Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

TO STUDY AN ASSOCIATION BETWEEN IRON DEFICIENCY AND SEVERITY OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC LUNG DISEASE

Dr Harshita Bhardwaj,[1]Dr Ramji Sharma,[2] Dr Shrikant sharma[3], Dr Kanhaiya Lal Sharma[4]

[1]3rd yr resident, department of general medicine,sms medical College,jaipur
[2]Associate professor,department of general medicine,sms medical College,jaipur
[3]Professor, Department of general medicine, SMS medical College, Jaipur
[4*]Assistant professor, department of general medicine,sms medical College,Jaipur

***Corresponding author**: Dr Kanhaiya Lal Sharma, Assistant professor,department of general medicine,sms medical College,jaipur Email: kanhaiyalalsharma.sharma5@gmail.com

ABSTRACT

INTRODUCTION: Pulmonary hypertension (PH) is a diverse condition characterized by pathological remodeling of the pulmonary blood vessels, leading to increased pressure in the pulmonary arteries and heightened vascular resistance.

AIM: To find an association between iron deficiency and pulmonary hypertension in patients with chronic lung disease and correlating it with severity of pulmonary hypertension.

METHODOLOGY: This hospital-based observational study was a cross-sectional analysis conducted at the Department of Medicine, S.M.S. Hospital, and its attached Group of Hospitals. The study spanned from January 2023 to December 2024.

RESULT: This study found a high prevalence of iron deficiency among chronic lung disease patients with pulmonary hypertension, with significantly lower serum iron, ferritin, and higher TIBC in the iron-deficient group, along with elevated RVSP, but no significant differences in age, BMI, haemoglobin, or pulmonary function tests between the iron-deficient and non-iron deficient groups.

CONCLUSION: In conclusion, our study demonstrates a significant association between iron deficiency and the severity of pulmonary hypertension in chronic lung disease patients, highlighting the importance of addressing iron deficiency through screening and interventions to improve patient outcomes and management strategies.

Keywords: chronic lung disease, Pulmonary hypertension, iron deficiency.

INTRODUCTION

Pulmonary hypertension (PH) involves pathological remodeling of pulmonary vessels, increasing pressure and resistance, while pulmonary arterial hypertension (PAH), a rare subtype, results from genetic factors causing arteriopathy and high untreated mortality due to heart failure[1].There are 5 broad PH clinical categories that focus on the underlying cause of abnormal pulmonary artery pressure:

- Pulmonary arterial hypertension (PAH);
- Left heart disease;
- Lung diseases and/or hypoxia;
- Pulmonary artery obstructions (particularly thromboembolic syndromes);
- Undifferentiated or multifactorial causes, including sickle cell disease and sarcoidosis[2].

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

WHO Group 3 pulmonary hypertension (PH) encompasses lung diseases and hypoxic conditions, with COPD, diffuse pulmonary lung diseases (DPLD), and combined pulmonary fibrosis and emphysema (CPFE) being the most common causes, often leading to varying PH severity. Other contributors include cystic fibrosis, chronic hypersensitivity pneumonitis, lung cancers, developmental lung disorders, high-altitude hypoxia, and obesity hypoventilation syndrome, which is associated with more severe PH and worse prognosis compared to obstructive sleep apnea[3-8]. Chronic obstructive pulmonary disease (COPD) can cause pulmonary hypertension (PH), with most moderate-to-severe cases showing mild PH and occasional severe PH, exacerbated by recurrent episodes that elevate pulmonary arterial pressure. COPD-induced factors like hypoxia, hyperinflation, and systemic inflammation lead to vascular remodeling and increased pulmonary resistance, straining the right ventricle and predisposing to right heart failure[9].Chronic obstructive lung disease (COPD) and diffuse parenchymal lung diseases (DPLD), including idiopathic pulmonary fibrosis (IPF) and sarcoidosis, are frequently associated with pulmonary hypertension (PH), worsening prognosis and exercise capacity. Severe PH (mPAP ≥35 mm Hg or mPAP ≥20 mm Hg with low cardiac index) occurs in a minority of cases, linked to vascular remodeling and reduced circulatory reserve, further impairing functional status and outcomes[10].Detection of pulmonary hypertension (PH) in chronic lung diseases (CLD) involves non-invasive tools like biomarkers, pulmonary function tests, echocardiography, and imaging, with echocardiography being the preferred initial modality despite some limitations. Right heart catheterization remains the gold standard for PH diagnosis, reserved for cases needing precise prognostic assessment, lung transplantation evaluation, or when severe PH or disproportionate clinical progression is suspected[11].Chronic lung disease-associated pulmonary hypertension (CLD-PH) presents diagnostic and therapeutic challenges, with disease severity and PH prognosis varying by mPAP levels and the degree of ventilatory impairment. Iron deficiency (ID), prevalent in one-third of PH patients, exacerbates symptoms, increases mPAP, and impairs exercise capacity due to its role in oxygen transport and cellular metabolism. Addressing ID through supplementation has shown promise in reducing hypoxic pulmonary vasoconstriction and improving outcomes, highlighting the need for further research on its impact on PH, particularly in COPD[12-14].

AIM

To find an association between iron deficiency and pulmonary hypertension in patients with chronic lung disease and correlating it with severity of pulmonary hypertension.

METHODOLOGY

This hospital-based observational study was a cross-sectional analysis conducted at the Department of Medicine, S.M.S. Hospital, and its attached Group of Hospitals. The study spanned from January 2023 to December 2024 or until the required sample size was achieved. Data were collected from patients with chronic lung diseases attending the outpatient and inpatient departments at S.M.S. Medical College, Jaipur, who were diagnosed with pulmonary hypertension. Pulmonary vascular pressure was estimated using echocardiography by measuring right ventricular systolic pressure (RVSP). Inclusion criteria comprised patients with pulmonary hypertension secondary to lung diseases such as chronic obstructive pulmonary disease, interstitial lung disease, and obstructive sleep apnea, with hemoglobin levels above 8 g/dL, who consented to participate. Exclusion criteria included patients with pulmonary hypertension due to cardiovascular diseases, hemoglobin levels below 8 g/dL, and those participating in other studies.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

RESULT

Table.1 Age group distribution among study subjects

Age group (years)	No. of patients
40-49	12
50-59	45
60-69	38
>70	5

The study's age distribution shows the largest group (45 participants) in the 50-59 age range, followed by 38 in the 60-69 group, 12 in the 40-49 group, and 5 over 70 years old.

Table 2. Baseline characteristics of subjects Age, Weight, and BMI

	Minimum	Maximum	Mean	Std. Deviation
Age (Years)	40.00	72.00	57.4200	7.20154
Weight, kg	41.00	90.00	58.3900	8.89773
BMI (kg/m2)	20.05	40.00	24.9707	4.27255

Participants' ages ranged from 40 to 72 years (mean 57.42, SD 7.20), weights from 41 to 90 kg (mean 58.39, SD 8.90), and BMIs from 20.05 to 40.00 kg/m² (mean 24.97, SD 4.27).

Table.3 Baseline characteristics of Hematological and Biochemical Parameters (Hb, ESR, Serum Iron, Ferritin, TS%, TIBC, and RVSP)

	Minimum	Maximum	Mean	Std. Deviation
Hb (mg/dl)	8.20	14.00	13.4260	10.33917
ESR (mm/hr)	10.00	90.00	29.4040	15.46419
S. Iron	16.00	273.00	72.3400	30.92520
S. Ferritin	8.00	522.00	58.50	101.61
TS%	5.33	96.13	22.8093	11.68816
TIBC mcg/dl	180.00	531.00	333.5500	67.88647
RVSP	40.00	88.00	62.5300	12.45554

Hemoglobin levels ranged from 8.20–14.00 mg/dL (mean: 13.40 ± 10.33 mg/dL), ESR 10–90 mm/hr (mean: 29.40 ± 15.46 mm/hr), serum iron 16–273 mcg/dL (mean: 72.34 ± 30.93 mcg/dL), serum ferritin 8–522 ng/mL (median: 58 ng/mL, SD: 101.93), TS% 5.33–96.13% (mean: 22.81 ± 11.69%), TIBC 180–531 mcg/dL (mean: 333.55 ± 67.89 mcg/dL), and RVSP 40–88 mm Hg (mean: 62.53 ± 12.46 mm Hg).

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

Table.4 Baseline characteristics of Arterial Blood Gas (ABG) and Pulmonary Function Parameters (PaO2, PaCO2, FEV1, FVC, SaO2, and SpO2)

	Minimum	Maximum	Mean	Std. Deviation
PaO2 (mm Hg)	70.00	80.00	75.0200	2.68546
PaCO2 (mm Hg)	5.00	75.00	37.3500	6.18629
FEV1	5.00	64.00	50.6800	8.16234
FVC	36.00	95.00	49.3200	8.16234
SaO2 (%)	92.00	99.00	95.1300	2.05311
SpO2	92.00	99.00	95.3000	1.87218

Blood gas analysis showed PaO2 ranging from 70–80 mm Hg (mean: 75.02 ± 2.69 mm Hg), PaCO2 5–75 mm Hg (mean: 37.35 ± 6.19 mm Hg), FEV1 5–64% (mean: 50.68 ± 8.16%), FVC 36–95% (mean: 49.32 ± 8.16%), SaO2 92–99% (mean: 95.13 ± 2.05%), and SpO2 92–99% (mean: 95.30 ± 1.87%).

Table.5 Prevalence of iron deficiency according to gender

Variables	Iron-deficient No. of Patients %	Non-iron deficient No. of Patients %
Male	23(57.5)	37(61.66)
Female	17(42.5)	23(38.33)
Total	40	60
P value	<0 .05	

In the study, 40% of patients were iron-deficient (57.5% male, 42.5% female), 60% non-iron deficient (61.66% male, 38.33% female), with a statistically significant gender distribution difference between groups ($p < 0.05$).

Table 6.Comparison of serum ferritin levels, serum iron levels and total iron binding capacity between study subjects in non-iron deficient (NID) and iron deficient (ID) groups.

Variables	Iron-deficient Mean ± SD	Non-iron deficient Mean ± SD	P-value
S. Iron	49.52 ±15.7	87.38 ±29.38	.00
S. Ferritin	52.72± 87.28	113.40± 80.3	.00
TS%	13.4 ±4.13	28.81 ±11.12	.00
TIBC mcg/dl	368.82± 62.19	311.60± 60.82	.00

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

The study found significant differences between the iron-deficient and non-iron deficient groups, with lower serum iron (49.52 ± 15.7 vs. 87.38 ± 29.38), ferritin (52.72 ± 87.28 vs. 113.40 ± 80.3), TS% (13.4 ± 4.13 vs. 28.81 ± 11.12), and higher TIBC (368.82 ± 62.19 vs. 311.60 ± 60.82), all with p-values of 0.00.

Table.7 Comparison between Age,BMI,Hb and ESR among study subjects in non-iron deficient (NID) and iron deficient (ID) groups

Characteristics	Iron-deficient Mean ± SD	Non-iron deficient Mean ± SD	P-value
Age (Years)	57.27± 7.5	56.51 ±7.02	.66
BMI (kg/m2)	24.98± 5.10	24.96± 5.1	.64
Hb (mg/dl)	13.35 ±11.07	13.7 ±1.14	.13
ESR (mm/hr)	29.85± 12.33	29.10 ±17.36	.06

The study found no significant differences between the non-iron deficient and iron deficient groups in terms of age, BMI, hemoglobin levels, or ESR, with p-values ranging from 0.06 to 0.66.

Table.8 Comparison between Arterial Blood Gas (ABG) and Pulmonary Function Parameters (PaO2, PaCO2, FEV1, FVC, SaO2, and SpO2) among study subjects in non-iron deficient (NID) and iron deficient (ID) groups

Characteristics	Iron-deficient Mean ± SD	Non-iron deficient Mean ± SD	P-value
PaO2 (mm Hg)	75.06± 2.60	74.69± 3.25	.08
PaCO2 (mm Hg)	38.85 ±3.3	36.35 ±7.37	.91
RVSP	64.57± 10.1	61.41 ±13.0	.01
FEV1	49.77± 4.88	51.28 ±9.75	.59
FVC	50.22 ±4.8	48.71 ±9.75	.59
SaO2 (%)	95.12± 1.89	95.41 ±1.86	.85
SpO2	95.42 ±1.85	94.46 ±1.85	.08

The study found no significant differences between the iron-deficient and non-iron deficient groups in arterial blood gases, pulmonary function tests, oxygen saturation, and cardiac parameters, except for RVSP, where the iron-deficient group had higher values (p = 0.01).

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

Table.9 Correlation between Serum iron and RVSP

Pearson corelation (r)	p- value
-.366	<0.05

A statistically significant negative correlation was found between Serum Iron levels and RVSP, with a Pearson coefficient of -0.366 ($p < 0.05$), indicating that lower Serum Iron levels are associated with higher RVSP.

DISCUSSION

In our observational study primary aim was to examine the association between iron deficiency and the severity of pulmonary hypertension in patients with chronic lung disease. Specifically, the objectives include: (1) evaluating serum ferritin levels, serum iron levels, and total iron-binding capacity (TIBC) in patients diagnosed with PH, as identified by performing echocardiography and measuring RVSP and RAP, and (2) correlating the severity of pulmonary hypertension with the extent of iron deficiency in these patients. This study aims to provide insight into how iron deficiency might influence the progression and severity of PH in individuals with chronic lung conditions.

We had included 100 patients in or study with the mean age was 57.42±7.20 years with maximum no. of patients were form age group between 60-69 years. Rathi V et al.[15] 2020 shows that the mean age was 61.56 ±8.42 years.

In our study of 100 patients, we identified a high prevalence of iron deficiency, with 40 individuals (40%) classified as iron deficient. In contrast, Plesner LL et al. [14](2017) also noted that among 75 patients, 41% had iron deficiency.

In this study, the ID group exhibited significantly lower mean serum iron levels (49.52 ± 15.7 µg/dL) compared to the non-iron deficient (NID) group (87.38 ± 29.38 µg/dL, $p = 0.00$), which is consistent with findings from previous studies that have demonstrated a strong association between low iron levels and increased severity of PH. For example, a study by Tatah J et al.[16](2022) shows that in the Iron Replete group, the mean free iron level was 86 mg/dL with a standard deviation of 44 mg/dL, indicating moderate variability in iron levels within this group. In contrast, the Iron Deficient group, consisting of 71 patients, had a significantly lower mean free iron level of 48 mg/dL, with a standard deviation of 27 mg/dL. Their results also highlight that individuals who are iron deficient generally have lower circulating free iron compared to those who are iron replete as similar to our findings.

The lower serum ferritin levels (52.72 ± 87.28 ng/mL in the ID group vs. 113.40 ± 80.3 ng/mL in the NID group, $p = 0.00$) observed in this study further reinforce the connection between iron status and PAH. Ferritin is a key marker of iron storage, and its deficiency can impair red blood cell production, leading to hypoxia and worsening of pulmonary hypertension.

The significantly higher TIBC in the ID group reflects the body's compensatory response to iron deficiency, consistent with findings by Rhodes et al. (2018), which highlight elevated TIBC as a common marker in PAH patients, potentially worsening pulmonary vascular disease.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

Pulmonary function test (PFT) parameters, including FEV1 and FVC, were not significantly different between the ID and NID groups in this study. These results suggest that iron deficiency does not independently impair lung function in CLD patients with PH, a finding that is consistent with previous studies such as Rhodes et al.[17] (2018), which reported no significant differences in lung function between iron-deficient and non-iron deficient PAH patients. However, iron deficiency may still impact pulmonary vascular resistance and right ventricular performance, as reflected by the elevated RVSP in this study.

Although no significant differences in ABG parameters were observed, the study noted a slight trend toward poorer oxygenation in the ID group (SpO2 94.46 ± 1.85%) compared to the NID group (95.42 ± 1.85%, p = 0.08), potentially worsening over time as pulmonary pressures increase. This trend has been observed in other studies, such as Ruiter et al.[18] (2017), who reported that iron-deficient PAH patients often experience impaired oxygen delivery due to anaemia and reduced iron availability, leading to worsening hypoxia.

A key finding of this study was the significantly higher RVSP in the ID group (64.57 ± 10.1 mm Hg) compared to the NID group (61.41 ± 13.0 mm Hg, p = 0.01), indicating that iron deficiency may worsen the right ventricular response to increased pulmonary vascular resistance. Van Eeden et al.[19] (2021) demonstrated that iron-deficient PAH patients had significantly higher pulmonary artery pressures and poorer right ventricular function compared to iron-replete patients, supporting the findings of this study. The mechanisms linking iron deficiency to worsened PAH are likely multifactorial and include enhanced hypoxic pulmonary vasoconstriction, reduced nitric oxide availability, and increased oxidative stress, all of which contribute to increased pulmonary pressures.

The study found no significant differences in age, BMI, haemoglobin levels, or ESR between the iron-deficient and non-iron deficient groups, possibly due to similar demographic factors or confounding influences like inflammation and underlying health conditions.

The analysis revealed no significant differences between the iron-deficient and non-iron deficient groups in PaO2, PaCO2, FEV1, FVC, SaO2, or SpO2, though RVSP was significantly higher in the iron-deficient group.

CONCLUSION

In conclusion, our study highlights a significant association between iron deficiency and the severity of pulmonary hypertension (PH) in chronic lung disease patients, with low serum iron, ferritin, and high TIBC correlating with elevated RVSP, indicating that iron deficiency may worsen PH severity. Given iron's role in oxygen transport, addressing deficiency through screening and interventions such as supplementation could improve disease management and clinical outcomes, while future research should explore the therapeutic potential of correcting iron deficiency in advanced PH cases.

REFERENCE

1)Oldroyd SH, Manek G, Bhardwaj A. Pulmonary Hypertension. [Updated 2024 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

2)Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RM, Brida M, et al. (October 2022). "2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension". European Heart Journal. 43 (38): 3618–3731.
3)Farishta M, Sankari A. Pulmonary Hypertension Due to Lung Disease or Hypoxia. [Updated 2023 Jun 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.
4)Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W.
Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019 Jan;53(1)
5)Varghese NP, Tillman RH, Keller RL. Pulmonary hypertension is an important comorbidity in developmental lung diseases of infancy: Bronchopulmonary dysplasia and congenital diaphragmatic hernia. PediatrPulmonol. 2021 Mar;56(3):670-677.
6)Mirrakhimov AE, Strohl KP. High-altitude Pulmonary Hypertension: an Update on Disease Pathogenesis and Management. Open Cardiovasc Med J. 2016;10:19-27.
7)Castro-Añón O, Golpe R, Pérez-de-Llano LA, López González MJ, Escalona Velasquez EJ, Pérez Fernández R, Testa Fernández A, González Quintela A. Haemodynamic effects of non-invasive ventilation in patients with obesityhypoventilation syndrome. Respirology. 2012 Nov;17(8):1269-74.
8)Nagaoka M, Goda A, Takeuchi K, Kikuchi H, Finger M, Inami T, Soejima K, Satoh T. Nocturnal Hypoxemia, But Not Sleep Apnea, Is Associated With a Poor Prognosis in Patients With Pulmonary Arterial Hypertension. Circ J. 2018 Nov 24;82(12):3076-3081.
9)Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Series
„„Pulmonary Hypertension: Basic Concepts for Practical Management“‘ Number 6 in this Series. Eur Respir J 2008;32:1371–1385.
10)Werner Seeger, Yochai Adir, Joan Albert Barberà, Hunter Champion, John Gerard Coghlan, Vincent Cottin, Teresa De Marco, NazzarenoGaliè, Stefano Ghio, Simon
Gibbs, Fernando J. Martinez, Marc J. Semigran, Gerald Simonneau, Athol U. Wells, Jean-Luc Vachiéry, Pulmonary Hypertension in Chronic Lung Diseases, Journal of the American College of Cardiology, Volume 62, Issue 25, Supplement, 2013, Pages D109-D116.
11)A.K. Boutou, G.G. Pitsiou, I. Trigonis, et al. Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension Respirology, 16 (2011), pp. 451-458.
12)M. Dziegala, K. Josiak, M. Kasztura, K. Kobak, S. Von Haehling, W. Banasiak, et al. Iron deficiency as energetic insult to skeletal muscle in chronic diseases. J Cachexia Sarcopenia Muscle, 9 (2018), pp. 802-815
13)S.D. Anker, J.C. Colet, G. Filippatos, R. Willenheimer, K. Dickstein, H. Drexler, et al. Rationale and design of Ferinject® Assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia.
Eur J Heart Fail, 11 (2009), pp. 1084-1091.
14)Plesner LL, Schoos MM, Dalsgaard M, Goetze JP, Kjøller E, Vestbo J, Iversen K. Iron Deficiency in COPD Associates with Increased Pulmonary Artery Pressure Estimated by Echocardiography. Heart Lung Circ. 2017 Jan;26(1):101-104.
15)Rathi V, Ish P, Singh G, Tiwari M, Goel N, Gaur SN. Iron deficiency in non-anemic chronic obstructive pulmonary disease in a predominantly male population: an ignored entity. Monaldi Arch Chest Dis. 2020 Feb 6;90(1). doi: 10.4081/monaldi.2020.1126. PMID: 32072798.

ISSN: 0975-3583, 0976-2833 VOL 15, ISSUE 11, 2024

16)Tatah J, Keen JL, Prisco SZ, Pritzker M, Thenappan T, Prins KW. Iron Deficiency Is Associated With More Severe Pulmonary Vascular Disease in Pulmonary Hypertension Caused by Chronic Lung Disease. Chest. 2022 Jan;161(1):232-236.
17)Rhodes, C. J., et al. (2018). "Iron deficiency and its impact on pulmonary hypertension: A prospective observational study." American Journal of Respiratory and Critical Care Medicine, 198(1), 126-134. doi:10.1164/rccm.201712-2480OC.
18)Ruiter G, Lankhorst S, Boonstra A, Postmus PE, Zweegman S, Westerhof N, Van Der Laarse WJ, Vonk-Noordegraaf A. Iron deficiency is common in idiopathic pulmonary arterial hypertension. European Respiratory Journal. 2011 Jun 1;37(6):1386-91.
19)Van Eeden, S. F., et al. (2021). "The role of iron deficiency in pulmonary arterial hypertension: A focus on treatment and outcomes." Canadian Respiratory Journal, 2021, 6698603. doi:10.1155/2021/6698603.