The Egyptian Journal of Bronchology

RESEARCH

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Incidence of pulmonary hypertension in COPD and its relation to inflammatory marker interleukin-1

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Abstract

Background Many COPD patients present with severe PH defined by a pulmonary vascular resistance (PVR) > 5 WU as measured by right heart catheterization (RHC), and inflammation is thought to be contributing strongly to pulmonary vascular remodeling in COPD besides hypoxia. Interleukin-1 (IL-1) is thought to be a major cytokine that may be involved in development of PH in these patients.

Objective This study aimed to identify the incidence of PH in COPD and its relation to inflammatory marker IL-1.

Patients and methods One-hundred COPD patients underwent echocardiography and serum IL-1 analysis, and patients with high probability of PH underwent pulmonary artery catheterization using Swan-Ganz catheter.

Results The mean serum IL-1 level was 82 pg/ml ± 22 pg/ml (the normal IL-1 serum level is known to be 0:5 pg/mL), 51% of the participants were categorized as having a low probability of PH, 35% was intermediate, and 14% was high. RHC results were as follows: mild combined pre- and postcapillary PH was diagnosed in 14.3% of the patients. Mild precapillary PH was found in 42.9%, making it the most common type. Severe combined pre- and postcapillary PH was noted in 21.4% of the patients. Severe precapillary PH was present in 14.3%. A significant positive correlations were observed between serum IL-1 and tricuspid regurgitation velocity (TRV) ($r = 0.409$, $P < 0.001$), estimated systolic pulmonary artery pressure (ESPAP) ($r = 0.508$, $P < 0.001$), and mean pulmonary artery pressure (mPAP) ($r = 0.410$, $P = 0.140$).

Conclusion Serum IL-1 is a potent predictor of a high probability of PH in COPD patients, and there was significant positive correlation between serum IL-1 and echocardiographic findings and PH probability and RHC findings in COPD patients.

Keywords COPD, Pulmonary hypertension, Interleukin-1

Introduction

Pulmonary hypertension (PH) diagnosis is established when the mean pressure of pulmonary artery (mPAP) is ≥ 20 mmHg at rest as assessed by right heart catheterization (RHC) [1]. In group III PH, patients are classified to severe and non-severe PH, and pulmonary vascular resistance (PVR) more than 5 WU is recently considered a better prognostic factor than mPAP in PH associated with COPD patients [1].

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RHC is considered the gold standard in the diagnosis of PH, and it is essential in assessing the severity of hemodynamic impairment which is important for categorization of the patients of pH associated with COPD and can give a clue to the cause like cardiac comorbidities which are common in this group [2].

Interleukin-1 (IL-1) is a major cytokine that shows marked overexpression in cases of PH and is thought to have an important role in proliferation and inflammation of the smooth muscle cells of the pulmonary artery [3].

Patients and methods

This was a prospective interventional study and was conducted on 100 COPD patients who presented to the pulmonology department in Benha University hospitals, during the period between February 2022 and December 2023, and an informed written consent was fulfilled from all patients, after approval by the local ethics committee with ethical approval *code number: (MD 13-11-2021)*.

Inclusion criteria

The diagnosis of COPD patients included in the study was established by clinical examination together with spirometry (according to *GOLD 2020* guidelines) [4].

Exclusion criteria

Patients with other pulmonary diseases affecting pulmonary vasculature or causing hypoxia (as IPF); patient diagnosed with other types of PH, left-sided heart failure, and chronic kidney diseases; and patients who refused to share in the study

Methods

All patients have undergone the following: Full history of the disease, complete general and local physical examination, laboratory investigations (CBC, creatinine, ALT, AST, ABG), spirometery (FEV1, FVC, FEV1/FVC), high-resolution CT chest, serum level of interleukin-l, echocardiography with assessment of right heart, and probability of PH. Patients with high probability of pulmonary hypertension according to echocardiography criteria underwent pulmonary artery catheterization with Swan-Ganz catheter.

Serum interleukin-1 level

Quantitative measurement of serum interleukin-1β using ELISA technique. Using the kits: human interleukin-1β Elisa kit manufactured by INNOVA BIOTECH CO., LTD, China; Cat. No. In-Hu2151.

Echocardiography

Using a *Philips EPIQ 7C machine* with the *S5-1 probe* to assess the following.

- *Assessment of the right side of the heart*:
- *Assessment of PH probability* (according to recommendations of *2022 ESC/ERS* guidelines) [1] tricuspid regurge velocity (TRV), estimated systolic pulmonary artery pressure (ESPAP), additional echocardiographic signs suggestive of PH [1], and determination of PH probability to low, intermediate and high [1]
- *Assessment of the left side of the heart*

Right heart catheterization (RHC)

Patients found to have high probability of PH according echocardiographic criteria have undergone RHC with "Swan-Ganz catheter: TD Tourque-Line Catheter, 7F, 4 lumen, 110 Cm, Heparin coated designed by ICU medical, USA" to confirm diagnosis and assess hemodynamic characteristics and severity of pulmonary artery pressure.

Procedures

After fulfilling the consent, the catheter and the patient were prepared by unpacking the catheter, testing and flushing the ports under complete sterile condition, preparing the pressure monitor and transducer, sterilization of the site of puncture with povidone iodine solution, and inserting the introducer sheath in selected vein. The system is zeroed and calibrated to the reference point aligned to the 4th intercostal space, midaxillary line which parallels the midpoint of the left atrium (LA).

Insertion of Swan-Ganz catheter: The performed curve by the packaging of the catheter is used to facilitate directing it towards the tricuspid valve. Monitor pressure waveform changes connected to the distal port while advancing the catheter. The balloon is inflated slowly with air, when the catheter reaches the right atrium (RA) approximately at 20-cm mark, to allow blood flow to direct the catheter into the proper pathway to reach pulmonary artery (PA) and then obtain pulmonary artery wedge pressure (PAWP). Once the PAWP is obtained, make sure the PAWP pattern is reproducible by deflating balloon and regaining pulmonary artery pressure waves, and then a mixed central venous sample is taken through catheter side port.

Measurements

We measured the following: The systolic, diastolic, and mean pressures of RA, RV, and PA and then PAWP and mixed central venous O2 saturation (SvO2).

Cardiac output (CO) was calculated using direct Fick method [5].

*VO2 total oxygen consumption (ml/min), *CO cardiac output (l/min)

*Ca and Cv, the arterial and venous oxygen content (ml/l)

Cardiac index (CI) is calculated as follows [6]:

*CI cardiac index (l/min/m2), *CO cardiac output (l/min)

*BSA body surface area (m2)

PVR is calculated as follows [7]:

*PVR pulmonary vascular resistance (wood unit)

*mPAP mean pulmonary arterial pressure (mmHg)

*PAWP pulmonary artery wedge pressure (mmHg)

Statistical methods

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, USA). Quantitative data were compared according to PH probability using the independent t-test or Mann-Whitney U-test. ROC analysis was done for serum IL-1 to predict high probability of PH.

Results

The result of this study on 100 patients showed that their mean age was 60 ± 10 years. Most participants were males (88%). A total of 86% of the patients were smokers. The distribution of COPD phenotypes was chronic bronchitis (58%) and emphysema (42%). Regarding the severity of COPD, most participants fell into the moderate category (72%), 18% were severe, and 10% were mild (Table 1).

The mean serum IL-1 level was 82 pg/ml ± 22 pg/ml (normal IL-1 serum level = 0:5 pg/ml) [8] (Table 2).

Regarding echocardiographic findings, TRV was 2.79 m/s ± 0.43 m/s. The ESPAP was 33 mmHg ± 9 mmHg. Regarding the RV morphology, 9% of the participants showed evidence of RV hypertrophy or dilatation. In terms of the probability of PH, 51% of the participants were categorized as having a low probability, 35% as intermediate, and 14% as high (Table 3).

Findings of RHC showed mPAP was 34 mmHg ± 11 mmHg. The PVR had a median value of 3.5. The median PAWP was 12 mmHg. CO had a mean value 5.24 l/min ± 0.76 l/min. The CI had a mean of 2.72 l/min/m^2 ± 0.39 l/min/m^2. Regarding the diagnosis after catheterization, mild combined pre- and postcapillary PH was diagnosed in 14.3% of the patients. Mild precapillary PH was found in 42.9%, making it the most common type. Severe combined pre- and postcapillary PH was noted in 21.4% of the patients. Severe precapillary PH was present in 14.3%. Only 7.1% of the patients did not have PH (Table 4) (Fig. 1).

Patients with a high probability of PH revealed significantly higher levels of serum interleukin-1 (98 ± 21) compared to those without high probability (80 ± 21) ($P = 0.003$), and ALT showed lower levels (25 ± 8) than those without a high probability (31 ± 10) ($P = 0.041$) (Table 5).

ROC analysis for serum IL-1 to predict high probability of PH revealed a significant AUC of 0.722, with

Table 1 General characteristics of the studied patients

General characteristics		
Age (years)	**Mean ± SD**	**60 ± 10**
Sex		
Males	*n* (%)	88 (88)
Females	*n* (%)	12 (12)
Smoking	*n* (%)	86 (86)
Smoking index	Median (range)	600 (180–1800)
COPD phenotype		
Chronic bronchitis	*n* (%)	58 (58)
Emphysema	*n* (%)	42 (42)
Severity of COPD		
Mild	*n* (%)	10 (10)
Moderate	*n* (%)	72 (72)
Severe	*n* (%)	18 (18)

COPD chronic obstructive pulmonary disease

Table 2 Laboratory findings of the studied patients

Laboratory findings		
Hemoglobin	**Mean ± SD**	**13.1 ± 1.7**
TLC	Median (range)	9.2 (3.8–22.5)
Platelets	Median (range)	237 (106–671)
AST	Median (range)	28 (12–78)
ALT	Mean ± SD	30 ± 10
Creatinine	Mean ± SD	0.82 ± 0.23
Serum interleukin-1 (Pg/ml)	Mean ± SD	82 ± 22

SD, standard deviation; *TLC*, total leukocyte count; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase

Table 3 Echocardiographic findings of the studied patients

Echo findings		
TRV	**Mean ± SD**	**2.79 ± 0.43**
ESPAP	Mean ± SD	33 ± 9
RV hypertrophy/dilatation	*n* (%)	9 (9)
Probability*		
Low probability	*n* (%)	51 (51)
Intermediate	*n* (%)	35 (35)
High	*n* (%)	14 (14)

TRV, tricuspid regurgitation velocity; *ESPAP*, estimated systolic pulmonary artery pressure; *RV*, right ventricular; *n* (%), number (percentage).

*Probability of PH: low: *TRV* < 2.8 with no additional signs, intermediate: *TRV* = (2.8:3.4) with no additional signs or < 2.8 with additional signs, and high:^{TRV} > 3.4 or (2.8:3.4) with additional signs[1]

Table 4 Pulmonary artery catheterization findings

PA catheterization		
mPAP	**Mean ± SD**	**34 ± 11**
PVR	Median (range)	3.5 (1.9–8.6)
PAWP	Median (range)	12 (5–23)
CO	Mean ± SD	5.24 ± 0.76
CI	Mean ± SD	2.72 ± 0.39
Diagnosis*		
Mild combined pre- and postcapillary PHtn	*n* (%)	2 (14.3)
Mild precapillary PHtn	*n* (%)	6 (42.9)
Severe combined pre- and postcapillary PHtn	*n* (%)	3 (21.4)
Severe precapillary PHtn	*n* (%)	2 (14.3)
No PHtn	*n* (%)	1 (7.1)

mPAP, mean pulmonary artery pressure; *PVR*, pulmonary vascular resistance; *PAWP*, pulmonary artery wedge pressure; *CO*, cardiac output; *CI*, cardiac index; *PHtn*, pulmonary hypertension. Precapillary *PAWP* < 15 mmHg, postcapillary *PAWP* > 15[1]

*Severe *PH PVR* > 5 WU, mild PH *PVR* < 5 WU[1]

Precapillary *PAWP* < 15 mmHg, postcapillary *PAWP* > 15[1]

a 95% confidence interval ranging from 0.575 to 0.869 ($P = 0.008$). The best cutoff point was > 86, at which sensitivity was 78.6% and specificity was 58.1% (Table 6) (Fig. 2).

Regarding correlation of serum IL-1 with echocardiography and pulmonary catheterization findings, a significant positive correlations were observed between TRV ($r = 0.409$, $P < 0.001$) and ESPAP ($r = 0.508$, $P < 0.001$), and a positive correlation was noted between mPAP and serum IL-1 ($r = 0.410$) with *P*-value ($P = 0.140$) (Table 7).

Discussion

In patients with COPD, pulmonary vascular remodeling emerges as a primary contributor to PH. Multiple factors are believed to result in this remodeling such as hypoxia, loss of capillary bed in emphysema, and inflammation [9].

IL-1 is a key cytokine that is involved in chronic inflammation that stands out as a characteristic feature in various forms of PH and also is emerging as a major player in the initiation and persistence of inflammation in COPD [10].

The average age of participants in this study was 60 years ± 10 years. Most participants were males (88%). A total of 86% of the patients were smokers. The prevalence of COPD between Egyptians is approximately 10% as concluded in *Said* et al. [11], so it constitutes a serious health problem in Egypt. The distribution of COPD phenotypes in this study was chronic bronchitis (58%) and emphysema (42%). Regarding the severity of COPD, most participants fell into the moderate category (72%), 18% were severe, and 10% were mild. These findings are coinciding with what is expected as the common age group, gender, and history of smoking in COPD patients but differ slightly than *Fabricius* et al. [12], who showed that mild cases represented 35% of the study that was conducted on 6236 patients; while moderate

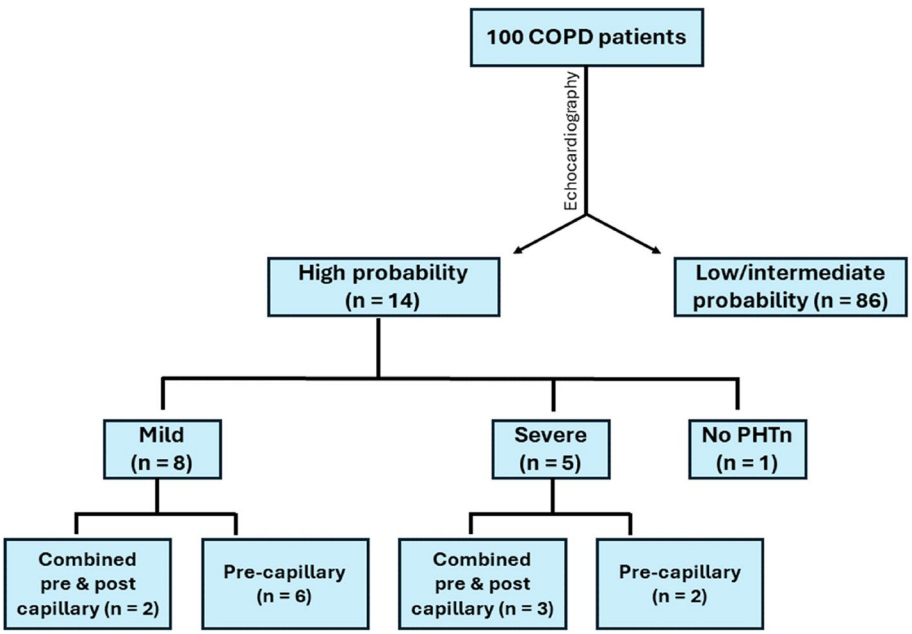

Fig. 1 Flow chart of the studied COPD patients

Table 5 Correlation of laboratory findings to probability of pulmonary hypertension

		High probability		
		Yes ($n=14$)	No ($n=86$)	*p*-value
Hemoglobin	**Mean ± SD**	**13.4 ± 2.1**	**13.1 ± 1.6**	**0.504**
TLC	Median (range)	9.4 (6.5–22.5)	9.2 (3.8–22)	0.913
Platelets	Median (range)	222 (150–336)	246 (106–671)	0.205
AST	Median (range)	25 (15–41)	28 (12–78)	0.058
ALT	Mean ± SD	25 ± 8	31 ± 10	**0.041***
Creatinine	Mean ± SD	0.8 ± 0.21	0.83 ± 0.23	0.621
Serum interleukin-1 (Pg/ml)	Mean ± SD	98 ± 21	80 ± 21	**0.003***

SD, standard deviation; *TLC*, total leukocyte count; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase

Table 6 ROC analysis of serum interleukin-1 to predict high probability of pulmonary hypertension

ROC characteristics	
AUC	**0.722**
95% CI	0.575–0.869
Best cutoff	> 86 pg/ml
Sensitivity	78.6%
Specificity	58.1%
P-value	0.008

AUC, area under the curve; *CI*, confidence interval; *PPV*, positive predictive value; *NPV*, negative predictive value

cases represented 52% and severe cases represented 11% only, these differences are thought to be mostly due to that this study was conducted on cases that presented to hospital only.

In this study, echocardiography illustrated that TRV was 2.79 m/s ± 0.43 m/s. The ESPAP was 33 mmHg ± 9 mmHg. Regarding the RV morphology, 9% of the participants showed evidence of RV hypertrophy or dilatation. In *Kovacs* et al. [13], study on 142 patients resulted that the mean ESPAP was 35 mmHg, and this was close to our results as mentioned.

In terms of the probability of pulmonary hypertension, 51% of the participants were categorized as having a low probability, 35% as intermediate, and 14% as high.

Patients with a high probability of pulmonary artery hypertension underwent pulmonary artery catheterization. The mPAP was 34 mmHg ± 11 mmHg. The PVR had a median value of 3.5, ranging from 1.9 to 8.6. The median PAWP was 12 mmHg, ranging from 5 to 23 mmHg. CO had a mean value 5.24 l/min ± 0.76 l/min. The CI had a mean of 2.72 l/min/m^2 ± 0.39 l/min/m^2. Regarding the diagnosis after catheterization, mild combined pre- and postcapillary PH was diagnosed in 14.3% of the patients. Mild precapillary PH was found in 42.9%, making it the most common type. Severe combined pre- and postcapillary PH was noted in 21.4% of the patients. Severe precapillary PH was present in 14.3%. Only 7.1% of the patients did not have PH. But in *Kovacs* et al. [13], the mean mPAP was 35 mmHg ranging from 27 to 43 mmHg, the mean PVR was 4.3 WU ranging from 2.9 to 7.4 WU, and the mean PAWP was 10 mmHg ranging from 8 to 13 mmHg.

The wide differences between the two studies in this category are thought to be due to the relatively small number of patients that was subject to right heart catheterization in our study.

In *Soliman* et al. [14], a study was performed on 51 COPD patients, 17 of them have undergone RHC, the mean mPAP was 35.27 ± 7.8 mmHg, and the mean PAWP was 7.18 ± 1.6. Patients with severe PH constituted 4% of the cases compared to our results that severe cases are constituting 5% of all the studied cases, so the results of *Soliman* et al. [14], strongly support our results.

The mean serum IL-1 level was 82 pg/ml ± 22 pg/ml, and while correlating IL-1 to the probability of PH, serum IL-1 was significantly higher in patients with high probability (98 ± 21) compared to those without high probability (80 ± 21) ($P=0.003$); this finding is in line with the understanding of IL-1 as it means that serum level IL-1 are generally higher in COPD patients as it was resulted in *Palomera* et al. [15], that a group of 27 controls showed serum level of IL-1 7.78 ± 2.26 pg/ml.

Similarly, in *Humbert* et al. [16], study on serum levels of IL-1β, IL-6, and TNF-α in different patient groups, severe primary pulmonary hypertension (PPH) (29 patients), COPD-associated PH group (9 patients) and normal group (15 patients), serum levels of TNF alpha did not show differences between groups, but there was marked elevation in serum IL-1β level in severe PPH group (118 + / − 36 pg/ml), while other groups did not show similar elevations; also, there was notable increase in serum IL-6 level in PPH group only (66 + / − 20 pg/ml), and this was not recorded in COPD-PH group or control group.

The findings observed by *Humbert* et al. [16], that serum IL-1β has great rises in PPH group only sparing the COPD-PH group as well as control group do not coincide with the results of our study as we observe notable higher serum levels in COPD patients, in particular patients with high probability of PH. This variance is thought to be due to the difference in the number of the studied cases as *Humbert* et al.[16] have studied only nine COPD patients, and another possible cause

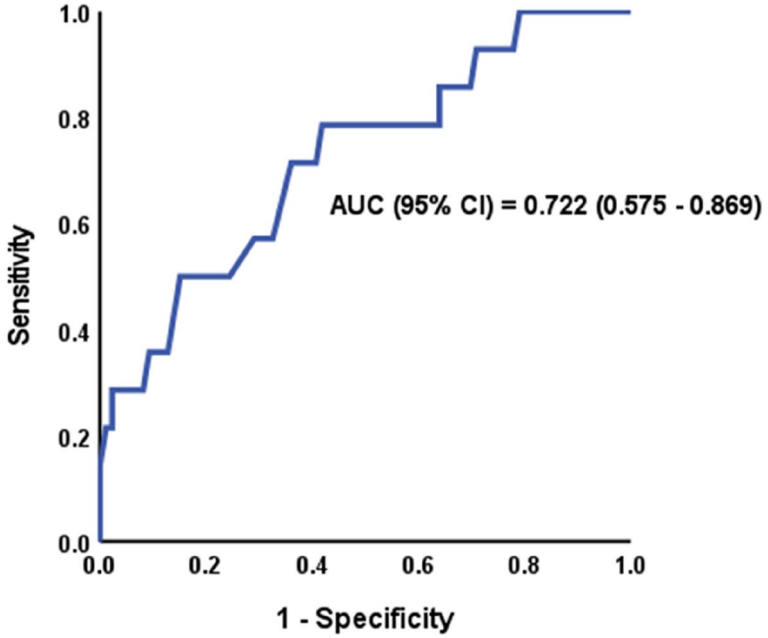

Fig. 2 ROC analysis of serum interleukin-1 to predict high probability of pulmonary hypertension

Table 7 Correlation of serum interleukin-1 with echo and pulmonary catheterization findings

	Serum interleukin-1 (Pg/ml)	
	R	*P*
TRV	0.409	< .001*
ESPAP	0.508	< .001*
mPAP	0.410	0.145
CO	0.18	0.538
CI	− 0.038	0.897
PVR	0.366	0.199
PAC PAWP	0.123	0.676

* Significant *P*-value; *TRV*, tricuspid regurgitation velocity; *ESPAP*, estimated systolic pulmonary artery pressure; *CO*, cardiac output; *CI*, cardiac index; *PVR*, pulmonary vascular resistance; *PAWP*, pulmonary artery wedge pressure

may be the different ethnic groups of the two studies, taking into account that IL-1 overexpression may vary depending on COPD phenotypes or etiology as discussed in *Osei* et al. [10].

ROC analysis was done for serum IL-1 to predict high probability of PH. The established cutoff point for IL-1 levels (> 86 pg/ml) in predicting PH showed a sensitivity of 78.6% and specificity of 58.1%. A sensitivity of 78.6% means that IL-1 levels above 86 pg/ml correctly identified approximately 79% of patients who did have PH. However, the specificity of 58.1% indicates that about 42% of patients without PH would still test positive (false positives). This lower specificity suggests that while elevated IL-1 is indicative of PH, it should not be the sole criterion for diagnosis [17].

When key echocardiographic and pulmonary catheterization parameters in COPD patients were evaluated for PH, significant positive correlations were observed between serum IL-1 levels and both TRV and ESPAP, as evidenced by correlation coefficients of $r = 0.409$ ($P < 0.001$) and $r = 0.508$ ($P < 0.001$), respectively. Also, there was a positive correlation between mPAP and serum IL-1 ($r = 0.410$) with a p-value of 0.140. These correlations are significant, suggesting that elevated IL-1 levels are associated with increased TRV and ESPAP, and mPAP measured with RHC in cases who were subjected to catheterization.

These correlations suggest that systemic inflammation in COPD can be assessed by serum IL-1 levels, and it may be involved in the pathophysiology of PH in these patients.

These findings coincide with the results of *Agrawal* et al. [18], who revealed a strong positive correlation between PH associated with heart failure with preserved ejection fraction (HFpEF) and serum levels of IL-1β measured in venous blood, PA blood, and PAWP blood; also, *Agrawal* et al. [18], confirmed overexpression of IL-1β in neutrophils and activated monocytes in this group over the other group with no PH and stated that myeloid cells derived IL-1β has contributed to pulmonary vascular remodeling in cases of HFpEF-associated PH.

These findings not only underscore the potential of IL-1 as a biomarker for early detection and risk stratification of PH in COPD but also open new avenues for targeted therapeutic interventions. Focusing on IL-1 modulation could lead to more effective management strategies, shifting the treatment paradigm towards addressing underlying inflammatory processes in PH associated with COPD.

Conclusion

Our prospective study evaluates the relationship between COPD, PH, and the role of IL-1 in predicting a high probability of PH. In comprehensive investigations, and statistical analyses, we identified that serum IL-1 is as a potent predictor of a high probability of PH in COPD patients. There was significant positive correlation between serum IL-1 and echocardiographic findings, PH probability, and RHC findings in patients with COPD; these observations provide valuable insights into the underlying mechanisms of pulmonary complications in COPD.

Abbreviations

CI	Cardiac index
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
ESPAP	Estimated systolic pulmonary artery pressure
HFpEF	Heart Failure with preserved Ejection Fraction
IL	Interleukin
mPAP	Mean pulmonary artery pressure
PA	Pulmonary artery
PAWP	Pulmonary artery wedge pressure
Pg	Picogram
PH	Pulmonary hypertension
PPH	Primary pulmonary hypertension
PVR	Pulmonary vascular resistance
RA	Right atrium
RHC	Right heart catheterization
RV	Right ventricle
TNF	Tumor necrosis factor
TRV	Tricuspid regurge velocity
WU	Wood unit

Acknowledgements

Not applicable.

Authors' contributions

Authors contributed equally in the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The data will be accessible to the journal and reviewers from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all patients; the Benha University Ethics Committee gave its approval to the study with ethical approval code number: (MD 13–11-2021).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 6 February 2024 Accepted: 30 March 2024
Published online: 13 April 2024

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