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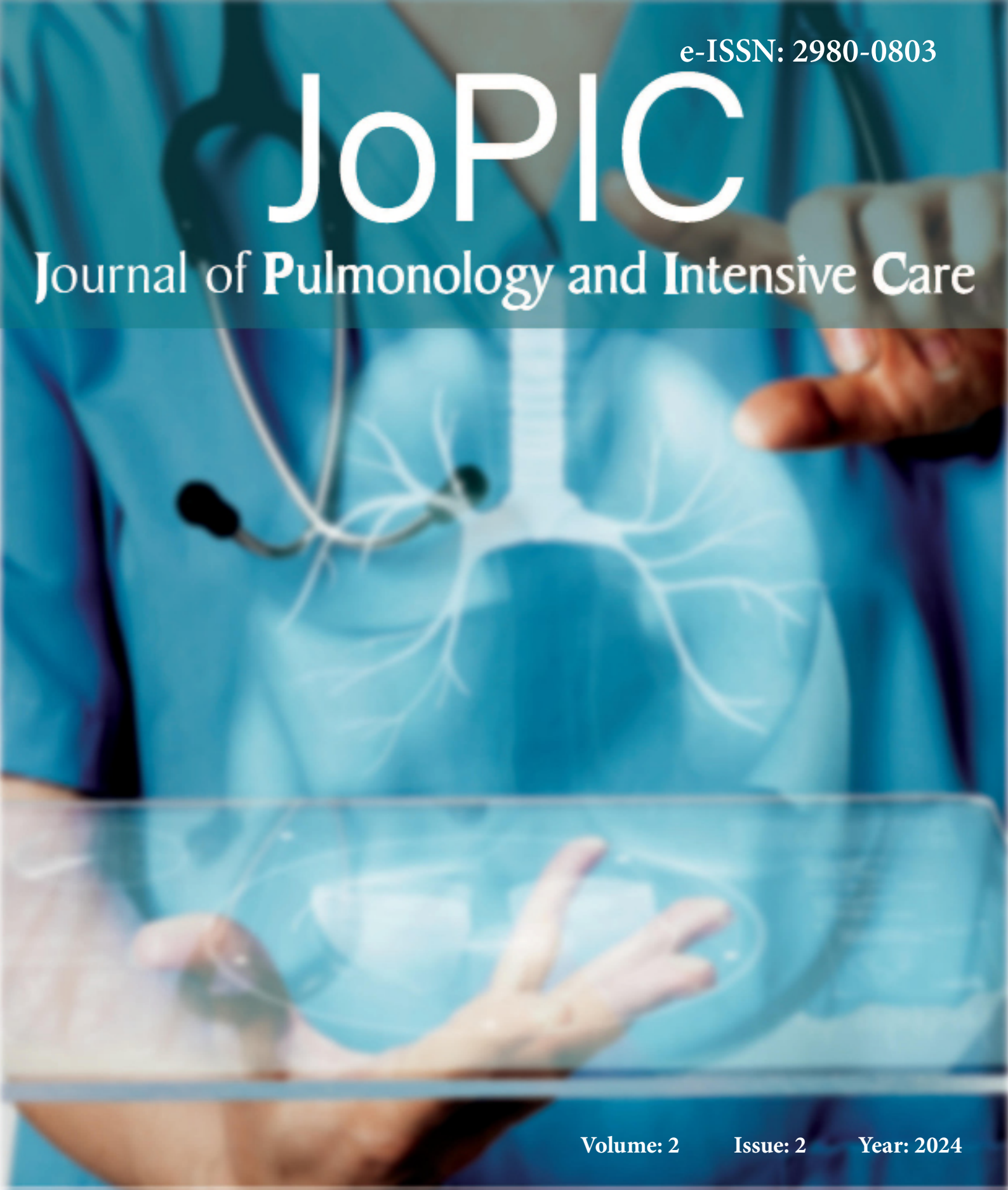

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Original Article

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Pulmonary vascular changes in interstitial lung diseases

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ABSTRACT

Aims: Pulmonary hypertension (PH) is commonly seen in patients with interstitial lung diseases (ILDs), and is associated with a worse prognosis. The aim of this study was to determine the prevalence of PH in patients with ILDs and identify the markers that may predict this complication without invasive procedures. For this purpose, the correlation between mean pulmonary artery pressures and diffusion test, functional assessments, such as six-minute walk test, was investigated.

Methods: The study group included 30 patients who were diagnosed interstitial lung disease between February 2010 and February 2011. Demographic and clinical characteristics, physiological studies, sixminute-walking test and high resolution computered tomography results were prospectively collected, and compared between patients with and without PH. Pulmonary hypertension was defined by right heart catheterization and results were compared between patients with PH and with non-PH.

Results: The study cohort consisted of 30 patients, of whom 14 patients (46.6%) had PH. When compared with non-PH subjects, patients with PH exhibited lower six-minutes-walk distance (415±41 m vs. 260±95 m, p<0.001), increased oxygen desaturation percentage during six-minutes-walk test (12.44±5,46 & 7.12±3.48), and decreased percentage of predicted FVC% (49±13.95 & 67±11.56), percentage of predicted FEV1% (52±13.2 & 73.5±12.43), and percentage of predicted DLCO% (38.8±13.7 & 65.3±11.23).

Conclusion: As a result, if there is a doubt about the decrease of pulmonary function tests and exercise capacity, patients with ILDs have to be investigated for pulmonary hypertension.

Keywords: Interstitial lung disease, pulmonary hypertension, six-minutes walk test, pulmonary functional tests

INTRODUCTION

The development of pulmonary hypertension (PH) in the context of interstitial lung diseases (ILDs) is a well-known complication of various ILDs. The pathogenetic concepts of pulmonary fibrosis have interesting commonalities with the pathogenetic mechanisms responsible for the development of PH. As a result of epithelial damage occurring in interstitial lung diseases, oxidative stress occurs, fibroblast proliferation is stimulated as a result of the released cytokines, and angiogenesis and neovascularization inevitably occur as a result of restructuring.[1] Clinically, PH can produce dyspnea, fatigue, and exercise limitation, which are also characteristic symptoms of ILDs. As a result, PH may not be noticed in patients with ILDs until signs of right heart failure develop.[2] Echocardiogram (ECHO) is a valuable noninvasive technique for diagnosis and follow-up. Regurgitation of the pulmonary valve on ECHO, shortening of the right ventricular ejection acceleration time, dilatation in the right heart chambers, functional and structural deterioration in the interventricular septum, increase in right ventricular wall thickness, and dilatation in the main pulmonary artery suggest pulmonary hypertension. However, echocardiography has limitations depending on the method and the person evaluating it and cannot provide a definitive diagnosis of pulmonary hypertension.[3] The gold standard diagnostic method for monitoring the degree of the disease, arranging the treatment and ensuring the response to treatment is right heart catheterization and measurement of pulmonary artery pressure.[4]

The aim of this study is to identify markers that can predict the presence of pulmonary hypertension in ILDs without invasive procedures. For this purpose, the correlation

between mean pulmonary artery pressures and diffusion test, functional assessments, such as 6-minute walk test (6MWT), was investigated.

METHODS

Ethics committee approval was obtained from Eskişehir Osmangazi University Faculty of Medicine (Date: 31.08.2010, Decision No: 2010/165). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of 30 patients who applied to our chest diseases department between February 2010 and February 2011 and were diagnosed with interstitial lung disease and agreed to participate in the study were evaluated. The final diagnoses of the patients were reached after clinical, radiological and histopathological examinations. Fifteen patients diagnosed with idiopathic pulmonary fibrosis, five patients diagnosed with stage 4 sarcoidosis, three patients diagnosed with asbestosis due to environmental exposure, three patients diagnosed with hypersensitivity pneumonitis, one patient diagnosed with nonspecific interstitial pneumonia, one patient diagnosed with lung disease due to rheumatoid arthritis, and two patients diagnosed with pneumoconiosis were included in the study. All patients underwent arterial blood gas analysis, 6MWT, carbon monoxide diffusion test and pulmonary function test. Oxygen saturation of the patients was monitored with a pulse oximeter before and during the 6MWT. Desaturation during the test was recorded. To evaluate whether pulmonary hypertension developed, right heart catheterization was performed in all patients. Pulmonary arterial pressure of 25 mmHg and above was considered as pulmonary hypertension.

Statistical Analysis

The data were analyzed using the SPSS 22 package program. Shapiro-Wilk test was used to determine distribution forms. Independent samples t-test was used to compare the means between groups. Yates Chi-square test was used to analyze cross-tables. ROC analysis was used to determine critical values, and specificity and sensitivity were determined. Stepwise logistic regression analysis (Backwardwald model) was used in the multivariate analysis of the data regarding the variables of 6MWT distance, desaturation during the test, expected FEV1%, expected FVC%, expected DLCO%, expected DLCO/VA% between the groups. Hosmer Lemeshow test were used to investigate the significance of the model. Data were summarized as mean±standard deviation. A value of $p<0.05$ was considered statistically significant.

RESULTS

30 patients diagnosed with interstitial lung disease were included in the study. Final diagnoses of the patients; idiopathic pulmonary fibrosis (n=15), asbestosis (n=3), chronic sarcoidosis (n=5), chronic hypersensitivity pneumonia (n=3) and unclassifiable (n=4). 15 of the patients were women and 15 were men. The average age of women was 60.6 (±13.8) years, and the average age of men was 62.5 (±12.5) years. Pulmonary hypertension was detected in 14 (46.6%) of the patients. Mean pulmonary artery pressures (PAP) were 25.03±9.07 mmHg in all cases, 32.9±6.8 mmHg in the group with PH and 18.2±3.5 mmHg in the group without PH. The mean PAP was measured as 28.4±10.0 mmHg in patients diagnosed with IPF, 20.33±6.11 mmHg in patients diagnosed with asbestosis, 18.4±5.17 mmHg in patients diagnosed with sarcoidosis, 27.0±11.3 mmHg in patients with hypersensitivity pneumonitis, and 22.75±4.34 in other patients (one patient diagnosed with nonspecific interstitial pneumonia, one patient diagnosed with lung disease due to rheumatoid arthritis, and two patients diagnosed with pneumoconiosis). The demographic characteristics of the patients, symptom durations, arterial blood gas analysis results, respiratory function test and diffusion test results, 6MWT results are summarized in Table 1, right heart catheterization results are summarized in Table 2. Presence of PH in terms of ILDs diagnoses are summarized in Table 3.

Tablo-1. The demographic characteristics of the patients with or without PH symptom durations, arterial blood gas analysis results (pO2, oxigene saturation, pCO2, pH), respiratory function test and diffusion test results, 6MWT results

	PH (-)	PH (+)	p value
Age (years)	60±12	63±14	
Gender Female Male	 9 (56,2%) 7 (43.8%)	 6 (42,9%) 8 (57.1%)	
Symptom durations(months)	20.7±13.6	41.2±36.8	0.047
pO2(mmHg)	68±8	53±10	<0.001
Oxygene saturation (%)	94±2	88±5	<0.001
pCO2 (mmHg)	35±4	37±7	0.406
pH	7.44±0.03	7.46±0.04	0.269
%FEV1	73,5±12,43	52±13,20	<0.001
%FVC	67,0±11,56	49,5±13,95	0.001
FEV1/FVC	88,5±11,40	89,1±11,32	0.890
%DLCO	65,3±11,23	38,8±13,72	<0.001
%KCO	110,4±28,94	75,6±37,80	0.010
6MWT distance (meter)	414,93±40,58	260,42±94,94	<0.001
Desaturation during 6MWT (%)	7,12±3,48	12,44±5,46	0.005

PH: Pulmonary hypertension, pO2: Oxygene pressure, pCO2: Carbon dioxide pressure, FEV: Forced expiratory volume, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, DLCO/VA: Diffusing capacity divided by the alveolar volume, 6MWT: Six-minute walk test)

Table 2. Right heart catheterization results

	PH (-)	PH (+)	p value
Right atrial pressure (mmHg)	3.4±2.6	6.6±5.3	0.050
Right ventricular Pressure (mmHg)	10.9±3.7	19.2±6.4	<0.001
Pulmonary arterial pressure	18.2±3.5	32.9±6.8	<0.001
Pulmonary capiller wedge pressure	6.5±2.9	9.4±2.7	0.009

To determine the presence of pulmonary hypertension, ROC analysis was used to determine cut-off values for FEV1%, FVC%, DLCO%, DLCO/VA%, 6MWT distance and the desaturation during the 6-MWT Table 4.

Multiple logistic regression analysis was performed. 6MWT distance, desaturation, FEV1%, FVC%, DLCO%, DLCO/

VA% variables were included in the analysis. Among the parameters examined, the most valuable variable in terms of determining pulmonary hypertension was found to be FEV1%. A weaker correlation was detected between the six-minute walk test distance and PH.

Table 3. Presence of pulmonary hypertension in terms of interstitial lung disease diagnoses

Final Diagnosis	PH (-)	PH (+)
Idiopathic pulmonary fibrosis (n=15)	6	9
Sarcoidosis (n=5)	4	1
Hypersensitivity pneumonitis (n=3)	0	3
Asbestosis (n=3)	3	0
Others (n=4)	3	1

Table 4. Specificity and sensitivity of cut-off values for FEV1%, FVC%, DLCO%, DLCO/VA%, 6MWT distance and desaturation

Parameter	Cut-off value	Specificity (%)	Sensitivity (%)
FEV1%	70	75	92.9
FVC%	50	93.7	71.4
DLCO%	53	87.5	85.7
DLCO/VA%	70	100	57.1
6MWT distance (meter)	330	100	78.6
Desaturation (%)	9.5	80	71.4

FEV: Forced expiratory volume, FVC: Forced vital capacity DLCO: Diffusing capacity of the lungs for carbon monoxide, DLCO/VA: Diffusing capacity divided by the alveolar volume, 6MWT: Six-minute walk test)

DISCUSSION

In this study, the clinical findings, respiratory functions and exercise capacities of 30 patients followed with the diagnosis of interstitial lung disease were evaluated, and the data of the cases with and without pulmonary hypertension detected as a result of right heart catheterization were compared. Pulmonary hypertension was determined by right heart catheterization in 14 (46.7%) of the 30 patients included in our study. In previous studies; It has been reported that pulmonary hypertension can be determined between 6-74% in sarcoidosis 5 and 3-86% in idiopathic pulmonary fibrosis.[6]

In interstitial lung diseases, pulmonary hypertension can develop without hypoxemia, but hypoxemia is frequently observed.[7] In our study, consistent with this information, the average PaO_2 was found to be 53 mmHg in the group with PH and 68 mmHg in the group without PH. Likewise, the average oxygen saturation was found to be 88% in the group with PH and 94% in the group without PH. This difference was found to be statistically significant.

In cases with interstitial lung disease, a decrease in respiratory function test parameters and diffusion capacities occurs, especially when fibrosis develops. Decreased DLCO indicates fibrosis of alveoli in patients with ILD and PH, respectively. The worsening of the DLCO value despite preservation of lung volumes should suggest the possibility of pulmonary vascular resistance.[8] In our study, FEV1%, FVC%, DLCO%, DLCO/VA% values of the cases were compared and the relationship of these values with the development of pulmonary hypertension was examined. Cut-off values were calculated using ROC analysis. The cut-off value for DLCO% in determining pulmonary hypertension was found to be 53%. The sensitivity of this value was found to be 85.7% and the specificity was 87.5%. Several studies have suggested that DLCO ranging from 30% to 45% can predict PH.[9-11] For the FVC% value, 50% was found to be the critical value in determining pulmonary hypertension. The sensitivity of this value was found to be 93.7% and the specificity was 71.4%. As a result, hypoxemia detected in low DLCO, FVC and deoxygenated blood gas is associated with a high probability of pulmonary hypertension. A disproportionate decrease in DLCO compared to FVC should prompt the clinician to consider the possibility of pulmonary hypertension.

In patients with interstitial lung disease, exercise limitation detected in exercise testing indicates pulmonary vascular changes better than respiratory function parameters.[12] A decrease in the six-minute walk test distance brings with it a decrease in the quality of life and mortality. Studies have shown that even minimal decreases in the 6-minute walk test result in statistically significant changes in patients' clinical conditions.[13] Many studies have shown that the 6MWT distance of ILD patients with PH is lower than that of ILD patients without PH.[14] In a study conducted on patients diagnosed with sarcoidosis, a lower 6MWT distance was found in the group with pulmonary hypertension compared to the group without it (280 meters versus 408 meters), and this statistically significant difference was found to be associated with quality of life and Saint George questionnaire.[15] In our study, exercise capacity limitation in people diagnosed with pulmonary hypertension and followed up with a diagnosis of interstitial lung disease was investigated. For this purpose, a 6-minute walk test was applied to the patients. A statistically significantly lower 6MWT distance was detected in the group with pulmonary hypertension. By calculating the threshold value for the 6-minute walk test distance using ROC analysis, it was aimed to predict pulmonary hypertension and reveal the need for further examination in patients followed with a diagnosis of interstitial lung disease. For the six-minute walk test distance, the value of 330 meters was found to have 78.6% sensitivity and 100% specificity. In a study evaluating tools that could predict the development of pulmonary hypertension in interstitial lung disease, this value was predicted to be 350 meters sarcoidosis.[5] In the study of Cahalin et al.,[16] which evaluated cases diagnosed with interstitial lung disease in need of transplantation, it was observed that the risk of developing pulmonary hypertension increased in cases with a 6-minute walking distance below 300 meters.

In this study, to determine hypoxemia during exercise, saturation records were taken during the 6-minute walk test and the lowest values detected at the beginning and during the test were compared. Hypoxemia was observed more clearly during exercise in the group with pulmonary hypertension. As a result, desaturation of more than 9.5% during the test was found to be associated with the development of pulmonary hypertension. Similarly, previous studies have reported that a decrease of more than 10% in saturation during the 6-minute walk test in patients with pulmonary hypertension may be a determinant of mortality.[17]

As a result of multiple logistic regression analysis, it was determined that among the expected FEV1%, expected FVC%, expected DLCO%, expected DLCO/VA%, 6MWT distance and desaturation parameters during 6MWT, the most valuable parameters to predict pulmonary hypertension in interstitial lung diseases were expected FEV1% and 6MWT distance. However, due to the small number of cases, the relationship between these values and the degree of pulmonary hypertension could not be examined. In a study by Bourbonnais and Samauati[18] evaluating patients with sarcoidosis, the expected DLCO%, 6MWT distance and desaturation during the test were found to be related to pulmonary hypertension, but the strongest predictor was the desaturation detected during the 6-minute walk test.

Limitaitons

Our study had some limitations. A small number of cases from many disease groups were included in the study. For this reason, evaluations regarding disease subgroups could not be made. The small number of cases in some disease groups was insufficient for comparison and statistical analysis. Since the follow-up period of the cases was not long (one year), the relationship between the development of pulmonary hypertension and mortality and morbidity could not be examined.

CONCLUSION

Cases diagnosed with interstitial lung disease with a decrease in respiratory function tests and exercise capacity should be investigated for pulmonary hypertension if there is clinical suspicion. If necessary, the diagnosis should be confirmed with right heart catheterization, which is the gold standard diagnostic method.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (Date: 31.08.2010, Decision No: 2010/165).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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An evaluation of noninvasive mechanical ventilation application in intensive care

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ABSTRACT

Aims: Noninvasive mechanical ventilation (NIMV) is a positive pressure treatment applied with a mask without the need for endotracheal intubation in patients with acute and chronic respiratory failure. C-reactive protein (CRP), procalcitonin (PCT), albumin, red blood cell distribution width (RDW), and mean platelet volume (MPV) are frequently used markers in clinical practice. Arterial blood gas (ABG) analysis is a standard method in clinical practice in intensive care, which is known to have a higher risk of complications than venous blood gas (VBG) analysis. Studies have shown a strong correlation between ABG and VBG with regard topH, partial arterial carbon dioxide pressure ($PaCO_2$), and serum bicarbonate (HCO_3). In this study, we aimed to evaluate the relationship between CRP, PCT, albumin, MPV, and RDW and in-hospital mortality and acute respiratory failure in patients undergoing NIMV. Our secondary aim was to evaluate the relationship between these parameters and VBG values.

Methods: Patients with acute hypoxemic and hypercapnic respiratory failure that underwent NIMV in intensive care unit (ICU) were evaluated retrospectively.

Results: The study included 99 patients with a mean age of 69.39±9.79 years. In-hospital mortality occurred in 5 (5.1%) patients. Hypercapnic respiratory failure was detected in 66 (66.7%), hypoxemic respiratory failure in 19 (19.2%), and hypoxemic + hypercapnic respiratory failure in 14 (14.1%) patients. PCT was significantly higher in patients with acute hypoxemic respiratory failure and MPV was significantly higher in patients with acute hypercapnic respiratory failure compared to other patients ($p<0.05$ for both). Both MPV and RDW were significantly higher in patients with in-hospital mortality ($p<0.05$). The baseline and 24-h PO_2/FiO_2 ratios were significantly lower in patients with acute hypoxemic+hypercapnic respiratory failure ($p<0.05$). The 24-h PO_2/FiO_2 ratio was significantly lower in patients with in-hospital mortality compared to patients without mortality ($p<0.05$).

Conclusion: Both RDW and MPV should be employed in predicting mortality in patients undergoing NIMV due to acute respiratory failure. Further multicenter, prospective studies are needed to evaluate the PaO_2/FiO_2 ratio particularly in VBG in patients receiving NIMV due to acute respiratory failure.

Keywords: Mean platelet volume, noninvasive mechanical ventilation, red blood cell distribution width, venous blood gas

INTRODUCTION

Noninvasive mechanical ventilation (NIMV) is a positive pressure treatment applied with a mask without the need for endotracheal intubation in patients with acute and chronic respiratory failure. Physiopathologically, NIMV promotes alveolar ventilation, reduces pulmonary workload, and provides improvement in the ventilation/perfusion ratio. NIMV is frequently administered in clinical practice without delaying invasive mechanical ventilation in acute hypoxemic or hypercapnic respiratory failure.[1,2] NIMV may help reduce the intubation rate, hospitalization period, and mortality. Moreover, NIMV is considered the gold standard, particularly in acute hypercapnic respiratory failure.[3] Within the first 1-2 hours of NIMV commencement, a number of significant contributions of NIMV including improvement in pH and partial arterial oxygen pressure (PaO_2) and reduction in respiratory rate and partial arterial carbon dioxide pressure ($PaCO_2$) can be observed.[4]

It is known that the pulmonary and systemic inflammatory response is increased in patients receiving invasive

mechanical ventilation (IMV). Additionally, increased inflammatory markers have been reported in patients with chronic obstructive pulmonary disease (COPD) receiving long-term NIMV at home.[3] Serum procalcitonin (PCT) is a polypeptide of a small molecular weight substance synthesized by C cells of the thyroid gland. Additionally, PCT has also been shown to be secreted in bacterial infections and severe systemic reactions and it is practically used to differentiate bacterial infections. C-reactive protein (CRP) is an acknowledged acute inflammatory response marker. Studies have shown that both PCT and CRP increase as a result of oxidative stress and inflammatory immune response.[1] In some other studies, PCT levels have been shown to be higher in patients that received NIMV in intensive care unit (ICU) compared to patients that did not. Moreover, in exacerbation of COPD, both PCT and CRP levels have been found to be higher in the group with NIMV failure.[5] Red blood cell distribution width (RDW) and mean platelet volume (MPV) are well-known complete blood count (CBC) measures routinely used in clinical practice and are also acute phase parameters associated with inflammation and used to predict mortality. MPV is an indicator of platelet activation and may be detected at low levels in the inflammation site in clinical conditions such as sepsis since it is a marker of accumulation in that site. There are studies reporting on an association between the RDW value assessed during ICU admission and respiratory failure. In a retrospective study by Zheng et al.[6], high CRP and MPV values in IMV were associated with weaning failure.[7] Similarly, high CRP and low albumin levels have been associated with NIMV failure in patients receiving NIMV in ICU.[4]

Arterial blood gas (ABG) and venous blood gas (VBG) are frequently used parameters in ICU practice. Although ABG analysis is a standard method, it has a higher risk of complications than VBG analysis. In a study evaluating 246 patients admitted to the emergency department, 196 of whom had respiratory failure, a high degree of correlation was found between venous and arterial pH estimation.[8] Moreover, in a study that evaluated 132 patients with COPD, a strong correlation was found between ABG and VBG with regard to pH, PaCO2, and serum bicarbonate (HCO_3).[9]

In this retrospective study, we aimed to evaluate the relationship between the CRP, PCT, albumin, MPV, and RDW values measured at the time of admission and in-hospital mortality and acute respiratory failure in patients undergoing NIMV [bilevel-positive airway pressure (BiPAP)] due to acute hypoxemic and hypercapnic respiratory failure. Our secondary aim was to evaluate the relationship between these values and VBG values.

METHODS

After obtaining an ethics committee approval from Pamukkale University Non-interventional Clinical Researches Ethics Committee (Date: 03.07.2019, Decision No: 60116787-020/45998), patients that underwent NIMV due to acute hypercapnic and hypoxemic respiratory failure in ICU were evaluated retrospectively. Patients aged below 18 years, pregnant women, and those with NIMV contraindications (e.g. cardiac and respiratory arrest, hemodynamic instability, myocardial infarction, arrhythmia, trauma, craniofacial anomalies, encephalopathy, surgery, upper gastrointestinal bleeding), and patients with IMV were excluded from the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The CRP, PCT, albumin, RDW, and MPV values measured at ICU admission were recorded for each patient. The Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment Score (SOFA) scores of the patients were retrieved from hospital databases.[10] Since all the patients included in the study had VBG values, the pH, $PaCO_2$, PaO_2 and oxygen saturation (SO_2) values were measured from venous blood samples. Due to the retrospective nature of the study, ABG samples could not be obtained at the 24th hour of ICU admission. For this reason, the ratio of PaO_2 to the inspired oxygen (FiO_2) at admission and at the 24th hour was calculated according to the PaO_2 measured from venous blood samples. CBC was performed using the photometric method, the CRP and albumin levels were assessed using the turbidimetric method, and PCT levels were measured using the immunoassay method. Normal ranges of RDW, MPV, CRP, and albumin were 11.6-17.2%, 7.8-11 fL, 0-5 mg/L, and 3.5-7.2 mg/L, respectively. All the patients included in the study received NIMV with BIPAP-ST in ICU. In all patients, the tidal volume was adjusted to 6 ml per kilogram of predicted body weight. During NIMV, the initial pressure support ventilation (PSV), positive end-expiratory pressure (PEEP), and FiO_2 values were recorded for each patient. Respiratory failure was defined as PaO_2 below 60 mmHg and $PaCO_2$ above 45 mmHg in ABG. Patients were divided into two groups: (i) hypoxemic and (ii) hypercapnic respiratory failure. Hypoxemic respiratory failure was defined as PaO_2<60 mmHg and hypercapnic respiratory failure was defined as $PaCO_2$>45 mmHg.[11]

Statistical Analysis

Data were analyzed using IBM SPSS for Windows version 27.0 (Armonk, NY: IBM Corp.). Continuous variables were expressed as mean±standard deviation (SD) and categorical variables were expressed as frequencies (n) and percentages (%). Normal distribution of continuous variables was assessed using Kolmogorov-Smirnov test.Two groups were compared using Mann-Whitney U test or independent samples t-test as appropriate. Three or more groups were compared using Kruskal-Wallis H test or one-way ANOVA test as appropriate. For all analyses, a p value of <0.05 was considered significant.

RESULTS

The study included 99 patients (26.3% female and 73.7% male) with a mean age of 69.39±9.79 years. In-hospital mortality occurred in 5 (5.1%) patients. IMV was used in 17 (17.2%) patients within the first 24 hours of ICU admission. Of all patients, 18 (18.2%) had pneumonia and 81 (81.8%) had COPD. Hypercapnic respiratory failure was detected in 66 (66.7%), hypoxemic respiratory failure in 19 (19.2%), and hypoxemic+hypercapnic respiratory failure in 14 (14.1%) patients. Sedation was performed in 11 (11.1%) patients. Mean APACHE II and SOFA scores were 17.11±5.66 and 5.20±2.46, respectively. Mean serum levels of CRP, PCT, RDW, MPV and albumin were 72.80±85.20 mg/ml, 0.57±1.83 ng/ml, 17.16%±4.84%, 9.21±1.23 fl, and 32.94±5.33 g/L, respectively. Mean PSV, PEEP, and FiO2 values were 19.42±7.53, 7.60±1.48, and 60.58±16.54, respectively. Table 1 presents the laboratory parameters measured at admission.

Table 1. Baseline laboratory parameters

Variables	Mean±SD
PO_2(mmHg)/FiO_2	72.08±31.48
PO_2(mmHg)/FiO_2 (24-h)	88.55±32.88
VBG-pH	7.33±0.09
VBG- PCO_2 (mmHg)	67.41±17.69
VBG-PO_2 (mmHg)	40.65±11.62
SO_2 (%)	65.34±14.66
CRP (mg/L	72.80±85.20
PCT (ng/mL)	0.57±1.83
RDW (%)	17.16±4.84
Albumin (g/L)	32.94±5.33
MPV (fL)	9.21±1.23

CRP: C-reactive protein, PCT: Procalcitonin, RDW: Red blood cell distribution width, MPV: Mean platelet volume, VBG: Venous blood gas, PO_2/FO_2: Ratio of partial oxygen pressure to inspired oxygen, PO_2: Partial oxygen pressure, PCO2: Partial carbon dioxide pressure, SO_2: Oxygen saturation, SD: Standard deviation

In patients with COPD, the SOFA score and the PO_2/FiO_2 ratio at 24 hours were significantly higher and the PCT values at admission were significantly lower than those of patients with pneumonia (p<0.05 for all). However, no significant difference was found between the two groups with regard to PSV, PEEP, and FiO_2 values (p=0.385, p=0.252, and p=0.293, respectively) Table 2. In patients that received sedation during NIMV, the APACHE II score and FiO_2 value were significantly higher and the PCT value was significantly lower than those of other patients (p=0.001, p=0.018, and p=0.020, respectively).

Table 2. Association of other parameters in COPD and pneumonia groups

Variables	Pneumonia (n=18)	COPD (n=81)	p
	Mean± SD	Mean± SD	
APACHE	17.28±8.00	17.07±5.06	0.960[b]
SOFA	4.78±3.80	5.30±2.08	0.043[b]
PO_2 (mmHg)/FiO_2	59.79±18.14	74.81±33.20	0.091[b]
PO_2 (mmHg)/FiO_2 (24-h)	74.73±28.06	91.66±33.23	0.048[a]
pH	7.31±0.10	7.34±0.09	0.284[a]
PCO_2 (mm/Hg)	60.90±21.83	68.85±16.45	0.085[a]
PO_2 (mm/Hg)	38.97±12.25	41.02±11.53	0.490[b]
SO_2 (%)	63.75±17.09	65.69±14.16	0.860[b]
NIMV PSV	18.17±3.76	19.70±8.13	0.385[b]
NIMV PEEP	7.22±1.52	7.68±1.47	0.252[b]
FiO_2 (%)	63.33±14.95	59.96±16.89	0.293[b]
CRP (mg/L)	104.29±102.16	65.80±80.01	0.127[b]
PCT (ug/L)	1.46±3.06	0.37±1.37	0.001[b]
RDW (%)	16.30±1.92	17.35±5.10	0.376[b]
Albumin (g/L)	33.13±6.40	32.90±5.10	0.866[a]
MPV (fL)	9.11±1.74	9.23±1.10	0.690[a]

p<0.05; a=T-Test; b=Mann Whitney-U Test
COPD: Chronic obstructive pulmonary disease, APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment score, CRP: C-reactive protein, PCT: Procalcitonin, RDW: Red blood cell distribution width, MPV: Mean platelet volume, VBG: Venous blood gas, PO2/FiO2: Ratio of partial oxygen pressure to inspired oxygen, PO2: Partial oxygen pressure, PCO2: Partial carbon dioxide pressure, SO2: Oxygen saturation, NIMV: Noninvasive mechanical ventilation, PSV: Pressure support ventilation, PEEP: Positive end-expiratory pressure, FiO2: Inspired oxygen, SD: Standard Deviation

In patients with acute hypoxemic respiratory failure, the SOFA score and the PCO_2 and PSV values were significantly lower and the PCT value was significantly higher than those in patients with acute hypercapnic respiratory failure and hypoxemic + hypercapnic respiratory failure (p<0.05 for all). Both the admission and 24-h PO_2/FiO_2 and MPV values were significantly higher in patients with acute hypercapnic respiratory failure compared to patients with acute hypoxemic and hypoxemic+hypercapnic respiratory failure (p<0.05). In patients with acute hypoxemic+hypercapnic respiratory failure, pH was significantly lower and FiO_2 was significantly higher in VBG compared to other patients (p<0.05) Table 3.

Table 3. Relationship between causes of acute respiratory failure and other parameters

Variables	Acute hypoxic respiratory failure (n=19)	Acute hypercapnic respiratory failure (n=66)	Acute hypercapnic +hypoxemic respiratory failure (n=14)	p
	Mean± SD	Mean± SD	Mean± SD	
APACHE II	15.79±7.81	17.15±4.58	18.71±6.82	0.125[b]
SOFA	4.32±3.28	5.32±1.95	5.86±3.18	0.043[b]
PO_2(mmHg)/ FiO_2	62.22±23.69	78.65±34.25	54.48±11.55	0.010[b]
PaO_2(mmHg)/ FiO_2 (24-h)	77.29±32.44	94.79±33.10	73.32±23.61	0.023[a]
pH	7.34±0.09	7.34±0.09	7.27±0.09	0.017[a]
PCO_2 (mmHg)	48.70±15.20	72.22±15.71	70.09±12.97	0.001[a]
PO_2 (mmHg)	38.52±12.76	41.58±11.82	39.16±9.02	0.505[b]
SO_2 (%)	58.29±17.03	67.30±13.73	65.63±13.53	0.109[b]
NIMV PSV	16.74±3.02	20.15±8.80	19.64±3.84	0.021[b]
NIMV PEEP	7.53±1.47	7.67±1.44	7.36±1.78	0.723[b]
FiO_2 (%)	64.74±17.12	57.08±15.77	71.43±14.06	0.003[b]
CRP (mg/L)	100.85±98.56	66.26±83.84	65.55 ±68.58	0.288[b]
PCT (ug/L)	1.34±3.01	0.40±1.51	0.31±0.22	0.032[b]
RDW (%)	18.19±10.13	16.77±2.26	17.58±2.48	0.265[b]
Albumin (g/L)	32.18±5.25	32.62±5.10	35.49±6.13	0.148[a]
MPV (fL)	8.56±1.70	9.45±1.03	8.96±1.08	0.014[a]

p<0.05; a=One-way ANOVA, b=Kruskal-Wallis Test
APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment score, CRP: C-reactive protein, PCT: Procalcitonin, RDW: Red blood cell distribution width, MPV: Mean platelet volume, VBG: Venous blood gas, PO2/FiO2: Ratio of partial oxygen pressure to inspired oxygen, PO2: Partial oxygen pressure, PCO2: Partial carbon dioxide pressure, SO2: Oxygen saturation, NIMV: Noninvasive mechanical ventilation, PSV: Pressure support ventilation, PEEP: Positive end-expiratory pressure, FiO2: Inspired oxygen, SD: Standard Deviation

In patients that underwent IMV, the PO_2/FiO_2 ratio and the pH and SO_2 values assessed at admission and 24 hours were significantly lower and the FiO_2 and admission PCT values were significantly higher than those in other patients (p=0.004, p=0.016, p=0.040, p=0.016, p=0.001, and p=0.004, respectively).

In patients with in-hospital mortality, the SOFA score, the PO_2/FiO_2 ratio at 24 hours, and the PO_2 and SO_2 values were significantly lower compared to those in patients without mortality (p<0.05 for all). Additionally, the admission RDW and MPV values significantly higher in patients with in-hospital mortality compared to other patients (p<0.05 for all) Table 4.

Table 4. Relationship between in-hospital mortality and other parameters

Variables	In-hospital mortality		
	No (n=94)	Yes (n=5)	p
	Mean± SD	Mean± SD	
APACHE II	17.10±5.64	17.40±6.66	0.923[b]
SOFA	5.31±2.47	3.20±1.30	0.038[b]
PO2 (mmHg)/FiO2	72.99±31.84	54.96±17.71	0.215[b]
PO2 (mmHg)/FiO2 (24-h)	90.03±32.72	53.75±9.05	0.030[a]
pH	7.33±0.09	7.33±0.06	0.996[a]
PCO2 (mmHg)	68.18±17.36	52.90±19.67	0.060[a]
PO2 (mmHg)	41.25±11.46	29.32±9.48	0.022[b]
SO2 (%)	66.35±13.93	46.26±16.49	0.011[b]
NIMV PSV	19.50±7.71	18.00±2.45	0.580[b]
NIMV PEEP	7.55±1.47	8.40±1.67	0.232[b]
FiO2 (%)	59.97±16.14	72.00±21.68	0.239[b]
CRP (mg/L)	71.36±85.95	99.80±71.74	0.150[b]
PCT (ug/L)	0.57±1.87	0.57±0.71	0.105[b]
RDW (%)	17.06±4.93	19.04±1.69	0.014[b]
Albumin (g/L)	33.03±5.43	31.20±2.17	0.456[a]
MPV (fL)	8.00±0.54	9.28±1.23	0.023[a]

p<0.05; a=T-test; b=Mann-Whitney U Test
APACHE II: Acute physiology and chronic health evaluation II, SOFA: Sequential organ failure assessment score, CRP: C-reactive protein, PCT: Procalcitonin, RDW: Red blood cell distribution width, MPV: Mean platelet volume, VBG: Venous blood gas, PO2/FiO2: Ratio of partial oxygen pressure to inspired oxygen, PO2: Partial oxygen pressure, PCO2: Partial carbon dioxide pressure, SO2: Oxygen saturation, NIMV: Noninvasive mechanical ventilation, PSV: Pressure support ventilation, PEEP: Positive end-expiratory pressure, FiO2: Inspired oxygen, SD: Standard Deviation

DISCUSSION

Our results indicated that the RDW and MPV values in patients with in-hospital mortality, the PCT values in patients with acute hypoxemic respiratory failure, and the MPV values in patients with acute hypercapnic respiratory failure were significantly higher compared to those in other patients. The admission and 24-h PO_2/FiO_2 ratio were significantly lower in patients with acute hypercapnic + hypoxemic respiratory failure compared to patients with acute hypoxemic respiratory failure and patients with acute hypercapnic respiratory failure. Moreover PCO_2 level was significantly higher in patients with acute hypercapnic+hypoxemic respiratory failure compared to patients with acute hypoxemic respiratory failure. However, the PO_2/FiO_2, PO_2, and SO_2 values were significantly lower in patients with in-hospital mortality compared to patients without mortality.

Studies suggest that VBG can be preferred over ABG, particularly in the evaluation of the acid-base balance.[8,9] It has also been shown that the SO_2/FiO_2 ratio can be preferred over the PaO_2/FiO_2 ratio in ICU patients receiving NIMV.[12-14] In a multicenter study evaluating patients admitted to hospital due to an acute illness, the SO_2/FiO_2 ratio was assessed on days 1, 2, 3, and 7 and the results indicated that the SO_2/FiO_2 ratios assessed on day 1 and 2 were useful in predicting in-hospital mortality.[15] Due to the retrospective nature of our study, the assessment of the parameters was performed by VBG analysis, which is frequently used in ICU practice. Instead of the SO_2/FiO_2 ratio, the PO_2/FiO_2 ratio obtained at admission and 24 hours was analyzed. To our knowledge, there is no study in the literature evaluating VBG-based parameters and the PO_2/FiO_2 ratio in patients undergoing NIMV due to acute respiratory failure. Our analyses indicated that the 24-h PO_2/FiO_2 and PO_2 values in patients with in-hospital mortality and both the admission and 24-h PO_2/FiO_2 ratios in patients with acute hypercapnic+hypoxemic respiratory failure were significantly lower than those in patients with acute hypoxemic respiratory failure and patients with hypercapnic respiratory failure. Nevertheless, in our study, the PO_2/FiO_2 ratio obtained in patients undergoing NIMV could not be compared with the data in the literature due to the lack of studies on the relationship between the PO_2/FiO_2 ratio and mortality or types of acute respiratory failure.

Serum albumin level is a significant parameter in malnutrition-related inflammatory response syndrome. The effects of serum albumin level on NIMV include hypoalbunemia, respiratory muscle weakness, and decreased lung function.[16] In a study evaluating patients with COPD hospitalized in ICU, a negative correlation was found between in-hospital mortality and serum albumin level <3 g/dL.[17] In another study that was conducted in patients with COPD, low serum albumin level was found to be associated with an increase in hospitalization, acute respiratory failure, and mortality.[18] However, in our study, no significant relationship was found between serum albumin level and mortality or types of acute respiratory failure. This finding could be attributed to the fact that serum albumin level was assessed with a single measurement and the parameters that could affect serum albumin level such as kidney and liver function tests and nutritional status were not evaluated.

CRP and PCT are acknowledged biomarkers frequently used in daily clinical practice. CRP increases in systemic inflammation although it has a low sensitivity and specificity. PCT, on the other hand, has been shown to be an indicator of both bacterial infection and oxidative stress. This biomarker is particularly used in antimicrobial treatment decisions. In a study conducted in patients with COPD, increased CRP and PCT levels were found to be significantly associated with NIMV failure. In some other studies, a PCT level of >0.24-0.25 ng/ml was found to be associated with increased mortality rate.[19,20] In a study conducted in patients with COPD, it was reported that an increase of over 50% in PCT was associated with the requirement of IMV during NIMV and with increased clinical mortality.[5] On the other hand, increased CRP has been shown to be an independent factor for mortality, particularly in patients with COPD.[20-22] In our study, CRP did not establish a significant relationship with acute respiratory failure types and mortality. In contrast, although PCT established no significant relationship with mortality, it was significantly higher in patients with acute hypoxemic respiratory failure. These findings are inconsistent with those reported in the literature ,which could be ascribed to the fact that the PCT level was assessed with a single measurement, its assessment could not be standardized due to the retrospective nature of the study, and the parameters that could affect the PCT level such as kidney and liver function tests were not evaluated.

Both RDW and MPV are routinely measured parameters in CBC analysis. Platelets are significant indicators of inflammation and immunity. MPV is a simple and practical

indicator of platelet functions. In some ICU studies, increased MPV and RDW levels have been shown to be poor prognostic factors particularly for diabetes mellitus, coronary artery disease, pulmonary thromboembolism, and COPD. In a study evaluating patients with IMV, increased MPV levels were detected in patients with weaning failure.[6] In another study, in-hospital mortality was found to be associated with increased MPV in patients followed up in ICU due to pneumonia. The authors also noted that the MPV value is affected by age, kidney functions, and the presence of peripheral arterial diseases.[23] In a study evaluating COPD patients receiving NIMV, increased RDW levels were found to be a negative prognostic factor and also an increase in RDW within the first three days of ICU hospitalization was found to be a poor prognostic factor for mortality.[24] In a study evaluating 153 hospitalized patients with community-acquired pneumonia, increased RDW and MPV values were associated with high mortality.[25] Similarly, in our study, both RDW and MPV values were significantly higher in patients with mortality and the MPV value was significantly higher in patients with acute hypercapnic respiratory failure. Although the RDW value was higher in patients with acute hypoxemic respiratory failure, the difference was statistically insignificant. These findings could not be compared with the literature since, to our knowledge, there is no study in the literature evaluating the relationship between RDW and MPV and types of acute respiratory failure.

Limitations

Our study was limited in several ways. First and foremost, it was a retrospective study and had a small number of patients. Second, serum levels of CRP, PCT, albumin, RDW, and MPV were assessed with a single measurement and no serial measurements were performed, and thus no standardization was established. Finally, in-hospital mortality was assessed independently.

CONCLUSION

Our study is a rare study that evaluated VBG in patients that underwent NIMV due to acute respiratory failure. The results indicated that RDW and MPV values should be taken into consideration in predicting mortality. Further multicenter, prospective studies are needed to evaluate the PO_2/FiO_2 ratio particularly in VBG.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Pamukkale University Non-interventional Clinical Researches Ethics Committee (Date:03.07.2019, Decision No: 60116784-020-45998).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Chronic thromboembolic pulmonary hypertension in acute pulmonary embolism: a risk factor evaluation study

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ABSTRACT*

Aims: Pulmonary thromboembolism (PTE) is a highly mortal disease, defined by presence of a thrombus partially or completely obstructing pulmonary arteries and/or veins, commonly originating from deep venous system. Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of PTE with high mortality if not treated properly. In recent studies, the incidence of CTEPH was found between 0.4-9.1%. Due to clinically silent PTE in roughly 50% of patients, it is difficult to pinpoint the exact incidence of CTEPH. This study aims to investigate PTE patients during their long-term follow up to observe CTEPH presence and evaluate CTEPH risk factors.

Methods: Patients who had been evaluated in emergency service and/or admitted to the pulmonary medicine ward between January 2014 and January 2017 with PTE diagnosis confirmed by computed tomography pulmonary angiogram (CTPA) were accepted retrospectively into the study. Their echocardiography, CTPA and lower extremity venous Doppler ultrasonography at 3rd, 6th and 12th months follow up were also included. In the patient group with pulmonary arterial pressure (PAP) above 50 mmHg and residual thrombosis at CTPA, ventilation-perfusion scintigraphy was performed and was added to the study. Among those suitable for CTEPH, right cardiac catheterization was done to confirm the diagnosis and accepted as CTEPH. In addition to this group, patients who were not found suitable for right cardiac catheterization but were clinically suitable for CTEPH are also included in the CTEPH group.

Results: The average age of patients included into the study was 62 (±16.5), with 71 (39%) being male and 111 (61%) female. As for risk factors, 130 (71.4%) had acquired, 16 (8.8%) had genetic and the rest 36 (19.8%) did not have any prominent risk factors. At the time of diagnosis, 10 patients were accepted as massive, 26 as sub massive and the rest 139 were considered non-massive PTE. Due to hemodynamic instability, 7 (3.8%) patients were given thrombolytic therapy. During 1 year follow-up, 5 (2.7%) patients were diagnosed with CTPH. When further investigation was performed on these 5 patients, atrial fibrillation (AF) and persistent thrombosis at 12-month follow up CTPA and PAP above 55 mmHg upon time of diagnosis were found significant risk factors (p being 0.001/0.023/0.009 respectively). In multivariate analysis, no independent predictive factors were found in regards to CTEPH diagnosis.

Conclusion: CTEPH is a preventable complication of PTE with severe mortality and morbidity if not properly treated. It might prove useful to utilize echocardiography and CTPA together, especially in high risk groups, to diagnose patients in the early stage of CTEPH with no evident signs or symptoms.

Keywords: Pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension, right cardiac catheterization

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INTRODUCTION

Pulmonary thromboembolism (PTE), a highly fatal disease that develops as a result of complete or partial occlusion of the pulmonary artery and/or its branches by a thrombus that breaks away from the deep venous system and reaches the pulmonary bed, occurs frequently but is difficult to diagnose.[1] Chronic thromboembolic pulmonary hypertension (CTEPH) develops when recurrent and organized PTE or in situ thrombosis occludes the pulmonary vascular bed and causes structural changes. CTEPH is diagnosed by visualizing residual perfusion defects in ventilation-perfusion (V/P) scintigraphy despite using anticoagulants at effective doses for at least three months after an acute pulmonary embolism

episode, detecting a mean pulmonary artery pressure of 20 mmHg or above, a pulmonary capillary wedge pressure (PCWP) of 15 mmHg or below and excluding other conditions that may cause pulmonary hypertension (PHT).[2] Although its true incidence remains unknown, its incidence after acute PTE has been found to range between 1% and 9%.[3] CTEPH is characterized by the presence of occlusive fibrotic thromboembolic material in large pulmonary vessels and accompanying microvascular arteriopathy.[4] Although PTE is the initiating event in CTEPH, vascular remodeling that develops in small vessels with the effect of the mediators released from cells found in thrombus has an important role in the pathogenesis.[5,6] These changes cause an increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) over time. Pulmonary hypertension (PHT) is a severe medical condition characterized by increased pulmonary artery pressure (PAP) which may frequently result in progressive right ventricular (RV) failure and death.[4] CTEPH is included in class 4 pulmonary hypertension, and is the only pulmonary hypertension subgroup that may be cured by pulmonary endarterectomy (PEA), a surgical treatment method.[7]

In this study we aimed to investigate the incidence of CTEPH development over long follow-up periods in patients with acute PTE, to define factors that predispose patients to CTEPH, which patients develop CTEPH, patients' profile, type of admission, clinical presentation, diagnostic methods applied, and treatment approaches, and to contribute to the literature on CTEPH.

METHODS

The ethical approval of the study was received from the ethics committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, where the study was conducted, on 19.02.2018 with the decision number of 46/12. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The medical records of patients who were admitted to University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Health Application and Research Center chest diseases outpatient clinic and diagnosed with acute PTE using thoracic computerized tomographic angiography (CTPA) between January 2014 and January 2017 were retrospectively reviewed. The files were scanned with the "I-26=Pulmonary Embolism" ICD diagnostic code using the Alpdata Medical Information System from the hospital information management system. Laboratory results, and radiology reports of patients diagnosed with PTE were reviewed. Patients with missing medical records, those who were younger than 16 years of age, and those who did not attend their follow-up appointments at 3rd, 6th, and 12th months after discharge due to any reason were excluded. A total of 182 patients with a minimal follow-up duration of 2 years were enrolled.

The patients' demographic characteristics, PTE-related risk factors, comorbidities, D-dimer (quantitative-PCR), troponin I, clinical probability scores (Wells, Modified Genova), site and diffuseness of PTE involvement in ECHO and CTPA, treatment methods and treatment durations were recorded.

The CTPA and ECHO results of the patients with PTE, both at admission and at 3rd, 6th, and 12th months of follow-up were recorded. Pulmonary hypertension was considered to have a low probability when PAP was below 36 mmHg; moderate probability when PAP was between 37 mmHg and 50 mmHg; and high probability when PAP was above 50 mmHg.[8] In patients with PAP above 36 mmHg despite effective anticoagulant use for more than 3 months, a V/P scan was performed to evaluate CTEPH when there were signs of chronic thrombus in pulmonary arteries on CTPA. Patients whose V/P could not be performed for any reason were evaluated for CTEPH using the CTPA result.

Patients with suspected CTEPH were evaluated further if residual thrombus persisted on CTPA at 3rd, 6th, and 12th month follow-up appointments despite effective anticoagulant use for more than three months. If residual thrombus were reported on CTPA, a V/P scan was performed in patients with a PAP over 36 mmHg on ECHO.

In patients who refused to give written consent for right heart catheterization or for whom invasive intervention was not considered appropriate due to hemodynamic disorders or comorbidities, CTEPH was diagnosed if PAP was >50 mmHg after anticoagulant use for at least three months and there were findings compatible with CTEPH on CTPA or V/P scintigraphy.[2]

IBM SPSS (Statistics Program for Social Scientists) 20 (USA) software was used for statistical analyses. Continuous data were reported as mean ± standard deviation. Categorical data were presented as percentage (%). Normality of data was tested with Kolmogorov Smirnov test. Mann Whitney U test and Student's t test were used to compare two independent groups with respect to non-normally and normally distributed data, respectively. Chi-square or Fisher's exact test was used to compare independent categorical variables; Cochrane's Q test was used for the comparison of dependent categorical variables. A ROC analysis was performed to determine the cut-off values of the tests that could be used to diagnose CTEPH. A p value of less than 0.05 was considered statistically significant.

RESULTS

The patients who were included in the study had a mean age of 62 (±16.5) years; 71 (39%) patients were male and 111 (61%) were female. As for the cause of pulmonary hypertension, 130 (71.4%) patients had acquired pulmonary hypertension and 16 (8.8%) had genetic risk factors while 36 (19.8%) patients had idiopathic PTE with no identifiable risk factor.

The ECHO findings and CTPA results of patients with acute pulmonary embolism included in the study were evaluated at control visits at 3rd, 6th, and 12th months. Forty-one patients were found to have residual pulmonary embolism on ECHO evaluation. Because there were mismatch defects compatible with CTEPH on V/P scintigraphy, the patients were evaluated with right heart catheterization. CTEPH was confirmed by detecting a mean PAP of 25 mmHg on right heart catheterization in one of the patients, and 50 mmHg in another patient. In two of the other three patients, invasive catheterization was not deemed appropriate by the

cardiology department due to comorbidities; one patient did not undergo catheterization because he did not give written consent.

The patients were considered to have CTEPH based on the ECHO results, imaging techniques, and clinical presentation. To conclude, residual pulmonary thrombus persisted despite effective anticoagulant therapy for 3 months in 41 of 182 patients with acute pulmonary embolism included in the study. Five of those 41 patients were diagnosed with CTEPH. In our strategy, the incidence of CTEPH after acute pulmonary embolism was calculated 2.7% (5 of 182 patients). The characteristics of the patients diagnosed with CTEPH are shown on Table 1.

Table 1. Characteristics of patients with CTEPH

	Sex	Age	Diagnosis sPAP (mmHg)	PTE clinical evaluation	Diagnostic method	RHC mPAP (mmHg)
Patient 1	Female	47	100	submassive	RHC	50
Patient 2	Male	75	85	submassive	RHC	25
Patient 3	Male	74	85	Non- massive	V/P scintigraphy	-
Patient 4	Female	68	70	Non-massive	V/P scintigraphy	-
Patient 5	Female	86	60	Non-massive	V/P scintigraphy	-

(sPAP: Systolic pulmonary artery pressure, RHC: Right heart catheterization, mPAP: Mean pulmonary artery pressure)

Five patients with CTEPH antd 36 patients without CTEPH but residual pulmonary thrombus despite anticoagulant therapy for 3 months after acute pulmonary embolism were compared with regard to the risk factors of CTEPH. The groups with and without CTEPH were not significantly different with respect to age, sex, Wells and Modified Genova scores, D-dimer, and troponin level. The median CRP level of the patients with CTEPH was significantly higher than the median CRP level of the patients who did not develop CTEPH (p:0.042).

No significant difference was found between the patients with and without CTEPH with respect to the rates of diabetes mellitus, hypertension, coronary artery disease, chronic pulmonary disease, and malignancy (p 0.066/1.00/1.00/0.299/1.00, respectively). All patients with AF were in the CTEPH group. The diagnosis of CTEPH was more frequent in patients with AF than those without (p:0.001).

An analysis of the patients by the presence of residual thrombus on CTPA showed that all patients with CTEPH had residual thrombus whereas 21% of patients without CTEPH had residual thrombus on 12th-month CTPA (p:0.023). No significant difference was found between the patients with and without CTEPH regarding the presence of residual thrombus on CTPA (p:0.579) Table 2.

The patients with CTEPH had a significantly higher mean PAP value both at the time of diagnosis and at 3rd, 6th, and 12th months than patients without CTEPH (p<0.001/0.043/<0.001/<0.001, respectively) (Table 3). A ROC analysis was done to determine the cut-off value of PAPs at the time of diagnosis, which was shown in Figure. The AUC value was 0.897, cut-off 55 mmHg, sensitivity 80, and specificity 83.3 Table 3.

Table 2. Comparison of patients with and without CTEPH by comorbidities

	CTEPH (+) n:5	CTEPH (-) n:36	p
Age, years (sd)	71 (±14.7)	63 (±15.5)	0.273
Sex			1.00
Female	3 (60)	23 (63.9)	
Male	2 (40)	13 (36.1)	
D-Dimer	869 (609-892)	1920 (153-17887)	0.222
CRP	31 (12-65)	15 (5-58)	0.042
Diabetes mellitus	2 (40)	2 (5.6)	0.066
Hypertension	1 (20)	10 (27.8)	1.00
Coronary artery disease	1 (20)	8 (22.2)	1.00
Chronic pulmonary disease	2 (40)	7 (19.4)	0.299
Atrial fibrillation	3 (60)	0 (0)	0.001
Presence of residual thrombus on CTPA thrombus on CTPA thrombus on CTPA			
6th month	1 (33.3)	17 (56.7)	0.579
12th month	0 (0)	15 (78.9)	0.023
sPAP levels at ECHO follow-ups (%)(mean±SD)			
sPAP at the time of diagnosis	77 (±23.6)	41 (±14.3)	<0.001
sPAP 3rd month	55 (±13.2)	38 (±12.8)	0.043
sPAP 6th month	71 (±19.4)	33 (±10.9)	<0.001
sPAP 12th month	71 (±11.1)	35 (±14.5)	<0.001

CRP: C-Reactive protein, CTPA: Computed tomography pulmonary angiogram, sPAP: Systolic pulmonary artery pressure, sd: Standard deviation

Table 3. Results of the ROC analysis of sPAP level at the time of diagnosis for the diagnosis of CTEPH

AUC	Cut-off	Sensitivity	Specificity	p
.897	55	80	83.3	0.004

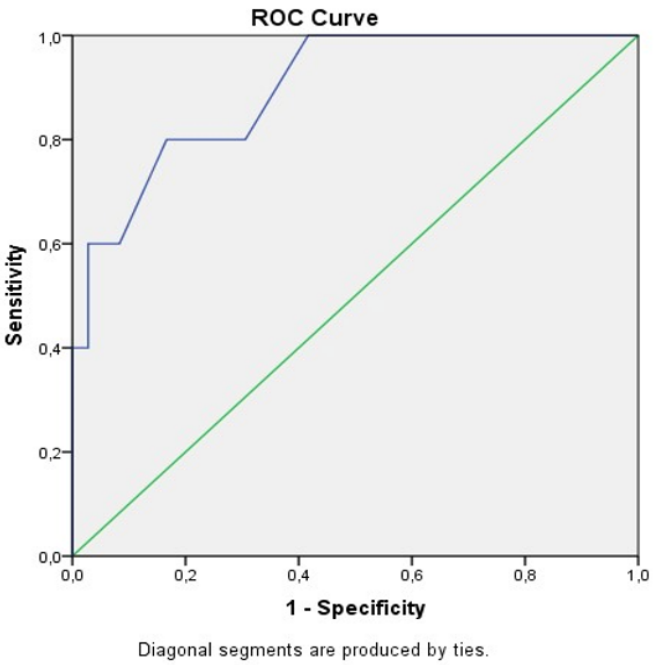

Figure. ROC curve for the PAPs value at the time of diagnosis for use in the diagnosis of CTEPH

A univariate analysis was performed to determine the risk factors for developing CTEPH, and its results are shown on Table 4. The statistically significant risk factors were AF, residual thrombus on CTPA taken at 12th month and the PAPs measured at the time of diagnosis (p 0.001/0.023/0.009, respectively). A multivariate analysis, however, failed to detect any independent predictive factor for CTEPH.

Table 4. Results of the univariate analysis for the risk factors of CTEPH

		CI		
	p	OR	Lower limit	Upper limit
Age	0.636	2.5	0.25	25.17
Gender (Male/Female)	1.00	1.2	0.17	7.99
Diyabetes mellitus	0.066	0.09	0.01	0.87
Hypertension	1.00	1.5	0.15	15.49
Coronary artery disease	1.00	1.1	0.11	11.72
Atrial fibrillation	0.001	-	-	-
Chronic pulmonary disease	0.299	0.36	0.05	2.59
Malignancy	1.00	-	-	-
Thrombophilia	1.00	-	-	-
Presence of residual thrombus on CTPA 6th month	0.579	0.38	0.03	4.68
Presence of residual thrombus on CTPA 12th month	0.023	-	-	-
Concomitant DVT	0.373	1.14	0.91	1.42
sPAP (at the time of diagnosis) ≥55	0.009	20	1.88	211.84

(CTPA: Computed tomography pulmonary angiogram, sPAP: Systolic pulmonary artery pressure)

DISCUSSION

Chronic thromboembolic pulmonary hypertension (CTEPH), which develops as a result of fibrous remodelling, is a long-term complication of acute pulmonary embolism that is uncommon but has high morbidity and mortality. In the present study we primarily aimed to determine the incidence of CTEPH in patients diagnosed with acute pulmonary embolism after long-term follow-up; our secondary aim was to determine the factors associated with CTEPH development. In that context, we calculated the incidence of CTEPH as 2.7% after a minimum follow-up of 12 months and a maximum follow-up of 24 months in 182 patients with acute pulmonary embolism. Our study determined that the presence of AF, residual thrombus on CTPA taken at the 12th-month follow-up, and an elevated sPAP measured at the time of diagnosis (55 mmHg or above) as risk factors for developing CTEPH.

The exact incidence after acute PTE is unclear; it was previously thought to be between 0.1% and 0.5%. However, recent studies have reported higher figures. In a study conducted with 91 patients, Dentali et al.[9] found an incidence of 8.8% over a follow-up of 6-12 months. In a study by Marti et al.,[10] which followed 110 patients for 2 years, the incidence was found 9.1%. A review of contemporary studies indicates that the incidence of CTEPH following acute pulmonary embolism ranges between 0.4% and 9.1%, with an average figure around 4%.[11-13] This variation on the incidence figures stems from the differing population sizes of the studies, diagnostic methods, cut-off levels used for the diagnosis, and follow-up durations. Some of the studies on the incidence of CTEPH after acute PTE have been prospectively conducted while some of them have been retrospectively conducted. While an echocardiographic study has been performed in all enrolled patients in some studies, some others have enrolled patients with symptoms compatible with CTEPH. It was found out that only symptomatic patients with persistent dyspnea are screened for pulmonary hypertension by ECHO in most studies.[11,12,14,15] In a study conducted by Surie et al.[16] with 110 patients, a questionnaire about the possible symptoms of CTEPH (new-onset dyspnea or dyspnea that worsened after PTE, which affects daily life activities etc.) was applied to the patients with a history of PTE 2-4 years after the acute event. Patients with suspected CTEPH were subjected to further evaluation using ECHO and V/P scintigraphy. After a mean follow-up duration of 3 years, the incidence was found to be 2.7%. All of our patients, whether symptomatic or not, regularly underwent echocardiographic evaluation. Although excluding asymptomatic patients is a cost-effective approach, it can be considered to cause finding a lower CTEPH incidence.

CTEPH is diagnosed by showing PAPm≥20 mmHg and PCWP≤15mmHg on right heart catheterization, at least one segmental perfusion defect on perfusion scintigraphy, or pulmonary artery obstruction on CTPA/conventional angiography after receiving effective anticoagulant treatment for at least 3 months. While the diagnosis of CTEPH was confirmed by catheterization in some studies, it was diagnosed by ECHO and V/P scintigraphy in most. Pengo et al. followed 223 patients with acute PTE for a mean period of 94.3 months (1-10 years); they examined patients with symptoms suggesting CTEPH with transthoracic echocardiography, and when there were ECHO signs compatible with CTEPH, they confirmed the diagnosis with V/P scintigraphy and pulmonary angiography.

Using these tests and examinations, they calculated a cumulative CTEPH incidence of 1% at 6 months after acute PTE, 3.1% at 1 year, and 3.8% at 2 years.[16] In a domestic study where 99 patients were followed for 2 years, the researchers applied right heart catheterization to patients with PAPs>30 mmHg or signs suggestive of CTEPH on CTPA or V/P scintigraphy. They found a CTEPH incidence of 5.5%.[17] In a study by Dentali et al.[9] with a small cohort consisting of 91 patients, the patients were examined with ECHO 6 and 12 months after acute PTE. CTEPH was diagnosed in patients with a PAPs>40 mmHg on ECHO and residual perfusion defects on perfusion scintigraphy, but the diagnosis was not confirmed by invasive diagnostic methods. That study found an incidence as high as 8.8%. Also in our study, the diagnosis of CTEPH was confirmed by right heart catheterization performed in our hospital in 2 patients. Catheterization could not be performed in a patient because he was taking high-intensity anticoagulant therapy due to a high CVA risk while two other patients refused to provide written informed consent for the invasive catheterization procedure. Those three patients were diagnosed with CTEPH because they had PAPs>50 mmHg and residual perfusion defects on V/P scintigraphy.

Pulmonary embolism is mostly considered an acute and reversible disease and the patients are considered to be cured altogether by appropriate anticoagulant therapy. However, studies have reported residual perfusion defects at 6th month follow-up scans after acute PTE in more than half of patients.[18] Failure in thrombus resolution or slow thrombus resolution after acute PTE brings about remodelling in the affected vessels. A proximal obstruction results in secondary vasculopathy and pulmonary hypertension.[19] Therefore, large perfusion defects and incompletely resolved PTE are considered risk factors for developing CTEPH. In a previous study, partial or unresolved PTE was observed in 35% of patients, most of whom were followed with an inferior vena cava filter without anticoagulant treatment, after 1 to 7 years of follow-up.[20] In a study from our country, conducted by Korkmaz et al.,[12] it was shown that residual chronic thrombi persisted on CTPA in 48%, 27.4%, and 18.2% of PTE patients on anticoagulant therapy at 3, 6, and 12 months after the acute event, respectively. It was reported that pulmonary hypertension was detected at the end of the first year in 19 of 29 patients with persistent residual thrombi on the CTPA taken at 12th month.

Yang et al.[21] found that an obstruction index of more than 30% three months after acute pulmonary embolism was significant. In our study, an evaluation of the patients for residual thrombus in the pulmonary arteries revealed that thrombus persisted on CTPA in 22.8%, 16.3% and 8.6% of the patients at the 3rd, 6th, and 12th months, respectively, after acute PTE. Five of 16 patients with persisting residual thrombus on CTPA at 12th month were found to have pulmonary hypertension. While residual thrombus was present on the CTPA at 12th month in all patients with CTEPH, residual thrombus existed in 21% of patients who were free of CTEPH. The univariate analysis in our analysis indicated that the presence of residual thrombus at 12th month was a risk factor for developing CTEPH (p=0.023).

One of the important risk factors for developing CTEPH are elevated PAP and right ventricular dysfunction, which are observed in approximately half of all patients with PTE and related to early mortality.[12,22-24] Studies have demonstrated that a sPAP of more than 50 mmHg during acute PTE is associated with the development of persistent PHT in the long term.[22,23] Korkmaz et al.[12] found high PAPs (>35 mmHg) and right ventricular dysfunction in 57% of patients with acute PTE; they also added that sPAP was higher in patients who developed CTEPH than those who did not. In a study by Yang et al.,[21] basal sPAP above 50 mmHg after acute PTE and a history of DVT were significantly related to CTEPH development. Our study showed a significantly higher basal PAPs level in patients who developed CTEPH than those who did not. In the ROC analysis to determine a cut-off level for sPAP to diagnose CTEPH, the cut-off level was found to be 55 mmHg (sensitivity 80, specificity 83.3). The mean sPAP at the time of diagnosis of the group that developed CTEPH was 77 (±23,6) mmHg; hence, a univariate analysis determined a high sPAP (sPAP≥55 mmHg) at the time of diagnosis was an important risk factor for developing CTEPH (p=0.009).

In a cohort study by Martinez et al.[25] from the UK it was reported that the presence of COPD, AF, and left heart failure may predict CTEPH in patients with a history of VTE. AF was considered to develop as a result of thrombus formation inside the atrium due to inadequate anticoagulant therapy after pulmonary embolism. Klok et al.[26] reported that the presence of DM as a comorbidity is associated hypercoagulability and comes forth as a risk factor for CTEPH. Three (60%) patients who developed CTEPH in our study had AF; a univariate analysis showed that AF caused statistically significant risk for CTEPH development (p=0.001).

Limitations

Our study has some limitations. The most important limitations are the inadequate number of patients with CTEPH for performing any statistical analysis and the single-centre nature of our study. Studies with greater sample size are thought to obtain more clear results about the incidence and risk factors of CTEPH.

CONCLUSION

Our single-centre retrospective study determined a CTEPH incidence of 2.7% after acute PTE. The presence of AF, residual thrombus on CTPA taken at the 12th-month follow-up, and elevated sPAP (55 mmHg or above) at the time of diagnosis after acute PTE were determined as the risk factors for developing CTEPH after acute PTE (0.001/0.023/0.009, respectively). A multivariate analysis, however, failed to determine any independent predictor of CTEPH. The diagnostic algorithms used in our study were consistent with the current publications.

CTEPH developed in a considerable number of patients with pulmonary embolism during follow-up. We therefore do not consider CTEPH a rare complication of acute PTE. Unlike other pulmonary hypertension groups, patients with CTEPH have a higher potential to improve with medical and surgical therapies. Thus, early diagnosis and treatment are extremely important in CTEPH. Regular and long-term screening of symptomatic and asymptomatic patients with ECHO and CTPA after acute PTE is important for early diagnosis and treatment of CTEPH; it will reduce mortality and morbidity rates and also provide a significant decrease in the financial burden of the disease. Additionally, increasing clinical awareness of CTEPH and directing patients to surgical treatment will contribute to efforts for improving their quality of life and extending their life expectancy.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethics Committe of Dışkapı Yıldırım Beyazıt Training and Research Hospital (*Date:19.02.2018, Decision No: 46/12*).

Informed Consentw

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Case Report

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Occupational papillary thyroid carcinoma and basal cell carcinoma coexistence: a case report

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ABSTRACT

Occupational cancers are cancers that result from exposure to carcinogens at work. Diagnosing occupational cancer expresses great importance in terms of public health. Because all occupational cancers are preventable as other occupational diseases. A detailed occupational history and careful questioning of exposure factors enable early diagnosis and prevention of occupational cancer. It is known that thyroid and skin cancers may occur due to occupational exposures. In this report, the coexistence of occupational thyroid cancer and occupational basal cell skin carcinoma is presented.

Keywords: Occupational cancer, papillary thyroid carcinoma, basal cell carcinoma, ionizing radiation

INTRODUCTION

Occupational cancers are described as cancers that result from exposure to carcinogens at work.[1] Occupational cancer diagnosis and treatment process are not different from cancers that occur without occupational exposure.[2] Diagnosing occupational cancer expresses great importance in terms of public health. Because all occupational cancers are preventable as other occupational diseases. Occupational history is often ignored when evaluating the patient. A detailed occupational history and careful questioning of exposure factors enable early diagnosis and prevention of occupational cancer.

In the study on occupational causes of cancer, 47 agents were identified as definite carcinogens in relation to 23 cancer types.[3] These occupational agents are chemicals and chemical mixtures; radiation and radionuclides; airborne particles and complex mixtures; metals and metal alloys. Documenting and minimizing exposure to occupational carcinogens is critical to prioritizing interventions and reducing the future cancer burden. Generating country-specific evidence for effective prevention is important in this regard.[4]

The biological effects of ionizing rays are very various. It is difficult to establish a causal relationship between occupational ionizing radiation exposure and cancer development since the stochastic effects of ionizing radiation, such as cancer, may occur many years after exposure, and the exposure doses could not always be recorded in the past. In this report, the coexistence of thyroid and skin cancer in a nurse with long-term exposure to low-dose ionizing radiation is presented.

CASE

The patient, who had no active complaints at the time of her application to the occupational diseases clinic, was operated on for a nevus in the right axillary region approximately 15 days ago. The pathology of the excised nevus was reported as basal cell carcinoma. The patient, who had previously been diagnosed with papillary thyroid carcinoma, applied with the suspicion of occupational cancer.

In the detailed anamnesis taken from the patient, it was learned that she had COVID two months ago. The patient had a 1-pack-year smoking history and had never smoked for the last five years. She has been diagnosed with hypertension for 17 years and diabetes mellitus for ten years. She had a cesarean section 17 years ago because of eclampsia. Total thyroidectomy was performed for papillarythyroid carcinoma in 2019, and in 2022, after nevus excision in the right axillary region, the pathology was reported as basal cell carcinoma.

In the patient's occupational history, it was learned that she started working as a nurse at 18, worked in the internal medicine service for three years, and then worked on the night shift for six years in the cardiovascular surgery intensive care unit. The patient, who started working in the coronary angiography unit at 28, mostly worked during the daytime hours. She had night shifts 3 or 4 times a month. An average of 50-60 angiography procedures were performed per day. She only wore a vest as personal protection and didn't always use head and neck protectors. She worked under these conditions for 21 years. She retired in 2019 after being diagnosed with papillary thyroid carcinoma. The patient declared that she used a dosimeter (but the measurement data could not be reached), and she was exposed to high levels of measurement sometimes.

In physical examination, there were incision scars in the right axillary region (2 cm) and the midline of the neck (approximately 4 cm). There were no pathological physical examination findings except scars. Thyroid function tests, complete blood count, and biochemistry parameters were within normal limits. The thyroid gland was not observed in the thyroid ultrasound, and no residue or recurrence was reported.

The pathology result of a total thyroidectomy performed in 2019 was reported as a follicular variant with classical-type papillary carcinoma in the right and left lobes. In 2022, the result of the right axillary nevus biopsy was reported as nodular-type basal cell carcinoma. Permission was obtained from the patient for the data used while writing this report.

DISCUSSION

The damage of ionized rays varies depending on the type of ray, the amount of energy, and the place exposed to the effect. Such rays adversely affect all other organs, especially the skin, thyroid, and hematopoietic system.[5] Some healthcare professionals, such as those working in the radiology department, may be repeatedly exposed to low levels of ionizing radiation throughout their working life. The probability of an adverse health effect due to ionizing radiation is proportional to the dose received.[6] Scientific studies have shown significant associations between cancer and radiation dose levels of approximately ten rem (0.1 Sv) or higher, and the risk of cancer increases as the radiation dose increases. For low-level radiation exposure [i.e., whole-body doses less than about ten rem (0.1 Sv)], statistical limitations in studies complicate cancer risk assessment.[7] However, the research report of the American National Research Council's health risks assessment committee in 2006 stated that the cancer risk continued linearly even at low doses. According to this, it is assumed that there is no safe threshold for cancer and that even low doses of ionizing radiation have the potential to cause an increased risk of cancer.[7,8]

Occupational skin cancers are less than 1% of all skin cancers. Although it is impossible to specify the prevalence of occupational skin cancers, it can be estimated that they are more common than diagnosed. The most common causes of occupational skin cancers are UV radiation, polycyclic aromatic hydrocarbons, arsenic, and ionizing radiation. Ionizing radiation is among the etiological factors of occupational skin cancer, especially in nuclear plant workers, X-ray technicians, and uranium miners.[9]

It has been well-known since the observations of thefirst scientists using X-ray and radiation sources to cause squamous cell skin cancer and other premalignant conditions.[5] Although ionizing radiation-related skin cancers have been reported less frequently using personal protective equipment in recent years, Freedman et al.'s[10] 2003 study reported that the risk of malignant melanoma increased in radiology technicians who did not use personal protective equipment before 1950. In addition, in a systematic review of 65719 radiology technicians by Lee et al.,[11] it was reported that the risk of basal cell skin cancer increased in healthcare workers who worked before 1960 and were exposed to ionizing radiation, especially under 30. The latent period can be two to three decades or longer.[12] Occupational-related skin tumors don't differ clinically from spontaneous skin tumors.

An increased risk of thyroid cancer has been observed due to certain occupational exposures. In a study by Dr. Ba et al.,[13] 462 patients diagnosed with thyroid cancer were included in the study, and it was observed that the risk of thyroid cancer is higher in occupational groups with high exposure to radiation, such as radiology technicians. There was a less consistent association with thyroid cancer risk in other occupational groups less likely to be exposed to radiation. It has been determined that the risk of thyroid cancer, especially papillary type, has increased significantly, especially among health professionals working under radiation exposure for more than ten years.

Our patient, who accompanied the angiography procedure for an average of 8 hours a day in the coronary angiography unit for 23 years as a nurse, didn't use personal protective equipment because of the absence of the equipment. At the same time, she was exposed to high dosimeter measurement levels sometimes. The latent period between the onset of the current disease and the beginning of exposure of the patient, who was diagnosed with thyroid cancer 23 years after starting the study, and basal cell skin cancer 26 years later, is consistent with the literature. In addition, the development of basal cell skin cancer in a skin area not exposed to sunlight (right armpit) where there is spontaneous UV radiation suggests that the malignant lesion may be associated with ionizing radiation exposure rather than UV radiation effect. The association of thyroid and skin cancer, the most common malignant lesions seen with the impact of ionizing radiation, also supports the possibility of malignancy developing with occupational exposure to ionizing radiation without protection. In addition, the absence of a known history of malignancy in first-degree and second-degree relatives also reduces the possibility of hereditary cancer.

CONCLUSION

By the current literature, clinical, radiological, and pathological findings of the patient whose diagnosis of thyroid and skin cancer is considered to be occupational have been presented to the literature to draw attention to the diagnosis of occupational cancer and thus to remind the need to produce common policies to improve preventive activities for those working with carcinogens.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Pulmonary aspergillosis after COVID-19: a case report

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ABSTRACT

COVID-19 is an infectious disease that spreads worldwide, can progress rapidly, affect individuals of all ages, and cause death, especially in the elderly and people with chronic diseases. It has predisposed a relatively high number of patients to acute respiratory distress syndrome, and co-infections are a frequent complication, especially during prolonged hospital stays. Bacterial or viral co-infections with SARS-CoV-2 have been reported in many studies, but knowledge of *Aspergillus* co-infection in patients with COVID-19 is limited. This study presents a 57-year-old male patient with COVID-19 who had had no lung disease before COVID-19 pneumonia. However, after COVID-19 pneumonia with sequels and treatments that include corticosteroids and IL-6 receptor antagonists, an invasive pulmonary *aspergillus* (IPA) cavity occurred immediately. In addition to the fact that COVID-19 infection progresses with destructive parenchymal damage and sequelae, the effectiveness of treatment is limited, and treatment-related side effects and complications can be examined. Therefore, clinical and radiological follow-up of patients whose symptoms persist after infection is essential.

Keywords: Aspergillosis, COVID-19, lobectomy, postcovid pulmonary aspergillosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which appeared in China in late 2019. Several opportunistic infections as *Aspergillus* spp., *Candida* spp., *Cryptococcus neoformans*, *Pneumocystis jiroveci* (*carinii*), mucormycosis, cytomegalovirus (CMV), Herpes simplex virus (HSV), *Strongyloides stercoralis, Mycobacterium tuberculosis,* and *Toxoplasma gondii* have been identified following severe respiratory viral infections in COVID-19 patients.[1,2] Especially the incidence of fungal infections is high.[3]

CASE

A 57-year-old male patient, who applied to our clinic with complaints of hemoptysis, was hospitalized for further examination and treatment due to a cavitary lesion in the right upper lobe. Nine months ago, he was treated for 55 days as non-intubation in the intensive care unit for five days due to COVID-19 pneumonia Figure 1. During this period, steroid treatment and four flacons of 162 mg tocilizumab (a monoclonal antibody against the interleukin-6 receptor) was given because of respiratory symptoms and sequelae COVID-19 pneumonia Figure 2.

Pulmonary rehabilitation and steroid therapy were continued for three months because dyspnea continuedin the patient whose treatment was terminated Figure 3.

In thorax Computed Tomography (CT), a cavitary lesionwas observed in the right upper lobe who administered withcomplaints of swelling in the legs and hemoptysis in thefourth month of his treatment Figure 4.

After taking a nonspecific culture, the patient continued prophylactic fungal treatment and steroid treatment due to dyspnea. Blood culture, sputum culture, urine culture, fungal culture, and tuberculosis tests, Aspergillom specific IgE, was negative, Total IgE was normal. On the 12th day of his treatment, the patient's general condition was good, and he was discharged after colchicine and steroid treatment were arranged. In the control HRCT after antibiotic treatment, the cavity persisted in the right upper lobe Figure 5.

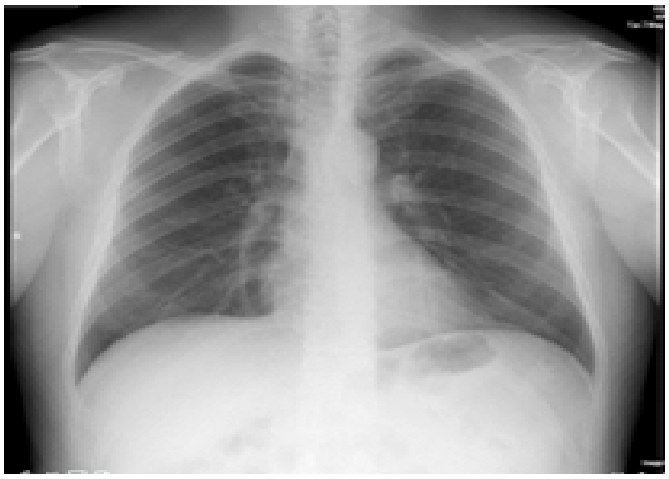

Figure 1. First hospital admission chest X-Ray

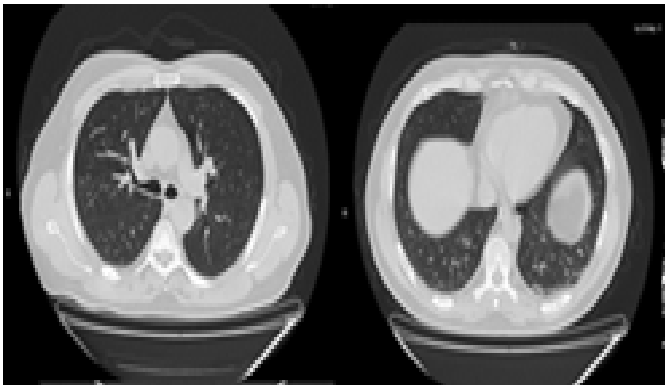

Figure 2. Thorax CT when the patient applied to the hospital for the second time, on 15th day: bilateral ground glass were determined

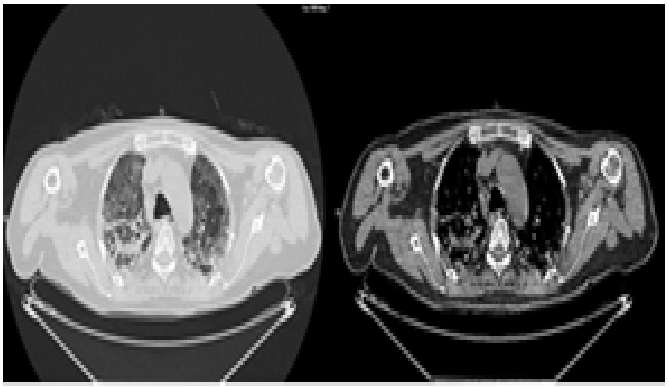

Figure 3. Thorax CT on the 45th day. Ground glass and fibrotic lesions, right upper thin-walled cystic lesion were determined

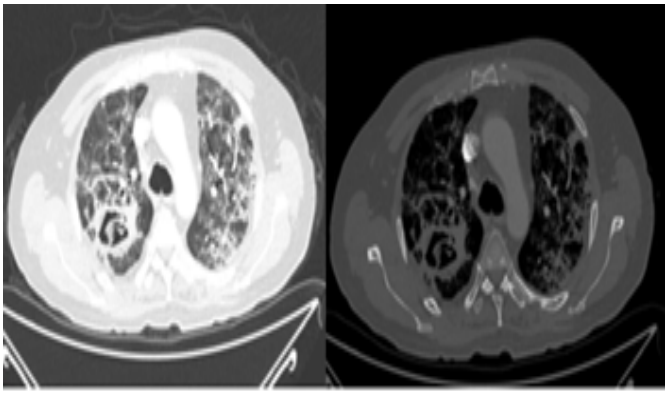

Figure 4. Right upper lobe cavitary lesion was detected in thorax CT angiograph

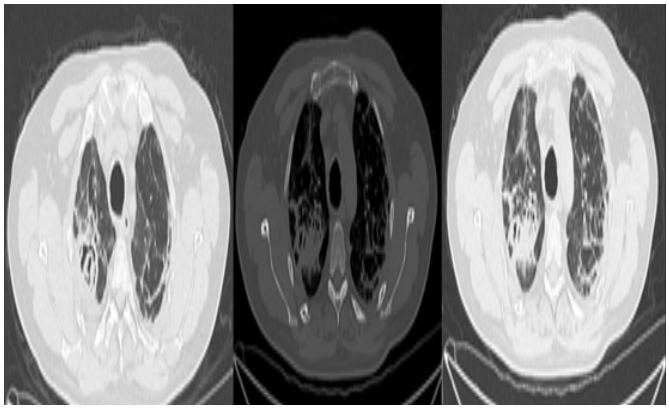

Figure 5. Right upper lobe cavity persisting on control thorax CT, one month after the treatment

Due to intermittent complaints of hemoptysis, right upper lobectomy via thoracotomy was performed. The postoperative pathology result was reported as Aspergilloma (Figure 6) and discharged on the seventh postoperative day without complications. He is in the third month of his follow-up, and any complications occurred.

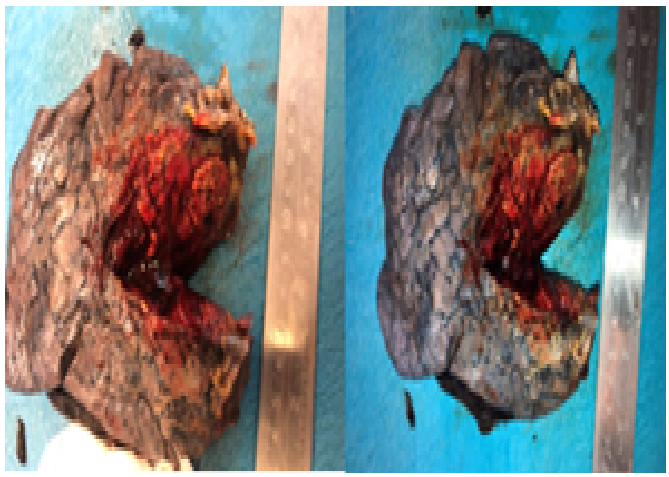

Figure 6. The macroscopic appearance of postoperative specimen of right upper lobectomy with aspergilloma

DISCUSSION

Since the new pneumonia was first recognized in Wuhan, China, at the end of 2019, the causative pathogen SARS-CoV-2 has been identified, and its associated infection, COVID-19, has rapidly evolved worldwide. While SARS-CoV-2 is responsible for severe pneumonia and ARDS, COVID-19 is associated with a wide variety of extrapulmonary complications; many other organs can be affected, including cardiovascular, immune, nervous, and gastrointestinal systems, therefore, can be considered a systemic disease. In addition to common bacteria and viruses, *Aspergillus* can cause co-infection in COVID-19 patients, especially in severe/critical illnesses. The possibility of co-infection with bacterial or fungal infections is higher in patients who require follow-up in intensive care units or require mechanical ventilation.4 Among the possible pathogens in COVID-19 patients, İnvasive pulmonary *aspergillosis* (IPA) carries more attention to *aspergillus* as it is challenging to diagnose and can be associated with high morbidity and mortality. In particular,

respiratory samples for mycological studies such as fungal culture, galactomannan test, and PCR from respiratory tract samples can help early diagnosis. In our case, the culture results of the patient who was followed up and treated with the non-intubated high flow for five days in the intensive care unit during this period were typical.

All studies of COVID-19 fungal infections have reported that they occur during COVID-19 infection, mostly 14 days after the onset of COVID-19 symptoms.[5] In this case, a cavitary lesion in the right upper lobe was observed in the fourth month of the patient's COVID-19 treatment.

In COVID-19-associated pulmonary aspergillosis, diabetes, immunosuppressive drug use, steroid therapy, and intubating are risk factors for patients followed. It also increases the risk of pulmonary aspergillosis in COVID-19 patients using IL-6 antagonists.[6] In our case, four vials of 162 mg tocilizumab were given on the 12th day of the patient's treatment. The patient had fibrotic lesions on the thorax CT, and dyspnea continued. The patient was followed up under steroid and colchicine treatment for about four months after discharge, and a cavitary lesion in the right upper lobe was observed in the fourth-month tomography.

Aspergillosis is one of the most common opportunistic fungal co-infections caused by certain Aspergillus species, mainly affecting immunocompromised individuals such as COVID-19 patients. It can critically affect the respiratory system, leading to a mild/serious lung infection known as pulmonary aspergillosis, a severe form of aspergillosis that worsens over time and has no effective treatment.

CONCLUSION

In patients with severe acute respiratory disease associated with SARS-CoV-2, invasive aspergillosis should be suspected in case of clinical worsening, even in immunocompetent patients. At the same time, aspergillosis should not be forgotten in patients with worsening after steroid and immunomodulator therapy. Pulmonary aspergillosis is a severe complication of COVID-19 patients that may not respond well to medical therapy. Pulmonary resection is the most effective treatment to control the disease.

ETHICAL DECLARATIONS

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

Referee Evaluation Process
Externally peer-reviewed.

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

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

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

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