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Pulmonary hypertension in patients with Philadelphia-negative myeloproliferative neoplasms: a single-center retrospective analysis of 225 patients

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Background
The prevalence of pulmonary hypertension (PH) in myeloproliferative neoplasms (MPNs) varies among studies. We analyzed the prevalence of PH in Korean patients with Philadelphia-negative (Ph^-) MPNs.

Methods
Medical records of patients with Ph^- MPNs [essential thrombocythemia (ET), polycythemia vera (PV), or primary myelofibrosis (PMF)] visiting a single hospital between 1993 and 2019 were reviewed retrospectively. Transthoracic echocardiographic examination (TTE) results were reviewed and PH was diagnosed according to established guidelines.

Results
Of the 320 MPN (179 ET, 107 PV, and 34 PMF) patients, 225 (121 ET, 83 PV, and 21 PMF) underwent TTE. Of these 225 MPN patients, 19 of 121 (15.7%) ET, 9 of 83 (10.8%) PV, and 6 of 21 (28.6%) PMF patients had PH. PV patients with PH were older [71 (42–85) vs. 61.5 (26–91) yr, respectively; P=0.049], predominantly female (male:female ratio, 0.29 vs. 1.96, respectively; P=0.010), had lower hemoglobin levels (15.9±2.6 g/dL vs. 18.4±2.6 g/dL, respectively; P=0.010), and higher platelet counts (616.6±284.2×10^9/L vs. 437.7±191.7×10^9/L, respectively; P=0.020) than PV patients without PH. PMF patients with PH had higher monocyte counts (1.3±0.5×10^9/L vs. 0.8±0.4×10^9/L, respectively; P=0.031) than those without PH. PH was a risk factor for poor survival in PV (HR, 12.4; 95% CI, 1.8–86.6).

Conclusion
PH is common in patients with Ph^- MPNs and hence, careful screening for PH is warranted.

Key Words Myeloproliferative neoplasm, Essential thrombocytopenia, Polycythemia vera, Primary myelofibrosis, Pulmonary hypertension

INTRODUCTION

Philadelphia-negative classical myeloproliferative neoplasms (Ph^- MPNs) have traditionally included polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) [1]. Vascular complications are commonly observed in Ph^- MPNs [2], and some patients may convert to myelodysplasia and/or acute leukemia [3].

Pulmonary hypertension (PH) is a progressive disease that often leads to premature death [4, 5]. PH is divided into five types according to its etiology [6]. The first type is pulmonary arterial hypertension (PAH), which causes several pathological changes within the pulmonary vasculature, leading to idiopathic, familial, drug-, or toxin-induced PAH and/or associated forms of PAH such as systemic sclerosis, portal hypertension, congenital heart disease, and/or human immunodeficiency virus-induced PAH. Other four types of

PH occur secondary to other conditions and are usually referred to as secondary PH.

MPNs have been linked to PH and are few of the causes for secondary PH [7]. However, these conclusions have been drawn primarily on the basis of early case reports and small case series with highly variable prevalence rates (5–50%) [8-22]. Recently, some studies including larger cohorts of MPN patients have been reported; however, the prevalence of PH varied markedly among these studies [23-26]. Furthermore, no studies have yet included the Asian populations. In this study, we analyzed the prevalence of PH and its clinical implications in Korean patients with Ph^- MPNs.

MATERIALS AND METHODS

Patients

The medical records of patients with ET, PV, or PMF who visited the Chungnam National University Hospital between January 1993 and June 2019 were reviewed retrospectively. MPNs were diagnosed according to the Polycythemia Vera Study Group criteria [27] in patients who visited before 2001, and the World Health Organization criteria in patients who visited thereafter [28-30]. MPN patients who underwent transthoracic echocardiographic examination (TTE) were enrolled in the study. The study was approved by the Institutional Review Board of Chungnam National University Hospital and was performed in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Declaration of Helsinki.

Diagnosis of PH

The results of TTE were reviewed by two cardiologists, and PH was diagnosed when the probability of PH was "high" according to the European Society of Cardiology/European Respiratory Society guidelines [31]. Briefly, PH probability was defined as "high" when the tricuspid regurgitation velocity was >3.4 m/sec or in the range of 2.9–3.4 m/sec accompanied by certain additional findings. PH patients with associated left heart failure and/or chronic obstructive lung disease were excluded.

Statistical analysis

Descriptive data are presented as mean±standard deviation, median (range), or percentage, and were analyzed using the Student's t test or the χ^2 test (Fisher's exact test). Survival analysis was performed using Kaplan–Meier plots and the log-rank test. Multivariate analysis of factors associated with survival was performed by Cox proportional hazard analysis. Overall survival was defined as time from MPN diagnosis until death due to any cause. Statistical analyses were performed using SPSS software (ver. 24.0, SPSS Inc., Chicago, IL, USA), and $P<0.05$ was considered to indicate statistical significance.

RESULTS

Overall prevalence of PH in MPN patients

MPNs were diagnosed in 320 patients (179 ET, 207 PV, and 34 PMF) during the study period. Of the 320 patients, 225 (121 ET, 83 PV, and 21 PMF) underwent TTE either at the time of diagnosis or during follow-up examinations [median, 4.5 yr (range, 0.1–25.5 yr)]. The baseline characteristics and clinical features, including age, gender, prognostic score, complete blood count, lactate dehydrogenase (LDH) levels, driver gene mutations, thrombotic events, and follow-up durations, did not differ between all patients and patients undergoing TTE (for all MPN subtypes; data not shown). Of the 225 patients undergoing TTE, 34 (15.1%) had PH of indeterminate etiology. Hence, it was defined as MPN-related PH. Thirteen (5.8%) patients with left heart failure-associated PH were excluded from the analysis. No cases of chronic obstructive lung disease-associated PH were reported. Of the 108 MPN patients who underwent TTE at the time of diagnosis, 8 (7.4%) had PH, indicating that majority of the patients developed PH during follow-up period (Table 1).

PH in ET patients

Of the 121 ET patients who underwent TTE, 19 (15.7%) had PH. Of the 57 ET patients who underwent TTE at the time of diagnosis, 2 (3.5%) had PH. Female ET patients were more likely to develop PH than male (male:female ratio, 0.45; P=0.062). *Calreticulin* (*CALR*) mutation was more prevalent in ET patients with PH than that in ET patients

Table 1. Prevalence of pulmonary hypertension in myeloproliferative neoplasms.

	MPN-associated PH, N (%)		Heart failure-associated PH, N (%)
	At diagnosis	Overall	
Essential thrombocythemia	2/57 (3.5)	19/121 (15.7)	7/121 (5.8)
Polycythemia vera	1/38 (2.6)	9/83 (10.8)	5/83 (6.0)
Primary myelofibrosis	5/13 (38.5)	6/21 (28.6)	1/21 (4.8)
Total	8/108 (7.4)	34/225 (15.1)	13/225 (5.8)

Abbreviations: MPN, myeloproliferative neoplasms; PH, pulmonary hypertension.

without PH (28.6% vs. 7.1%, respectively; *P*=0.080). The follow-up duration was significantly longer for ET patients with PH than that for ET patients without PH [7.1 (1.1–18.1) vs. 3.7 (0.1–21.4) yr, respectively; *P*=0.032]. The International Prognostic Score for Essential Thrombocythemia categories, hemoglobin levels, WBC counts, platelet counts, LDH levels, driver gene mutations, and comorbidities (diabetes mellitus, hypertension, chronic kidney disease, smoking, and/or thrombotic events) did not differ significantly between ET patients with and without PH (Table 2). Overall survival also did not differ significantly between the two groups (10-yr survival rate, 90% vs. 86%, respectively; *P*=0.510) (Fig. 1).

PH in PV patients

Of the 83 (10.8%) PV patients, 9 had PH. Of the 38 PV patients who underwent TTE at the time of diagnosis, 1 (2.6%) had PH. PV patients with PH were significantly older [71 (42–85) vs. 61.5 (26–91) yr, respectively; *P*=0.049] and were more likely to be female (male:female ratio, 0.29 vs. 1.96, respectively; *P*=0.010) compared to those without PH. The hemoglobin levels were significantly lower (15.9±2.6 vs. 18.4±2.6 g/dL, respectively; *P*=0.010), and platelet counts were significantly higher (616.6±284.2×10^9/L vs. 437.7±191.7×10^9/L, respectively; *P*=0.020) in PV patients with PH than those in PV patients without PH. LDH levels, driver gene mutations, and comorbidities (diabetes mellitus, hypertension, chronic kidney disease, smoking, and/or thrombotic events) did not differ significantly between PV patients with and without PH (Table 3). The follow-up duration of patients with PH did not differ significantly from patients without PH [2.5 (0.1–20.4) vs. 6.3 (0.1–25.5) yr, respectively; *P*=0.298]. PV patients with PH exhibited significantly shorter survival times than those without PH (10-yr survival rate, 94% vs. 53%, respectively; *P*=0.001) (Fig. 1). Multivariate Cox regression analysis confirmed that PH was a risk factor for poor survival [hazard ratio (HR), 12.4; 95% confidence interval (CI), 1.8–86.6; *P*=0.011], along with older age (HR, 1.4; 95% CI, 1.1–1.8; *P*=0.002), and high LDH level (HR, 11.3; 95% CI, 1.1–119.6; *P*=0.045) (Table 4).

PH in PMF patients

Of the 21 (28.6%) PMF patients, 6 had PH. Of the 13 PMF patients who underwent TTE at the time of diagnosis, 5 (38.5%) had PH. PMF patients with PH had significantly higher monocyte counts than those without PH (1.3±0.5×10^9/L vs. 0.8±0.4×10^9/L, respectively; *P*=0.031). International Prognostic Scoring System category, LDH level, driver gene mutations, and comorbidities (diabetes mellitus, hypertension, chronic kidney disease, smoking, and/or thrombotic events) did not differ significantly between PMF patients with and without PH (Table 5). The follow-up duration of patients with PH did not differ significantly from patients without PH [2.4 (0.4–4.1) vs. 2.8 (0.2–7.0) yr, respectively; *P*=0.529]. Overall survival showed no significant difference between the two groups (10-yr survival rate, 100% vs. 75%, respectively; *P*=0.671) (Fig. 1).

Table 2. Characteristics and clinical features of essential thrombocythemia patients with and without pulmonary hypertension.

	With PH (N=19)	Without PH (N=102)	*P*
Age (yr), median (range)	65 (22–79)	66 (29–88)	0.536
Gender, male:female	6:13	56:46	0.062
IPSET, N (%)			0.071
Low	1 (5.3)	26 (25.5)	
Intermediate	9 (47.4)	27 (26.5)	
High	9 (47.4)	49 (48.0)	
Laboratory findings, mean±SD			
WBC (×10^9/L)	11.4±4.6	12.9±6.2	0.398
Monocyte (×10^9/L)	0.6±0.2	0.8±0.6	0.429
Hemoglobin (g/dL)	13.1±2.6	13.9±2.1	0.176
Platelet (×10^9/L)	1,152.2±572.0	968.8±377.6	0.107
LDH (×UNL)	1.4±0.4	1.2±0.5	0.094
Driver gene mutations, N (%)			0.080
JAK2V617F	9/14 (64.3)	67/84 (79.8)	
CALR mutation	4/14 (28.6)	6/84 (7.1)	
Comorbidity, N (%)			
Diabetes mellitus	3 (15.8)	14 (13.7)	0.812
Hypertension	12 (63.2)	41 (40.2)	0.064
Chronic kidney disease	4 (21.1)	20 (19.6)	0.885
Smoking	2 (10.5)	26 (25.5)	0.363
Thrombotic events[a)]	8 (42.1)	37 (36.3)	0.797
Follow-up duration (yr), median (range)	7.1 (1.1–18.1)	3.7 (0.1–21.4)	0.032

[a)]Overall thrombotic events (before, at the time of, and after diagnosis).
Abbreviations: CALR, calreticulin; IPSET, International Prognostic Score for Essential Thrombocythemia; LDH, lactate dehydrogenase; PH, pulmonary hypertension; UNL, upper normal limit.

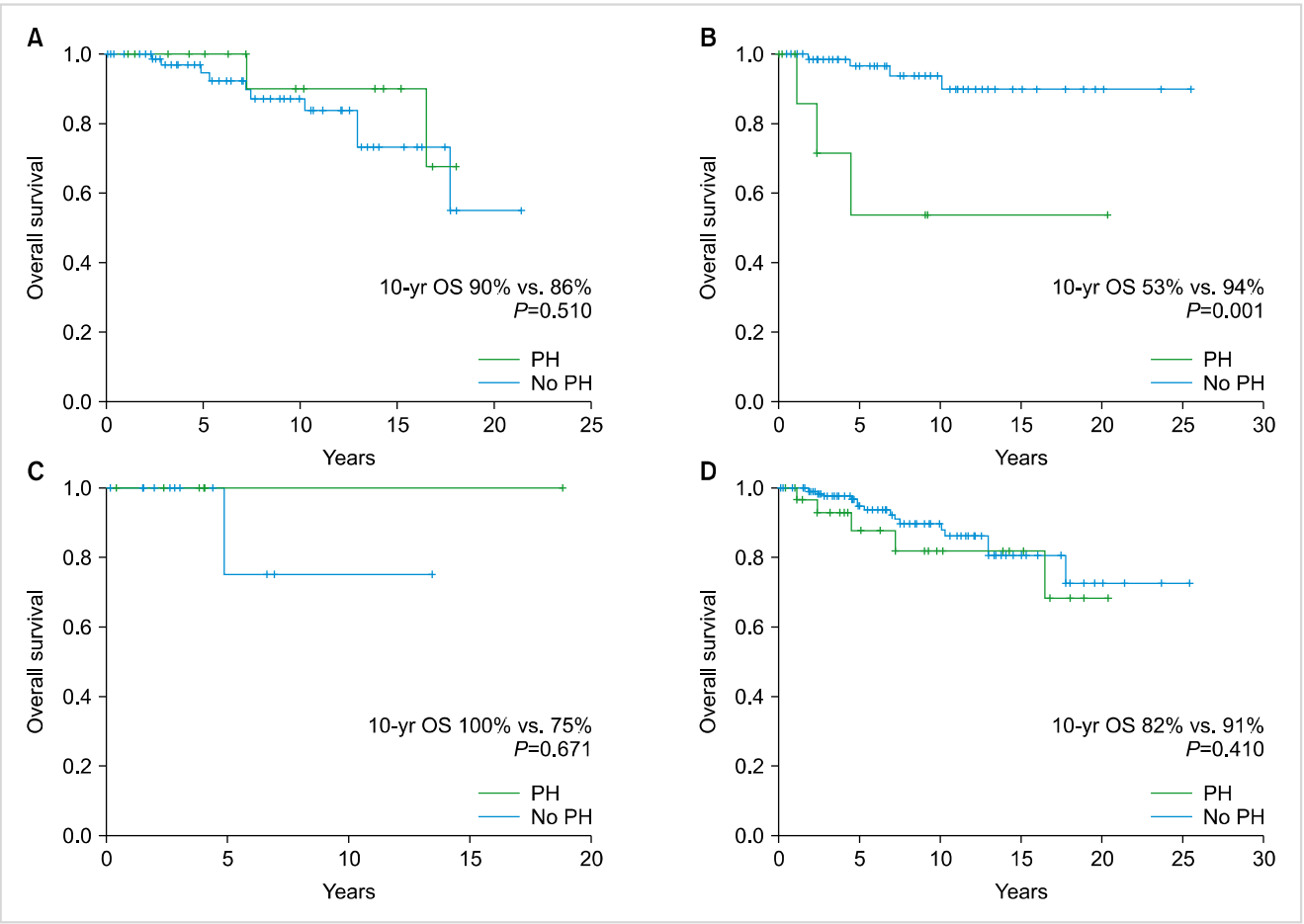

Fig. 1. Overall survival of patients with MPNs according to pulmonary hypertension. Essential thrombocythemia **(A)**. Polycythemia vera **(B)**. Primary myelofibrosis **(C)**. All MPN patients **(D)**.
Abbreviations: MPNs, myeloproliferative neoplasms; OS, overall survival; PH, pulmonary hypertension.

Table 3. Characteristics and clinical features of polycythemia vera patients with and without pulmonary hypertension.

	With PH (N=9)	Without PH (N=74)	*P*
Age (yr), median (range)	71 (42–85)	61.5 (26–91)	0.049
Gender, male:female	2:7	49:25	0.010
Laboratory findings, mean±SD			
WBC ($\times 10^9$/L)	17.2±7.5	14.5±7.4	0.330
Monocyte ($\times 10^9$/L)	0.9±0.3	0.7±0.4	0.200
Hemoglobin (g/dL)	15.9±2.6	18.4±2.6	0.010
Platelet ($\times 10^9$/L)	616.6±284.2	437.7±191.7	0.020
LDH (×UNL)	1.3±0.3	1.3±0.5	0.973
Driver gene mutations, N (%)			
JAK2V617F	8 (88.9)	59 (79.7)	0.396
JAK2 exon12 mutation	0 (0)	3 (4.1)	-
Comorbidity, N (%)			
Diabetes mellitus	2 (22.2)	20 (27.0)	0.556
Hypertension	6 (66.7)	44 (59.5)	0.486
Chronic kidney disease	4 (44.4)	24 (32.4)	0.355
Smoking	2 (22.2)	42 (43.2)	0.266
Thrombotic events[a]	2 (22.2)	22 (29.7)	0.723
Follow-up duration (yr), median (range)	2.5 (0.1–20.4)	6.3 (0.1–25.5)	0.298

[a]Overall thrombotic events (before, at the time of, and after diagnosis).
Abbreviations: LDH, lactate dehydrogenase; PH, pulmonary hypertension; UNL, upper normal limit.

PH detected at the time of MPN diagnosis

Eight patients (2 ET, 1 PV, and 5 PMF) had PH at the time of MPN diagnosis. The two ET patients were classified as "high risk" according to the revised International Prognostic Score for Essential Thrombocythemia-thrombosis, while two of the five PMF patients were classified as "high risk" according to the International Prognostic Scoring System. One PMF patient showed *CALR* mutation, and the remaining patients showed *JAK2V6217F* mutations. Two patients (1 ET and 1 PV) had experienced thrombotic events prior to MPN diagnosis. Five of the eight patients had comorbidities such as hypertension, diabetes mellitus, and/or chronic kidney disease. All patients are currently alive after a median follow-up duration of 2.4 years (range, 0.6–4.3 yr) (Table 6).

Table 4. Multivariate Cox regression analysis for overall survival in patients with polycythemia vera.

Variable	Hazard ratio (95% CI)	*P*
Old age	1.4 (1.1–1.8)	0.002
Gender, female	0.7 (0.1–9.9)	0.977
High LDH (>2 UNL)	11.3 (1.1–119.6)	0.045
Diabetes mellitus	1.8 (0.1–31.0)	0.906
Hypertension	0.5 (0.1–5.7)	0.784
Chronic kidney disease	1.1 (0.1–12.0)	0.976
Thrombotic events	1.8 (0.2–19.0)	0.794
Pulmonary hypertension	12.4 (1.8–86.6)	0.011

Abbreviations: LDH, lactate dehydrogenase; UNL, upper normal limit.

DISCUSSION

Here, we report the prevalence of PH in Korean patients with Ph⁻ MPNs. Overall, 15.1% Ph⁻ MPN patients had PH either at the time of diagnosis or during follow-up, which is clearly higher than the prevalence of PH in the general population [32, 33]. Notably, PH was most common in PMF patients.

It is intriguing that the prevalence of PH in Ph⁻ MPN patients shows variability among studies. All studies reported to date were retrospective in nature. In addition, majority of recent studies analyzed 20–50% candidates [23-26], and thus, may not have been representative of the entire patient population, leading to selection bias. In our study, 70% Ph⁻

Table 5. Characteristics and clinical features of primary myelofibrosis patients with and without pulmonary hypertension.

	With PH (N=6)	Without PH (N=15)	*P*
Age (yr), median (range)	77 (69–82)	68 (36–86)	0.067
Gender, male:female	3:3	9:6	1.000
Stage, N (%)			0.445
Prefibrotic/early	1 (16.7)	4 (33.3)	
Overt myelofibrosis	5 (83.3)	10 (66.6)	
IPSS, N (%)			0.398
Low	0 (0)	4 (26.7)	
Intermediate-1	3 (50.0)	8 (53.3)	
Intermediate-2	1 (16.7)	1 (6.7)	
High	2 (33.3)	2 (13.3)	
Laboratory findings, mean±SD			
WBC ($\times10^9$/L)	22.0±16.7	13.8±8.0	0.141
Monocyte ($\times10^9$/L)	1.3±0.5	0.8±0.4	0.031
Hemoglobin (g/dL)	10.8±1.2	11.6±3.5	0.590
Platelet ($\times10^9$/L)	965.0±615.0	586.3±437.8	0.126
LDH (×UNL)	2.6±1.6	2.4±1.6	0.755
Driver gene mutation, N (%)			
JAK2V617F	4/6 (66.7)	10/13 (76.9)	0.571
CALR mutation	2/6 (33.3)	3/13 (23.1)	0.811
Comorbidities, N (%)			
Diabetes mellitus	1 (16.7)	4 (26.7)	0.627
Hypertension	3 (50.0)	9 (60.0)	0.676
Chronic kidney disease	2 (33.3)	5 (33.3)	1.000
Smoking	1 (16.7)	2 (13.3)	0.844
Thrombotic events[a]	1 (16.7)	2 (13.3)	0.844
Follow-up duration (yr), median (range)	2.4 (0.4–4.1)	2.8 (0.2–7.0)	0.529

[a]Overall thrombotic events (before, at the time of, and after diagnosis).
Abbreviations: CALR, calreticulin; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; PH, pulmonary hypertension; UNL, upper normal limit.

Table 6. Characteristics and clinical features of MPN patients who had pulmonary hypertension at the time of diagnosis.

No.	Age (yr)/ gender	Diagnosis	Prognostication	Driver gene mutations	WBC ($\times10^9$/L)	Hb (g/dL)	Platelet ($\times10^9$/L)	LDH (×UNL)	Thrombotic events[a]	Comorbidities	TRV (m/sec)	RVSP (mmHg)	Late thrombotic events[b]	Follow-up duration (yr)	Alive/ dead
1	75/F	ET	R-IPSET-T high	*JAK2V617F*	16.5	11.1	2,299	1.2	None	None	3.0	41	No	4.3	Alive
2	79/F	ET	R-IPSET-T high	*JAK2V617F*	10.5	14.2	896	1.0	CI, IHD	HT, DL	3.7	60	No	1.2	Alive
3	80/F	PV	-	*JAK2V617F*	20.7	16.3	492	1.3	DVT	DM, HT	3.4	51	No	1.0	Alive
4	56/M	PMF	IPSS low	*JAK2V617F*	17.7	14.7	1,273	1.0	None	CKD	3.0	41	No	4.0	Alive
5	69/M	PMF	IPSS high	*JAK2V617F*	31.1	11.0	570	1.6	None	CKD	3.0	41	No	2.4	Alive
6	71/F	PMF	IPSS high	*JAK2V617F*	51.2	10.2	786	4.7	None	DM	4.1	72	No	4.1	Alive
7	79/M	PMF	IPSS intermediate -2	*CALR*	9.3	9.2	579	1.5	None	CKD	2.9	40	No	2.4	Alive
8	82/F	PMF	IPSS intermediate -1	*JAK2V617F*	19.7	12.2	2,178	1.6	None	None	3.1	43	No	0.6	Alive

[a]Thrombotic events prior to or at the time of diagnosis. [b]Thrombotic events after diagnosis.
Abbreviations: CALR, calreticulin; CI, cerebral infarction; CKD, chronic kidney disease; DL, dyslipidemia; DM, diabetes mellitus; DVT, deep vein thrombosis; ET, essential thrombocythemia; F, female; HT, hypertension; IHD, ischemic heart disease; IPSS, International Prognostic Scoring System; LDH, lactate dehydrogenase; M, male; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera; R-IPSET-T, revised International Prognostic Score for Essential Thrombocythemia-thrombosis; RVSP, right ventricle systolic pressure; TRV, tricuspid regurgitation velocity; UNL, upper normal limit.

MPN patients underwent TTE, and the characteristics and clinical features of these patients did not differ significantly from the whole patient population. Therefore, we believe that the patients enrolled in this study were representative of the whole MPN patient population. Nevertheless, some selection bias may have affected the prevalence as TTE was performed in selected patients before 2016 (thereafter, TTE was included in the baseline or follow-up studies for MPN patients). Most previous studies had analyzed the overall PH prevalence in MPN patients, instead of performing separate analyses by MPN subtype. Some studies even included patients with CML, which is different from Ph^- MPNs in terms of biology and clinical manifestations. Several studies had included more number of patients with certain MPN subtypes. Considering that PH prevalence in PMF was significantly higher than that in PV, both in this and a previous study [26], the subtype proportions of enrolled patients may affect the overall PH prevalence.

Several recent studies on PH prevalence in MPNs designed to overcome the limitations of previous studies including smaller cohorts have been reported. However, these studies also revealed a striking variability in PH prevalence. A Danish group observed 6 PH cases among 158 MPN patients [24]. However, all patients had conditions predisposing for PH, and 'true' MPN-related PH was not observed. Therefore, they concluded that screening for PH is not necessary in MPN patients. A French study reported 14 (7.7%) cases of primary PH among 183 MPN patients, including 28 with CML [23]. In contrast, two American studies reported high PH prevalence rates of >50% [25, 26]. Despite the retrospective nature, differences in diagnostic tools, and possible selection bias in these studies, such marked differences in PH prevalence among studies is difficult to understand. Therefore, regional or racial differences in PH prevalence can be speculated, which should be addressed in future well-designed international multicenter prospective studies.

Some overt causes of PH such as veno-occlusive disease, pulmonary thromboembolism, and extramedullary hematopoiesis in the lungs have been identified in some MPN patients [19, 21, 34]. However, the causative factors and mechanisms are not clear in most cases, although some experiments have suggested several underlying mechanisms. Similarly, characteristics and clinical features associated with the development of PH are not well defined. In our study, PH was predominant in female PV patients, and tended to be predominant in female ET patients, which is consistent with the female predominance of PAH reported previously [32]. Thrombotic events were not related to the development of PH in any MPN subtype, suggesting that thromboembolism may not be a major mechanism underlying PH. Only a small population of patients had PH at the time of diagnosis of ET and PV. In addition, hemoglobin levels were lower, and platelet counts were higher in PV patients with PH. Collectively, changes in biology with time or disease progression could be considered risk factors for PH. The monocyte count was higher in PMF patients with PH than that in those without PH; this is understandable because monocytes have been suggested to contribute to the vascular complications in MPNs [35, 36]. However, it remains unclear why monocytes are involved only in PMF-associated PH, and not in PH associated with ET or PV.

Our study had some limitations. First of all, PH was diag-

nosed by TTE. Considering that the standard diagnostic tool is right-heart catheterization, use of TTE alone may have led to an overestimation of PH. Additional limitations inevitable due to the retrospective nature of the study were that Ph- related symptoms and signs and changes in the severity and clinical implications of PH with time and treatment could not be examined. Further well-designed prospective studies are warranted to analyze these issues. Despite these limitations, it is clear that the overall survival in PV patients with PH is poorer than that in PV patients without PH. It also remains to be determined whether the effects of PH on survival are limited to patients with PV, or may affect ET and PMF patients as well. Eight patients (2 ET, 1 PV, and 5 PMF) had PH at the time of diagnosis. Four patients were not classified as "high risk" according to current prognostic scoring systems. Only two patients experienced thrombotic events, and two others had no comorbidities. These observations indicate that PH can exist in 'normal' MPN patients with an uncomplicated clinical course.

In conclusion, PH is common in patients with Ph- MPNs, and is associated with poor survival in PV. Therefore, vigilant screening for PH, not only at the time of diagnosis but also during follow-up, is warranted in patients with Ph- MPNs.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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