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Relationship Between Phenotypical and Echocardiographic Findings With Pulmonary Hypertension in COPD Patients

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ABSTRACT

Pulmonary hypertension in COPD patients and identifying accompanying factors in clinical decisions are very important. The current study aimed to determine the relationship between phenotypic and echocardiographic findings with the help of pulmonary artery pressure in patients with COPD. In this study, 100 COPD patients referred to a specialized clinic participated in the study. The prevalence of pulmonary hypertension (PH) and its relationship with phenotypic criteria, spirometry, laboratory findings, and echocardiography in COPD patients were investigated. Among the COPD patients, 76 cases were classified as having chronic bronchitis, nine as having emphysema, and 15 were classified as mixed phenotype by Chest high-resolution computed tomography (HRCT) methods. The prevalence of PH in the study was 36% (moderate 24% and severe 12%). The average pulmonary arterial pressure (PAP) was significantly difference in different phenotypes ($p < 0.001$). Heart rate and PAP significantly increase in mixed phenotypes $p = 0.029$ and $p = 0.002$, respectively. Also, the modified Medical Research Council scale (mMRC) and BODE index were significantly increase in mixed phenotypes of COPD patients ($p < 0.05$ to $p < 0.001$). Compared the factors related to PH in different phenotypes of patients with COPD indicated that PH are related with heart rate, PCO2, creatinine, triglycerides, 6MWT and BODE Index.

1 | Introduction

Pulmonary hypertension (PH) is a common phenomenon in chronic obstructive pulmonary disease (COPD) patients and is classified as group 3 by the World Health Organization (WHO). The pathophysiological processes in the occurrence of pulmonary hypertension begin from the onset of COPD; however, the severity of this complication does not depend only on the severity of the decrease in forced expiratory volume in 1 s (FEV1), but on various factors which affect its progress [1]. In these patients, PH is usually mild to moderate, as defined by a mean pulmonary artery pressure (mPAP) between 21 and 34 mmHg. Nevertheless, 6% to 8% of patients have severe PH (mPAP 25–35 mmHg). Identifying the associated factors or the phenotype of COPD patients, which is associated with pulmonary hypertension, is an important consideration in clinical decisions to improve the prognosis of patients. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study on 2164 COPD patients in stable condition helps us to identify different phenotypes of COPD patients and, while determining prognosis, classify patients for appropriate treatments [2]. For the phenotypic

classification of COPD disease, the emphasis is on valuing each phenotype in the face of clinical prognoses or response to treatment [3]. Considering the importance of pulmonary hypertension in COPD patients and its essential role in determining the prognosis of these patients, a study to determine which phenotype is more likely to have pulmonary hypertension will aid in identifying the appropriate treatment to give COPD patients quality improvement in prognosis and increased life expectancy. In the numerous articles and studies reviewed, no comprehensive and inclusive evaluation with specific results in this regard was found. While inflammatory factors, lung hyperventilation, and genetic factors are prominent risk factors in the development of PH, there is still no certainty about some factors such as polycythemia, hypercapnia, and acidosis [4, 5]. It is said that the main cause of pulmonary hypertension in COPD is vascular remodeling brought about in pulmonary vessels by chronic hypoxia, inflammation, and destruction of the vascular bed caused by advanced emphysema. While PH is a relatively common phenomenon in the course of COPD, no physical examination, radiography, electrocardiography, or laboratory results can predict the existence of PH. From the pathophysiological point of view, hypoxia is the most important factor, as it is known to cause PH [6]. The current study investigated the prevalence of PH in patients with COPD as well as the relationship between different COPD phenotypes (bronchitis, emphysema, or mixed phenotype) and clinical and laboratory conditions in COPD patients with an incidence of PH.

2 | Methods

2.1 | Study Design and Participants

In this descriptive-analytical study, 100 patients with COPD who were referred to a specialized clinic, Vali-Asr Hospital, Birjand, Iran were recruited by respiratory physicians from July 2021 to May 2022. The sample size of the current study was estimated according to the previous study [7]. The COPD patients were defined as forced expiratory volume in the first second/forced vital capacity ratio (FEV1/FVC) with post-bronchodilator $< 70\%$ and exposure to a risk factor (smoking 10 packs/year) [8].

After obtaining informed consent, demographic characteristics was collected by experts. A Persian questionnaire was used to evaluate the prevalence and severity of respiratory symptoms (wheezing, sputum, and cough) [9, 10].

Venus blood gases (VBG) due to less aggressive was performed used for assessment of the potential of hydrogen (pH), partial pressure of carbon dioxide (PCO2), partial pressure of oxygen (PO2), and bicarbonate (HCO3 −) according to the American Thoracic Society and European Respiratory Society (ERS) standards. Based on the COPD phenotype, participants were divided into three groups: Dominant emphysema, Dominant chronic bronchitis, and mixed (chronic bronchitis - emphysema) phenotypes [11]. COPD assessment test (CAT) score, modified Medical Research Council (mMRC) [12], and BODE Index were also used to evaluate patients.

Inclusion criteria for the current study were all subjects aged 40–75 years in stable condition (no history of exacerbation for the previous 4 weeks) with a diagnosis of COPD that willingness to participate in the study and were recruited by respiratory physicians.

Subjects with a main diagnosis of bronchiectasis, asthma, or any respiratory diseases with exacerbation in 1 month before the study, valvular disease, vascular collagen diseases, the body mass index (BMI) $> 30\ kg/m^2$, uncontrolled hypothyroidism and sleep apnea syndrome were excluded.

2.2 | Pulmonary Artery Pressure (PAP) Assessment

Echocardiography was performed for all participants. Systolic PAP (SPAP) was estimated by measuring tricuspid regurgitation velocity (TRV), evaluating multiple views, and searching for the best coverage and maximum velocity. The highest interval velocity was used to calculate TRV. Doppler was used to assess the presence of indirect signs of PH, such as right ventricular outflow Doppler acceleration time (RVOT) and late diastolic pulmonary regurgitation velocity, which were used as indicators of PH in people whose tricuspid regurgitation could not be easily assessed [13, 14]. An RVOT acceleration time of less than 105 ms and an early diastolic lung failure velocity > 2.2 m/s were considered markers of elevated PAP. Considering a 35-mmHg cut-off for systolic pulmonary arterial pressure, patients were divided into two groups those with and those without pulmonary hypertension, and patients with more than 60 mmHg were placed into the severe PH group [13].

2.3 | Blood Gas Analysis

Vein blood gas (VBG) was performed according to American Thoracic Society and European Respiratory Society (ERS) standards. Oxygen saturation was measured by pulse oximetry at rest [15].

2.4 | 6-Minute Walking Test (6 MWT)

The 6MWT is a reliable measure in people with chronic respiratory disease that was performed according to the protocol. Briefly, we asked Patients to walk as far as possible in 6 min along a flat corridor. The distance in meters is recorded. Standardized instructions and encouragement are commonly given during the test [16].

2.5 | Chest High-Resolution Computed Tomography (HRCT)

A helical computed tomography (CT) scanner (GE Medical Systems, Milwaukee, WI, USA) was employed to perform conventional contiguous imaging with a slice thickness of 10 mm for the detection of chest abnormalities. This was succeeded by high-resolution CT (HRCT) imaging conducted at full inspiration (total lung capacity level) with a 1-mm collimation, utilizing parameters of 120 kVp, 200 mA, and a pitch of 1.0 [17]. The patients with stable COPD ($FEV_1 \leq 80\%$) were examined by chest HRCT.

Traditionally, based on the findings of clinical appearance and physical examination, patients were classified into three groups: Pink Puffer (emphysema-predominant), Blue Bladder (non-emphysematous or bronchitis-predominant), and a combination form [18].

CT scan was performed to confirm emphysema and bronchitis based on visually defined emphysematous and bronchial wall thickness, respectively (Radiology report regardless of severity) [19]. In addition to assessment of parenchymal COPD change, antero-posterior chest diameter was also recorded on chest HRCT.

2.6 | BODE Index

The BODE index (BMI [B], degree of airflow obstruction (percent predicted FEV1) [O], degree of dyspnea [D], and exercise capacity (based on 6-min walk test [6-MWT]) [E]) as a multidimensional scale to better assess the morbidity and mortality associated with COPD [20].

2.7 | Statistical Analysis

The normality of variables was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) for normal variables or median and interquartile ranges for no normal variables as well as qualitative variables as n (percent). To assess differences between the groups PH (non-PH, Moderate PH, severe PH) and phenotypes of COPD (dominant bronchitis, dominant emphysema, and mixed phenotypes), we used Chi-square, ANOVA, and non-parametric Kruskal Wallis Test. p value < 0.05 was considered significant and analyses were performed using the statistical software SPSS 22.

3 | Results

3.1 | Characteristics of the COPD Patients

In this study, 100 samples with COPD were classified into three phenotypes of COPD: chronic bronchitis (76 participants), emphysema (9 participants), and mixed (15 participants). Slightly more males (61%) were included in the study and 79% of them were opium users (oral or inhalation). The prevalence of moderate PH in the entire studied population was 24 people (24%); severe PH was seen in 12 people (12%), and 64 people (64%) did not have PH. Their clinical and hemodynamic characteristics are presented in Table 1 and Figure 1.

3.2 | Blood Gas Analysis

Smoking history including; current smoking, pack-years, hookah, and opium consumption did not significantly change in the three groups of patients. In blood gas analysis, partial pressure of carbon dioxide (PCO2) was significantly increased in severe PH COPD patients ($p = 0.007$).

3.3 | Air Tapping

6-min Walk test (6MWT) in exercise capacity indicated that 6MWT significantly reduced in moderate and severe PH ($p < 0.001$), while the heart size compared to chest diameter was significantly increased in severe PH ($p = 0.017$).

COPD Assessment Test (CAT), modified Medical Research Council (mMRC) scale and the BODE index significantly increased in severe PH COPD patients ($p < 0.001$, for all cases). The laboratory parameters and Chest CT scan findings were not significant changes in three groups of disease, Table 2.

Weight and BMI significantly reduced in dominant emphysema and had clear statistical relationships with different disease phenotypes ($p < 0.001$). Heart rate and PAP significantly increase in mixed phenotype $p = 0.029$ and $p = 0.002$, respectively, Table 3.

The prevalence of opium consumption and increased sputum production increase in mixed phenotypes had a statistically significant relationship with the phenotype of the disease $p = 0.013$ and $p = 0.003$, respectively. Moreover, 6 MWT was reduced in the mixed phenotype of COPD patients ($p = 0.017$), while the anteroposterior diameter in Chest CT scan was increased in the bronchitis patients' group ($p = 0.021$). In addition, the modified Medical Research Council scale (mMRC) and BODE index significantly increased in mixed phenotype of patients ($p = 0.033$ and $p < 0.001$, respectively), Table 3 and Figure 2.

4 | Discussion

The current study describes the characteristics and outcomes of patients with PH in different phenotypes of COPD patients. The COPD patients with severe PH achieved worse outcomes than patients with moderate and non-PH in COPD. Based on the findings, PH is significantly increased among mixed phenotype of patients with COPD. Considering the pathophysiological factors in increasing pulmonary pressure, including hyperinflation and factors that increase pulmonary vascular resistance (pulmonary vascular remodeling, loss of small pulmonary vessels, epithelial dysfunction, inflammation and, hypoxia) it can be expected that in patients with mixed type of COPD, these factors are more in synergy with each other, and play a role in causing high pulmonary pressure [21].

The average EF in the entire studied population was not statistically significantly different among phenotypes, while the average BMI, Heart rate, PAP, mMRC and BODE Index, TG, and 6MWD values were related to different phenotypes of patients with COPD who had a significant increase in sputum production and hyperinflation. By examining factors related to PH in different phenotypes of patients with COPD, lung function tests, and echocardiography and laboratory parameters. We found PH association with EF and O2Sat, as well as severe PH was associated with patient O2Sat, HCO3, and PCO2 levels.

In a research, echocardiography revealed that the PH prevalence was 36% in COPD patients with moderate to severe PH severity ranging, these results are in line with previous studies showing that the prevalence of PH in 146 COPD patients was (36%) [22].

TABLE 1 | Patient Characteristics ($n = 100$).

Characteristics		Data
Age (year)		65.2 ± 12.1
Male, *n* (%)		61 (61%)
Female, *n* (%)		39 (39%)
Height (cm)		167.5 (159–175)
Weight (kg)		64.34 ± 14.75
BMI (kg/m^2)		22.9 ± 10.53
Smoking history		
Current cigarette smoker		69 (69%)
Hookah		69 (69%)
Opium uses	Oral	39 (39%)
	Inhalation	42 (42%)
BP, mm Hg		
Systolic, mm Hg		130 (120–140)
Diastolic, mm Hg		80 (80–85)
Heart rate, n		74 (65.25–84)
EF		55 (46.25–60)
PAP, mm Hg		30 (25–40)
TAPSE, mm		19 (16.75–23.92)
Respiratory symptoms		
Wheeze		32 (32%)
Sputum		71 (71%)
Cough		83 (83%)
Blood gas analysis		
PH		7.37 (7.33–7.4)
HCO3, Eq/l		24 (22–27)
PCO2, mm Hg		51.67 ± 9.6
SPO2, %		52.5 (44.25–67)
Severity of pulmonary hypertension		
None		64 (64%)
Moderate		24 (24%)
Severe		12 (12%)
Exercise capacity		
6MWD, m		235 (140–365)
Chest CT scan		
Anteroposterior diameter, mm		190 (170–220)
Transverse diameter, mm		239 (210–258.25)
Anteroposterior to transverse diameter ratio		0.83 ± 0.11
Chest in examination		
Anteroposterior diameter, mm		230 (210–260)
Transverse diameter, mm		280 (250–310)
Anteroposterior to transverse diameter ratio		0.84 ± 0.096
Air tapping		
Heart size compared to chest diameter, mm		0.44 (0.40–0.50)
The height of the semicircle of the diaphragm, mm		18.73 ± 6.55
Countable number of ribs, *n*		9 (8–9)
mMRC		2 (1–3)
BODE index		5 (3–7)
CAT		17.54 ± 7.6

Note: Data are presented as (%) or median (interquartile range) or Mean ± SD. Abbreviations: 6MWD, 6-min walk distance; ALT, aspartate alanine transferase; AST, aspartate aminotransferase; BMI, body mass index; CAT, COPD assessment test; Chol, cholesterol; Cr, Creatinine; CRP, C-Reactive Protein; EF, ejection fraction; ESR, Erythrocyte Sedimentation Rate; FBS, fasting blood sugar; HB, hemoglobin test; HCO3, bicarbonate; HDL, high density lipoprotein; HCT, Hematocrit test; LDL, low density lipoprotein; mMRC, modified Medical Research Council scale; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PAP, pulmonary arterial pressure; PH, pulmonary hypertension; PLT, Platelet test; SaO2, arterial oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; Tg, triglycerides; TSH, thyrois stimulating hormone; WBC, white Blood Cells.

The prevalence of PH in COPD depends on the severity of the disease and the definition of PH [22]. Additionally, Aguirre-Franco et al. reported the prevalence of PH in COPD patients was (31.6%) associated with a decrease in FEV1 and O2 saturation [7].

Smoking history including; current smoking, hookah, and opium consumption were not significantly changed in moderate and severe PH groups compared to the non-PH group. The previous study also indicated that current smoking and pack-years were not significantly changed in COPD without PH compared to the moderate and severe PH groups [23] that approved our results.

In blood gas analysis, PCO2 in the current study was significantly increased in severe PH COPD patients. The previous study also reported that PCO2 increased significantly as the severity of COPD class [24] similar to the current study. Also, 6MWT was significantly reduced in moderate and severe PH, while the cardiothoracic diameter was significantly increased in severe PH. A previous study showed that 6MWT was lower in severe PH ($n = 307$) compared to moderate PH ($n = 68$) in COPD patients [25]. The other study also confirmed these results in severe and moderate PH ($n = 74$ and 45, respectively) [23]. These results indicated that circulatory impairment in severe PH leaded to limitation in exercise capacity. Previous studies indicated that the development of PH (mPAP ≥ 35) is the result of lower values of lung capacity, reduced gas exchange, lower exercise capacity, and independent of lung function tests [22, 26]. Also have been demonstrated the influence of 6MWT in the prognosis of patients with PH, so 6MWT less than 400 m was associated with increased mortality [27].

In this study, CAT score, mMRC scale, and the BODE index significantly increased in patients with PH compared to non-PH. A study demonstrated that total CAT score and respiratory symptoms were higher in patients with PH compared to non-PH [28]. A recent study have led to the BODE index being significantly higher in COPD patients with PH compared to non-PH and there also was a negative correlation between sPAP and BODE index [29]. In

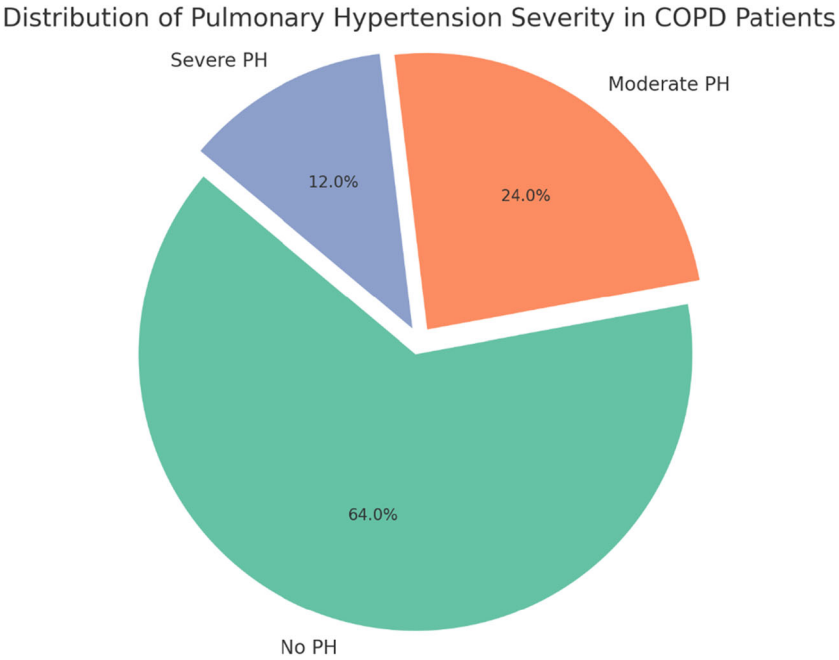

FIGURE 1 | Distribution of pulmonary hypertension severity among COPD Patients.

TABLE 2 | Characteristics for COPD patients with non PH, moderate and severe PH ($n = 100$).

Characteristics		Non PH $n = 64$	Moderate PH $n = 24$	Severe PH $n = 12$	p value
Age, y		63.9 ± 12.23	67.96 ± 11.9	66.4 ± 11.7	0.35
Male, *n* (%)		37 (58%)	15 (63%)	9 (75%)	0.563
Female, *n* (%)		27 (42%)	9 (37%)	3 (25%)	
Height, cm		167 (157.25–175)	168 (159.25– 173)	165.5 (157.75–181.75)	0.87
Weight, kg		66.172 ± 14.74	60.5 ± 12.7	62.25 ± 17.8	0.24
BMI, kg/m^2		23.7 ± 4.7	21.5 ± 4.2	21.4 ± 3.3	0.058
BP, mm Hg					
Systolic		130 (125–140)	130 (120–140)	130 (121.25– 140)	0.83
Diastolic		80 (80–85)	80 (72.5–85)	80 (76.25–85)	0.75
Heart rate		74 (65–83)	72 (64.25–86)	70 (66.5–87.5)	0.83
EF		55.5 (50–60)	50 (42.75– 58.75)	55 (46.25–59)	0.133
TAPSE		20 (18–24)	17.6 (16.1– 19.75)	17.65 (12.45– 27.25)	0.047
Smoking history					
Current cigarette smoker		44 (69%)	16 (67%)	9 (75%)	0.949
Hookah		44 (69%)	17 (71%)	8 (67%)	1.000
Opium uses	Oral	21 (33%)	10 (42%)	8 (67%)	0.087
	Inhalation	25 (39%)	14 (58%)	3 (25%)	0.124
Respiratory symptoms					
Wheeze		20 (31%)	10 (42%)	2 (17%)	0.349
Sputum		45 (70%)	16 (67%)	10 (83%)	0.680
Cough		52 (82.5%)	20 (83%)	11 (92%)	0.848
Blood gas analysis					
PH		7.36 (7.33–7.4)	7.38 (7.32–7.4)	7.34 (7.3–7.39)	0.616
HCO3		24 (22.25–26)	23.5 (21.25–26)	27.5 (23–30.75)	0.1

(Continues)

TABLE 2 | (Continued)

Characteristics	Non PH $n = 64$	Moderate PH $n = 24$	Severe PH $n = 12$	p value
PCO2	49.76 ± 9.28	53.4 ± 9.4	55.4 ± 8.6	0.009
SPO2	54 (45–69.75)	51 (44–60.75)	48.5 (43.5–67.5)	0.779
6MWT, m	290 (182.5– 427.5)	155 (91.5– 297.5)	76 (52.5–161.25)	< 0.001
Chest CT scan				
Anteroposterior diameter	190 (175– 228.75)	175 (161– 208.75)	197.5 (182.5– 230)	0.102
Transverse diameter	239 (210– 267.5)	227 (211.25– 249.5)	245 (205– 266.25)	0.549
Anteroposterior to transverse diameter ratio	0.83 ± 0.12	0.81 ± 0.11	0.85 ± 0.09	0.595
Chest in examination				
Anteroposterior diameter	235 (210–260)	220 (192.5– 237.5)	232.5 (220– 282.5)	0.082
Transverse diameter	285 (251.25– 317.5)	270 (246.25– 305)	285 (247.5– 338.75)	0.295
Anteroposterior to transverse diameter ratio	0.83 ± 0.09	0.83 ± 0.1	0.85 ± 0.08	0.794
Air tapping				
Heart size compared to chest diameter	0.44 (0.4–0.49)	0.44 (0.4–0.5)	0.51 (0.48–0.54)	0.007
The height of the semicircle of the diaphragm	19.75 ± 6.9	16.5 ± 5.7	17.75 ± 5.24	0.1
Countable number of ribs	9 (8–9)	9 (8–9)	9 (8.25–9.75)	0.519
mMRC	2 (1–3)	3 (2–3)	3 (3–3.75)	< 0.001
BODE Index	4 (2–6)	6 (4.25–7)	7.5 (6.25–9)	< 0.001
CAT	15.36 ± 7.37	19.5 ± 6.3	25.08 ± 5.9	< 0.001

Note: Data are presented as (%), median (interquartile range) or Mean ± SD.
Abbreviation: 6MWD, 6-Min walk distance; ALT, aspartate alanine transferase; AST, aspartate aminotransferase; BMI, body mass index; CAT, COPD assessment test; Chol, cholesterol; Cr, creatinine; CRP, C-Reactive protein; ESR, erythrocyte sedimentation rate; EF, ejection fraction; FBS, fasting blood sugar; HB, hemoglobin test; HCT, hematocrit test; HDL, high density lipoprotein; LDL, low density lipoprotein; mMRC, modified medical research council scale; PAP, pulmonary arterial pressure; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PLT, platelet test; PH, pulmonary hypertension; SaO2, arterial oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TSH, thyroid stimulating hormone; Tg, triglycerides; WBC, white blood cells.

addition, sPAP > 40 mmHg, FEV1 < 40% and 6MWD < 300 m were prognostic factors in COPD patients [30]. It has been reported that mMRC grade is higher in COPD-PH patients and a higher mMRC scale is associated with PH complications (OR 1.680, 95% CI) [31]. The evidence of other studied demonstrated higher mMRC scale and BODE index and lower 6MWT test in PH compared to non-PH [32]. These results indicated that an increase in PAP can lead to lower maximal workload, more dyspnea, and worse quality of life in COPD patients.

The COPD subtypes patients were classified as emphysema (pink puffer) with characteristics, of underweight and normal resting oxygen saturation, and bronchitis (blue bloater) with overweight, chronic bronchitis, and hypoxemia [33]. Regarding the phenotype rate, the most common type of phenotype was chronic bronchitis, followed by mixed, and emphysema phenotype. The phenotype distribution in the current study was similar to that found in other studies. The previous study performed in Spain with 3125 COPD patients found more than 50% to be non-exacerbator bronchitis, followed by exacerbator with chronic bronchitis and asthma-COPD overlap syndrome [34, 35].

Weight and BMI significantly reduce in dominant emphysema and have relationships with different disease phenotypes. The results of a study indicated that patients with the predominate emphysema had lower BMI and poor quality of life scores compared to those without or mild emphysema [36]. Also, BMI was significantly lower in the dominant emphysema and mixed phenotypes with a higher percent of low attenuation areas [37] which supports our data. It has been reported that weight loss in COPD is associated with high energy expenditure and low energy intake [38] and nutritional depletion can contribute to the development of emphysema.

Heart rate and PAP significantly increase in mixed phenotype compared to the bronchitis and emphysema phenotypes. Clinical characteristics of mixed phenotype was older, severe airway limitation and highly symptomatic (between clusters 1 and 3) [39].

The results of the current study showed heart rate and PAP significantly increased in mixed phenotypes. 6 MWD test, and cardiothoracic diameter in Chest CT scan were also reduced in mixed phenotype, while increased in bronchitis. In addition, mMRC and BODE index were significantly increased in mixed phenotype.

The results of a study showed mixed phenotype was older than two other groups, which confirmed the results of our study [40].

TABLE 3 | Characteristics of patients with different phenotypes of COPD ($n = 100$).

Characteristics		Dominant bronchitis $n = 76$	Dominant emphysema $n = 9$	Mixed $n = 15$	p value
Age, y		65.3 ± 12.45	59.67 ± 11.8	67.8 ± 9.95	0.278
Male, *n* (%)		45 (59%)	7 (78%)	9 (60%)	0.68
Female, *n* (%)		31 (42%)	2 (22%)	6 (40%)	
Height, cm		167.5 (159–175)	168 (159.25–173)	165.5 (157.75–181.75)	0.452
Weight, kg		68.04 ± 14.47	60.5 ± 12.7	62.25 ± 17.8	< 0.001
BMI, kg/m^2		24.03 ± 4.48	21.5 ± 4.2	21.4 ± 3.3	< 0.001
BP, mm Hg					
Systolic		130 (125–140)	120 (115–140)	130 (120–130)	0.085
Diastolic		80 (80–85)	80 (70–85)	80 (80–85)	0.544
Heart rate		71 (64–82)	72 (65.5–89)	84 (72–90)	0.037
EF		55 (45–60)	50 (50–57.5)	55 (50–60)	0.7
TAPSE		20 (17.37–23.9)	18 (16.05–25.5)	16.1 (14.4–28)	0.227
PAP		30 (22.87–36.5)	40 (30–55)	45 (35.8–60)	< 0.001
Smoking history					
Current cigarette smoker		50 (66%)	7 (78%)	12 (80%)	0.527
Hookah		53 (70%)	8 (89%)	8 (53%)	0.189
Opium uses	Oral	25 (33%)	3 (33%)	11 (73%)	0.015
	Inhalation	32 (42%)	3 (33%)	7 (47%)	0.831
Respiratory symptoms					
Wheeze		22 (29%)	3 (33%)	7 (47%)	0.377
Sputum		56 (74%)	2 (22%)	13 (87%)	0.002
Cough		64 (84%)	5 (63%)	14 (93%)	0.194
Blood gas analysis					
PH		7.37 (7.33–7.4)	7.4 (7.36–7.41)	7.35 (7.3–7.39)	0.107
HCO3		24 (22–26)	29 (21.5–31)	25 (23–29)	0.230
PCO2		50.7 ± 10.2	53.7 ± 5.2	55.3 ± 7.6	0.195
SPO2		53.5 (45–68.5)	49 (41–60.5)	52 (44–80)	0.676
Exercise capacity					
6MWT, m		260 (150.25–399)	190 (120–340)	140 (60–300)	0.027
Chest CT scan					
Anteroposterior diameter		190 (175–237.5)	200 (171.5–200)	172 (170–195)	0.079
Transverse diameter		240 (210–277.5)	240 (220.5–263)	225 (200–248)	0.319
Anteroposterior to transverse diameter ratio		0.84 ± 0.12	0.79 ± 0.089	0.8 ± 0.12	0.343
Chest in examination					
Anteroposterior diameter		240 (210–270)	220 (197.5–235)	220 (210–230)	0.048
Transverse diameter		290 (250–327.5)	275 (255–290)	270 (240–290)	0.097
Anteroposterior to transverse diameter ratio		0.84 ± 0.097	0.8 ± 0.088	0.84 ± 0.097	0.528
Air tapping					
Heart size compared to chest diameter		0.44 (0.4–0.5)	0.4 (0.38–0.47)	0.47 (0.4–0.5)	0.142
The height of the semicircle of the diaphragm		19.75 ± 6.9	18 ± 5.05	15.4 ± 6.4	0.082
Countable number of ribs		9 (8–9)	9 (8–9)	9 (8–10)	0.493

(Continues)

TABLE 3 | (Continued)

Characteristics	Dominant bronchitis $n = 76$	Dominant emphysema $n = 9$	Mixed $n = 15$	p value
mMRC	2 (1–3)	2 (1–3)	3 (2–3)	0.037
BODE Index	4 (3–6)	6 (4–8)	7 (6–9)	< 0.001
CAT	17.28 ± 7.9	17.89 ± 5.1	18.67 ± 7.5	0.808

Note: Data are presented as (%), median (interquartile range) or Mean ± SD.
Abbreviations: 6MWD, 6-min walk distance; ALT, aspartate alanine transferase; AST, aspartate aminotransferase; BMI, body mass index; CAT, COPD assessment test; Chol, cholesterol; Cr, creatinine; CRP, C-Reactive protein; ESR, erythrocyte sedimentation rate; EF, ejection fraction; FBS, fasting blood sugar; HB, hemoglobin test; HCO3, bicarbonate; HDL, high density lipoprotein; HCT, hematocrit test; LDL, low density lipoprotein; mMRC, modified medical research council scale; PAP, pulmonary arterial pressure; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; PH, pulmonary hypertension; PLT, platelet test; SaO2, arterial oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; Tg, triglycerides; TSH, thyroid stimulating hormone; WBC, white blood cells.

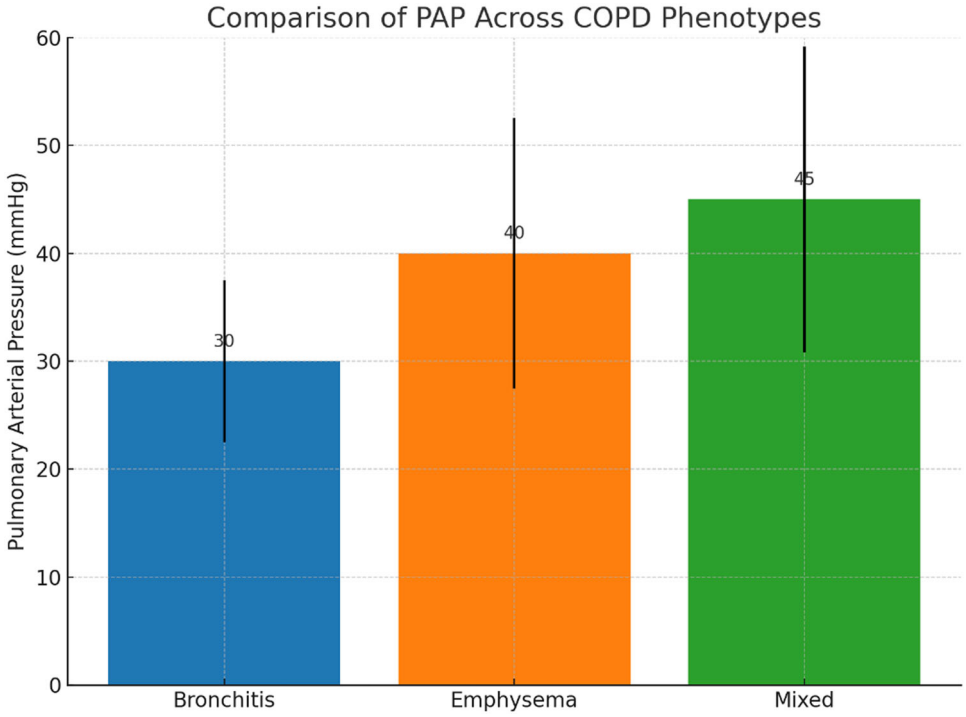

FIGURE 2 | Comparison of Mean Pulmonary Arterial Pressure (PAP) Across Different COPD Phenotypes.

Additionally, COPD patients with mixed phenotype had the highest percentage of mMRC grade compared to the other phenotypes that were associated with more frequent hospitalizations [41]. The mixed phenotype (emphysema and airway disease) has more frequent adverse clinical outcomes with higher blood neutrophil count, which has been associated with repeated exacerbations [42]. It has also been reported that the body mass and BODE index were significantly higher in dominant emphysema than in chronic bronchitis similar to the current study [43]. In a previous study, a significant relationship between COPD stages and the BODE index was reported. In addition, a significant association between systemic biomarkers and components of the BODE index was shown. Moreover, a significant and inverse correlation between inflammatory cytokines and the BODE index with FEV1 was observed [44]. Like our study, studies by kalkan et al. [45] and Regueiro et al. [46] have shown a significant correlation between 6MWT, CAT score, mMRC, BODE Index and severity in COPD patients. The current study highlights important clinical implications, such as the association between mixed phenotype and higher PAP, heart rate, mMRC, and BODE index. These findings could guide clinical decisions and improve patient management. However, the study does not discuss potential interventions or treatment strategies based on these findings.

4.1 | Limitations

This study has several limitations that should be considered when interpreting the findings. First, its cross-sectional design precludes causal inference, and potential biases such as reverse causality, incidence-prevalence bias, and unmeasured confounding may have influenced the results. Second, the relatively small sample size in the moderate and severe PH subgroups may have limited the statistical power to detect certain associations. Third, the number of patients in the emphysema phenotype group was notably low ($n = 9$), which may have affected the robustness of comparisons across phenotypes. This imbalance reflects the natural distribution of COPD phenotypes in our clinical setting, where chronic bronchitis is more prevalent.

Finally, heterogeneity in medication use among participants may have introduced additional variability. Future studies with larger, more balanced populations and prospective designs are warranted to confirm and expand upon these findings.

5 | Conclusions

This study demonstrated that the severe PH was associated with the lower 6MWT test while, it was associated with higher PCO2, mMRC, the BODE Index, CAT score, and higher heart size compared to chest diameter. The mixed phenotypes of COPD patients also showed an increase in heart rate, PAP, mMRC, and BODE Index as well as lower in 6MWD.

Author Contributions

Sayyed Gholamreza Mortazavi Moghaddam: Conceptualized the study, obtained the data, and prepared the manuscript. **Fahime Nosrati:** helped with the study design, and was involved in the collection of data. **Fateme Mahdizadeh:** assisted in analyzing the data, and drafting the manuscript. **Toba Kazemi:** Conceptualized, and obtained the data. **Mohammad Reza Khazdair:** is responsible for study design, drafting, and revising the manuscript. All authors read, and approved the final manuscript.

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Ethics Statement

The researcher filled out demographics and questionnaires form via face-to-face interviews and informed consent was signed by all patients. The patients were assured that the information were confidential and used only for research purposes. The study protocol was approved by the Ethics Committee of the Vice-Chancellery for Research and Technology of Birjand University of Medical Sciences. All subjects consented and filled out the form. The investigation fits in the principles outlined in the Declaration of Helsinki (Ethical committee code: IR. BUMS. REC.1399.325).

Conflicts of Interest

The authors declare no conflicts of interest.

Guarantor

Sayyed Gholamreza Mortazavi Moghaddam.

Data Availability Statement

The datasets during the current study are available from the corresponding author upon reasonable request.

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