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Original Research Article

Risk Assessment in Severe PH Due to ILD– A Cross Sectional Study

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Abstract:

Background: Pulmonary hypertension (PH) complicates the management of individuals with ILD, leading to diminished functional status & adverse outcomes. Timely identification of PH in ILD is crucial for commencing treatment & evaluating lung transplantation options. The aim of present study was "to assess the suitability of a reduced ESC/ERS risk categorization model to forecast the long-term prognosis in individuals with severe PH resulting from ILD".

Methods: The present cross-sectional study was conducted 60 among patients of ILD suspicious of PH at department of pulmonary medicine of a tertiary care centre for a period of one year & follow up was done upto two years. Risk stratification analyses were conducted on patients according to guidelines. Statistical analysis was done by using SPSS version 25.0.

Results: Out of 60 patients 10 had low risk, 35 had intermediate risk & 15 had high risk. During the follow-up, one patient was lost to follow-up. The TF survival rates for patients with SPH related to ILD were 58% at 1 year & 31% at 2 years. "SvO2, RA area, BNP, WHO functional class, & the ESC/ERS risk score were important predictors of TFS". Nonetheless, the ESC/ERS risk score emerged as the most robust predictor.

Conclusion: A condensed iteration of the ESC/ERS risk classification paradigm for PAH may predict TFS in patients with advanced PH due to ILD.

Keywords: CLD, ILD, PH, Pulmonary Fibrosis, Risk Stratification, Survival.

Introduction

The World Health Organization has classified PH (PH) into five separate groups based on similarities in pathogenesis, clinical presentation, & therapeutic choices. PH associated with hypoxia &/or pulmonary disorders, including ILD, COPD, & sleep-related breathing disorders, is classified as group 3.[1] The incidence of PH (PH) has been documented in as many as 86% of individuals with ILD, contingent upon the definition of PH, the specific form of ILD, & the diagnostic methodology employed to identify PH.[2,3] The analysis of PH in subjects with ILD is established through RHC, characterized by a resting mPAP exceeding 20 mmHg & a pulmonary vascular resistance of at least 3. Wood Units are obligatory, as recently revised during the "6th World Symposium on Pulmonary Hypertension." [1,4]

PH with ILD is linked to diminished functional status, the necessity for supplemental oxygen, & adverse outcomes. [5-8] PH can also manifest in several ILDs apart from IPF, with a severe phenotype of PH-ILD characterized by a diminished cardiac index reported in extensive European investigations. [9,10] The emergence of PH in patients with ILD correlates with diminished survival rates & heightened morbidity. Song et al. reported a 1-year death rate of 61.2% for patients with idiopathic pulmonary fibrosis (IPF) & PH identified via echocardiography, in contrast to 19.9% for those without PH. [11] Nadrous et al similarly observed a median survival of 0.7 years for patients with idiopathic pulmonary fibrosis (IPF) with pulmonary artery systolic pressure over 50 mmHg as determined by echocardiography. [12]

Notwithstanding its significance, there is a lack of unanimity on showing for PH in ILD. The early identification of ILD-PH relies on the clinical acumen of the attending physician, & the confirmation of the diagnosis frequently presents difficulties. To date, treatment has been exclusively supportive, encompassing OT(Oxygen Therapy), diuretics, & the appropriate management of the underlying pulmonary condition. [13] Nonetheless, emerging medicines shown in recent trials may address this area of unmet clinical need. Therefore, we sought "to assess the suitability of a reduced

ESC/ERS risk categorization model to forecast the long-term prognosis in individuals with severe PH resulting from ILD".

Material & Methods

The present cross-sectional study was conducted among patients of ILD at department of pulmonary medicine of a tertiary care centre for a period of one year & follow up was done upto two years. Ethical clearance was taken from institutional ethics committee of allied institute. Patients were asked to sign an informed consent form.

Through consecutive sampling a total of 60 patients with ILD suspected of PH were selected on the basis of inclusion & exclusion criteria. The primary end-point was TFS.

Inclusion Criteria

Patients with age above 18 years, diagnosed with ILD according to current guidelines, undergoing right heart cathertization at department, patients willing to participate in the study.

Exclusion Criteria

Patients with age less than 18 years, having ILD but not having risk of PH& did not sign ant consent form for the study.

"Hemodynamic classification- The presence & severity of PH were assessed in accordance with the current guidelines. [1] Severe PH (PH) was characterized by a mPAP of ≥35 mm Hg or a mPAP of ≥25 mm Hg accompanied with a cardiac index of <2.0 liters/min/m².

RS analyses were performed on patients with data for at least two of the following variables: "World Health Organisation (WHO) functional class, 6-minute walk distance, brain natriuretic peptide (BNP) level, right atrial (RA) area, presence of pericardial effusion, RA pressure, cardiac index, & mixed venous oxygen saturation (SvO2)". Patients were categorised into low, intermediate, & high-risk groups based on these eight features, employing a condensed version of the risk stratification method specified in the latest ESC/ERS guidelines.[14] As previously stated, each variable was designated a grade of 1, 2, or 3, indicating low, intermediate, or high risk, respectively. The sum of all grades was subsequently divided by the number of available variables & rounded to the nearest integer to determine the risk class. Risk stratification analyses were performed using baseline & follow-up data.

Statistical analyses were performed utilising SPSS 25.0 (IBM, Armonk, NY). Patient characteristics were summarised using appropriate descriptive statistics. We evaluated the relationship between risk stratification &TFS by Kaplan−Meier analyses. The association of each risk stratification parameter with TFS was assessed using univariate Cox regression analysis. In all trials, a p-value below 0.05 was considered significant".

Results

Of the 60 patients, 10 were classified as LR, 35 as IR, & 15 as HR. The baseline characteristics are presented in Table 1. The primary causes of ILD included IPF, non-specific interstitial pneumonia, hypersensitivity pneumonitis & rheumatoid-inflammatory diseases, representing 30%, 21%, 10%, & 11% of the examined population, respectively. The average age of the patients was 64 ± 10 years. The TLC, FVC, & DLCO demonstrated considerable impairment, recorded at 58% ± 21%, 70% ± 22%, & 40% ± 15%, respectively, whereas the FEV in one second to maximum VC ratio remained within normal parameters (≥75%). Lung function showed no significant differences among the ESC/ERS risk categories ($p > 0.05$ for TLC, FVC, & DLCO).

Table 1: Fundamental Attributes of Patients with Severe Pulmonary Hypertension As a result of ILD

Parameter	All (n=60)	LR (n=10)	IR (n=35)	HR (n=15)
Age, years	64±10	61±12	65±10	63±11
BMI, kg/m^2	28.1±6.1	26.1±9.2	27.1±4.6	25.1±8.4
Male	34	8	14	12
Female,	26	6	12	8
Etiology,				
Idiopathic pulmonary fibrosis	18	4	8	6
Hypersensitivity pneumonitis	13	1	9	3
Non-specific interstitial pneumonia	6	1	4	1
Rheumatoid-inflammatory diseases	7	1	4	2
Sarcoidosis	6	1	4	2
Combined pulmonary fibrosis & emphysema	5	0	4	1
Other	5	1	3	1
mPAP, mmHg	41±6	40±4	42±2	46±1
RA pressure, mmHg	5±1	4±1	4±2	6±1
CI, liter/min/m^2	2.1±0.4	2.0±0.4	2.1±0.3	1.5±0.1

SvO_2, %	61±6	68±3	61±5	53±9
6MWD, m	213±110	262±104	218±111	153±09
WHO functional class, n				
II	5	1	3	2
III	46	3	42	1
IV	9	1	7	1
RA area, cm^2	20±3	12±4	20±1	34
Pericardial effusion, n				
No	13	5	6	2
Minimal	18	0	12	6
Yes	29	0	13	16
FEV1, % predicted	60±20	53±16	60±20	64±21
FEV1/VC max, % predicted	82±13	78±12	84±11	80±21
TLC, % predicted	70±22	73±21	69±21	70±10
FVC, % predicted	57±21	53±20	52±21	52±21
DLCO, % predicted	40±15	45±21	46±12	35±3

All 60 patients with severe PH resulting from ILD were incorporated into the RSA; 10 were classified as LR, 35 as IR, & 15 as HR according to the shortened ESC/ERS risk classification framework. Baseline data for BNP values, WHO functional class, & 6-minute walk distance were accessible for all patients. Data from right cardiac catheterization &ECG were accessible for 100% & 84% of the patients, respectively. 98% of the patients had data accessible for a minimum of five risk categorization factors. The median duration from initial diagnosis to subsequent evaluation was 18 months. During the follow-up, one patient was lost to follow-up. The TFS rates for patients with severe PH related to ILD were 58% at 1 year& 31% at 2 years.

Each risk stratification factor was tested for its predictive significance for severe PH related to ILD using univariate Cox regression models. TFS prognosis was influenced by "BNP, SvO2, WHO functional class, RA area, & ESC/ERS risk score". Table 2 shows that the ESC/ERS risk score was the most accurate predictor.

Table 2: "Univariate Cox regression study investigating the association between risk stratification parameters & mortality/transplantation in patients with ILD & severe PH".

Parameter	Risk Category	Hazard Ratio
WHO functional class	Intermediate	0.713
	High	1.871
6 MWD	Intermediate	1.554
	High	2.435
BNP	Intermediate	1.678
	High	2.346
Right atrial area	Intermediate	1.542
	High	0.821
Pericardial effusion	Intermediate	1.194
	High	0.632
Right atrial pressure	Intermediate	0.921
	High	1.679
Cardiac index	Intermediate	0.983
	High	1.435
SvO2	Intermediate	1.654
	High	2.134
ESC/ERS score	Intermediate	1.892
	High	3.189

Discussion

Interstitial lung disease is a collective term encompassing a diverse array of over 150 pulmonary disorders that share basic functional traits, such as restricted physiology & compromised gas exchange, yet exhibit a broad spectrum of etiologies, pathological & clinical presentations, imaging features, & varying prognoses. [15] Notwithstanding the considerable variability of ILD , the pulmonary alveolar walls are predominantly penetrated by various inflammatory cell types & exhibit proliferation of certain cells, such as fibroblasts & myofibroblasts. IPF & several other ILDs are characterized by lung

interstitium fibrosis that leads to permanent fibrosis & impaired gas exchange, regardless of the cause. Progressive fibrosing ILDs cause exercise intolerance, respiratory failure, increased oxygen needs, & death due to morphological & pathophysiological changes. [16,17]

The present cross-sectional study was conducted among 60 patients of ILD at department of pulmonary medicine of a tertiary care centre for a period of one year & follow up was done upto five years. We sought "to assess the suitability of a reduced ESC/ERS risk categorization model to forecast the long-term prognosis in individuals with severe PH resulting from ILD". We applied a reduced ESC/ERS risk classification scheme to a real-world cohort of ILD-related severe PH patients. Our study found that the risk stratification model may predict TFS in patients with severe PH from ILD at diagnosis & throughout follow-up.

The majority of evidence on PH in patients with ILD is derived from publications pertaining to idiopathic pulmonary fibrosis. Typically, PH in patients with ILD is mild to moderate & seldom severe. In a substantial experiment involving patients with IPF, 46% of individuals with severe ILD exhibited mPAP over 25 mmHg, whereas only 9% demonstrated mPAP surpassing 40 mmHg. [18] It is noteworthy that the majority of data utilized in earlier studies adhered to the old definition of PH, which employed a mean pulmonary arterial pressure cutoff of 25 mmHg. A distinct cohort of 70 patients with IPF underwent receiver operating characteristic analysis, indicating that a mean pulmonary arterial pressure of 17 mmHg serves as the optimal predictor of mortality. [19,20] The reported prevalence of IPF varies from 14 to 43 per 100,000 individuals, while PH is identified in up to 30–50% of this cohort. [21] The prevalence of IPF escalates with advancing age, often manifesting in the sixth & seventh decades of life. [22] PH is linked to a threefold elevation in mortality relative to individuals with pulmonary disease who do not have PH. [23] According to the "COMPERA registry", there is no disparity in survival rates across the various kinds of ILD linked with PH. [4,9]

We documented TFS in our cohort; nevertheless, transplants were comparatively rare, & our survival rates are inferior than the overall survival statistics from prior studies of patients with PH resulting from chronic lung disease &/or hypoxia. [24,25] There is no content to rewrite. Trammell et al. studied 18,382 US veterans with PH resulting from chronic lung illness &/or hypoxia, reporting overall survival rates of 86.2%, 67.4%, & 52.3% at 1 year, 3 years, & 5 years, respectively. [24] Nevertheless, they failed to distinguish between COPD & ILD, despite the significant effect on survival. [25] In the registry for Assessing the Spectrum of PH at a referral center, the overall three-year survival rate was 44% for patients with PH attributable to lung illnesses, & merely 16% for those with PH resulting from ILD. [24,25] Moreover, neither research distinguished between severe & non-severe PH in subjects with ILD.

The TFS of patients with severe PH related to ILD in our study was significantly inferior than that previously documented in patients with pulmonary arterial hypertension in the Giessen PH registry. [26] Patients with high-risk PAH have lately demonstrated significantly reduced overall survival rates. [27,28] Consequently, individuals with high-risk pulmonary arterial hypertension should have intensive initial therapy with prompt evaluation for lung transplantation. [28] The low-risk cohort of patients with severe PH due to ILD had a comparable reduction in TFS, whereas the high-risk subgroup had a much greater drop. Due to a lack of comparison trials, PAH-specific treatment for these people is unclear.. [1]

We found that the ESC/ERS risk categorization is useful for monitoring during therapy since the risk classes at follow-up were prognostically significant. This risk stratification method's main feature is its simplicity in commencing & escalating medication & tracking therapy progress. Moreover, employing a risk stratification framework may facilitate the standardization of study protocols, particularly for randomized controlled trials, hence enhancing comparability among investigations. A risk classification framework could elucidate the beneficial or detrimental impacts of PAH-specific medication in individuals with ILD.

Conclusion

PH is an under-recognized condition in people with ILD& negatively impacts FC & survival. The diagnosis is complex, requiring a heightened level of suspicion, & there are no established guidelines for patient screening or the most effective screening methods. RHC is the benchmark for a conclusive diagnosis, although it is only required when it is expected to influence the management approach.

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