Frequency and etiology of pulmonary hypertension in patients with myeloproliferative neoplasms

Brabrand, Mette; Hansen, Knud Nørregaard; Laursen, Christian B; Larsen, Thomas Stauffer; Vestergaard, Hanne; Abildgaard, Niels

Published in:
European Journal of Haematology

DOI:
10.1111/ejh.13197

Publication date:
2019

Document version
Accepted manuscript

Citation for published version (APA):

Terms of use
This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk
Frequency and etiology of pulmonary hypertension in patients with myeloproliferative neoplasms

Running title: Pulmonary hypertension and MPN

Mette Brabrand1*, Knud Nørregaard Hansen2, Christian B. Laursen3, Thomas Stauffer Larsen1, Hanne Vestergaard1 and Niels Abildgaard1

1Department of Haematology, Odense University Hospital, Denmark

2Department of Cardiology, Odense University Hospital, Denmark

3Department of Respiratory Medicine, Odense University Hospital, Denmark

*Corresponding author. E-mail: mette.brabrand@rsyd.dk. Telephone: +45 66 11 33 33.
Abstract

**Objective:** Pulmonary hypertension (PH) has been reported to be associated with myeloproliferative neoplasms (MPN), affecting 5-48% of MPN patients. With the aims to describe the prevalence of PH in Ph-MPN patients and explore the cause in identified subjects, we performed a prospective cohort study of Ph-MPN patients.

**Method:** Transthoracic echocardiography (TTE) was performed on all patients. When the TTE was abnormal, further investigations were performed according to current guidelines from the European Society of Cardiology. The primary endpoint was the frequency of PH. The secondary endpoint was causes of PH.

**Results:** We included 158 patients, median age was 65 years. Fifty percent had polycythemia vera, 34% essential thrombocytosis, and 11% primary myelofibrosis, 3% post-ET-myelofibrosis, and 2% post-PV-myelofibrosis. Only six patients (3.8%) were found to have a high probability of PH. They were all examined with right heart catheterization and all met the invasive criteria for PH. In all six patients other causes than MPN for PH were identified, although some contribution from the MPN could not be ruled out in three patients.

**Conclusion:** In the largest study ever reported, we found a lower prevalence of PH (3.8%) than previously reported. Screening for PH in unselected MPN patients is not justified.

**Keywords:** Myeloproliferative neoplasms, pulmonary hypertension, prevalence, etiology
Introduction

Pulmonary hypertension (PH) has been reported to be associated with myeloproliferative neoplasms (MPN) in several case reports and retrospective studies (1-7). According to these reports, PH affects between 5% and 48% of patients with MPN, where the large variability seems caused by the retrospective reporting of rather small patient cohorts. In 2001, Dingli et al. (8) published a register-based study identifying 26 patients in contrast to the expected 0.53 patients with both MPN and PH, demonstrating a higher co-occurrence of these rare diseases than expected. The mortality was high in these patients with an observed median survival of 18 months after the diagnosis of PH, and in the majority of patients the cause of death was cardiopulmonary (8).

Based on these observations the 2015 guidelines for the diagnosis and treatment of pulmonary hypertension from the European Society for Cardiology (ESC) and European Respiratory Society (ERS) recognized MPN as a specific cause of PH of unclear and/or multifactorial mechanisms (9).

The causes for PH in Philadelphia chromosome negative myeloproliferative neoplasms (Ph-MPN) patients are thought to be multifactorial. Cortelezzi et al. (3) report the obstruction of pulmonary vessels by circulating megakaryocytes, smooth muscle hyperplasia due to platelet-derived growth factor (PDGF), and altered angiogenic status as potential causes. Adir et al. and Guilpain et al. (10, 11) primarily refer to an increased risk for thromboembolic events, and thus a high risk of pulmonary embolism leading to PH. Extramedullary haematopoiesis, which is a well-known complication of PMF, may
also cause PH. Garcia-Manero et al. (12) have revealed myeloid metaplasia and fibrosis on autopsies and pulmonary biopsy. Steensma et al. (13) have shown that Technetium-99m sulfur colloid scintigraphy demonstrated diffuse pulmonary uptake consistent with extramedullary haematopoiesis and showed that whole-lung external beam radiotherapy in a single fraction reduced symptoms and decreased pulmonary artery systolic pressure. This effect is probably due to extramedullary haematopoiesis, or the presence of circulating marrow progenitors in lung parenchyma, contributing to the pathogenesis of PH in MPN.

In this paper we report a prospective, population based study of a large cohort of Ph-MPN patients to clarify the occurrence and causes of PH in this patient population. The specific aims were 1) to identify the prevalence of PH in Ph-MPN patients and 2) to explore the causes of PH in identified subjects.

Methods

This was a prospective observational cohort study. From March 2015 through June 2016, we included patients with MPN (regardless of co-morbidity) followed at the Department of Hematology at Odense University Hospital, Denmark. We included patients with classical Philadelphia chromosome negative myeloproliferative neoplasms (Ph-MPN), encompassing essential thrombocytosis (ET), polycythemia vera (PV), post-essential thrombocytosis myelofibrosis (post-ET MF), post-polycythemia vera myelofibrosis (post-PV MF) and primary myelofibrosis (PMF). We excluded all other MPN diagnoses (chronic myelogenous leukaemia (CML), chronic neutrophilic leukaemia, chronic eosinophilic leukaemia and mastocytosis). As unclassifiable
myelodysplastic/myeloproliferative neoplasm is a very heterogeneous group, we also excluded this entity.

We excluded patients incapable of giving informed consent (e.g. dementia or non-Danish speaking patients). A total of 342 patients with Ph-MPN are regularly seen in the outpatient clinic. Patients were asked for participation by the treating physician at a scheduled outpatient visit. Unfortunately, due to workload and other circumstances, not all patients were offered inclusion during the inclusion period.

The Ph-MPN diagnosis was established using the standard hematological criteria following the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (14). Data were extracted from the electronic medical records. Missing data from the health records could not be reconstructed. In a few cases with uncertain hematological diagnoses, two board certified hematologists reviewed the full medical records and blood tests and agreed on a diagnosis based on the available information.

We extracted data on current anti-coagulant and platelet aggregation inhibitor treatments for all patients.

An experienced cardiologist (KNH) performed transthoracic echocardiography (TTE) on all patients after inclusion into the study. All examinations were saved digitally and could be analyzed later. All TTEs were performed according to the guidelines of the European Society of Cardiology (9), recommending the measurements of peak tricuspid regurgitation velocity (TRV) by continuous wave Doppler as the main variable for assessing PH. Additionally, the guidelines recommend use of other echocardiographic signs of PH (i.e. assessment of right ventricular size and pressure overload, diameter of...
the pulmonary artery and the flow pattern out of right ventricle and estimate of the pressure in the right atrium).

The World Health Organization (WHO) groups PH into five groups (9): 1) Pulmonary Arterial Hypertension (PAH), which can be idiopathic, heritable, related to drugs or associated with other diseases such as connective tissue disease, congenital heart disease, liver disease or HIV infection, 2) Pulmonary Hypertension due to left heart disease, 3) Pulmonary Hypertension due to lung disease or hypoxia, 4) Pulmonary Hypertension due to chronic thromboembolic pulmonary disease and 5) Pulmonary Hypertension due to unclear or multifactorial mechanisms. Hematological disorders (e.g. MPN and chronic haemolytic anaemia) are categorized in group 5.

Patients with a high probability of PH by echocardiography were further examined with right heart catheterization (RHC), which is the “gold standard” for final diagnosis of PH. We also wished to assess if the patients had pulmonary arterial hypertension (PAH). PAH was defined as mean pulmonary arterial pressure (PAPm) > 25 mmHg (9), a pulmonary arterial wedge pressure (PAWP) < 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units in the absence of other causes of pre-capillary PH. PAH is a severe life-limiting condition seen in idiopathic PAH and can be associated with other diseases (e.g. scleroderma) (15).

In identified subjects with PH the cause was explored by additional testing according to the abovementioned guidelines. Once the etiology behind PH was definitely established, no further tests were performed as part of this study.
The primary endpoint was frequency of PH and the secondary endpoint was cause of PH.

The Regional Committees on Health Research Ethics for Southern Denmark approved the study (S-20130075) and all patients gave written, informed consent. The study was conducted in accordance with the Declaration of Helsinki and will be presented in accordance with the STROBE guidelines (16).

We present data descriptively as median (range) or number (proportion) as appropriate. Missing data is reported as such. No additional statistical tests were performed.

Results

Patients

In total, 278 patients (81.2% of the population) were screened and either excluded (13.7%) or offered participation in the study and 158 patients were included, 18.8% were not offered inclusion due to either time or staff factors in the clinic (Figure 1). The characteristics of included patients are shown in Table 1. Fifty-five (34.8%) had ET, 79 (50.0%) PV, four (2.5%) post-ET MF, three (1.9%) post-PV MF and 17 (10.8%) PMF. Median age was 65 years (range 27-87) and 80 (50.6%) were female. The median age at Ph-MPN diagnosis was 58 years (range 20-83) and median duration of Ph-MPN at inclusion was four years (range 0-24). JAK2 mutation analysis was performed in all patients and the mutation was identified in 117 (74.1%) patients. Patients were not
routinely tested for the presence of other driver mutations. Only 28 patients were analyzed for the presence of CAL-R mutations and six were found positive.

At time of inclusion 43 patients (29.1%) had regular phlebotomy, 54 (34.2%) received Interferon-alfa, 51 (32.3%) Hydroxyurea, 18 (11.4%) received Anagrelid, 10 (6.3%) Ruxolitinib, one (0.6%) Busulfan, five (3.2%) received erythropoietin and 18 (11.4%) received no cytoreductive treatment; see Table 1 for more details. A total of 149 (94.3%) patients were treated with anticoagulants or platelet aggregation inhibitors, 114 (72.1%) received acetylsalicylic acid (ASA), 22 (13.9%) Clopidogrel, 17 (10.8%) Warfarin, seven (1.1%) new oral anticoagulants (NOAC), five (3.2%) Dipyridamol, one (0.6%) Ticagrelor. Nine (5.7%) were not prescribed anticoagulants or platelet aggregation inhibitors. All patients received anti-platelet inhibition as recommended unless directly contradicted (17), and some were treated with anticoagulants as presented in Table 1. The reasons for anticoagulants were stroke in most of the patients, atrial fibrillation in some and former DVT/PE in others (Table 4).

Association between PH and MPN

The echocardiographic findings of all included patients are shown in Table 2 and six patients were found to have a high probability of PH according to the 2015 ESC/ERS guidelines defined in Table 2. All six patients were examined with right heart catheterization (RHC) (Table 3), and all six patients had mean pulmonary pressures above 25 mmHg, and thus met the invasive diagnostic criteria for PH. One patient had RHC performed previously. As part of the study we therefore only performed RHC on
five of six patients (Table 3). These patients experienced no complications related to RHC.

Of the six patients with PH, one had ET, two had PV and three had PMF. Median age was 70.5 years (65-83) and three were female. Median age at diagnosis was 65 years (50-82) and median time from diagnosis to enrollment was four years (0-22), (Table 4). Five patients had had symptomatic disease (dyspnea, oedema) at some point prior to inclusion, and five of the six patients had TEE performed at some earlier time-point.

Five of six patients underwent additional diagnostic tests (Table 5).

Of the six patients, three had a cardiac etiology for PH, one pulmonary, one thromboembolic and one had a restrictive ventilatory defect due to extrapulmonary disease.

Patient no. 1: 69 years (at inclusion) old female patient with PMF diagnosed in 2013. In 2006, using RHC, she was diagnosed with chronic thromboembolic pulmonary hypertension with bilateral peripheral pulmonary emboli not suitable for surgery, and was medically treated; at that time point blood counts were normal. The diagnosis of PMF was established 7 years later. She was treated with Ruxolitinib, Erythropoietin and blood transfusions. Data in table 3 originates from the 2006 RHC.

Patient no. 2: 71 years (at inclusion) old male patient who was diagnosed with ET in 2000 and progressed to post-ET-MF in 2010. He was treated with Erythropoietin. He had a restrictive ventilatory defect due to severe thoracic kyphoscoliosis since childhood. This is a rare but well established cause of PH (18). The patient suffered from multiple comorbidities and eventually died from infection.
Patient no. 3: 80-years (at inclusion) old female patient with PMF since 2009. She suffered from severe cardiac congestion, but also had significant splenomegaly of 20 cm. She has just resumed Ruxolitinib treatment with a perceived reduction in the size of her spleen thus reducing the massively increased plasma volume. Through this, we hope to reduce cardiac preload and thus improve her cardiovascular performance, but we still do not know the full effect of the initiated treatment at the end of study.

Patient no. 4: 85-years (at inclusion) old male patient with ET since 2014. He had since diagnosis been well treated with Hydroxyurea. He had significant bilateral hypertrophy of the ventricles and a myocardial biopsy confirmed amyloidosis.

Patient no. 5: 73-year-old male patient with PV since 1994 treated with phlebotomy. He had aortic valve stenosis as cause of PH.

Patient no. 6: 67-year-old female patient with PV since 2015 treated with phlebotomy. She had reversible PH as the pressure in the pulmonary artery normalized during RHC when additional oxygen was given. Later additional medical history, autoimmune testing and high resolution computed tomography scanning of the lungs showed the patient was suffering from smoking-related interstitial lung disease (SR-ILD), subtype desquamative interstitial pneumonia (DIP). Additional invasive procedures were contraindicated due to reduced DLCO and low paO2. The final diagnosis was established at a multi-disciplinary team conference at our institution’s center for interstitial lung disease.

By August 2017, with a median follow-up of 20 months from inclusion (range 14-30 months), eight (5.1%) patients had died, but only one of these patients had PH. Time to death from inclusion was 17 months (range 2-25).
Discussion

The primary aim of our study was to clarify the prevalence of PH in Ph-MPN patients, and surprisingly, we only found PH in six of 158 unselected patients (3.8%), half of whom had MF. All six were extensively investigated and we identified a specific etiology in all patients; three had a cardiac cause, one pulmonary, one thromboembolic and one had pulmonary disease from extra pulmonary causes. Only the patient (no. 1) with thromboembolic disease had PH that could be directly related to the MPN diagnosis, but patients no. 2 and 3 had advanced MF that potentially may have contributed to the PH. None of the patients had PAH. A total of eight (5.1%) patients died within the follow-up period, only one of these had PH. Four died from thromboembolic disease and the cause of death therefore could be related to Ph-MPN (19-21). The patient with PH and confirmed Ph-MPN died from infection.

To our knowledge, this is the largest cohort of Ph-MPN patients screened for PH. It was performed prospectively and inclusion of patients were population based. It is the first study where all identified subjects underwent extensive diagnostic evaluation to identify the cause of PH. We found a much lower proportion of PH than reported in previous studies. In previous reports, patients with known heart and lung disease were excluded. If we had done so as well, four out of six patients would have been excluded, giving a proportion of PH of only 1.3%.

Previous studies were mostly small screening studies and case reports (1-7, 11, 12). In most prior studies MPN patients were screened for PH using TTE (1-7). Patients with known secondary causes for PH were excluded and only in one study did the authors screen for unknown secondary causes of PH (3), RHC was performed in none of the
studies. The studies included 22-68 patients (if only including patients with classical Ph-negative MPN and excluding patients with other diagnoses, e.g. myelodysplastic syndromes, CML etc.) and found a prevalence of PH of 4-52 % using TTE. The previous studies did not report how patients were identified for screening and therefore could be influenced by selection bias. Some of the studies had a larger proportion of PMF patients than in the current study, but previous studies have not reported associations between a high proportion of PMF patients and high levels of PH (1-7, 11, 12). Our cohort is representative for the distribution of diagnoses with Ph-MPN (22).

Two out of 253 (0.8%) patients died (one from cardiopulmonary reason and one from infection) in these previous studies (4). The low reported mortality rate, however, might be caused by a short period of follow-up; these were not reported in most studies. With a median follow-up of 17 months we observed a mortality of 5.1 % in our cohort. Only one of these patients had PH. The few observed deaths do not make it possible to analyze the prognostic importance of PH in Ph-MPN patients.

Two previous studies only included patients with known MPN and PH (11, 12) and the register based study by Dingli et al. included patients with diagnoses compatible with MPN and PH (8). Most patients in these three studies had RHC performed, and in many patients, secondary causes for PH were identified. Overall, mortality in these studies was high. Between 67 and 100% of the patients died within 12 months, mostly from cardiopulmonary causes (8, 11, 12). Thus, according to these studies PH is associated with an adverse prognosis.
There could be different explanations to why we found a weak association between Ph-MPN and PH. First of all, our cohort was unselected. Also, as we had fewer patients with PMF, post-ET-MF and post-PV-MF than reported in other studies, thus we could suffer from recruitment bias. Despite our intentions, we were not able to include all patients attending our outpatient clinic. This introduced a risk for selection bias.

Patients who were excluded or refused to take part in the study may differ from those who were included. Non participants were older (median age 75 years) and the proportion of MF patients was higher (eight out of 54 MF patients refused to take part and eight were excluded, five patients were excluded due to dementia, two were considered too frail to be offered participation (this would include extra hospital visits) and one patient was non-Danish speaking). Median time from diagnosis to end of study did not differ significantly between included patients (5.9 years) vs. non-included patients (6.6 years) (p=0.14), data not presented.

Although, this unselected study cohort showed a representative distribution of MPN patients, the number of patients with advanced stage disease (post-ET, post-PV MF and PMF) was only 24, corresponding to 15% of the study cohort, and only 44% of the MF patients were included. Therefore we may have underestimated the prevalence of PH in MF. The generalizability of our study is also limited by the fact that almost all patients were Danish and thus Caucasian making the study findings less applicable in a more heterogeneous population. Lastly, only one cardiologist reviewed the ECHOs.
However, our study also has strengths. All patients were offered the same extensive diagnostic procedure, ensuring identification of the existence and cause of PH in all. Our cohort is homogenous and representative for the expected distribution of Ph-MPN entities, and we excluded patients with uncertain diagnoses.

Conclusion

In this large, prospective, population based cohort study of Ph-MPN patients we found a lower prevalence of PH than previously reported. In five of six cases with PH, causes other than Ph-MPN were identified, although MPN to some degree could have contributed to PH in two more patients. None of our patients had PAH. Standard screening for PH in asymptomatic Ph-MPN patients cannot be recommended. In Ph-MPN patients where PH is suspected or identified a multidisciplinary approach is recommended to establish the cause and optimal treatment.

References


This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.


Figure legend

Figure 1 – Flow chart of patient inclusion
Table 1 – Characteristics of 158 patients with myeloproliferative neoplasm included in pulmonary hypertension screening study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (100.0%)</th>
<th>ET (34.8%)</th>
<th>PV (50.0%)</th>
<th>Post-ET MF (2.5%)</th>
<th>Post-PV MF (1.9%)</th>
<th>PMF (10.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n (%)</td>
<td>158</td>
<td>55</td>
<td>79</td>
<td>4</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>80 (50.6%)</td>
<td>32 (59.3%)</td>
<td>38 (48.1%)</td>
<td>1 (25.0%)</td>
<td>2 (66.7%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Median age at inclusion, years (range)</td>
<td>65 (27-87)</td>
<td>64 (27-85)</td>
<td>63 (33-87)</td>
<td>59.5 (57-69)</td>
<td>76 (70-80)</td>
<td>70 (50-84)</td>
</tr>
<tr>
<td>Median duration of disease at inclusion, years (range)</td>
<td>4 (0-24)</td>
<td>3 (0-18)</td>
<td>4 (0-22)</td>
<td>11.5 (7-16)</td>
<td>13 (9-24)</td>
<td>2 (0-15)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>8 (5.1%)</td>
<td>3 (5.5%)</td>
<td>2 (2.5%)</td>
<td>1 (25.0%)</td>
<td>0 (0.0%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Anti thrombotic treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ASA</td>
<td>114 (72.1%)</td>
<td>41 (74.5%)</td>
<td>57 (72.2%)</td>
<td>3 (75.0%)</td>
<td>2 (66.7%)</td>
<td>11 (64.7%)</td>
</tr>
<tr>
<td>- Clopidogrel</td>
<td>22 (13.9%)</td>
<td>6 (10.9%)</td>
<td>14 (17.7)</td>
<td>1 (25.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- NOAC</td>
<td>7 (1.1%)</td>
<td>1 (1.8%)</td>
<td>2 (2.5%)</td>
<td>0</td>
<td>0</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>- Warfarin</td>
<td>17 (10.8%)</td>
<td>6 (10.9%)</td>
<td>9 (11.4%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>- Dipyridamol</td>
<td>5 (3.2%)</td>
<td>2 (3.6%)</td>
<td>3 (3.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- Ticagrelor</td>
<td>1 (0.6%)</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- None</td>
<td>9 (5.7%)</td>
<td>4 (7.3%)</td>
<td>3 (3.8%)</td>
<td>1 (25.0%)</td>
<td>1 (25.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Cytoreductive treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hydroxyurea</td>
<td>51 (32.3%)</td>
<td>19 (34.5%)</td>
<td>25 (31.6%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>6 (35.3%)</td>
</tr>
<tr>
<td>- Interferon</td>
<td>54 (34.2%)</td>
<td>17 (31.0%)</td>
<td>30 (38.0%)</td>
<td>2 (50.0%)</td>
<td>0</td>
<td>5 (29.4%)</td>
</tr>
<tr>
<td>- Ruxolitinib</td>
<td>10 (6.3%)</td>
<td>0</td>
<td>3 (3.8%)</td>
<td>1 (25.0%)</td>
<td>3 (100%)</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>- Busulfan</td>
<td>1 (0.6%)</td>
<td>1 (1.8%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>- Anagrelid</td>
<td>18 (11.4%)</td>
<td>12 (21.8%)</td>
<td>3 (3.8%)</td>
<td>2 (50.0%)</td>
<td>0</td>
<td>1 (5.9%)</td>
</tr>
<tr>
<td>- None</td>
<td>30 (19.0%)</td>
<td>7 (12.7%)</td>
<td>19 (24.1%)</td>
<td>0</td>
<td>0</td>
<td>4 (23.5%)</td>
</tr>
</tbody>
</table>
ET = essential thrombocytosis

PV = polycythemia vera

Post-ET MF = post-essential thrombocytosis myelofibrosis

Post-PV MF = post-polycythemia vera myelofibrosis

PMF = primary myelofibrosis

ASA = acetylsalicylic acid

NOAC = novel oral anticoagulant

Table 2

Echocardiographic screening for pulmonary hypertension in 158 patients with myeloproliferative neoplasms

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity (m/s)</th>
<th>Presence of additional signs of PH*</th>
<th>Number of patients</th>
<th>Probability of PH **</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.8 or not measurable</td>
<td>No</td>
<td>149</td>
<td>Low</td>
</tr>
<tr>
<td>&lt; 2.8 or not measurable</td>
<td>Yes</td>
<td>0</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9 – 3.4</td>
<td>No</td>
<td>3</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2.9 – 3.4</td>
<td>Yes</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>&gt; 3.4</td>
<td>Yes or No</td>
<td>4</td>
<td>High</td>
</tr>
</tbody>
</table>

* right ventricular size and pressure overload, diameter of the pulmonary artery and the flow pattern out of right ventricle and estimate of the pressure in right atrium

** according to 2015 ESC/ERS guidelines for diagnosis and treatment of pulmonary hypertension

PH = pulmonary hypertension
Table 3

Right heart catheterization of 6 patients found with high probability of pulmonary hypertension by screening of 158 patients with myeloproliferative neoplasms

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Mean PAP mmHg</th>
<th>PCW mmHg</th>
<th>CI L/body surface</th>
<th>PVR Wood Unit</th>
<th>Final diagnosis And WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>41</td>
<td>10</td>
<td>3.6</td>
<td>4.7</td>
<td>CTEPH WHO group 4</td>
</tr>
<tr>
<td>(done in 2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>41</td>
<td>14</td>
<td>4.9</td>
<td>3.0</td>
<td>Lung disease/hypoxia WHO group 3</td>
</tr>
<tr>
<td>Patient 3</td>
<td>42</td>
<td>16</td>
<td>3.2</td>
<td>4.9</td>
<td>Left heart disease WHO group 2</td>
</tr>
<tr>
<td>Patient 4</td>
<td>28</td>
<td>22</td>
<td>2.4</td>
<td>1.4</td>
<td>Left heart disease WHO group 2</td>
</tr>
<tr>
<td>Patient 5</td>
<td>38</td>
<td>20</td>
<td>5.0</td>
<td>1.8</td>
<td>Left heart disease WHO group 2</td>
</tr>
<tr>
<td>Patient 6</td>
<td>34</td>
<td>11</td>
<td>4.4</td>
<td>2.9</td>
<td>Lung disease/hypoxia WHO group 4</td>
</tr>
</tbody>
</table>

Mean PAP = Mean pulmonary arterial pressure  
PCW = Pulmonary capillary wedge pressure  
CI = Cardiac index  
PVR = Pulmonary vascular resistance  
CTEPH = Chronic thromboembolic pulmonary hypertension
Table 4 – Characteristics of 6 patients with pulmonary hypertension and myeloproliferative neoplasm

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age at inclusion/Sex</th>
<th>Diagnosis</th>
<th>Year of diagnosis</th>
<th>Last bone marrow sample</th>
<th>White cell count/platelets at inclusion</th>
<th>Treatment</th>
<th>Anticoagulant</th>
<th>Vital status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/F</td>
<td>PMF</td>
<td>2013</td>
<td>2014</td>
<td>4.3/196</td>
<td>Ruxolitinib, EPO, transfusions</td>
<td>NOAC (former PE)</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>71/M</td>
<td>Post ET-MF</td>
<td>2000</td>
<td>2010</td>
<td>7.6/382</td>
<td>EPO</td>
<td>ASA</td>
<td>Deceased</td>
</tr>
<tr>
<td>3</td>
<td>80/F</td>
<td>PMF</td>
<td>2009</td>
<td>2017</td>
<td>12.6/331</td>
<td>Ruxolitinib, EPO</td>
<td>ASA</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>85/M</td>
<td>ET</td>
<td>2014</td>
<td>2015</td>
<td>5.6/298</td>
<td>Hydrea</td>
<td>Warfarin (Atrial fibrillation)</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>73/M</td>
<td>PV</td>
<td>1994</td>
<td>2017</td>
<td>17.0/156</td>
<td>Phlebotomy</td>
<td>ASA</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>67/F</td>
<td>PV</td>
<td>2015</td>
<td>Only 1 performed</td>
<td>9.8/368</td>
<td>Phlebotomy</td>
<td>ASA</td>
<td>Alive</td>
</tr>
</tbody>
</table>

ASA = acetylsalicylic acid, NOAC = novel oral anticoagulant, EPO = erythropoietin, M = male, F = female, PE = pulmonary embolism
Table 5 – Additional diagnostics of patients with pulmonary hypertension confirmed by right heart catheterization.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>TTE main findings</th>
<th>Myocardial biopsy</th>
<th>HRCT</th>
<th>Pulmonary scintigraphy</th>
<th>Pulmonary function tests</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LVEF: 70% TRV: 3.2 m/s TAPSE: 2.1 cm</td>
<td>Not performed</td>
<td>Not performed</td>
<td>2006 multiple segmental and subsegmental pulmonary emboli</td>
<td>Not performed</td>
<td>Pulmonary emboli</td>
</tr>
<tr>
<td>2</td>
<td>LVEF: 89% TRV: 4.2 m/s TAPSE: 1.7 RA and RV dilatation Flattening of IVS</td>
<td>Not performed</td>
<td>Mosaic perfusion with large areas of lucency, consistent with vascular disease. Severe thoracic kyphoscoliosis.</td>
<td>No signs of pulmonary embolism</td>
<td>Restrictive pattern. Reduced transfer factor but near normal transfer coefficient.</td>
<td>Restrictive ventilatory defect due to severe thoracic kyphoscoliosis HRCT findings consistent with PH</td>
</tr>
<tr>
<td>3</td>
<td>LVEF: 35% Mild mitral insufficiency TRV: 4.0 m/s TAPSE 1.2 cm RA and RV dilatation</td>
<td>Not performed</td>
<td>Mosaic perfusion. Uncharacteristic lucency pattern, radiologist unable to differentiate whether mosaic perfusion is due to vascular or obstructive disease</td>
<td>No signs of pulmonary embolism</td>
<td>Slightly reduced transfer factor and transfer coefficient</td>
<td>Primary respiratory disease unlikely, findings consistent with PH due to extrapulmonary disease, i.e. congestive heart failure</td>
</tr>
<tr>
<td>4</td>
<td>LVEF: 85% TRV: 3.6 m/s LA and RA dilatation Significant bilateral hypertrophy Amyloidosis</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Cardiac amyloidosis</td>
</tr>
<tr>
<td>5</td>
<td>LVEF: 62% TRV: 3.5</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Not performed</td>
<td>Aortic valve stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m/s TAPSE: 3.5 cm LA and RA dilatation LV-hypertrophy Aortic valve stenosis (peak gradient 24 mmHg, valve area 1.2 cm²)</td>
<td>ed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LVEF: 66% TRV 3.1 m/s RA and RV dilatation</td>
<td>Not performed</td>
<td>Bilateral, patchy ground-glass opacities. Discrete interlobular septal thickening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No signs of pulmonary embolism</td>
<td>Reduced expiratory volumes without signs of obstruction Supranormal static lung volumes. Reduced transfer factor but near normal transfer coefficient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Final diagnosis established by multidisciplinary team conference: desquamative interstitial pneumonia (DIP)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease, DIP = desquamative interstitial pneumonia, IVS = intra ventricular septum, LV = left ventricle, LVEF = left ventricular ejection fraction, HRCT = high resolution computed tomography, RA = right atrium, RV = right ventricle, TRV = tricuspid regurgitation velocity, TAPSE = tricuspid annular plane systolic excursion.
342 patients followed in outpatient clinic

- 37 excluded due to dementia or inability to give informed consent
- 44 refused participation
- 3 withdrew consent
- 36 did not respond to offer of inclusion

64 was not offered inclusion with time span

158 included