European Journal of Internal Medicine 68 (2019) 71–75

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Pulmonary hypertension in patients with myeloproliferative neoplasms: A large cohort of 183 patients

Geoffroy Venton[a,b], Mihai Turcanu[a,n], Julien Colle[a,b], Franck Thuny[c,d], Safia Chebrek[e], Laure Farnault[a], Cédric Mercier[a,f], Vadim Ivanov[a], Raphaëlle Fanciullino[g,h], Pierre Suchon[i,j], Pierre-André Jarrot[k,l], Karim Aissi[m], Pauline Roche[a], Jennifer Cautela[c,d], Robin Arcani[a,*], Regis Costello[a,b]

[a] Hematology and Cellular Therapy Department, La Conception, University Hospital of Marseille, France
[b] Aix-Marseille University, INSERM, UMR1090 TAGC, Marseille F_13288, France
[c] Aix-Marseille University, Assistance Publique – Hopitaux de Marseille, Mediterranean University Cardio-Oncology Center, Unit of Heart Failure and Valvular Heart Diseases, Department of Cardiology, Hôpital Nord, Marseille, France
[d] Aix-Marseille University, Inserm, Inra, Centre for Cardio-Vascular and Nutrition research (C2VN), Marseille, France
[e] Hematology Department, Hospital of Avignon, Marseille, France
[f] UMR-911 INSERM, Toxicokinetics and Pharmacokinetics Laboratory, Pharmacological Faculty, Marseille, France
[g] SMARTc Unit, Pharmacokinetics Laboratory, UMR_911 CRO2 AMU, Marseille, France
[h] Pharmacy Unit, La Conception, University Hospital of Marseille, APHM, Marseille, France
[i] Hematology Laboratory, La Timone, University Hospital of Marseille, France
[j] UMR 1062 NORT, INSERM, Marseille, France
[k] Internal Medicine and Clinic Immunology Department, La Conception, University Hospital of Marseille, France
[l] Center for Cardiovascular and Nutrition Research, INRA 1260, INSERM _S1263, Aix-Marseille University, France
[m] Internal Medicine Department, North Hospital, University Hospital of Marseille, France
[n] General Medicine Department, Aix-Marseille University, France

ARTICLE INFO

Keywords:
Chronic myeloproliferative neoplasms
Pulmonary hypertension
Transthoracic echocardiography

ABSTRACT

Background: Chronic myeloproliferative neoplasms (MPN) are recognized as a cause of pulmonary hypertension (pH). We ought to describe the prevalence and characteristics of PH in a cohort of MPN who were screened using transthoracic echocardiography (TTE).

Methods: One hundred eighty-three newly diagnosed consecutive MPN patients were prospectively evaluated using TTE to detect PH.

Results: Two patients were diagnosed with chronic eosinophilic leukemia, two patients had post-essential thrombocythemia (ET) myelofibrosis (MF), two patients had post-polycythemia vera (PV) MF, 11 patients had primary myelofibrosis (PMF), 28 patients had chronic myeloid leukemia (CML), 51 patients had PV, and 87 patients had ET. TTE was used to determine PH, and PH was suspected in 16 of 183 patients as follows: four with PV, seven with ET, two with PMF, and three with CML. Two patients with ET were excluded because of global cardiac failure. Three patients underwent right heart catheterization to confirm PH. The 14 (7.7%) patients with PH had no cardiac or lung disease that directly involved MPN in PH development.

Conclusion: In this large cohort of 183 MPN patients, TTE was used to diagnose PH, and 14 patients (7.7%) developed PH. This prevalence was lower than expected based on previously reported data, but it remains higher than in the general population.

Abbreviations: MPN, Chronic myeloproliferative neoplasms; PH, pulmonary hypertension; WHO, World Health Organization; mPAP, mean pulmonary artery pressure; RHC, right heart catheterization; PAWP, pulmonary artery wedge pressure; WU, Wood units; sPAP, systolic pulmonary artery pressure; TTE, transthoracic echocardiography; TRV, tricuspid regurgitation velocity; TKIs, tyrosine kinase inhibitors; PDGF, platelet-derived growth factor; ET, essential thrombocythemia; PV, polycythemia vera; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; ESC, European Society for Cardiology; ERS, European Respiratory Society; TR, tricuspid regurgitation; CEL, chronic eosinophilic leukemia; MF, myelofibrosis; OS, overall survival

* Corresponding author at: Hematology and Cellular Therapy Department, La Conception, University Hospital of Marseille, 147 Boulevard Baille, 13005 Marseille, France.
E-mail address: robin.arcani@ap-hm.fr (R. Arcani).

https://doi.org/10.1016/j.ejim.2019.08.004
Received 1 April 2019; Received in revised form 5 August 2019; Accepted 7 August 2019
Available online 14 August 2019

1. Introduction

Chronic myeloproliferative neoplasms (MPN) are recognized as a cause of pre-capillary pulmonary hypertension (PH) in the World Health Organization (WHO) 2016 classification of myeloid neoplasm [1] and since the 4th World Symposium held in Dana Point (2008, California, USA), they have belonged to the group 5 clinical classification of PH [2]. PH is defined as an elevation in the mean pulmonary artery pressure (mPAP) that is greater than or equal to 25 mmHg, which was measured at rest via right heart catheterization (RHC) [3]. Pre-capillary PH is characterized by a pulmonary artery wedge pressure (PAWP) $\leq$15 mmHg and a pulmonary vascular resistance > 3 Wood units (WU) in the absence of other causes of pre-capillary PH [3]. RHC is required to confirm the PH diagnosis. However, besides obvious cost issues, it is not possible to perform RHC in all patients with suspected PH and to expose all of them to potential serious iatrogenic events [4]. Since Yock and Popp first demonstrated in 1984 that systolic pulmonary artery pressure (sPAP) can be accurately estimated using Doppler transthoracic echocardiography (TTE), recent advances in non-invasive imaging led Doppler TTE to become the most widespread and well-recognized technique for non-invasive sPAP evaluation and the screening modality of choice for evaluating PH [5–8]. sPAP estimation is based on peak tricuspid regurgitation velocity (TRV) at rest and in the presence of additional pre-specified echocardiographic variables that are suggestive of PH [3]. Although sPAP measurement is critical in evaluating pulmonary hemodynamics using TTE, a strong relationship between mPAP and sPAP has been documented and the threshold of 35 mmHg is most commonly used to estimate the PH [3,9]. PH in MPN can be secondary mainly to thromboembolic events or portal hypertension resulting from massive splenomegaly, or it can be caused by treatment such as tyrosine kinase inhibitors (TKIs). However, case reports and small series have identified patients without secondary causes, which suggested direct MPN involvement in PH development [10,11].

For the physiopathology of primary PH in MPN, various hypotheses have been proposed: lung myeloid metaplasia, obstruction of pulmonary vessels by circulating megakaryocytes, artery smooth muscle hyperplasia resulting from a high level of platelet-derived growth factor (PDGF), increased angiogenesis, and an abnormal circulating endothelial cell-to-endothelial progenitor cell ratio [12].

Through many studies that had a small number of patients (from 24 to 46), the PH prevalence was evaluated as 44% in essential thrombocythemia (ET), 22% in polycythemia vera (PV), 37% in primary myelofibrosis (PMF), and 25% in chronic myeloid leukemia (CML), with an average prevalence of 38% [13–16]. This surprisingly high prevalence of primary PH in MPN led Chebrek et al. [17], in 2014, to study the PH prevalence in the largest cohort in the literature (103 patients). Five of 103 patients (4.9%) were evaluated for PH using TTE in this research, but none of them had an RHC. These results were lower than expected based on previous publications, but they were significantly higher than in the general population [17]. Based on these observations, the 2015 guidelines from the European Society for Cardiology (ESC) and European Respiratory Society (ERS) on the diagnosis and treatment of PH recognized MPN as a specific cause of PH that has unclear and/or multifactorial mechanisms [3].

With 80 patients more than in Chebrek et al.'s cohort [17] (183 patients), we propose a new study to describe the prevalence and characteristics of PH in patients with MPN.

2. Materials and methods

From May 2008 to May 2018, 512 consecutive MPN patients were newly diagnosed at the Hematology and Cellular Therapy Department of University Hospital of Marseille (France), and 183 of these patients were included in this study. The study was approved by the institutional review board of the Assistance Publique des Hôpitaux de Marseille.

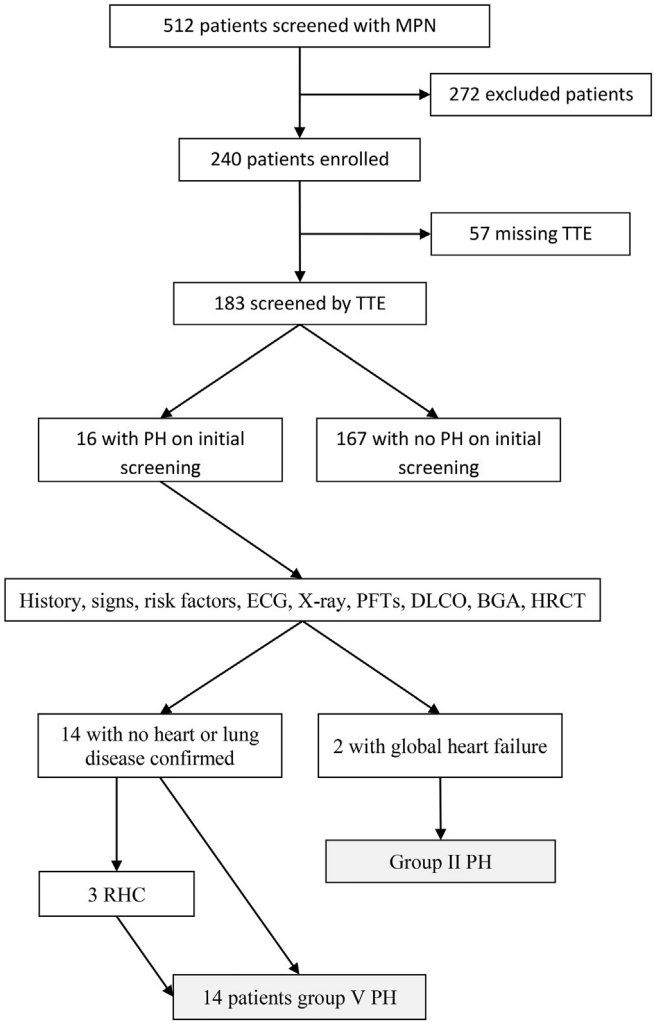

Fig. 1. Flow chart of patients inclusion and diagnosis.
BGA = blood gas analysis; DLCO = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; HRCT = high-resolution computer tomography; MPN = myeloproliferative neoplasms; PFTs = pulmonary functional tests; pH = pulmonary hypertension; RHC = right heart catheterism; TTE = trans thoracic echocardiography; X-ray = chest radiography.

Written informed consent was obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki. No selection was performed regarding asymptomatic and symptomatic patients, because the only inclusion criterion was the presence of MPN. MPN was diagnosed according to standard hematological criteria established by the WHO 2016 classification for myeloid neoplasms [1].

The exclusion criteria were as follows: patients with missing data, refusal to participate, patients incapable of providing informed consent (e.g. dementia or non-French speaking patients), patients who were being followed at another center, patients with missing TTE results, patients with unclassifiable myelodysplastic/myeloproliferative neoplasms, and patients with an ischemic cardiopathy and/or pulmonary thromboembolism history or any obvious identified cause of PH other than MPN.

PH was established mainly by TTE that was performed by two experienced cardiologists. All TTEs were performed according to the ESC guidelines, which recommended measuring the peak TRV using continuous-wave Doppler as the main variable for assessing PH. In the absence or presence of severe tricuspid regurgitation (TR), additional pre-specified echocardiographic variables that were suggestive of PH were used as follows: pulmonary artery diameter, ventricular diameter ratio, flattening of the interventricular septum, right ventricle and

Table 1
Patients and treatment characteristics.

Diagnosis	PV	ET	PMF	Post-ET MF	Post-PV MF	CML	Others	Total MPN
n	51	87	11	2	2	28	2	183
Sex M/F, n	34/17	31/56	5/6	1/1	1/1	15/13	2/0	89/94
Median age at diagnosis of MPN (range)	59 (26–89)	61 (20–93)	64 (31–79)	72 (65–79)	66 (62–70)	54 (20–88)	55 (52–58)	61 (20–93)
Number of PH diagnosed, n (%)	4 (7.8%)	5 (5.7%)	2 (18.2%)	0 (0%)	0 (0%)	3 (10.7%)	0 (0%)	14 (7.7%)
Median age at diagnosis of PH (range)	76 (50–89)	80 (71–92)	76 (72–79)	NA	NA	79 (74–85)	NA	79 (50–92)
Median delay between MPN and PH diagnosis, months (range)	2.5 (0–289)	37 (14–181)	3 (0–6)	NA	NA	59 (6–77)	NA	22.5 (0–289)
Death at 5 years, n (%)	0 (0%)	4 (4.6%)	2 (18.1%)	0 (0%)	0 (0%)	1 (3.5%)	0 (0%)	7 (3.8%)
MPN driver mutation profile, n (%)								
JAK2	47 (92.2%)	73 (83.9%)	6 (54.5%)	2 (100%)	2 (100%)	0 (0%)	0 (0%)	131 (71%)
TN	1 (1.9%)	3 (3.4%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (2.7%)
CALR	0 (0%)	4 (4.6%)	3 (27.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (3.8%)
MPL	0 (0%)	2 (2.3%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1.6%)
BCR-ABL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	28 (100%)	0 (0%)	28 (15.3%)
FIP1L1-PDGFRA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2 (1.1%)
ND	3 (5.9%)	5 (5.7%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (4.9%)
Anti-thrombotic treatment, n (%)								
None	7 (13.7%)	9 (10.3%)	8 (72.7%)	1 (50%)	1 (50%)	22 (78.5%)	1 (50)	49 (26.7%)
ASA	41 (80.3%)	66 (75.8%)	2 (18.1%)	1 (50%)	1 (50%)	5 (17.8%)	1 (50%)	117 (64%)
Clopidogrel	1 (1.9%)	10 (11.5%)	1 (9.1%)	0 (0%)	0 (0%)	1 (3.5%)	0 (0%)	13 (7.1%)
NOAC	2 (3.9%)	3 (3.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (2.7%)
Other	7 (13.7%)	6 (6.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (7.1%)
Cytoreductive treatment, n (%)								
Hydroxyurea	29 (56.8%)	63 (72.4%)	3 (27.2%)	2 (100%)	1 (50%)	6 (21.4%)	0 (0%)	104 (56.8%)
Interferon	2 (3.9%)	2 (2.3%)	1 (9.1%)	0 (0%)	0 (0%)	2 (7.1%)	0 (0%)	7 (3.8%)
Anagrelid	2 (3.9%)	14 (16.1%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	18 (9.8%)
6-mercaptopurine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Etoposide	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pipobroman	1 (1.9%)	5 (5.7%)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	8 (4.3%)
Tyrosine Kinase Inhibitors, n (%)								
Ruxolitinib	7 (13.7%)	4 (4.6%)	4 (36.3%)	1 (50%)	1 (50%)	1 (3.5%)	0 (0%)	18 (9.8%)
Imatinib	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	24 (85.7%)	2 (100%)	27 (14.7%)
Bosutinib	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (17.8%)	0 (0%)	5 (2.7%)
Dasatinib	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (53.5%)	0 (0%)	15 (8.2%)
Nilotinib	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (25%)	0 (0%)	7 (3.8%)
Ponatinib	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.5%)	0 (0%)	1 (0.54%)
Other, n (%)								
Bleeding	20 (39.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (10.9%)
Erythropoietin	0 (0%)	1 (1.14%)	3 (27.2%)	0 (0%)	0 (0%)	1 (3.5%)	0 (0%)	5 (2.7%)
Lenalidomide	0 (0%)	1 (1.14%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)
Allogenic SCT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.5%)	0 (0%)	1 (0.54%)
Omacetaxine	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (7.1%)	0 (0%)	2 (1.1%)
Melphalan	0 (0%)	1 (1.14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.54%)

MPN, myeloproliferative neoplasms; M, male; F, female; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; MF, myelofibrosis; CML, chronic myeloid leukemia; PH, pulmonary hypertension; ASA, acetylsalicylic acid; NOAC, new oral anticoagulant; EPO, erythropoietin; G-CSF, granulocyte-colony-stimulating factor; Allogenic SCT, allogenic stem cell transplantation.

pulmonary artery hemodynamics, and inferior vena cava and right atrium dimensions. With a peak TRV ≤ 2.8 m/s or not measurable in the absence of another echo "PH sign", there is a low probability of PH [3]. Because the mPAP cannot be estimated by TTE in all patients and according to multiple studies published that confirmed the mPAP-sPAP correlation and the Doppler method's reliability to screen for PH, by convention, we considered an elevation of sPAP that was greater than or equal to 35 mmHg to be a sign of PH [3,7,18]. A thorough study of all TTEs was performed to prevent some possible sources of error that were related to the echocardiographic method such as cardiac remodeling after myocardial infarction, difficulty in estimating sPAP in the absence or in case of severe TR, the necessity to measure all pressures at the end of expiration, misdiagnosis of pulmonary valve stenosis, or right ventricle outflow tract obstruction. The TTEs were centrally reviewed and discussed in a blinded manner. RHC was performed in only three patients.

3. Results

Our initial screening included 512 patients with MPN who were treated at the Hematology and Cellular Therapy Department at the University Hospital of Marseille (France) between May 2008 and May 2018. Among these 512 patients, 272 patients were not included: 60 patients refused to participate, 171 patients had missing data, and 41 patients were followed-up at other centers. Two hundred forty patients agreed to participate in our study but only 183 were screened using TTE. The flow chart of patients' inclusion and diagnosis is shown in Fig. 1.

The median age at MPN diagnosis was 61 years (range, 20–93 years). Two patients (1%) had chronic eosinophilic leukemia (CEL), two patients (1%) had post-ET myelofibrosis (MF), two patients (1%) had post-PV MF, 11 patients (6%) had PMF, 28 patients (15%) had CML, 51 patients (28%) had PV, and 87 patients (47%) had ET. All patients' characteristics, mutations, and treatments are summarized in Table 1.

Based on the ESC guidelines, we found signs of PH in 16 patients (8.8%) among our 183 patients who were screened using TTE: four with PV (25%), seven with ET (43.8%), two with PMF (12.5%), and three with CML (18.8%). Two patients with ET were excluded because of global cardiac failure: one with severe mitral regurgitation and one with ischemic cardiomyopathy. The remaining 14 patients had no cardiac or lung disease and no history of thromboembolic disease.

Table 2
Characteristics of patients with pulmonary hypertension.

Characteristic	UPN1	UPN2	UPN3	UPN4	UPN5	UPN6	UPN7	UPN8	UPN9	UPN10	UPN11	UPN12	UPN13	UPN14
Age	67	89	53	90	85	71	80	92	84	75	80	79	73	85
Sex	M	F	M	F	F	M	F	F	F	M	F	M	M	F
Diagnosis	PV	PV	PV	PV	ET	ET	ET	ET	ET	PMF	PMF	CML	CML	CML
Follow up (months from MPN diagnosis)	50	120	40	19	120	34	41	60	112	43	15	15	67	86
Thrombosis history	No	Yes	No	Yes	No	Yes	No	No	Yes	No	Yes	No	No	No
Dyspnea	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No
Splenomegaly	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No
Hepatomegaly	No	No	No	No	No	No	No	No	No	No	No	No	No	No
WBC (G/L)	11	14	8	10.13	22.38	8.9	7.71	20.22	7.3	6.9	22	3.79	7.9	4
Hemoglobin (g/dL)	18.3	13.8	18.6	17.1	8.7	12.5	10.3	16.8	14	13.3	9.6	10.2	12.4	11.1
Platelets (G/L)	449	489	456	535	622	490	518	1542	345	259	291	112	285	79
Pericardial effusion	No	No	No	No	No	No	No	No	No	No	No	No	Grade I	No
LAD	N	45	N	N	N	N	N	N	N	N	N	42	N	N
LVPW	N	N	N	N	N	N	N	N	N	11.5	12	N	14	N
IVSDd	N	12	N	N	N	N	N	N	N	12	13	N	13	N
LVDd	N	52	N	N	N	N	N	58	N	N	N	N	N	N
LVDs	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FS (%)	N	N	N	N	N	N	NA	N	N	N	N	N	N	N
EF (%)	55	50	60	N	65	N	NA	N	68	70	N	68	65	65
sPAP (mmHg)	85	50	70	40	65	40	40	60	36	35	55	45	48	40
RAP (mmHg)	N	15	N	N	N	N	N	N	N	N	N	N	N	N
Valvular abnormalities	No	AR II	No	No	MR I	No	No	MR II	MR II	No	No	No	MR I	MR I
Portal/splanchnic HT	No	No	No	No	No	No	No	No	No	No	No	No	No	No
IC thrombosis Worsened HP at TTE revaluation	No Yes	No No	No No	No No	No No	No No	No No	No No	No No	No No	No Yes	No Yes	No Yes	No Yes
Treatment	ASA VKA Ruxolitinib	VKA	ASA HU	ASA HU	P2Y12I HU Pipobroman	ASA HU	NOAC EPO Revlimid	ASA HU Melphalan	ASA VKA HU	EPO	EPO P2Y12I	HU TKI	TKI	ASA HU TKI

UPN, unique patient number; M, male; F, female; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; HT, hypertension; IC, Intracardiac thrombosis; HU, hydroxyurea; ASA, acetylsalicylic acid; P2Y12I, P2Y12 receptor inhibitors; VKA, vitamin K antagonist; NOAC, new oral anticoagulant; EPO, erythropoietin; TKI, tyrosine-kinase inhibitor; LAD, left atrium diameter, N = 30–40 mm for M, 27–38 mm for F; LVPW, left ventricular posterior wall, N = 7–11 mm; IVSDd, end-diastolic interventricular septal dimension, N = 7–11 mm; LVDd, end-diastolic left ventricular diameter, N = 36–56 mm; LVDs, end-systolic left ventricular diameter, N = 20–40 mm; FS, fractional shortening, N = 25–50%; EF, ejection fraction, N = 55–70%; sPAP, systolic pulmonary artery pressure; RAP, right atrial pressure, N = 5–10 mmHg; MR, mitral regurgitation, grades I-III; AR, aortic regurgitation, grades I-III; TTE, transthoracic echocardiography.

Three patients underwent an RHC with confirmation of the pre-capillary PH in the absence of comorbidities for left heart disease or "borderline" hemodynamics. All the RHC procedures were performed during the 6 months after the first TTE suggested PH, and two patients had a second RHC within the following 2 years. The median age of the 14 pH patients was 77.5 years (range, 50–88 years) at MPN diagnosis and 79 years (range, 50–92 years) at PH diagnosis. The median follow-up after MPN diagnosis was 46.5 months (range, 15–120 months) and the median delay between MPN diagnosis and PH diagnosis was 22.5 months (range, 0–118 months). The median follow-up since PH diagnosis was 10 months (range, 0–97 months). Two patients with PH were dead at the last check-point in our study (May 2018): one died of ET (pneumonia complicated by SARS) and one died of PMF (acute myeloid leukemia transformation). The median sPAP for the 14 patients with PH was 46.5 mmHg (range, 35–85 mmHg) based on TTE estimations and 64 mmHg (range, 59–96 mmHg) based on the three RHC measured pressures.

During the follow-up, all PH patients benefited from an echocardiographic revaluation: five (36%) of the 14 pH patients had worsening of sPAP (mean increase of 16 ± 3 mmHg).

Only two (14%) of the 14 pH patients received specific therapy to treat PH, which occurred because of disabling dyspnea. One patient was successfully treated using epoprostenol and sildenafil, and the other patient was treated with an ineffective treatment, bumetanide.

Forty-eight patients had thrombotic events at diagnosis or during the study duration (15 myocardial infarctions, 11 distal venous thrombosis, seven cerebral vascular accidents, five pulmonary embolisms, and five other) but only three of them had PH (cerebral vascular accidents for all three). There was no significant difference (p = .2) in overall survival (OS) at 60 months between MPN patients with (two patients died) or without (no patient died) PH. As expected, with a median follow-up of 46.5 months (range, 15–120 months), the median OS was not reached in both groups. Detailed clinical and TTE data from PH patients are summarized in Table 2.

4. Discussion

According to the different countries and the different epidemiologic studies, the scientific literature reports that the prevalence of PH ranges from 25.9 to 52 pH patients per million adults [19,20]. There have been no epidemiologic studies on the prevalence of group 5 pH in the general population. In the MPN patient population, the PH prevalence was significantly higher than that in the general population. To the best of our knowledge, our work presents the largest cohort in the literature of MPN patients who were evaluated using TTE to diagnose PH. With 14 (7.7%) diagnosed with PH among the 183 patients who were assessed, our results are different from previous studies that showed a 38% global prevalence of PH in MPN patients [12–16,21,22]. This discrepancy may have different explanations. First, the previous data reported were based on small size series or cases reports [12–16]. Moreover, in our work, patients with obvious secondary causes of PH such as left heart disease (group 2 WHO clinical classification of PH) were excluded. Another possible bias could be the referral of symptomatic patients to specialist PH centers with experienced university cardiologists who rigorously follow the experts' guidelines [10]. All previous studies included only asymptomatic patients during screening for PH. In our study, no selection was performed for asymptomatic and symptomatic patients. Among the 14 pH patients, three were symptomatic at the

diagnosis. Moreover, the PH rate may be greatly overestimated using TTE evaluation of sPAP or mPAP because the quality of the acquired continuous-wave Doppler signal is the major limitation of the method [23,24]. Furthermore, contrary to most previous studies that included a larger proportion of PMF, post-ET, and post-PV MF patients, in our study, only 11 (6%), one (1.1%), and one (1.1%) patients were included, respectively. However, there was no significant association between a high proportion of PMF patients and high levels of PH in the previous studies [12–16]. Another important issue is the use of TKIs because these compounds are responsible for causing PH in some cases, especially second-generation TKIs (dasatinib, nilotinib) [25]. A pretherapeutic cardiac assessment in CML patients seems to be necessary before starting treatment with TKIs [26]. For the three CML patients with PH who were treated with dasatinib and the PV patient with PH who was treated with ruxolitinib, we chose to include them in our cohort because the PH diagnosis was made before treatment initiation using second-generation TKIs.

Finally, there seems to be no difference in OS between patients with or without PH. However, the number of patients in each group is too disproportionate (16 pH patients vs. 167 patients without PH) to draw any conclusions.

Although this cohort is the largest ever reported, our work has two main limitations. First, RHC remains the gold standard for PH diagnosis [3]. Only three of our 14 pH patients benefited from this invasive procedure to confirm the suspicion of PH and it is unclear to what extent the PH prevalence may be overestimated in our cohort. The low number of RHC procedures performed is mainly explained by the patients' refusal of this procedure because it did not have a direct individual benefit or immediate therapeutic involvement. Another limitation in our study was the median duration of follow-up, which was only 46.6 months, and the time from MPN diagnosis to TTE, which was only 22.5 months. Thus, we detected predominantly early cardiovascular events. This suggests the need for a longer follow-up because, based on previous studies, the delay between MPN and PH diagnosis varies from 37 to 96 months [15,23].

5. Conclusion

In this large cohort, 183 MPN patients were evaluated using TTE to diagnose PH, and among them, 16 patients (8.8%) developed PH. Among these 16 pH patients, two had global cardiac failure and were assigned the group 2 pH classification at diagnosis, whereas the remaining 14 (7.7%) patients had no cardiac or lung disease and no history of thromboembolic disease that directly involved MPN in PH development. Although the PH prevalence in our study was lower than expected based on previously reported data, it was higher than that in the general population. Because early detection of PH is of pivotal importance for treatment success, we recommend systematic screening for PH in MPN patients even when they are asymptomatic.

Declaration of Competing Interest

None.

References

[1] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
[2] Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62(25):D34–41. Suppl.
[3] Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46(4):903–75.
[4] Rudski LG. Point: can Doppler echocardiography estimates of pulmonary artery systolic pressures be relied upon to accurately make the diagnosis of pulmonary hypertension? Yes. Chest. 2013;143(6):1533–6.
[5] Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation. 1984;70(4):657–62.
[6] Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(25):D42–50. Suppl.
[7] D'Alto M, Bossone E, Opotowsky AR, et al. Strengths and weaknesses of echocardiography for the diagnosis of pulmonary hypertension. Int J Cardiol 2018;263:177–83.
[8] Lafitte S, Pillois X, Reant P, et al. Estimation of pulmonary pressures and diagnosis of pulmonary hypertension by Doppler echocardiography: a retrospective comparison of routine echocardiography and invasive hemodynamics. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr 2013;26(5):457–63.
[9] Chemla D, Humbert M, Sitbon O, Montani D, Hervé P. Systolic and mean pulmonary artery pressures: are they interchangeable in patients with pulmonary hypertension? Chest. 2015;147(4):943–50.
[10] Adir Y, Elia D, Harari S. Pulmonary hypertension in patients with chronic myeloproliferative disorders. Eur Respir Rev Off J Eur Respir Soc 2015;24(137):400–10.
[11] Costello R. Pulmonary arterial hypertension and malignant hematologic disorders. Rev Med Interne 2010;31(9):621–5.
[12] Cortelezzi A, Gritti G, Del Papa N, et al. Pulmonary arterial hypertension in primary myelofibrosis is common and associated with an altered angiogenic status. Leukemia. 2008;22(3):646–9.
[13] Altintas A, Karahan Z, Pasa S, et al. Pulmonary hypertension in patients with essential thrombocythemia and reactive thrombocytosis. Leuk Lymphoma 2007;48(10):1981–7.
[14] Gupta R, Perumandla S, Patsiornik Y, Niranjan S, Ohri A. Incidence of pulmonary hypertension in patients with chronic myeloproliferative disorders. J Natl Med Assoc 2006;98(11):1779–82.
[15] Kadikoylu G, Onbasili A, Tekten T, Barutca S, Bolaman Z. Functional and morphological cardiac changes in myeloproliferative disorders (clinical study). Int J Cardiol 2004;97(2):213–20.
[16] Garypidou V, Vakalopoulou S, Dimitriadis D, et al. Incidence of pulmonary hypertension in patients with chronic myeloproliferative disorders. Haematologica. 2004;89(2):245–6.
[17] Chebrek S, Aïssi K, Francès Y, et al. Pulmonary hypertension in patients with chronic myeloproliferative neoplasms. Leuk Lymphoma 2014;55(1):223–5.
[18] Greiner S, Jud A, Aurich M, et al. Reliability of noninvasive assessment of systolic pulmonary artery pressure by Doppler echocardiography compared to right heart catheterization: analysis in a large patient population. J Am Heart Assoc 2014;3(4).
[19] Peacock AJ, Murphy NF, McMurray JJV, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. Eur Respir J 2007;30(1):104–9.
[20] Hoeper MM, Huscher D, Pittrow D. Incidence and prevalence of pulmonary arterial hypertension in Germany. Int J Cardiol 2016;203:612–3.
[21] Guilpain P, Montani D, Damaj G, et al. Pulmonary hypertension associated with myeloproliferative disorders: a retrospective study of ten cases. Respir Int Rev Thorac Dis 2008;76(3):295–302.
[22] García-Manero G, Schuster SJ, Patrick H, Martinez J. Pulmonary hypertension in patients with myelofibrosis secondary to myeloproliferative diseases. Am J Hematol 1999;60(2):130–5.
[23] Dingli D, Utz JP, Krowka MJ, Oberg AL, Tefferi A. Unexplained pulmonary hypertension in chronic myeloproliferative disorders. Chest. 2001;120(3):801–8.
[24] Schneider M, Pistritto AM, Gerges C, et al. Multi-view approach for the diagnosis of pulmonary hypertension using transthoracic echocardiography. Int J Cardiovasc Imaging 2018;34(5):695–700.
[25] Shah NP, Wallis N, Farber HW, et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol 2015;90(11):1060–4.
[26] Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukemia. Leuk Res 2009;33(6):861–4.