remains challenging for clinicians. Scoring systems and algorithms designed to support prognostic decisions regarding transfer to palliative care or the ICU remain insufficient. Physicians have limited legal protection regarding withholding or withdrawing life-sustaining treatment, which may contribute to increased ICU utilization among terminally ill patients.

This study aimed to evaluate ICU outcomes, survival, ICU stay duration, and the impact of palliative care implementation on ICU referral rates in patients with advanced lung cancer and COPD in a tertiary chest diseases hospital.

## METHODS

This study was conducted with the approval of the Clinical Researches Ethics Committee of the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 29.07.2021, Decision No: 2021-138). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Due to the retrospective design of the study, informed consent could not be obtained.

This single-center, retrospective and cross-sectional study included patients with malignancy or COPD who were transferred to ICU between January 2013 and January 2019. The relevant data were retrieved from the hospital's electronic medical records system.

Our study focused on the pre-COVID-19 period, as ICU utilization increased significantly during the pandemic, rendering it a distinct and atypical phase. Therefore, the pandemic period was excluded because patient characteristics and ICU utilization patterns substantially differed from the study population. Additionally, patients referred to the ICU for pneumonia, acute respiratory distress syndrome (ARDS) or other pandemic-related conditions were excluded.

A total of 731 patients were included (**Figure 1**). Our hospital is a tertiary referral center specializing in chest diseases and thoracic surgery. During the study period, the hospital had approximately 300 beds and a 14-bed ICU. Because ICU capacity was limited, some patients requiring intensive care were transferred to external centers. A 14-bed palliative care unit was established in November 2016. Patients are admitted to the inpatient clinics following an initial observation period in the ED.

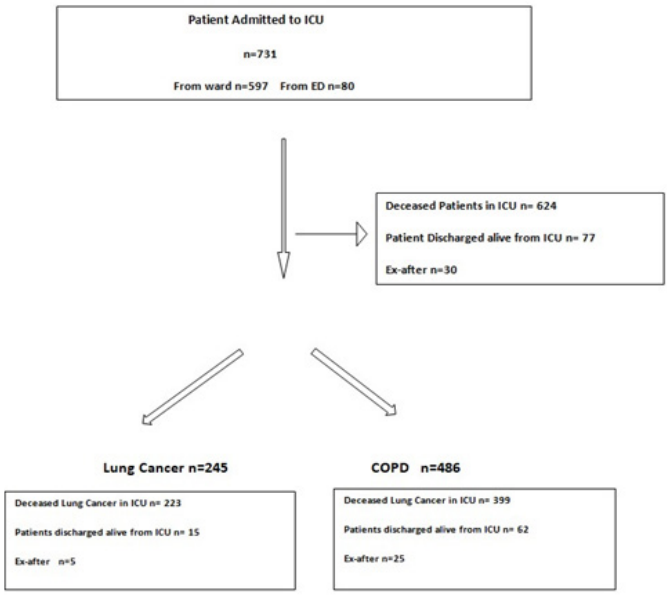


**Figure 1.** Flowchart of the patients
ICU: intensive care unit, COPD : Chronic obstructive pulmonary disease

During the study period, annual ED visits ranged between 50.000 and 60.000. The average number of patients admitted to inpatient wards was approximately 11.000 per year. Among these, 45-50% were diagnosed with COPD, while 20-25% had accompanying malignancies, most commonly lung cancer. Annual mortality rates in inpatient wards outside the ICU ranged between 450 and 470. In November 2016, a 14-bed palliative care unit was established in our hospital to provide specialized support for patients in advanced stages of illness.

### Recorded Data and Study Design

For all cases, demographic and clinical data, including age, sex, primary diagnosis, comorbidities, dates of hospitalization, ICU admission and discharge, and date of death, were systematically recorded. Mortality outcomes for patients discharged from the ICU were verified through the national death notification system and incorporated into our dataset. Patients were classified according to ICU outcome as: survived, died in the ICU or died after ICU discharge (ex-after). To assess the impact of the establishment of the palliative care unit on ICU transfers, monthly and annual ICU transfer rates before and after the establishment of the unit were compared.

### Statistical Analysis

Continuous variables were presented as mean±standard deviation, median, minimum, and maximum values. Categorical variables were summarized as frequencies and percentages. Independent samples t-tests were used to compare ICU referral rates before and after the establishment of the palliative care unit. A p-value <0.05 was considered statistically significant.

## RESULTS

Of all 731 patients, the mean age was 70.1±11.3 (Min: 19, Max: 99) and 81.7% (n=597) were male. Among all patients, 33.5% had lung cancer (n=243) and 66.5% had COPD (n=486). Most ICU transfers occurred during inpatient follow-ups (89%, n=651) while the others were transferred directly from the ED.

Patients' comorbidity rates was 14.1% (n=103), most commonly due to concurrent malignancies in other organs (9.7%, n=71) (**Table 1**). Malignancies other than lung cancer presented with either pleural effusion or parenchymal involvement in the lungs. The spectrum of primary cancers included breast, stomach, prostate, brain, pancreas, ovary, and liver cancers. Additionally, 11 patients had cancer of unknown primary origin.

The mean duration of ICU stay was 10.2±12.8 (min: 0-max: 95, median: 6) days. The mean ICU stay was 7.8±9.6 days in lung cancer patients and 11.6±14.2 days in COPD patients. Among patients diagnosed with lung cancer, 91.8% (n=223) died during their ICU stay, 5 patients were classified as ex-

**Table 1.** Patients and comorbidities

| ICU transfer | | Frequency | Percent |
|---|---|---|---|
| | Service | 651 | 89.0 |
| | Emergency department | 80 | 11.0 |
| | Total | 731 | 100.0 |
| | Female | 134 | 18.3 |
| | Male | 597 | 81.7 |
| | Total | 731 | 100.0 |
| Lung cancer | | 245 | 33.5 |
| COPD | | 486 | 66.5 |
| Total | | 731 | 100.0 |
| **Comorbidity** | | | |
| Congestive heart failure | | 8 | 1.1 |
| Renal failure | | 14 | 1.9 |
| Other malignancies | | 71 | 9.7 |
| No comorbidity | | 638 | 87.3 |
| Total | | 731 | 100.0 |

ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease

after and only 6.1% (n=15) survived. In COPD patients, ICU mortality was 82% (n=399), 5.1% (n=25) were classified as ex-after and 12.7% were discharged alive (**Table 2**). Among cancer patients who were discharged from the ICU to the ward and later died during hospitalization, 2 had initially been admitted to the ICU due to chemotherapy and radiotherapy-related complications related to, 3 due to heart failure, and 1 due to a cerebrovascular event. Two patients admitted because of postoperative respiratory failure and hypotension were still alive at the time of data collection. Seven patients admitted to the ICU due to respiratory failure and infection were discharged alive to the ward but subsequently died during the same hospitalization period. These cases were distinguished from ex-after mortality cases because death occurred shortly after ICU discharge during ward follow-up. The mean age of patients who later died was 67.0±10.9 years.

**Table 2.** Outcome of patients at ICU

| Outcome of patients | | Frequency | Percent |
|---|---|---|---|
| | Alive | 77 | 10.5 |
| | Ex | 624 | 85.4 |
| | Ex after ICU | 30 | 4.1 |
| | Total | 731 | 100.0 |

ICU: Intensive care unit

Ex-after cases were excluded from the statistical analysis and only in-hospital mortality analysis were performed (**Table 3**). The mean survival time of the patients were 16.6±21.8 days (range: 0-391; median: 11 days) (**Table 4**).

The palliative care unit in our hospital was established in November 2016. he monthly distribution of ICU admissions according to the time of first hospital admission is shown in **Figure 2A**. Comparison of the two-year periods before and after the establishment of the palliative care unit showed no significant difference in ICU referral rates. Similarly, the monthly and yearly distributions of ICU admissions according to disease groups remained comparable throughout the study period (**Table 5**, **Figures 2-4**).

**Table 3.** Outcome of Patients at ICU according to diseases

| | | Alive | Ex | Ex after ICU | Total |
|---|---|---|---|---|---|
| Disease | Lung cancer | 15 | 225 | 5 | 245 |
| | COPD | 62 | 399 | 25 | 486 |
| Total | | 77 | 624 | 30 | 731 |
| | **Mean** | **SD** | **Min** | **Max** | **Median** |
| Age | 70.50 | 11.30 | 19 | 99 | 71 |
| Days in ICU | 10.22 | 12.84 | 0 | 95 | 6 |
| Survival | 16.58 | 21.35 | 0 | 391 | 11 |

COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, SD: Standard deviation, Min: Minimum, Max: Maximum

**Table 4.** ICU stay duration and survival according to disease (days)

| | | | |
|---|---|---|---|
| ICU days | Lung cancer | Mean | 7.8161 |
| | | Standard deviation | 9.56567 |
| | | Minimum | .00 |
| | | Maximum | 73.00 |
| | | Range | 73.00 |
| | COPD | Mean | 11.5714 |
| | | Standard deviation | 14.19743 |
| | | Minimum | .00 |
| | | Maximum | 95.00 |
| | | Range | 95.00 |
| Survival days | Lung cancer | Mean | 16.2915 |
| | | Standard deviation | 29.08190 |
| | | Minimum | .00 |
| | | Maximum | 391.00 |
| | | Range | 391.00 |
| | COPD | Mean | 16.7393 |
| | | Std. Deviation | 15.51680 |
| | | Minimum | .00 |
| | | Maximum | 101.00 |
| | | Range | 101.00 |

ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease

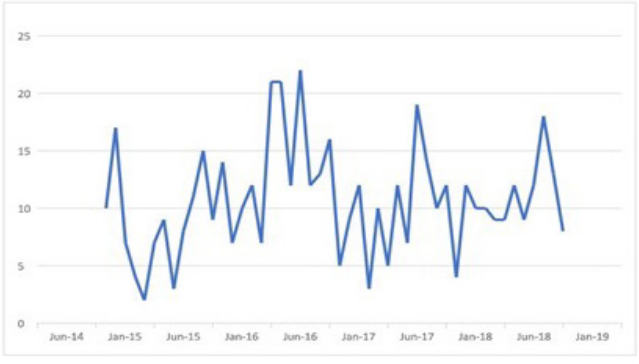


**Figure 2A.** The monthly distribution of intensive care patients according to the time of first admission to the hospital

## DISCUSSION

The present study reveals high ICU transfer rates with a significantly high mortality rate in patients with malignancy and COPD. However, the establishment of palliative care services did not significantly reduce mortality or ICU transfer rates.

**Table 5.** The monthly and annual distribution of patient admission to hospital according to disease

| Disease | | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | |
|---|---|---|---|---|---|---|---|---|---|
| Lung cancer | Jan | 1 | 2 | 4 | 3 | 4 | 2 | 1 | 17 |
| | Feb | 0 | 5 | 1 | 2 | 2 | 3 | 0 | 13 |
| | Mar | 0 | 5 | 0 | 2 | 6 | 4 | 0 | 17 |
| | Apr | 0 | 2 | 3 | 7 | 4 | 3 | 0 | 19 |
| | May | 0 | 8 | 2 | 8 | 2 | 3 | 0 | 23 |
| | Jun | 0 | 3 | 1 | 6 | 2 | 3 | 0 | 15 |
| | Jul | 0 | 3 | 3 | 4 | 3 | 7 | 0 | 20 |
| | Aug | 0 | 0 | 5 | 3 | 7 | 8 | 0 | 23 |
| | Sep | 0 | 4 | 4 | 6 | 5 | 6 | 0 | 25 |
| | Oct | 0 | 0 | 8 | 9 | 2 | 4 | 0 | 23 |
| | Nov | 5 | 6 | 4 | 3 | 1 | 5 | 0 | 24 |
| | Dec | 3 | 4 | 1 | 5 | 3 | 4 | 0 | 20 |
| | Total | 9 | 42 | 36 | 58 | 41 | 52 | 1 | 239 |
| COPD | Jan | 0 | 23 | 3 | 7 | 8 | 8 | | 49 |
| | Feb | 1 | 18 | 3 | 10 | 1 | 7 | | 40 |
| | Mar | 0 | 11 | 2 | 5 | 4 | 5 | | 27 |
| | Apr | 0 | 13 | 4 | 14 | 1 | 6 | | 38 |
| | May | 1 | 11 | 7 | 13 | 10 | 9 | | 51 |
| | Jun | 0 | 11 | 2 | 6 | 5 | 6 | | 30 |
| | Jul | 0 | 9 | 5 | 18 | 16 | 4 | | 52 |
| | Aug | 0 | 5 | 6 | 9 | 7 | 9 | | 36 |
| | Sep | 0 | 8 | 11 | 7 | 5 | 7 | | 38 |
| | Oct | 1 | 7 | 1 | 7 | 10 | 4 | | 30 |
| | Nov | 11 | 4 | 10 | 2 | 3 | 7 | | 37 |
| | Dec | 19 | 13 | 6 | 4 | 9 | 7 | | 58 |
| | Total | 33 | 133 | 60 | 102 | 79 | 79 | | 486 |

COPD: Chronic obstructive pulmonary disease

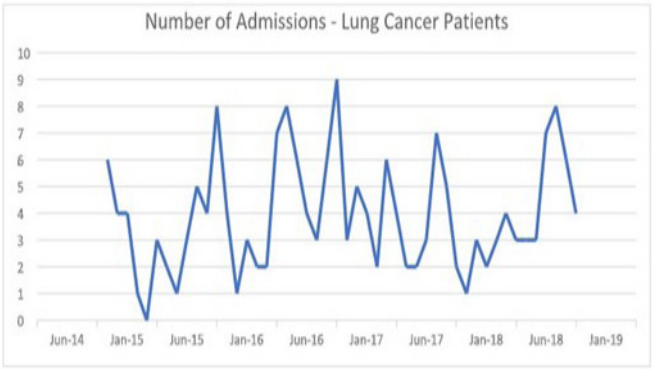


**Figure 2B.** The monthly distribution of intensive care patients according to the time of first admission to the hospital

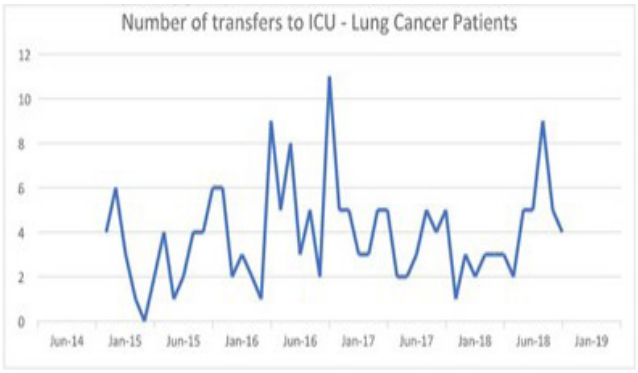


**Figure 3B.** The distribution of patients according to the transfer date to ICU
ICU: Intensive care unit

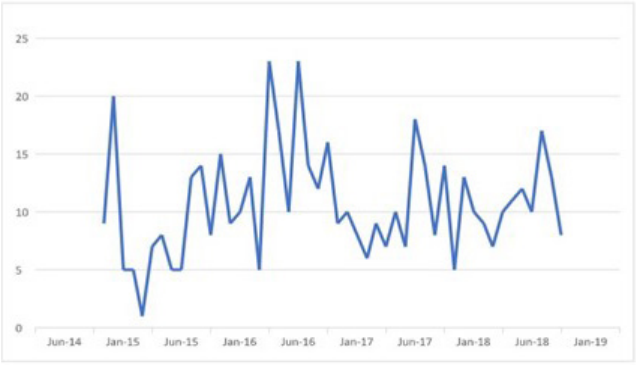


**Figure 3A.** The distribution of patients according to the transfer date to ICU
ICU: Intensive care unit

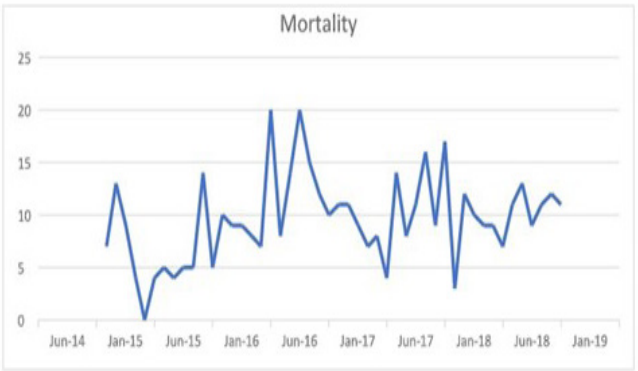


**Figure 4.** Mortality of the patients according to 6-months periods

In our study, irrespective of disease type, 89.5% of patients died during their ICU stay, while 10.5% survived. The patients who survived the ICU and were discharged from the hospital exhibited significantly longer survival times. In their meta-analysis involving cancer patients who underwent in-hospital cardiopulmonary resuscitation (CPR), Reisfield et al.[19] reported an overall survival of hospital discharge of 6.2%, and survival rates were 9.5% in patients with localized disease and 5.6% in metastatic disease cases. While the meta-analysis by Reisfield et al.[19] encompassed all cancer types, our study focused specifically on lung cancer and revealed comparable ICU survival rates. However, a notable distinction emerged: Even after ICU discharge, the majority of our patients died within less than two months. Champigneulle et al.[20] conducted a study involving cancer patients who received cardiopulmonary resuscitation (CPR) either in-hospital or out-of-hospital and were subsequently admitted to the ICU. They reported an ICU mortality rate of 74%, with a six-month survival rate of 14%. These six-month survival rates did not significantly vary based on cancer type or the location of resuscitation. The patients in our cohort experienced a high mortality rate during their ICU stay.

In their 23-year study evaluating lung cancer patients, Al-Dorzi et al.[21] observed a decline in ICU mortality rates after 2015. Although they reported that the mortality rate was between 55.6-66.7% in the period before 2015 and decreased by 28.0% after 2015, with variations over the years. We did not detect a meaningful bifurcation of decline/fall over the years; the rather short duration covered in our study may be the reason why. The aforementioned study also included patients with non-invasive use in the ICU. Moreover, in their study, according to hospital policy, patients whose treatment limitations were determined by three specialist physicians, the patient and their guardian and those with do-not-resuscitate (DNR) orders were not intubated. In contrast, all of our cases are intubated. Furthermore, the ICU mortality rate for intubated lung cancer patients was 79.1%, while 87.0% of patients with DNR died in hospital wards. On the other hand, our study revealed a higher ICU mortality rate of 91.7% among lung cancer patients. The relatively lower ICU mortality rate reported by Al-Dorzi et al.[21] may be attributed to structural and procedural improvements, including the establishment of a dedicated cancer center with inpatient beds, early observation and management of patients prior to ICU admission, the use of non-invasive mechanical ventilation even in end-stage cases and the practice of not intubating patients with DNR orders.

In Turkiye, there are no specialized centers dedicated to the continuous monitoring of cancer patients throughout all stages of their disease. Additionally, inpatient oncology services capacity remain insufficient. Patients are hospitalized across multiple centers. Recently, as respiratory problems have increased, our hospital, a referral center for chest diseases, is assigned more advanced-stage cases. Prior to intubation, we already have experience with non-invasive mechanical ventilation in the chest diseases ward. The intubated patients in our study had significant disability, underwent non-invasive ventilation, and began symptomatic and curative treatments upon admission.

In Turkiye, end-of-life decision-making remains legally and ethically challenging. Current healthcare regulations do not provide a clear legal framework regarding withholding or withdrawing life-sustaining treatment or formal DNR practices. This situation may contribute to increased ICU admissions and invasive interventions in terminally ill patients. Furthermore, limited palliative care infrastructure and insufficient public awareness may delay appropriate end-of-life planning. Contributing factors such as limited public health education, insufficient grief counseling resources and the prevalence of violence against healthcare professionals have led to increased intubation rates among terminally ill patients and increased reliance on intensive care services. National policies and institutional regulations supporting palliative care integration and physician-guided end-of-life decision-making are needed to reduce futile ICU utilization and improve quality of care.

In our cohort, the overall survival time for cancer patients was 16.5 days. In the study by Al-Dorzi et al.,[21] 87% of DNR cases died in the ward.The mean age of our cancer patients who died in the ICU was determined to be 70.5. At our hospital, a significant number of end-stage cancer patients are hospitalized in the ED and clinical services. Both in-patient and ICU deaths are quite high among these patients. Moreover, our cohort exhibited a high rate of metastatic involvement. Given this context, decisions regarding the transfer of terminally-ill patients to the ICU are guided by consultation with a board of specialists as well a professional consultation with their families. There is a pressing need for comprehensive legal and institutional regulations in Turkiye to address this issue. Intensive care should be a priority for cancer patients in the early stages of disease, those newly diagnosed or individuals experiencing acute complications related to chemotherapy or radiotherapy. Furthermore, possibilities should be discussed with the patient from the moment of diagnosis. The relatives who may serve as legal guardians or primary caregivers should be actively involved in the decision-making process.

Among the 486 patients admitted to the ICU with terminal-stage COPD, 82% (n=399) died during their ICU stay, while 12.7% (n=62) were discharged alive. While 5.1% (n=25) of the surviving cases died later, many of them died in the early period (n=37). In some studies, deaths in ICU (25%) of COPD patients were reported at a lower rate than in our study. In studies examining COPD exacerbations in all stages, it was determined that the high acute physiology score (APACHE III) was associated with decreased survival in intensive care.[22]

The decision to initiate mechanical ventilation in patients with terminal-stage COPD presents a significant challenge for physicians. In our study, COPD patients demonstrated a higher likelihood of being discharged alive from the ICU compared to cancer patients. However, because COPD patients were terminally ill, their ICU mortality rate was higher (82% mortality) compared to other studies. Gadre et al.[22] reported that mechanically ventilated patients with acute exacerbation of COPD had significantly lower ICU mortality (27%) and hospital mortality (17%) compared to patients admitted for other causes of respiratory failure.

Detailed evaluation of our patients admitted to the ICU demonstrates that they were patients with advanced stage COPD, who had frequent ED admisions and hospitalizations due to exacerbations, who were transferred to intensive care due to respiratory failure and who were receiving non-invasive mechanical ventilation during their treatment. These characteristics likely account for the shorter survival times observed in our cohort compared to other studies.

Our analysis revealed no statistically significant difference between the intervals with palliative care service establishment. Such lack of variation may be due to the rather small number of beds in our palliative service. However, Romano et al.[23] emphasize in their study that early initiation and continued palliative care in cancer patients reduce intensive care admissions. As noted above, the absence of clear legal regulations in Turkiye to protect healthcare professionals in end-of-life decision-making contributes to the frequent transfer of terminally ill patients to ICU due to last-minute evaluations with patients and their relatives and the inability to complete the grieving process. We also observed a notable lack of palliative care awareness across our hospital during the study period. This reflects a broader national shortage of dedicated palliative care services and trained specialists, as well as insufficient education in primary palliative care principles among physicians. The absence of legal regulations again appears as an obstacle here. A more clear legal policy could incentivize larger adoption of palliative care both by hospital management/staff and the public.

In a study conducted at another center in Turkiye, researchers developed a statistical model to identify candidates for early transfer from ICU to palliative services. Using parameters such as duration of hospital stay, history of cancer, previous hospitalizations and sequential organ failure, they calculated a probability score (>0.5). Patients with a score greater than 0.5 were classified as candidates for palliative transfer. In this way, the unnecessary use of ICU can be prevented.[24-26] Another study also reported that an effective palliative evaluation was cost-effective.[18] In a previous study we conducted with our patients in the palliative service, a positive correlation was detected between short life expectancy and the ratio of CRP, leukocytes, neutrophils, and the ESAS (Edmonton Symptom Scale) showing symptom burden and the presence of liver, brain and distant metastases. In that study, the application of artificial neural networks demonstrated that 30-day survival could be predicted with an accuracy of 89.3% using these parameters.[25]

In our study, the mean age of patients who survived was 68.4 years. Among those who died during the study period, the mean age was 70.5 years, while patients who died at a later stage had a mean age of 67 years. As demonstrated in multiple studies, age alone is not significantly associated with mortality or weaning outcomes in the ICU. Therefore, age should not be considered a limiting factor when evaluating candidates for ICU admission. However, COPD, pulmonary hypertension, and the presence of malignancy in pulmonary fibrosis are factors that make extubation difficult in elderly patients.[26,27]

### Limitations

Accessing sufficient data was a challenge for the research due to the distribution of patients across multiple ICU. The retrospective design of our study caused methodological limitations. Furthermore, the availability of biochemical data within ICU was limited and the information regarding whether cancer patients received chemotherapy prior to or during their ICU stay was incomplete. We also observed that documentation of pre-existing comorbidities was inconsistently recorded. However, cancer patients who survived intensive care were examined individually and meticulously.

## CONCLUSION

In conclusion, our study revealed that our hospital, serving a large population of patients with high mortality risk, continues to experience a high rate of ICU transfers. ICU admissions in malignancy and COPD were associated with extremely high mortality and limited long-term survival. The establishment of a palliative care unit alone did not significantly reduce ICU transfer rates. We believe a structured decision-making framework involving specialist physicians, patients, and their families should be established to guide ICU transfer decisions. Development of effective palliative care systems, structured end-of-life decision-making strategies, and clear legal regulations protecting both patients and healthcare professionals may help reduce unnecessary ICU utilization and improve quality of care in terminally ill patients.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This study was conducted with the approval of the Clinical Researches Ethics Committee of the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital (Date: 29.07.2021, Decision No: 2021-138).

### 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

Conceptualization: GA, TMZ, DK, FTA; Methodology: GA, TMZ; Data Collector: GA, TMZ, DK, FTA; Statistical Analysis: GA, DK; Writing Original Draft: GA, TMZ;

Supervision: GA, TNZ, DK, FTA; Writing Review and Editing: GA, TMZ, TMZ, DK.

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# A case of early-stage lung cancer diagnosed concurrently with dasatinib-induced pleural effusion in a patient with chronic myeloid leukemia

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## ABSTRACT

Advancements in cancer therapies have increased patient survival rates but have also brought about a higher risk of secondary malignancies. Dasatinib, a tyrosine kinase inhibitor commonly used in the treatment of chronic myeloid leukemia, is known to be associated with adverse effects such as pleural effusion. In this report, we present a case of a patient who developed pleural effusion during dasatinib therapy and was subsequently diagnosed with early-stage lung cancer upon further investigation. This case underscores the importance of a multidisciplinary approach in oncologic follow-up and highlights the need for vigilance regarding secondary primary malignancies.

**Keywords**: Secondary neoplasms, thoracic neoplasms, drug toxicity, diagnostic imaging, multidisciplinary approach

## INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal hematologic malignancy driven by the BCR-ABL1 fusion gene, and the advent of tyrosine kinase inhibitors (TKIs) has significantly prolonged survival in affected patientS.[1] Among second-generation TKIs, dasatinib is known for its high efficacy but has also been associated with non-hematologic adverse effects, most notably pleural effusion, in certain patients.[2] However, attributing new symptoms that arise during treatment solely to drug side effects-particularly in patients who achieve long-term survival-may lead to diagnostic delays and missed clinical opportunities. In this context, the possibility of a second primary malignancy should be carefully considered, especially in individuals with additional risk factors such as a history of smoking. This case report discusses the diagnosis of early-stage lung adenocarcinoma in a patient receiving dasatinib for CML, discovered during the evaluation of a newly developed pleural effusion. The case underscores the importance of thorough clinical assessment of new findings in patients undergoing TKI therapy to enable early detection of secondary primary malignancies.

## CASE

A 54-year-old male patient with a 40 pack-year smoking history, under follow-up for one year with a diagnosis of CML, presented to the pulmonology outpatient clinic with progressively worsening dyspnea over the past few weeks. The patient had been receiving dasatinib at a dose of 100 mg/day consistently. Systemic review revealed no symptoms such as fever, cough, sputum production, weight loss, or hemoptysis. Physical examination showed markedly diminished breath sounds and dullness to percussion in the lower right hemithorax. Vital signs were stable, and the patient's oxygen saturation was 94% at rest, decreasing to 89% with mild exertion. Routine laboratory tests revealed normal levels of leukocytes, hemoglobin, and platelets, while C-reactive protein (CRP) was approximately twice the upper limit of normal. Chest X-ray demonstrated a significant pleural effusion in the right lower zone (**Figure 1**). Diagnostic thoracentesis yielded 250 ml of clear, straw-colored fluid. Analysis revealed exudative characteristics, with a protein level of 4.1 g/dl and LDH of 360 U/L. Cytological analysis showed a lymphocyte-predominant (>80%) inflammatory cell profile. No malignant cells were detected in any of the three cytology samples, and microbiological studies were negative.

Given that the patient was in hematologic remission and in the chronic phase of CML, the pleural effusion was not attributed solely to dasatinib therapy, and further diagnostic work-up was pursued. Chest computed tomography (CT) revealed multiple solid nodules with irregular margins in the posterior segment of the right upper lobe, the largest measuring 7×5 mm (**Figure 2**). Fiberoptic bronchoscopy was performed, revealing an irregular, infiltrative lesion with disrupted mucosal surface on the posterior wall of the right upper lobe bronchus. Histopathological examination of biopsy samples confirmed a diagnosis of adenosquamous carcinoma. Subsequent PET/CT imaging showed FDG

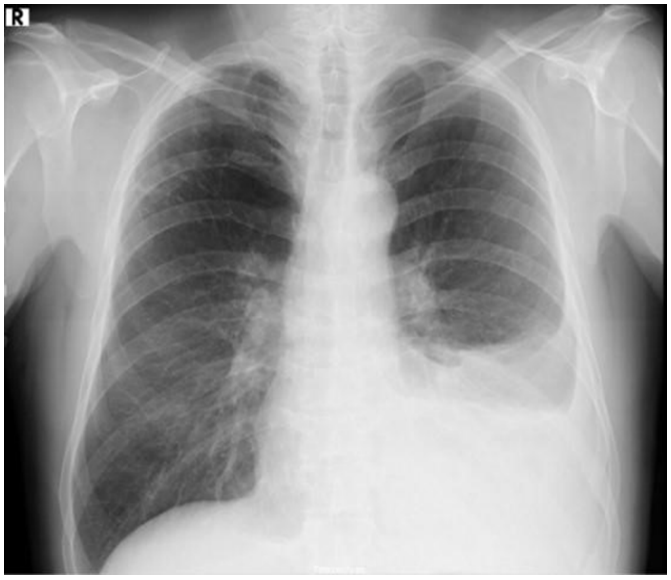

**Figure 1.** Chest radiograph of the patient at the time of presentation

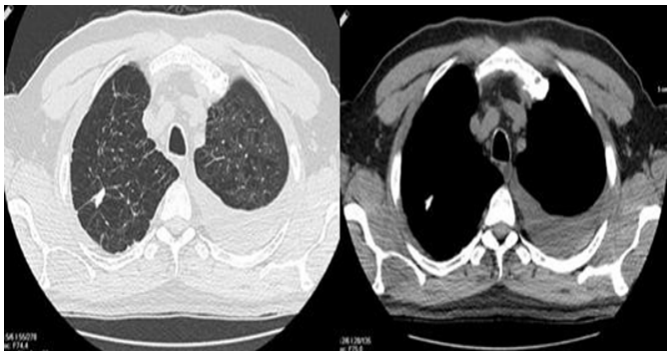

**Figure 2.** Computed tomography scan of the patient's chest

uptake in the right upper lobe nodule with a SUVmax of 5.8. The likelihood of malignant effusion was considered low due to the absence of FDG uptake in the fluid area on PET/CT and repeated negative cytology results. Culture results were negative, and there was no clinical evidence supporting infection. Therefore, an invasive pleural biopsy was not deemed necessary. No extrathoracic involvement or lymph node metastasis was observed. The disease was staged as T1N0M0, corresponding to stage IA1. Pulmonary function tests showed $FEV_1$: 2.85 L (81% predicted), FVC: 3.60 L (85% predicted), and DLCO: 78%, indicating no functional contraindication to surgery. Following a multidisciplinary evaluation with the hematology department, it was decided that the patient would continue dasatinib therapy and be referred to the thoracic surgery department for management of lung cancer. Considering that the most probable cause of the pleural effusion was drug toxicity related to dasatinib, the hematology team reduced the treatment dose and scheduled the patient for regular follow-up to monitor for fluid accumulation. There was no indication for radiotherapy or adjuvant chemotherapy. The thoracic surgery team planned a primary surgical resection, and the patient underwent right upper lobectomy. The postoperative histopathological examination was reported to be consistent with adenosquamous carcinoma.

## DISCUSSION

CML is now considered one of the hematologic malignancies with long-term survival, largely due to the efficacy of TKIs. However, the treatment course extends beyond disease control, as new clinical challenges such as non-hematologic adverse effects and secondary primary malignancies have emerged during long-term follow-up.[3] Among second-generation TKIs, dasatinib offers high molecular response rates but is also associated with adverse effects such as pleural effusion.[4] Although these effusions are often considered benign, in some cases they may represent the initial manifestation of a more serious underlying pathology.

Second primary cancers are among the most significant late complications observed in oncology patients with prolonged survival. Following disease recurrence, they rank second among treatment-related late mortality causes and substantially increase morbidity during follow-up.[5] Factors contributing to this risk include cumulative exposure to radiotherapy and chemotherapy, age at treatment, time elapsed since therapy, family history, and smoking.[6] Among individuals who are long-term survivors of hematologic malignancies, lung cancer is one of the most commonly encountered secondary solid tumors.[7] Lung cancer remains the leading cause of cancer-related mortality worldwide.[8] When detected at an early stage, the likelihood of cure and overall survival increases significantly; therefore, incidental detection or diagnosis prompted by concomitant clinical conditions is of great prognostic value.[9] In the presented case, a patient receiving dasatinib therapy for CML was diagnosed with early-stage lung cancer following a thorough evaluation of newly developed pleural effusion. This case highlights the importance of not attributing new respiratory symptoms solely to drug-related side effects in patients undergoing TKI therapy. Particularly in individuals with known risk factors, a multidisciplinary approach is crucial for the timely diagnosis of second primary malignancies.

## CONCLUSION

In patients undergoing long-term targeted therapy for chronic diseases, newly emerging clinical findings should not be attributed solely to drug-related adverse effects; instead, other potential underlying causes must be thoroughly investigated. As demonstrated in this case, detailed evaluation of pleural effusion developed during dasatinib therapy led to the diagnosis of asymptomatic, early-stage lung cancer. This highlights that clinical vigilance and a multidisciplinary approach can enable timely intervention, which may significantly influence survival and prognosis. Therefore, in patients-particularly those with a history of smoking-new-onset respiratory symptoms should be assessed comprehensively, as this is crucial for the early detection of secondary malignancies.

## ETHICAL DECLARATIONS

### Informed Consent

Written informed consent was obtained from the patient(s) 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: MA[1], BK, MA[2]; Design: MA[1], BK; Control: BK; Data Collection and/or Processing: MA[2]; Analysis and/or Interpretation: MA[2]; Literature Review: MA[1], BK; Article Writing: MA[1], BK; Critical Review: All Authors.

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# Clinical and radiological presentation of multiple intracranial tuberculomas mimicking brain metastases: a case report

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## ABSTRACT

Cases of brain tuberculoma frequently misdiagnosed as primary or metastatic brain tumors, causes to delay in diagnosis. The delay in diagnosis is even common in patients without a history of pulmonary tuberculosis. In the present case, the patient's history of testicular cancer one year prior, the absence of recent clinical findings suggestive of an infectious process, lack of cough, and the absence of radiological findings indicative of tuberculosis on thoracic CT imaging led clinicians away from considering central nervous system (CNS) tuberculosis in the differential diagnosis. This case is particularly significant in demonstrating that, especially in patients with a known history of malignancy and no evidence of pulmonary tuberculosis, the diagnosis of CNS tuberculosis may be delayed and easily confused with intracranial metastases.

**Keywords**: Tuberculosis, tuberculoma, intracranial tumor

## INTRODUCTION

Tuberculosis, although a preventable and treatable infectious disease, affects more than 10 million individuals worldwide each year and causes over 1 million deaths annually. This makes tuberculosis one of the leading causes of death attributable to a single infectious agent and places it among the top ten causes of mortality globally.[1,2] Approximately 90% of individuals diagnosed with tuberculosis are adults, and the disease is more prevalent in men than in women. Tuberculosis most commonly affects the lungs (pulmonary tuberculosis); however, it may also involve many extrapulmonary organs.[3]

Brain tuberculoma is one of the most severe forms of extrapulmonary tuberculosis and predominantly affects individuals under the age of 40. Nonspecific clinical symptoms and non-characteristic radiological features frequently lead to misdiagnosis.[4] Central nervous system (CNS) involvement represents one of the most serious manifestations of extrapulmonary tuberculosis. While its prevalence in the general population ranges from 2% to 15%, it is observed more frequently in patients with AIDS.[5] CNS tuberculosis accounts for approximately 1% of all tuberculosis cases and is associated with significant morbidity and mortality.[6] Brain parenchymal involvement occurs in 50% of disseminated tuberculosis cases and in approximately 1 out of every 300 untreated pulmonary tuberculosis cases.[7] Studies have shown that more than 75% of patients diagnosed with CNS tuberculosis had a history of pulmonary tuberculosis 6 to 12 months prior to diagnosis. However, pulmonary tuberculosis is absent in 25% to 30% of patients with brain tuberculosis.[8]

Delayed diagnosis and initiation of treatment may be attributed to the absence of a prior tuberculosis history in more than half of patients and the presence of an ambiguous clinical presentation.[9] Tuberculomas can mimic conditions such as glioblastoma, brain metastases, intracranial hemorrhage, and abscesses. The most common radiological appearance of a tuberculoma is a ring-enhancing lesion resulting from the absence of blood flow in the central area of caseous necrosis. However, similar imaging findings may also be observed in other conditions, including thrombosis, toxoplasmosis, bacterial abscesses, cryptococcosis, syphilis, sarcoidosis, inflammatory or vascular abnormalities, and various intracranial tumors.[7]

When treatment is initiated early, more than 85% of tuberculoma cases can be successfully treated. First-line antituberculous therapy consists of isoniazid, rifampicin, ethambutol, and pyrazinamide administered for two months, followed by dual therapy with isoniazid and rifampicin.[10] Corticosteroid therapy is recommended in cases of significant cerebral edema or concomitant meningeal involvement.[10]

Therefore, cases of brain tuberculoma frequently misdiagnosed as primary or metastatic brain tumors, causes to delay in diagnosis. The delay in diagnosis is even common in patients without a history of pulmonary tuberculosis. In this case report, it is aimed to discuss a patient diagnosed with intracranial tuberculoma mimicking multiple cranial metastases, by focusing on diagnostic challenges and differential diagnosis.

## CASE

A 60 year old male patient recording of heart failure (ejection fraction: 25%) and adrenal insufficiency had undergone surgical treatment for testicular cancer one year prior. He went to external emergency department with complaints of intermittent syncopal episodes, somnolence, weakness in the extremities, urinary incontinence, and loss of appetite. Upon reviewing the patient's medical history, it was noted that they had no complaints of cough, phlegm, shortness of breath or haemoptysis. During the initial evaluation, cranial computed tomography (CT) and diffusion magnetic resonance imaging (MRI) were performed. The reports of cranial CT revealed hypodense areas consistent with ischemic changes, and the repot of diffusion MRI demonstrated multiple lesions on T2-weighted sequences involving both the parietal and frontal lobes as well as both cerebellar hemispheres (**Figure 1**). Due to the widespread and multifocal distribution of the lesions (hypointense nodular lesions measuring 16×12 mm in the right parietal lobe, 10×9 mm in the left frontal lobe, 6×5 mm in the left cerebellum, and 10×9 mm in the posterior right cerebellum), the findings were interpreted as being consistent with metastatic brain involvement. On chest CT scans, emphysematous changes are present in both lungs, with millimetre-sized nodular infiltrative opacities noted in the upper and middle zones

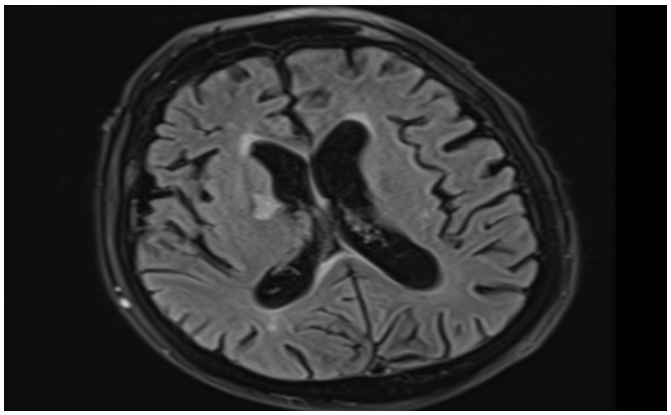

**Figure 1.** Cranial magnetic resonance imaging (MRI)
MRI: Magnetic resonance imaging

Based on these findings, consultations were requested from the neurology, neurosurgery, and departments as a result, dexamethasone treatment was recommended to reduce intracranial oedema, and no surgical intervention was planned for the patient and the patient was admitted to the medical oncology service. So far, surgical intervention was not a planned option. While during clinical monitoring in the medical oncology unit, positron emission tomography-computed tomography (PET-CT) was performed, which revealed pathologically increased metabolic activity in multiple paraaortic and iliac lymph nodes in the abdomen and pelvis (SUV: max 14.19) (**Figure 2**). Numerous millimetre-sized nodular areas of increased density and infiltration were observed in the upper and middle zones of both lungs, with low metabolic activity (SUV max: 2.90).

A paraaortic lymph node biopsy was performed as a result of the findings. Due to the patient's acute deterioration in consciousness and the presence of strong clinical and radiological findings suggestive of metastases of unknown

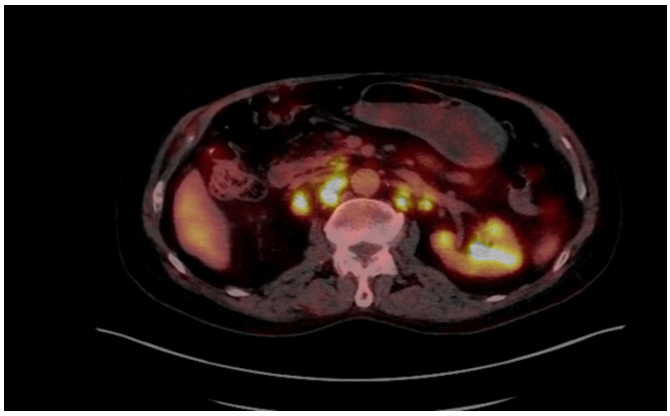

**Figure 2.** Positron emission tomography-computed tomography (PET-CT)

primary origin, radiotherapy was initiated without awaiting the pathology results, and a total of eight sessions were administered.

During inpatient clinical monitoring after radiotherapy, the patient's fever increased and a marked deterioration in the level of consciousness. As the Glasgow Coma Scale (GCS) score was assessed as 9, admission to the intensive care unit (ICU) was indicated. The patient was subsequently transferred from the external center to our ICU. During ICU hospitalization, the patient was monitored while receiving oxygen support via face mask. Isocoric pupils with bilaterally positive light reflexes were determined during neurological examination and no lateralized motor or sensory deficits were observed in the upper extremities. In addition to absence of neck stiffness, minimal motor responses were elicited in all four extremities with minimal stimulation.

The results of laboratory evaluation revealed a C-reactive protein (CRP) level of 54 mg/L and a procalcitonin level of 0.12 ng/Ml. Moreover, the result of anteroposterior chest radiograph wes normal (**Figure 3**). Based on findings, septic emboli, cerebral vasculitis, and CNS infection were considered in the initial differential diagnosis. Empirical treatment with vancomycin, ceftriaxone, sulbactam, and acyclovir, which had previously been initiated due to suspected CNS infection, was continued following consultation with the infectious diseases department.

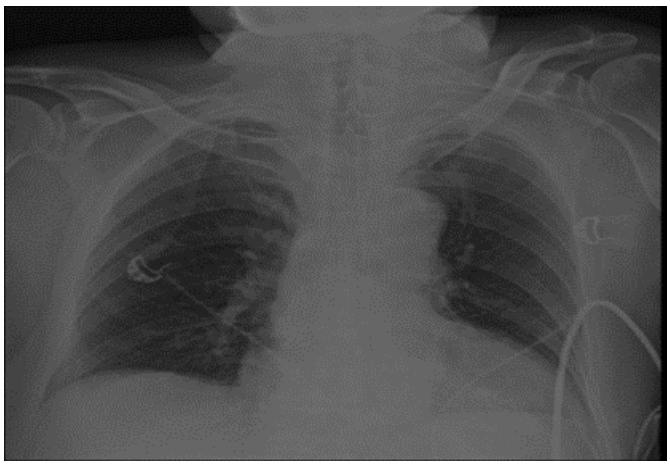

**Figure 3.** Anteroposterior chest radiograph (PA-AC)

On the second day of antibiotic therapy, histopathological examination of the paraaortic lymph node biopsy revealed granulomatous inflammation composed of extensive

necrosis, small lymphocytes, epithelioid histiocytes, and giant cells. Accordingly, sputum samples were obtained for acid-fast bacilli (AFB) staining, mycobacterial culture, and tuberculosis polymerase chain reaction (PCR) testing. The sputum sample was positive for tuberculosis PCR, and microscopic examination of the sputum AFB smear revealed 1-9 bacilli per 100 fields. Antibiotic susceptibility testing has shown sensitivity to isoniazid, streptomycin and rifampicin.

As a result of reevaluation, the cranial MRI findings metastasis were considered to be consistent with intracranial tuberculoma. However, the cranial MRI findings initially interpreted in favor of metastasis. Therefore, antituberculous therapy consisting of pyrazinamide, rifampicin, isoniazid, and ethambutol hydrochloride was initiated. In addition, treatment with dexamethasone 4 mg four times daily has been initiated for cerebral oedema. The treatment regimen was adjusted following consultation with the Department of Infectious Diseases and Tuberculosis. Given the extensive cranial involvement, the severity of the clinical presentation, and the patient's need for intensive care, an expanded antimicrobial treatment strategy was adopted in addition to the standard antituberculous regimen. In this context, after consultation with the tuberculosis clinic, amikacin, linezolid, and moxifloxacin were added to the treatment regimen to ensure adequate CNS penetration and to cover potential drug resistance.

On the fifth day of ICU hospitalization, the marked improvement was shown in clinical condition of patient. The patient's level of consciousness fully recovered, and the GCS score was assessed as 15. New developed focal neurological deficits were not observed on neurological examination. The findings of laboratory examination demonstrated a CRP level of 24 mg/L and a procalcitonin level of 0.04 ng/ml. After clinical and laboratory improvement, the patient was transferred to the tuberculosis service.

## DISCUSSION

CNS tuberculosis, also known as neurotuberculosis, is a severe form of extrapulmonary tuberculosis that develops as a result of the dissemination of Mycobacterium tuberculosis into the cerebrospinal fluid (CSF) and meninges.[10] The most common clinical presentation of neurotuberculosis is tuberculous meningitis. Other manifestations include brain tuberculoma, encephalopathy, brain abscess, Pott's paraplegia, meningoencephalitis, arteritis, and arachnoiditis.[11] CNS tuberculosis accounts for approximately 1-2% of all tuberculosis cases worldwide and is associated with high rates of morbidity and mortality, with more than 100,000 new cases reported annually.[12,13] Current treatment regimens involve prolonged courses of high-dose oral antituberculous medications, typically lasting six to nine months.[14]

One of the primary challenges in establishing a diagnosis in these cases is the presence of nonspecific and ambiguous clinical manifestations, such as altered consciousness, seizures, headache, and focal neurological deficits. The diagnosis of tuberculoma is often based on neuroimaging modalities, including brain CT and MRI; however, no radiological finding is pathognomonic or confirmatory for tuberculoma. Tuberculomas may occur in any intracranial location and can present as solitary or multiple lesions. While infratentorial involvement is more common in children, adults typically exhibit supratentorial localization. Therapeutic challenges include the management of cerebral edema, hydrocephalus, seizures, psychosis, and vasculitis. Moreover, the recent increase in drug-resistant tuberculosis cases has further complicated the treatment of CNS tuberculosis.[15] Long-term antituberculous therapy remains the cornerstone of treatment and is frequently supplemented with corticosteroids to control inflammation and prevent complications such as hydrocephalus. Treatment duration may range from 9 to 24 months, and when initiated early, the prognosis is generally favorable.[16]

In the present case, the patient's history of testicular cancer one year prior, the absence of recent clinical findings suggestive of an infectious process, lack of cough, and the absence of radiological findings indicative of tuberculosis on thoracic CT imaging led clinicians away from considering CNS tuberculosis in the differential diagnosis. Consequently, the lesions observed on cranial imaging were interpreted as mass lesions rather than intracranial tuberculomas. Additionally, the presence of multiple lesions on cranial MRI, a distribution pattern frequently associated with metastatic brain involvement in the literature, further strengthened the preliminary diagnosis of metastasis. However, following the detection of caseating granulomatous inflammation on histopathological examination and a positive tuberculosis PCR result in the sputum sample, reevaluation revealed that the imaging findings were consistent with intracranial tuberculoma.

## CONCLUSION

This case is particularly significant in demonstrating that, especially in patients with a known history of malignancy and no evidence of pulmonary tuberculosis, the diagnosis of CNS tuberculosis may be delayed and easily confused with intracranial metastases. In the differential diagnosis of multiple intracranial lesions, even when clinical and radiological findings strongly suggest metastatic disease, the possibility of intracranial tuberculoma should always be considered in regions where tuberculosis is endemic.

## ETHICAL DECLARATIONS

### Informed Consent

Written informed consent was obtained from the patient(s) 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: HÇA, EBÇ; Design: Control: HÇA, EBÇ; Data Collection and/or Processing: HÇA, EBÇ; Analysis and/or Interpretation: HÇA, EBÇ; Literature Review: HÇA, EBÇ; Article Writing: HÇA, EBÇ; Critical Review: HÇA, EBÇ.

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# *Pandoraea* spp. infection in the course of post-COVID pulmonary fibrosis: a rare case report

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## ABSTRACT

*Pandoraea* species are rare, Gram-negative, aerobic bacilli classified in the *Burkholderiaceae* family. They are increasingly recognized as pathogens in both cystic fibrosis (CF) and non-CF patients, frequently associated with chronic pulmonary infections and multidrug resistance. These organisms can cause significant inflammatory responses and exacerbate pre-existing structural lung diseases. A 32-year-old female with a history of allergic asthma presented with had worsening cough, shortness of breath, and fatigue following a COVID-19 infection. Chest computed tomography revealed bilateral fibrotic changes and cystic bronchiectasis, in addition to nodular lesions predominantly in the upper lobes. Bronchoscopy and bronchoalveolar lavage (BAL) were performed. In BAL culture, *Pandoraea* spp. exhibiting sensitivity to amikacin, cefepime, ciprofloxacin, gentamicin, piperacillin, aztreonam, and imipenem were identified. The patient was treated with ciprofloxacin for a month, resulting in significant clinical and radiological improvement and a reduction in inflammatory markers. Post-COVID pulmonary fibrosis can facilitate the proliferation of opportunistic bacterial infections. *Pandoraea* species can exacerbate chronic lung damage and inflammation thru biofilm formation and the induction of pro-inflammatory cytokines (IL-6, IL-8). This case highlights the importance of considering Pandoraea spp. as a potential cause of unresolved pulmonary infections, particularly in patients with pre-existing viral lung damage or bronchiectasis. Although rare, *Pandoraea* infections can complicate post-COVID pulmonary pathology and mimic chronic infection processes. Early microbiological identification and appropriate antimicrobial therapy are crucial for optimal patient outcomes.

**Keywords**: Bronchiectasis, opportunistic infection, *Pandoraea* species

## INTRODUCTION

The genus *Pandoraea* is a Gram-negative, obligately aerobic, rod-shaped bacterium belonging to the *Burkholderiaceae* family.[1] *Pandoraea* species are a recently identified pathogen in patients both with and without cystic fibrosis. *Pandoraea* isolates have been detected in various clinical samples, including blood, sputum, urine, upper respiratory tract, and lung tissue, from patients both with and without cystic fibrosis (CF). These isolates may contribute to respiratory tract infections and other systemic infections, indicating a wide range of clinical presentations.[2] *Pandoraea* species can trigger inflammatory responses by activating the immune system when they encounter lung epithelial cells. Specifically, these bacteria can increase the secretion of interleukin 6 (IL-6) and interleukin 8 (IL-8) in lung tissue. This can lead to tissue damage and an extensive inflammatory response, increasing the infection's severity. Moreover, certain *Pandoraea* isolates possess the ability to traverse the monolayer barrier established by lung epithelial cells in vitro. This condition suggests that the bacteria exhibit a pathogenic property that can cause more serious damage to lung tissue.[3-5] Pandorea species have been shown to be resistant to many antimicrobials, including drugs such as penicillins, cephalosporins, cefoxitin, meropenem, aminoglycosides, and chloramphenicol. Their resistance to fluoroquinolones is inconsistent. This circumstance complicates the treatment of infections induced by *Pandoraea*.[6] This report concerns a patient who visited our clinic with dyspnea and cough resulting from post-COVID acquired bronchiectasis, with respiratory samples revealing the presence of *Pandoraea* spp.

## CASE

A thirty-two-year-old female patient presented to our outpatient clinic with a cough, fatigue, and shortness of breath that had been ongoing for many years, particularly increasing in the last two months. The only known condition is allergic asthma, and the patient was not adhering to her medication regimen. There was no history of smoking. The patient's history revealed a COVID-19 infection in February 2022, and with symptoms persisting since that time.

Pulmonary function testing demonstrated mild airflow limitation, with a forced expiratory volume in one second ($FEV_1$) of 1.88 L, forced vital capacity (FVC) of 2.62 L, and an

$FEV_1$/FVC ratio of 72%. The bronchodilator reversibility test was negative.The chest X ray showed reticulary and nodullary infiltrations in bilateral lower zones (**Figure 1**).

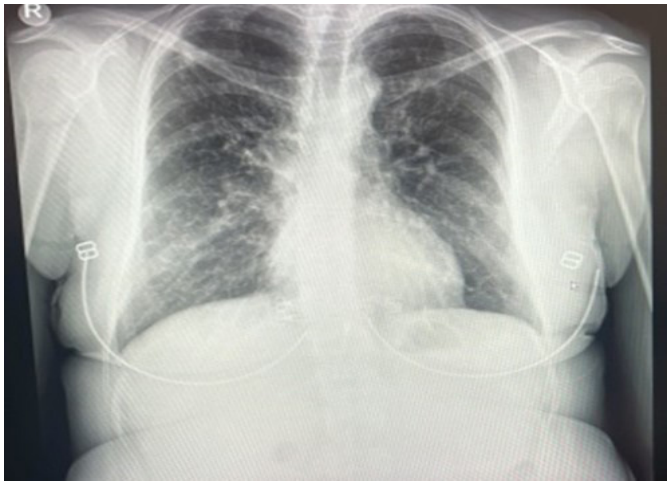

**Figure 1.** The chest X ray showed reticulary and nodullary infiltrations in bilateral lower zones, February 2022

Upon reviewing the patient's medical history, a CT scan conducted during her outpatient appointment in December 2022 revealed chronic reticular, fibrotic changes in both lung apices, tubular cystic cylindrical bronchiectasis in all lobes of the right lung and the lower lobe of the left lung. Additionally, several pleural-based irregular, limited nodular soft tissue density lesions located in the right lung apex and upper lobe posterior segment. The largest nodule's measures were approximately 27x17 mm (**Figure 2**, **3**).

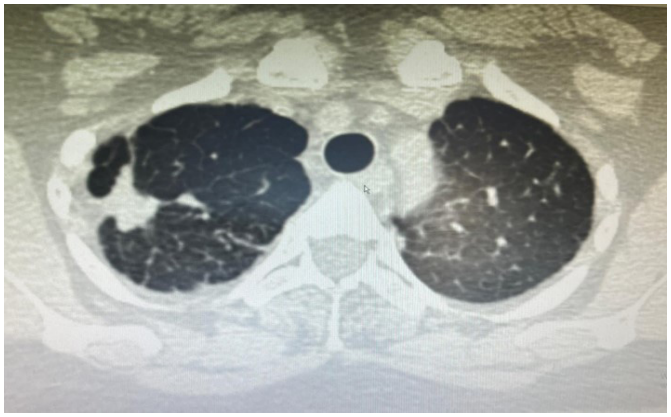

**Figure 2.** Irregular limited nodular lesions

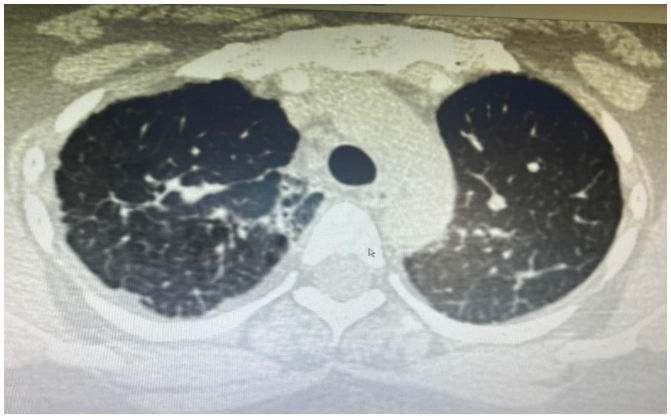

**Figure 3.** Cystic cylindrical bronchiectasis

There was a 9 mm diameter parenchymal nodule in the right lung lower lobe too. Given the presence of multiple nodular lesions on chest CT, positron emission tomography-computed tomography (PET-CT) was performed to further characterize the lesions and primarily to exclude an underlying malignancy. There were no pathological FDG uptake values in PET-CT report, and it was evaluated as post-COVID fibrosis. The patient was given bronchodilator treatment containing beclomethasone dipropionate and formoterol for mosaic perfusion patterns in parenchyma. An annual nodule follow-up scheduled. High-resolution lung tomography (HRCT) conducted in January 2024. The HRCT revealed that sequelae fibrotic changes in the apical segment of both upper lobes, widespread cystic cylindrical bronchiectasis in the right lung parenchyma, an irregular nodular lesion measuring 27x19 mm in the apical segment of the right upper lobe, and minimal pleural thickening. The patient underwent fiberoptic bronchoscopy (FOB). Chest computed tomography revealed bilateral fibrotic changes and cystic bronchiectasis with additional nodular lesions predominantly in the upper lobes. Because of persistent respiratory symptoms and suspicious radiological findings, bronchoscopy with bronchoalveolar lavage (BAL) was performed for microbiological evaluation and differential diagnosis, including tuberculosis/non-tuberculous mycobacterial infection, fungal infection, opportunistic bacterial pathogens, and malignancy. All bronchi and segments were open and subsegmental orifices were seen as open. No endobronchial lesions were detected. A BAL of right upper lobe was performed outpatiently. BAL samples were submitted for microbiological evaluation. The organism was identified as *Pandoraea* spp. by 16S rRNA gene sequencing, a molecular method widely used for accurate identification of non-fermenting Gram-negative bacteria. The identification was confirmed by the microbiology laboratory based on sequencing analysis. Given the high bacterial burden in BAL culture together with compatible clinical and radiological findings, the isolate was considered indicative of active infection rather than simple colonization. It was found to be sensitive to antibiotics containing amikacin, cefepime, ciprofloxacin, gentamicin, piperacillin, aztreonam, and imipenem. Based on antimicrobial susceptibility testing, the patient was started on oral ciprofloxacin (500 mg twice daily). During follow-up, the patient demonstrated significant improvement in respiratory symptoms, including decreased cough and sputum production, indicating a favorable clinical response to the treatment. A regression was observed in laboratory tests for infection parameters. There was no major differences between 2022 and 2025 chest X rays (**Figure 4**).

## DISCUSSION

The literature has shown that respiratory diseases such as atypical pneumonia caused by viruses may damage to lung tissue, and this infection results in abnormal inflammatory responses, persistent lesions, and the development of fibrosis. Specifically, it has been observed that fibrotic lung infection following COVID-19 infection, as in this case, causes symptoms of dyspnea, cough, and fatigue. Studies on the interaction of the *Pandoraea* strain with lung epithelial cells and its in vitro biofilm formation capabilities have shown that it elicits a strong pro-inflammatory response,

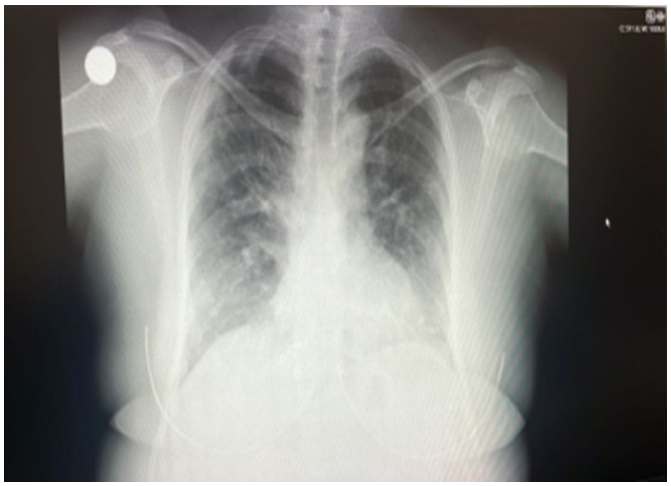

**Figure 4.** There was no major differences between 2022 and 2025 chest X rays, December 2025

and that *Pandoraea's* inflammatory effects likely exacerbate chronic inflammation resulting from infection with other pathogens, leading to lung damage.[7] This characteristic enables the bacterium to colonize structurally abnormal lung tissue and become resistant to antibiotics, leading to chronic infections. The genetic and phenotypic diversity observed within the *Pandoraea* population during chronic colonization can result in serious clinical consequences, such as evasion of host defenses and treatment failure.[8] In our patient, chronic inflammation after COVID-19 and sequelae changes observed on HRCT were also noted. In this case, in addition to lung pathology following COVID-19, we wanted to show that treating *Pandoraea*, which pathogenesis is not fully understood, is difficult in this group of patient. The pro-inflammatory effects of *Pandoraea*, combined with the inflammatory characteristics triggered by COVID-19 may worsen lung pathology.

## CONCLUSION

This case is significant as it represents one of the rare reports of a *Pandoraea* infection developing on a background of post-COVID pulmonary fibrosis. The bronchiectasis and fibrotic changes that developed after the COVID-19 infection created a suitable environment for the proliferation of opportunistic pathogens like *Pandoraea*. Although co-infections with COVID-19 have been previously reported in the literature, our case demonstrates that a *Pandoraea* infection can also present as a condition that mimics or exacerbates the sequelae of structural lung damage occurring in the post-COVID period. This underscores the importance of considering rare bacterial agents in the differential diagnosis, particularly in patients with prolonged respiratory symptoms and radiological progression following a viral infection.

## ETHICAL DECLARATIONS

### Informed Consent

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

### Peer Review Process

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### Conflict of Interest

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### Financial Disclosure

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### Author Contributions

Concept: AY, HL; Design: AY, FİS, DÇ, ÖY; Control: HL, ÖY; Data Collection and/or Processing: AY, FİS, DÇ; Analysis and/or Interpretation: AY, FİS, DÇ, HL, ÖY; Literature Review: AY, FİS; Article Writing: AY, FİS, DÇ, HL; Critical Review: All Authors.

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