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Study of Pulmonary Hypertension in Patients with Primary Myelofibrosis in Sohag University Hospital

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Abstract

Background: Pulmonary hypertension (PH) is a serious complex pathophysiological disorder that may be related to multiple clinical conditions and associated with high morbidity and mortality rates. It is a major complication of myeloproliferative neoplasms (MPNs) including primary myelofibrosis (PMF) mainly in advanced disease. Development of PH in PMF patients has a bad impact on prognosis of the disease and on the survival in those patients. PH prevalence in PMF and predictors for the disorder are not well established.

Objective: The main objective of this thesis is to determine the prevalence of pulmonary hypertension in patients with primary myelofibrosis and to find different parameters that can predict PH in those patients.

Results: Our results revealed that 13 patients out of 28 studied PMF patients had PH. There was a significant relationship between old age, long PMF duration since diagnosis at time of evaluation, presence of thrombotic events mainly portal vein thrombosis, anemia, and hyperuricemia and occurrence of PH. The two groups (PH & Non-PH groups) did not differ significantly in terms of gender, comorbidities, WBCs count, platelets count, serum lactate dehydrogenase level, and splenic diameter measured by abdominal ultrasound, presence of JAK 2 & Calreticulin (CALR) gene mutation.

Conclusion: PH prevalence in PMF patients in our study was 46.4%. Our findings suggest that old age, long PMF duration since diagnosis, and hyperuricemia appear to be valuable for predicting the development of PH in those patients.

Keywords: Pulmonary hypertension, Myeloproliferative neoplasms**,** Primary myelofibrosis, JAK2 gene mutation.

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Introduction

Pulmonary hypertension (PH) is a syndrome characterized by marked remodeling of the pulmonary vasculature and a progressive rise in the pulmonary vascular load, leading to hypertrophy and remodeling of the right ventricle. PH is a serious disorder caused by a heterogenous group of diseases and associated with high morbidity and mortality rates. It is now defined in terms of hemodynamic criteria by a mean pulmonary arterial pressure (mPAP) determined by right heart catheterization of more than 20 mm Hg at rest [(1)]. PH is classified according to world health organization (WHO) into five groups in terms of clinical and hemodynamic criteria and

response to treatment [2]. PH is one of the major complications of myeloproliferative neoplasms (MPNs) including primary myelofibrosis (PMF), which are classified within group 5 PH, corresponding to PH with an unclear and/or multifactorial etiology. MPNs are a wide group of disorders characterized by uncontrolled increased production of myeloid cells due to an abnormal clone of hematopoietic stem cells [3]

Pathogenesis of PH in PMF patients is multi-factorial including vasoconstriction of pulmonary vessels and their obstruction by megakaryocytes, extramedullary hematopoiesis, portopulmonary hypertension related to organomegaly, acute or chronic pulmonary emboli, congestion of pulmonary vascular bed, pulmonary myeloid infiltration, extensive bone marrow fibrosis, destruction of lung parenchyma and pulmonary vasculature, hyperviscosity, platelets activation, and thrombosis [4]. The development of PH in PMF has a bad impact on the course and prognosis of the disease and increases the morbidity and mortality rates in those patients, especially if advanced or complicated with right sided heart failure [5]. However, PH prevalence in PMF is highly heterogenous and its accurate estimates and predictors for the disorder are not well established [6]

Patients and Methods

Study population:

This study was a prospective cross-sectional cohort clinical based study, conducted on 28 patients diagnosed with primary myelofibrosis who attended the Outpatient Hematology Clinic at Sohag University Hospital in the peri-od from April 2021 to October 2022. All patients were divided according to systolic pulmonary artery pressure (SPAP) into two groups:

- **Group 1 :** 13 PMF patients who have echocardiographic evidence of pulmonary hypertension (SPAP value ≥ 40 mm Hg).
- **Group 2 :** 15 PMF patients who do not have echocardiographic evidence of pulmonary hypertension (SPAP value < 40 mmHg).

Inclusion Criteria:

- Age 18 years old or above.
- Patients diagnosed with primary myelofibrosis based on the diagnostic criteria of the revised 2016 WHO guidelines.

Exclusion Criteria:

- Patients less than 18 years old.
- Patients with cardiac diseases involving the left side of the heart.
- Patients having chronic lung illness.
- Patients with past or current pulmonary embolism.
- Patients with known primary pulmonary hypertension.
- Patients with chronic kidney disease.
- Patients with inherited and acquired chronic hemolytic anemia.
- Patients having autoimmune and connective tissue disorders.
- Patients having congenital heart diseases.

Methods:

All patients were subjected to detailed medical history including age, sex, associated comorbidity particularly diabetes mellitus and hypertension, duration of PMF since diagnosis, history of thrombotic complications such as ischemic stroke, acute myocardial infarction, unstable angina, peripheral arterial thrombosis, deep vein thrombosis, pulmonary embolism, portal vein thrombosis, and retinal artery or vein occlusion, symptoms related to PH, and treatment for PMF. Also, all patients were subjected to full clinical examination.

Laboratory investigations:
Complete blood count with differential, serum creatinine, serum uric acid, serum lactate dehydrogenase (LDH) level, JAK2V617F & CALR gene mutation assay by allele specific real-time PCR technique [7] using AB Step One Plus RT PCR (Thermo Fisher Scientific Massachusetts, USA), BCR-Abl fusion gene assay (Philadelphia chromosome) by PCR for exclusion of CML, bone marrow aspiration through sternal puncture under local anesthesia bone marrow trephine biopsy from the posterior superior iliac spine using the Jamshidi needle under general anesthesia [8]

Abdominal ultrasound was done for all patients to assess splenic diameter.

Pulmonary function tests and CT chest was done for patients with suspected COPD and interstitial lung disease.

Transthoracic echocardiography (TTE): for diagnosis of PH by estimation of SPAP. The echocardiography was done with Toshiba device, Japan (Nemio SSA-550A) at the Outpatient Echocardiography Clinic in Sohag University Hospital. The echocardiogramphic evidence of PH was established depending on measures by transthoracic echocardiography and Doppler study. The evidence of PH was determined if SPAP value was ≥ 40 mmHg. PH is best defined in terms of hemodynamic criteria by mPAP determined by right heart catheterization of more than 20 mm Hg at rest [1]. SPAP value of 40 mmHg typically signifies that mPAP is more than 25 mmHg [9]. SPAP can be estimated by measuring the peak tricuspid regurge velocity (TRVmax) obtained with continuous-wave Doppler echocardiography. The peak tricuspid regurge pressure gradient can be determined by applying the modified Bernoulli equation, $P = 4V^2$ where P represents the peak tricuspid regurge pressure gradient, and V represents the peak tricuspid regurge velocity. SPAP can be calculated by adding estimated right atrial pressure (eRAP) to the TRV-derived pressure gradient. [10] applying the modified Bernoulli equation, $SPAP = 4V^2 + eRAP$. RAP is currently calculated by measuring inferior vena cava (IVC) diameter and its collapsibility during inspiration indicated as caval index or collapsibility index[11]. If IVC diameter is less than 2.1 cm and collapses by more than 50% with inspiration, this means that RAP is of normal value ranging from 0 to 5 mmHg. If IVC diameter is more than 2.1 cm and collapses by less than 50% with inspiration, this means that RAP is of high value ranging from 10 to 20 mmHg. The other cases are assumed to be of intermediate values ranging from 5 to 10 mmHg [12]

Ethical approval

The study was approved by medical research ethics committee in the Faculty of Medicine, Sohag University under registration number: Soh-Med-21-04-15. Any data taken from the patients either from the history, the examination or from the investigations were dealt with in a confidential manner. Every patient was informed about the nature and steps of the study. The aim and value of the work were explained in a simplified manner for all patients. An informed written consent was taken from each participant.

Statistical analysis

All the data were analyzed using Statistical Package for Social Sciences (SPSS) version 24. Quantitative data were represented as mean ± standard deviation to measure the degree of dispersion of data around their mean. Data were analyzed using student

t-test to compare means of two groups. Qualitative data were presented in terms of number and percentage. Chi square test and fisher exact test were used to compare these qualitative data. Excel program was used to produce graphs. *P* value was considered significant if it was less than 0.05.

Results

A total of 28 participants were enrolled in the study. They were divided into two groups based on the presence of PH; PMF patients with PH (13) and PMF patients without PH (15). Age of PMF patients in PH group were significantly higher than that of patients in non-PH group (66.69 ± 6.87 years vs. 57.87 ± 10.32 years; $p = 0.01$) **(figure 1)**. Also, disease duration since diagnosis was significantly longer among PMF patients with PH, compared to those without PH (54.46 ± 20.41 months vs. 25 ± 18.86 months; $p < 0.001$) **(figure 2)**. Portal vein thrombosis as a thrombotic complication was significantly more common in PMF patients who had PH than in PMF patients in non-PH group ($p = 0.03$). PH group had significantly lower mean hemoglobin level than non-PH group (10.76 ± 2.53 mg/dl vs. 12.52 ± 1.41 mg/dl; $p = 0.02$) and significantly lower hematocrit value (31.16 ± 7.46 % vs. 36.14 ± 4.18 %; $p = 0.03$). Mean serum uric acid level is higher among PMF patients in PH group than in those in non-PH group ($p < 0.001$) **(figure 3)**.

There was no statistically significant difference between the two groups as regard sex, comorbidities, WBCs count, platelets count, serum lactate dehydrogenase level, and splenic diameter measured by abdominal ultrasound. JAK 2 gene mutation was less common in PMF patients in PH group compared with those PMF patients in non-PH group without significant difference among patients in the two groups (61.5% vs. 73.3%, $p = 0.39$) while calreticulin (CALR) gene mutation was found to be more prevalent in PMF patients who had PH, compared to PMF patients in non-PH group, also without significant difference among both groups (30.8% vs. 13.3%, $p = 0.32$) as shown in **table (1)**.

On multivariate logistic regression analysis of clinical and laboratory findings; old age (OR = 1.22, 95% CI: 1.19-2.44, $p = 0.03$), longer disease duration since diagnosis (OR = 1.71, 95% CI: 1.33-3.01, $p < 0.001$) and hyperuricemia (OR = 1.67, 95% CI: 1.01-2.12, $p < 0.001$) were found to be predictors for PH among PMF patients **(table 2)**.

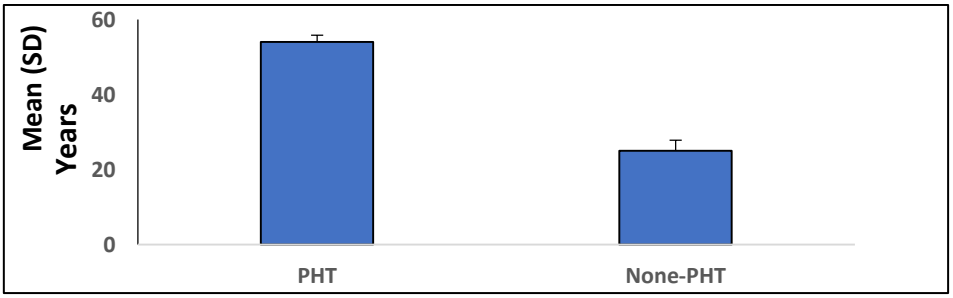

Figure (1): Mean age of PMF patients based on presence of PH

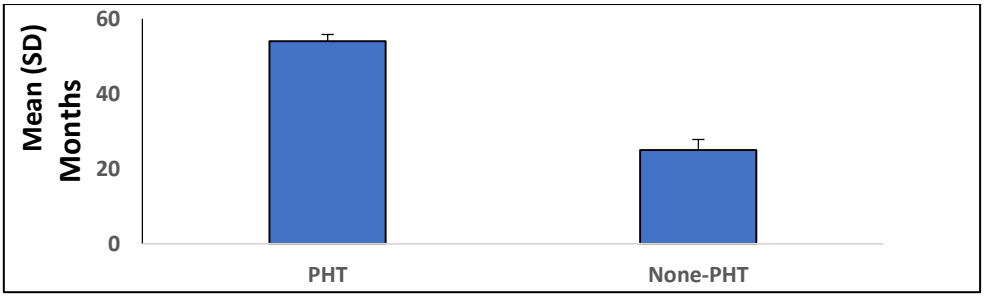

Figure (2): Mean disease duration in PMF patients based on presence of PH

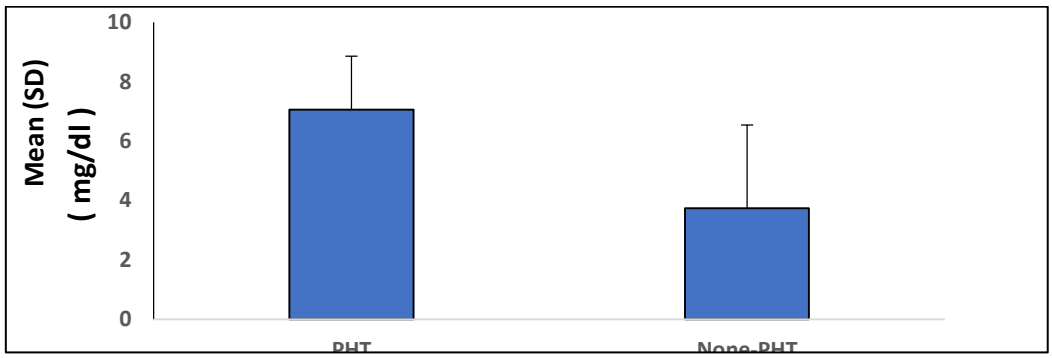

Figure (3): Mean serm uric acid level in PMF patients based on presence of PH

Table (1): Characteristics of PMF patients based on presence of PH :-

Variable	Pulmonary hypertension		*P* value
	(+) (n = 13)	(-) (n =15)	
Age (years)	66.69 ± 6.87	57.87 ± 10.32	**0.01**
Sex			0.06
Male	9 (69.2%)	5 (33.3%)	
Female	4 (30.8%)	10 (66.7%)	
Comorbidities			
Diabetes mellitus	9 (69.2%)	12 (80%)	0.41
Hypertension	6 (46.2%)	8 (53.3%)	0.50
None	0	3 (20%)	0.13
Thrombotic events	4 (30.8%)	0	**0.03**
Disease duration (months)	54.46 ± 20.41	25 ± 18.86	**0.001**
Hemoglobin (g/dl)	10.76 ± 2.53	12.52 ± 1.41	**0.02**
Hematocrit value (%)	31.16 ± 7.46	36.14 ± 4.18	**0.03**
WBCs (10^9/L)	19.63 ± 17.31	12.46 ± 9.89	0.18
Platelets (10^9/L)	319.23 ± 148.9	244.93 ± 88.7	0.11
Uric acid (mg/dl)	7.06 ± 1.68	3.74 ± 1.41	**< 0.001**
Lactate dehydrogenase (u/L)	663.15 ± 312.9	651.87 ± 238.9	0.91
Splenic diameter (Cm)	18.98 ± 3.41	17.78 ± 5.22	0.48
JAK 2 mutation	8 (61.5%)	11 (73.3%)	0.39
CALR mutation	4 (30.8%)	2 (13.3%)	0.32
SPAP (mmHg)	60.31 ± 8.36	16.2 ± 3.12	**< 0.001**

Data expressed as number (percentage) and mean ± SD. **PH**: pulmonary hypertension; **PMF**: primary myelofibrosis; **SPAP**: systolic pulmonary artery pressure. *P* value was significant if < 0.05.

Table (2): Multivariate logistic regression analysis of clinical and laboratory variables for prediction of PH among PMF patients:-

Variable	**Odd's ratio**	**95% CI**	***P* value**
Age (years)	**1.22**	**1.19-2.44**	**0.03**
Disease duration (months)	**1.71**	**1.33-3.01**	**< 0.001**
Thrombotic events	0.45	0.33-1.01	0.10
Hemoglobin (g/dl)	0.91	0.70-1.90	0.07
Hematocrit value (%)	1.56	0.80-2.11	0.40
Uric acid (mg/dl)	**1.67**	**1.01-2.12**	**< 0.001**

PH: pulmonary hypertension; **PMF**: primary myelofibrosis**; CI:** confidence interval. *P* value was significant if < 0.05.

Discussion

When performing analysis of data of PMF patients in the current study, we found that PH prevalence among PMF patients was 46.4%. this result was in corcordance with that reported by Cortelezzi et al., Lee et al., and Yaylali et al. [13-15] who showed a high PH prevalence in PMF patients of 36%, 28.6%, and 63.6% respectively. In contrast, the previous studies in PMF found PH prevalence of 14% and 17.3% in the studies based on SPAP reported by Lopez-Mattei et al. and Austin et al. [6 & 16], respectively and 17.6% and 18.1% in studies based on 2015 ESC/ERS guidelines reported by Brabrand et al. and Venton et al. [17&18], respectively. This striking wide variability and high heterogeneity between studies may be explained by differences in PH diagnostic modality, the median age of patients, PMF duration since diagnosis at time of evaluation, differences in study design nature, possible selection bias, and regional, ethnic or racial differences. On comparison between PMF patients with (13 patients) and without PH (15 patients) as regard baseline clinical and laboratory characteristics, we found that the mean age of PMF patients with PH at time of TTE evaluation was significantly higher compared to those without PH (66.69 ± 6.87 years vs. 57.87 ± 10.32 years; $p = 0.01$). This matches the result of a previous American retrospective study conducted by Lopez-Mattei et al. [6]. Conversely, Lee et al. [15] and Austin et al. [16] found no significant correlation between age and PH. Also, we found a statistically significant difference between PMF patients in PH and non-PH groups as regard disease duration since diagnosis with a mean of (54.46 ± 20.41 months vs. 25 ± 18.86 months; $p < 0.001$). This finding came in contrast with Lopez-Mattei et al. [6] and Cortelezzi et al. [14]. In our study, thrombotic events mainly portal vein thrombosis were significantly more prevalent in PMF patients in PH group compared to non-PH group, in contrast with Lee et al. [15] who found no significant correlation between presence of thrombotic events and PH in PMF patients.

The two groups in the current study did not differ significantly as regard sex and co-morbid diseases. These results match with that revealed by Cortelezzi et al., Austin et al., and Lee et al. [14,16,15]. On the contrary, Lopez-Mattei et al. [6] found that male gender and hypertension were significantly different between PMF patients with and without PH.

Regarding analysis of laboratory hematological parameters in PMF patients, we found a significant correlation between severity of anemia and development of PH in those patients. Mean hemoglobin level and mean hematocrit value were significantly lower in PH group than in non-PH group (p = 0.02 & 0.03, respectively). Similar finding was observed in a study by Lopez-Mattei et al. [6]. Conversely, Lee et al [15] reported no statistically significant difference among patients in the two groups in terms of mean hemoglobin level. Furthermore, we found that mean serum uric acid level was significantly higher among PMF patients in PH group than in those in non-PH group. According to our study, there was no significant difference between the two groups as regard mean platelets count, WBCs count, serum LDH levels, splenic diameters measured by abdominal ultrasound, and presence of driver genetic mutations either JAK2 or calreticulin (CALR) gene mutations. These results match that reported by Lee et al. and Lopez-Mattei et al. [15, 6]

On multivariate logistic regression analysis of significant clinical and laboratory variables in PMF patients, we found that old age, longer duration from PMF diagnosis to TTE evaluation, and hyperuricemia may be the only independent predictors of PH among those patients. This result came in contrast with Lopez-Mattei et al. [6] who reported that female gender was protective and N-terminal prohormone brain natriuretic peptide (NT-proBNP) was a significant predictor of PH in PMF.

Conclusion

This study showed that the prevalence of PH among PMF patients was 46.4%. Our findings suggest that old age, long PMF duration since diagnosis, and hyperuricemia appear to be valuable for predicting occurrence of PH in patients with PMF. Further well-designed prospective studies with a larger sample size, longer follow-up duration and confirmation of PH by right heart catheterization are warranted. Meta-analysis of these studies all together is important to define the exact prevalence and the significant predictors of PH in patients with PMF. Also, larger prospective studies are needed to explain the long-term impact of PH on survival and to identify predictors of mortality in those patients.

Recommendations

Based on the results of our study, we recommend careful systematic non-invasive screening for PH by TTE in patients with PMF at diagnosis as well as during follow up period, particularly those at high risk for PH mainly elderly patients, patients with long disease duration, and patients with hyperuricemia. This allows early detection and treatment of PH in PMF patients which is essential for treatment success to get a better outcome, prognosis and survival in those patients.

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