Characterization and prognostic implication of pulmonary hypertension among patients with myeloproliferative neoplasms

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Abstract

Pulmonary hypertension (PH) is a frequent complication of Philadelphia-negative myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). However, its prognostic significance is understudied. We, therefore, aimed to evaluate the effect of PH identified by echocardiography on the risk of progression to secondary MF or acute leukemia in MPN patients. We conducted a multicenter, retrospective cohort study of MPN patients with ≥1 echocardiogram from 2010-2023. PH was defined as pulmonary artery systolic pressure ≥40 mmHg. Outcomes were progression to secondary MF or leukemia, major adverse cardiovascular events (MACE) and all-cause mortality. Multivariable Fine-Gray competing-risk regression analysis was used to estimate subdistribution hazard ratios (SHR) of hematologic progression and MACE. Five hundred and fifty-five patients were included (42.7% with PV, 41.1% with ET, 16.2% with MF) or whom 195 (35.1%) had PH. Over a median follow-up period of 51.2 months, PH was associated with an increased risk of secondary MF progression (adjusted SHR [aSHR], 95% confidence interval [95% CI]: 1.25-4.59), leukemia progression (aSHR=3.06, 95% CI: 1.13-8.25), and MACE (aSHR=1.59, 95% CI: 1.01-2.49) but not all-cause death (adjusted hazard ratio=1.48, 95% CI: 0.96-2.26). In patients with PH, absence of left heart disease was associated with a higher risk of secondary MF progression among patients with ET or PV (aSHR=2.76, 95% CI: 1.19-6.38) and leukemia progression among patients with MF (aSHR=7.18, 95% CI: 1.59-32.46). Prospective studies are needed to assess the role of echocardiography in MPN-specific prognostication.

Introduction

Philadelphia-negative myeloproliferative neoplasms (MPN) are a group of chronic hematopoietic neoplasms that include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (MF) and are associated with cardiovascular disease, including pulmonary hypertension (PH).[1-3] PH is a recognized complication of MPN, though the prevalence varies widely in the literature (47% to 67%), depending on the diagnostic modality used (echocardiography *versus* right heart catheterization) and pressure cut-offs applied to define PH.[4,5] PH is characterized by elevated pulmonary artery pressures and is defined by a mean pulmonary artery pressure >20 mmHg but is a heterogenous entity that can be classified by etiology and hemodynamic characteristics.[6] The World Health Organization (WHO) classifies PH by etiology and MPN-associated PH is generally classified as group 5 (PH due to unclear and/or multifactorial mechanisms); however, patients with MPN are also at risk of PH from left heart disease (LHD; group 2) and from chronic thromboembolism (group 4). PH can also be classified by hemodynamic characteristics, including pre-capillary (PH due to increased resistance at the level of the pulmonary arterioles or pulmonary arteries), post-capillary (PH due to increased left heart pressures), or combined pre- and post-capillary PH.[6] Patients with MPN are at increased risk of both pre-capillary

and post-capillary PH given the high prevalence of other cardiovascular diseases in this population, including heart failure.[1,2,4,7] In a study of predominantly pre-capillary PH, the most common etiology of PH among patients with ET or PV was chronic thromboembolism (group 4).[7] However, patients with MF were more likely to have group 5 PH, suggesting a different pathophysiology of PH in patients with MF.[2] Additionally, a study of patients with MPN with underlying cardiovascular disease found an association between PH and increased risk of progression to secondary MF or acute leukemia.[4] However, both of these studies evaluated specific populations of patients (MPN patients with cardiovascular disease or known PH) and their findings may not, therefore, be generalizable to all MPN patients.

Echocardiography is a non-invasive and widely available tool that is used for the screening of PH as well as structural heart disease. We aimed to characterize risk factors associated with the development of PH in MPN patients and the impact of PH on clinical outcomes, in particular long-term hematologic and cardiovascular outcomes in patients who underwent at least one transthoracic echocardiogram (TTE) at two academic institutions.

Methods

Patients

This was a multicenter, retrospective cohort study of patients ≥18 years of age meeting WHO 2016 criteria for MPN (ET, PV or MF) who had undergone one or more TTE after their diagnosis of MPN at two academic hospitals.[8,9] Patients who underwent their first TTE from January 1, 2010 to January 1, 2023 were included. Patients who progressed to acute leukemia or underwent bone marrow transplantation prior to their first TTE or who had not undergone testing for driver mutational status were excluded (*Online Supplementary Figure S1*).

Data on up to two follow-up TTE performed ≥12 months apart after a diagnosis of MPN were analyzed. TTE data after progression to acute leukemia or bone marrow transplantation were excluded. Baseline characteristics at the diagnosis of MPN, prior to the first TTE and at the time of a subsequent TTE, including age, co-morbidities, MPN type, driver mutation, presence of non-phenotypic driver mutations, and spleen size (as measured by largest cranio-caudal dimension on cross-sectional imaging or ultrasound if performed within 3 months of TTE or MPN diagnosis) were captured.

Laboratory values were also captured at the time of MPN diagnosis and subsequent TTE. The H2FPEF score was calculated for every patient at the time of the index TTE. The H2FPEF score incorporates patients' factors including age, body mass index, history of atrial fibrillation, and echocardiographic parameters and was originally developed as a risk score for heart failure with preserved ejection fraction but has been shown to predict major adverse cardiovascular events (MACE) in patients with cardiovascular disease.[10-14] Cardiac output was estimated non-invasively using echocardiographic left ventricular outflow tract diameter, velocity time integral, and heart rate as per American Society of Echocardiography guidelines.[15] This study was approved by the New York University and Massachusetts General Hospital Institutional Review Boards (IRB numbers s22-00849 and 20-005, respectively). Given the retrospective nature of the study, informed consent was not required.

Outcomes

Outcomes were identified through chart review. The primary outcomes were progression to secondary MF and acute leukemia. Secondary outcomes included MACE, which is defined as a composite of arterial or venous thrombosis, heart failure hospitalization, or cardiovascular death (death due to thrombosis, heart failure, arrhythmias, or sudden cardiac death), all-cause mortality and individual components of MACE. Arterial thrombosis was defined as either myocardial infarction, ischemic stroke, or peripheral arterial thromboembolism.

Statistical analysis

In the primary analysis, patients with PH, defined as an estimated pulmonary artery systolic pressure (PASP) ≥40 mmHg calculated using tricuspid regurgitation maximum velocity and approximate right atrial pressure, as per American Society of Echocardiography guidelines, on their first TTE were compared with patients without PH.[16] Categorical variables were compared using a χ^2 or Fisher exact test, as appropriate. Continuous variables were compared using the Student *t* test or Wilcoxon rank-sum, as appropriate.

A Fine-Gray competing-risk regression analysis was performed to estimate the risk and hazard ratio (HR) or subdistribution hazard ratio (SHR) and 95% confidence interval (95% CI) of secondary MF progression, leukemia progression and MACE of patients with PH, with all-cause death and non-cardiovascular deaths as competing risks, respectively. To estimate the risk of all-cause death, Cox proportional hazards regression was utilized. Given the heterogeneity in prognosis and disease trajectory, the entire cohort of MPN patients together and stratification by MPN phenotype (ET or PV and MF) were analyzed. For analyses of the entire cohort and ET or PV subanalysis, the models for secondary MF and leukemia transformation were adjusted for variables associated with MPN progression, such as age, MPN type, driver mutation, presence of high molecular risk mutations (including *ASXL1, SRSF2, EZH2, LDH1/2,* and *U2AF1*), time from MPN to first TTE, white blood cell count at first TTE, and spleen size.[4,17,18] Given the smaller number of patients and events, the leukemia progression model for ET or PV patients was not adjusted. The models for MACE and all-cause death for the entire cohort and ET or PV patients were adjusted for variables included in hematologic progression models and variables associated with MACE in prior literature, such

as left ventricular ejection fraction, left atrial dilation, hypertension, prior heart failure, prior atrial fibrillation, prior atherosclerotic cardiovascular disease (including coronary artery disease, peripheral arterial disease, and prior ischemic stroke), indication and setting of first TTE, H2FPEF score, aspirin, anticoagulation, anti-hypertensives and statin use, white blood cell count at first TTE, hemoglobin concentration at first TTE, and creatinine level at first TTE.[1,19-24] Given the small number of patients with MF, all outcomes were adjusted for age and Mutation-Enhanced International Prognostic Scoring System (MIPSS70) score.[18]

A sensitivity analysis was performed in order to evaluate the association between PH and MPN disease progression (secondary MF or leukemia). Patients who underwent right heart catheterization within 6 months of their first TTE were analyzed and PH was defined as a mean pulmonary artery pressure >20 mmHg. Kaplan-Meier survival curves of MPN disease progression were constructed and curves were compared using the log-rank test.

Given that PH may be associated with LHD, we compared outcomes of patients with PH on any TTE after MPN diagnosis with or without LHD. LHD was defined as an H2FPEF score >5, left atrial enlargement, left ventricular ejection fraction <50%, or at least moderate aortic or mitral stenosis or regurgitation. A Fine-Gray competing-risk regression was performed to estimate the risk and SHR of secondary MF progression, leukemia progression and MACE of patients with PH as above. Models were adjusted for the same variables as the primary analysis with the exception that left ventricular ejection fraction, left atrial size and H2FPEF score were not included in the models given that they were used to define groups..

To identify patient and echocardiographic characteristics associated with MPN disease progression (either secondary MF or leukemia) among patients with PH, a backward stepwise Fine-Gray competing-risk regression was performed. Variables that were statistically significant (P<0.05) between patients with and without hematologic progression were added to the multivariable Fine-Gray competing-risk regression. Variables that remained statistically significant, as well as age, MPN type and MPN driver mutation, were kept in the final model. All tests were two-tailed, and a P value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 29.0 (IBM) and STATA version 15 (STATA).

Results

Incidence of pulmonary hypertension, baseline patients' characteristics and echocardiographic parameters at the time of the first echocardiograph

A total of 555 patients were included, of whom 195 (35.1%) had PH on their index TTE after the MPN diagnosis. Patients with PH were older at MPN diagnosis (median age 71 *vs.* 66 years, P<0.001) and had a longer time from MPN diagnosis to first TTE (median 50.5 *vs*. 33.7 months, P=0.003). The proportions of females and non-White subjects were similar in the different groups. At the time of the first TTE, patients with PH were less likely to have PV (36.9% *vs*. 45.8%) or ET (37.4% *vs*. 43.1%) and more likely to have MF (25.6% *vs*. 11.1%) compared with patients without PH. The proportion of driver mutations, including *JAK2* (82.6% *vs*. 76.7%, P=0.13) were similar in the two groups. Driver mutation variant allele frequency (median 50.1% *vs*. 40.7%, P=0.002) and spleen size (median 13.7 *vs*. 12.0 cm, P<0.001) were greater in patients with PH. Patients with PH had higher rates of cardiovascular co-morbidities and risk factors including prior hospitalizations for heart failure (15.4% *vs*. 3.3%, P<0.001) and atrial fibrillation (29.7% *vs*. 15.6%, P<0.001). The patients' characteristics are summarized in Table 1.

The indication for first TTE was more likely to be heart failure (24.6% *vs*. 5.0%, P<0.001) and less likely to be for screening (9.7% *vs*. 24.4%, P<0.001), and in the outpatient setting (63.1% *vs*. 81.1%, P<0.001) for patients with PH compared with those without PH. Patients with PH had a higher median white blood cell count (11.8 *vs*. 8.8x10^9/L, P<0.001), creatinine concentration (1.1 *vs*. 0.9 mg/dL, P<0.001), and B-natriuretic peptide level (511 *vs*. 142 pg/mL, P<0.001).

Compared to patients without PH, patients with PH were more likely to have a left ventricular ejection fraction <50% (10.3% *vs*. 3.9%, P=0.005). Furthermore, patients with PH were more likely to have markers of structural heart disease including moderate or greater left atrial dilation (37.9% *vs*. 11.1%, P<0.001) and right atrial dilation (23.1% *vs*. 1.7%, P<0.001), and left ventricular hypertrophy (25.1% *vs*. 16.7%, P=0.019). Patients with PH also had higher rates of valvular disease and higher H2FPEF scores (median 4 *vs*. 2, P<0.001). Echocardiographic parameters are summarized in *Online Supplementary Table S1*.

Hematologic and cardiovascular outcomes after the first echocardiograph in patients with or without pulmonary hypertension

Among the whole cohort and after a median follow-up time of 51.2 months, 55 (15.0%) patients had secondary MF progression, 25 (4.5%) had leukemia progression, 150 patients had MACE, and 198 (35.7%) had died of any cause. Secondary MF progression (14.4% *vs*. 7.5%, P=0.012), leukemia progression (8.7% *vs*. 2.2%, P=0.001), MACE (41.5% *vs*. 19.2%, P<0.001), and all-cause death (55.4% *vs*. 25.0%, P<0.001) occurred more frequently in patients with PH. After multivariable Fine-Gray competing-risk regression analysis, PH on first TTE was associated with increased risk of secondary MF progression (adjusted SHR=2.40, 95% CI: 1.25-4.59), leukemia progression (adjusted SHR=3.06, 95% CI: 1.13-8.25) and MACE (adjusted SHR=1.59, 95% CI: 1.01-2.49). PH was not associated with increased risk of

Table 1. Baseline characteristics of patients with or without pulmonary hypertension on first echocardiogram after the myeloproliferative neoplasm diagnosis.

Characteristics	All patients N=555	PASP <40 mmHg N=360	PASP ≥40 mmHg N=195	*P*
Demographics and clinical features				
Age at MPN diagnosis, years, median (IQR)	68 (59-77)	66 (56-74)	71 (64-80)	<0.001
Female sex, N (%)	286 (51.5)	188 (52.2)	98 (50.3)	0.72
Non-white race, N (%)	73 (13.2)	49 (13.6)	24 (12.3)	0.70
Time from MPN diagnosis to first TTE, months, median (IQR)	38.8 (12.8-85.3)	33.7 (9.8-78.2)	50.5 (19.2-99.8)	0.0025
Follow-up since first TTE, months, median (IQR)	51.2 (29.5-79.8)	54.3 (35.3-82.3)	38.5 (18.6-69.8)	<0.001
Spleen size, cm, median (IQR)	12.9 (10.3-15.5)	12.0 (9.9-14.8)	13.7 (11.4-17.2)	<0.001
MPN characteristics				
MPN type at first TTE, N (%)				
Polycythemia vera	237 (42.7)	165 (45.8)	72 (36.9)	<0.001
Essential thrombocythemia	228 (41.1)	155 (43.1)	73 (37.4)	
Myelofibrosis	90 (16.2)	40 (11.1)	50 (25.6)	
Driver mutation, N (%)				
JAK2	435 (78.4)	276 (76.7)	159 (81.5)	0.054
CALR	55 (9.9)	42 (11.7)	13 (6.7)	
MPL	16 (2.9)	7 (1.9)	9 (4.6)	
Triple-negative	49 (8.8)	35 (9.7)	14 (7.2)	
Driver mutation VAF, %, median (IQR)	45.1 (20.5-72.0)	40.7 (17.3-61.8)	50.1 (32.6-85.7)	0.002
Non-phenotypic driver mutations, N (%)				
Any	145 (26.1)	84 (23.3)	61 (31.3)	0.044
HMR[a]	54 (9.7)	31 (8.6)	23 (11.8)	0.23
DTA[b]	81 (14.6)	46 (12.8)	35 (18.0)	0.10
R*UNX1*	10 (1.8)	3 (0.8)	7 (3.6)	0.038
*TP*53	15 (2.7)	6 (1.7)	9 (4.6)	0.054
Other	65 (11.7)	39 (10.8)	26 (13.3)	0.41
Treatment for MPN, N (%)				
Any	416 (75.0)	265 (73.6)	151 (77.4)	0.36
Hydroxyurea	276 (49.7)	176 (48.9)	100 (51.3)	0.60
Ruxolitinib	43 (7.7)	24 (6.7)	19 (9.7)	0.24
Phlebotomy	111 (20.0)	77 (21.4)	34 (17.4)	0.32
Anagrelide	29 (5.2)	17 (4.7)	12 (6.2)	0.55
Co-morbidities, N (%)				
Prior heart failure	42 (7.6)	12 (3.3)	30 (15.4)	<0.001
Prior atherosclerotic cardiovascular disease[c]	217 (39.1)	131 (36.4)	86 (44.1)	0.084
Hypertension	340 (61.3)	204 (56.7)	136 (69.7)	0.003
Atrial fibrillation	114 (20.5)	56 (15.6)	58 (29.7)	<0.001
Chronic kidney disease	65 (11.7)	34 (9.4)	31 (15.9)	0.027
Prior venous thromboembolism	82 (14.8)	46 (12.8)	36 (18.5)	0.080
Diabetes	75 (13.5)	47 (13.1)	28 (14.4)	0.70
Current or former smoker	260 (46.8)	164 (45.6)	96 (49.2)	0.42
Obstructive sleep apnea	34 (6.1)	25 (6.9)	9 (4.6)	0.35
Chronic lung disease	60 (10.8)	34 (9.4)	26 (13.3)	0.20
Medications at time of TTE, N (%)				
Aspirin	385 (69.4)	255 (70.8)	130 (66.7)	0.33
P2Y12 inhibitor	48 (8.6)	41 (11.4)	7 (3.6)	0.001
Anticoagulant	136 (24.5)	68 (18.9)	68 (34.9)	<0.001
Statin	254 (45.8)	163 (45.3)	91 (46.7)	0.79
Antihypertensive	394 (71.0)	235 (65.3)	159 (81.5)	<0.001
Type of antihypertensive, N (% of pts on antihypertensives)				
ACE-I/ARB	188 (47.7)	118 (50.2)	70 (44.0)	0.23
Calcium-channel blockers	132 (33.5)	85 (36.2)	47 (29.6)	0.17
Thiazide diuretic	58 (14.7)	34 (14.5)	24 (15.1)	0.88
Metoprolol	138 (35.0)	75 (31.9)	63 (39.6)	0.12
Carvedilol	23 (5.8)	12 (5.1)	11 (6.9)	0.45
Other β-blocker	64 (16.2)	35 (14.9)	29 (18.2)	0.40
Laboratory values at TTE, median (IQR)				
White blood cell count, $x10^9$/L	9.5 (6.7-13.9)	8.8 (6.5-11.7)	11.8 (7.8-17.7)	<0.001
Hemoglobin, g/dL	12.9 (10.9-14.4)	13.4 (11.7-14.7)	12.0 (9.9-13.6)	<0.001
Platelet count, $x10^9$/L	428 (285-630)	430 (306-630)	421 (239- 614)	0.20
Creatinine, mg/dL	1.0 (0.8-1.2)	0.9 (0.8-1.1)	1.1 (0.9-1.4)	<0.001
Lactate dehydrogenase, U/L	327 (227-547)	304 (213-508)	371 (244-600)	0.003

Continued on following page.

[a]Presence of *ASXL1, SRSF2, EZH2, LDH1/2*, or *U2AF1Q157*.[b]Presence of *DNMT3A*, *TET2* or *ASXL1* mutations. [c]Prior coronary artery disease, peripheral vascular disease, or ischemic stroke. PASP: pulmonary artery systolic pressure; MPN: myeloproliferative neoplasm; IQR: interquartile range; TTE: transthoracic echocardiogram; VAF: variant allele fraction; HMR: high molecular risk; DTA: *DNMT3A*, *TET2* or *ASXL1* mutations; pts: patients; ACE-I: angiotensin-converting enzyme inhibitor; ARB: aldosterone receptor blocker.

all-cause death (adjusted HR=1.48, 95% CI: 0.96-2.26) (Table 2). Kaplan-Meier cumulative incidence curves of secondary MF progression, leukemia progression, MACE, and overall survival of patients with PH compared with those without PH are shown in Figure 1.

Among patients with either ET or PV (N=465), 55 (11.8%) had progression to secondary MF, 16 (3.4%) had progression to leukemia, 126 (27.1%) had MACE, and 151 died (32.5%). Secondary MF progression (19.3% *vs*. 8.4%, *P*=0.002), leukemic progression (7.6% *vs*. 1.6%, *P*=0.002), MACE (44.1% *vs*. 19.4%, *P*<0.001), and all-cause death (54.5% *vs*. 22.5%, *P*<0.001) occurred more frequently in patients with PH. PH was associated with increased risks of secondary MF progression (adjusted SHR=2.39, 95% CI: 1.25-4.60) and leukemia progression (unadjusted SHR=4.90, 95% CI: 1.69-14.20) but not MACE (adjusted SHR=1.42, 95% CI: 0.86-2.37) or all-cause mortality (adjusted HR=1.50, 95% CI: 0.89-2.52).

Among patients with MF (N=90), 14 (15.6%) had progression to leukemia. There was no difference in leukemic progression (18.0% *vs*. 12.5%, *P*=0.57), MACE (17.5% *vs*. 26.7%, *P*=0.096), and all-cause death (58.0% *vs*. 45.0%, *P*=0.29) between patients with or without PH. PH was not associated with leukemia progression (adjusted SHR=3.04,

Table 2. Outcomes of patients with or without pulmonary hypertension.

Outcomes, N (%)	**All patients**	**PASP <40 mmHg**	**PASP ≥40 mmHg**	***P***	**Hazard ratios (95% CI)**	
All MPN patients	**N=555**	**N=360**	**N=195**		**Unadjusted SHR or HR (95% CI)**	**Adjusted SHR or HR (95% CI)[b]**
Secondary MF progression	55 (15.0)	27 (7.5)	28 (14.4)	0.012	2.10 (1.24-3.56)	2.40 (1.25-4.59)
Leukemic progression	25 (4.5)	8 (2.2)	17 (8.7)	0.001	4.34 (1.88-10.02)	3.06 (1.13-8.25)
MACE[a]	150 (27.0)	69 (19.2)	81 (41.5)	<0.001	2.66 (1.93-3.67)	1.59 (1.01-2.49)
All-cause death	198 (35.7)	90 (25.0)	108 (55.4)	<0.001	3.03 (2.29-4.02)	1.48 (0.96-2.26)
ET or PV patients	**N=465**	**N=320**	**N=145**	***P***	**Unadjusted SHR or HR (95% CI)**	**Adjusted SHR or HR (95% CI)[c]**
Secondary MF progression	55 (11.8)	27 (8.4)	28 (19.3)	0.002	2.34 (1.37-3.98)	2.39 (1.25-4.60)
Leukemic progression	16 (3.4)	5 (1.6)	11 (7.6)	0.002	4.90 (1.69-14.20)	-
MACE[a]	126 (27.1)	62 (19.4)	64 (44.1)	<0.001	2.72 (1.92-3.86)	1.42 (0.86-2.37)
All-cause death	151 (32.5)	72 (22.5)	79 (54.5)	<0.001	3.01 (2.18-4.15)	1.50 (0.89-2.52)
MF patients	**N=90**	**N=40**	**N=50**	***P***	**Unadjusted SHR or HR (95% CI)**	**Adjusted SHR or HR (95% CI)[d]**
Leukemic progression	14 (15.6)	5 (12.5)	9 (18.0)	0.57	1.75 (0.44-7.01)	3.04 (0.88-10.54)
MACE[a]	24 (26.7)	7 (17.5)	17 (34.0)	0.096	2.64 (1.06-6.57)	2.18 (0.83-5.68)
All-cause death	47 (52.2)	18 (45.0)	29 (58.0)	0.29	2.01 (1.10-3.68)	1.60 (0.84-3.03)

[a]Composite of cardiovascular death, myocardial infarction, stroke, peripheral arterial thrombosis, venous thromboembolism, or hospitalization for heart failure. [b]Secondary MF and leukemia progression adjusted for age, MPN type, driver mutation, HMR mutation, time from MPN to first TTE, white blood cell count at first TTE, spleen size; MACE and all-cause death adjusted for the same variables as hematologic progression in addition to DTA mutations, MPN treatment, left ventricular ejection fraction, left atrial dilation, hypertension, prior heart failure hospitalization, prior atrial fibrillation, prior atherosclerotic cardiovascular disease, heart failure or dyspnea indication of TTE, setting of first TTE, H2FPEF score, aspirin use, anticoagulation, anti-hypertensive use, statin use, and creatinine. [c]Secondary MF adjusted for age, MPN type, driver mutation, HMR mutation, time from MPN to first TTE, white blood cell count at first TTE, and spleen size. [d]All outcomes adjusted for age and Mutation-enhanced International Prognostic Scoring System score. PASP: pulmonary artery systolic pressure; SHR: subdistribution hazard ratio; HR: hazard ratio; 95% CI: 95% confidence interval; MF: myelofibrosis; MACE: major adverse cardiovascular events; ET: essential thrombocythemia; PV: polycythemia vera; MPN: myeloproliferative neoplasm; HMR: high molecular risk; TTE: transthoracic echocardiography; DTA: *DNMT3A, TET2* or *ASXL1* mutations; H2FPEF: Heart Failure with Preserved Ejection Fraction.

95% CI: 0.88-10.54), MACE (adjusted SHR=2.18, 95% CI: 0.83-5.68), or all-cause death (adjusted HR=1.60, 95% CI: 0.84-3.03) (Table 2). Kaplan-Meier cumulative incidence curves of secondary MF and acute leukemia progression in patients by MPN type are shown in Figure 2.

Sensitivity analyses: impact of pulmonary hypertension on right heart catheterization and disease progression

A total of 49 (8.8%) of patients underwent right heart catheterization within 6 months of their first TTE, of whom 41 (83.7%) had PH (mean pulmonary artery pressure >20 mmHg). Among patients with PH, isolated pre-capillary (18; 43.9%) and combined pre- and post-capillary (13; 31.7%) PH were the most common hemodynamic types of PH. Patients with PH had a similar burden of co-morbidities as patients without PH (*Online Supplementary Table S2*). More patients with PH had MPN disease progression compared with those without PH (29.3% *vs*. 0, log-rank *P*=0.050). Kaplan-Meier curves of progression-free survival are shown in *Online Supplementary Figure S2*.

Characteristics and outcomes of patients with pulmonary hypertension with or without left heart disease

A total of 266 patients had PH (PASP ≥40 mmHg) on at least one TTE after the diagnosis of MPN, of whom 172 (64.7%) had LHD at the time of the PH diagnosis. Patients with LHD were older at PH diagnosis (median age 81 *vs.* 77 years, *P*<0.001), more likely to have atrial fibrillation

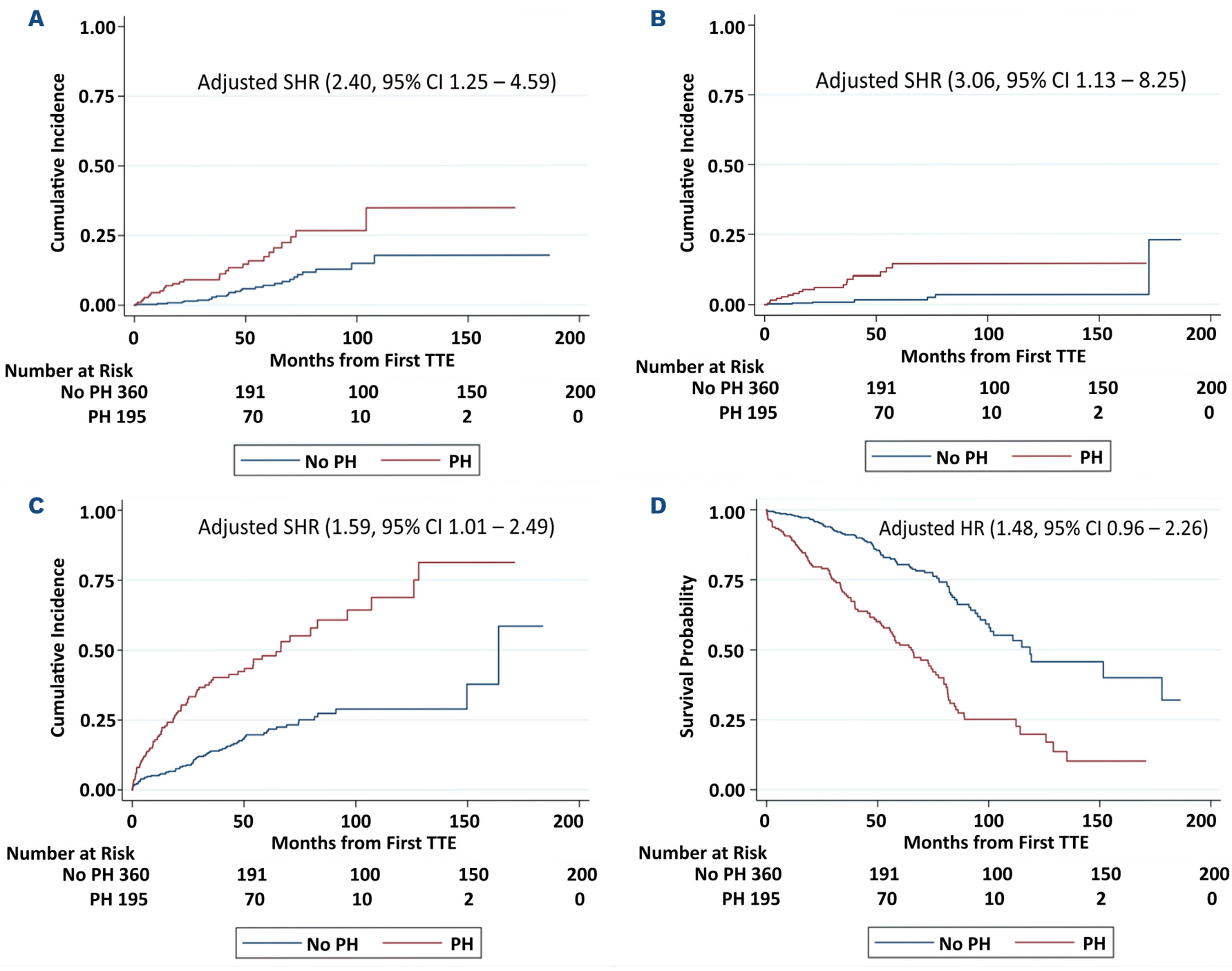

Figure 1. Outcomes of patients with or without pulmonary hypertension at first echocardiogram after the diagnosis of a myeloproliferative neoplasm. (A-D) Kaplan-Meier estimates of secondary myelofibrosis progression (A), acute leukemia progression (B), major adverse cardiovascular events (C) and overall survival (D) of patients with pulmonary hypertension (pulmonary artery systolic pressure ≥40 mmHg) compared with those without on the first transthoracic echocardiogram after being diagnosed with a myeloproliferative neoplasm. SHR: subdistribution hazard ratio; 95% CI: 95% confidence interval; TTE: transthoracic echocardiogram; PH: pulmonary hypertension; HR: hazard ratio.

(40.7% *vs*. 4.3%, *P*<0.001), chronic kidney disease (20.3% *vs*. 8.5%, *P*=0.014), and have higher B-natriuretic peptide levels (median 584 *vs*. 158, *P*<0.001) (*Online Supplementary Table S3*). Patients with LHD also had higher median PASP (51 *vs*. 46 mmHg, *P*<0.001).

Among the entire cohort, patients without LHD had higher rates of secondary MF progression (21.3% *vs*. 10.5%, *P*=0.027) but lower rates of MACE (41.5% *vs*. 57.6%, *P*=0.015) and no difference in leukemia progression (9.6% *vs*. 5.2%, *P*=0.20) a all-cause death (56.4% *vs*. 55.3%, *P*=0.90) compared with patients with LHD. After Fine-Gray competing-risk regression, absence of LHD on TTE at time of PH diagnosis was associated with a higher risk of secondary MF progression (adjusted SHR=3.29, 95% CI: 1.45-7.25) but lower MACE (adjusted SHR=0.56, 95% CI: 0.34-0.95). There was no association between absence of LHD and leukemia progression (adjusted SHR=2.32, 95% CI: 0.91-5.90) or all-cause mortality (adjusted HR=1.02, 95% CI: 0.63-1.64).

Among patients with ET or PV (N=204), absence of LHD was associated with a higher risk of secondary MF progression (adjusted SHR=2.76, 95% CI: 1.19-6.38) but not leukemia progression (adjusted SHR=1.09, 95% CI: 0.31-3.84), MACE (adjusted SHR=0.70, 95% CI: 0.40-1.24) or all-cause mortality (adjusted HR=1.09, 95% CI: 0.60-1.98) compared to the risks in those with LHD. Among patients with MF (N=62), absence of LHD was associated with a higher risk of progression to acute leukemia (adjusted HR=5.56, 95% CI: 1.41-21.94) but not MACE (adjusted SHR=0.51, 95% CI: 0.17-1.56) or all-cause mortality (adjusted HR=1.25, 95% CI: 0.59-2.66) compared with the risks in patients with LHD (Table 3). Kaplan-Meier cumulative incidence curves of hematologic progression among patients with *versus* without LHD are depicted in Figure 3.

Clinical and echocardiographic predictors of myeloproliferative neoplasm disease progression among patients with pulmonary hypertension

Among our cohort, 266 patients had PH at any time of whom 59 (22.2%) developed MPN disease progression

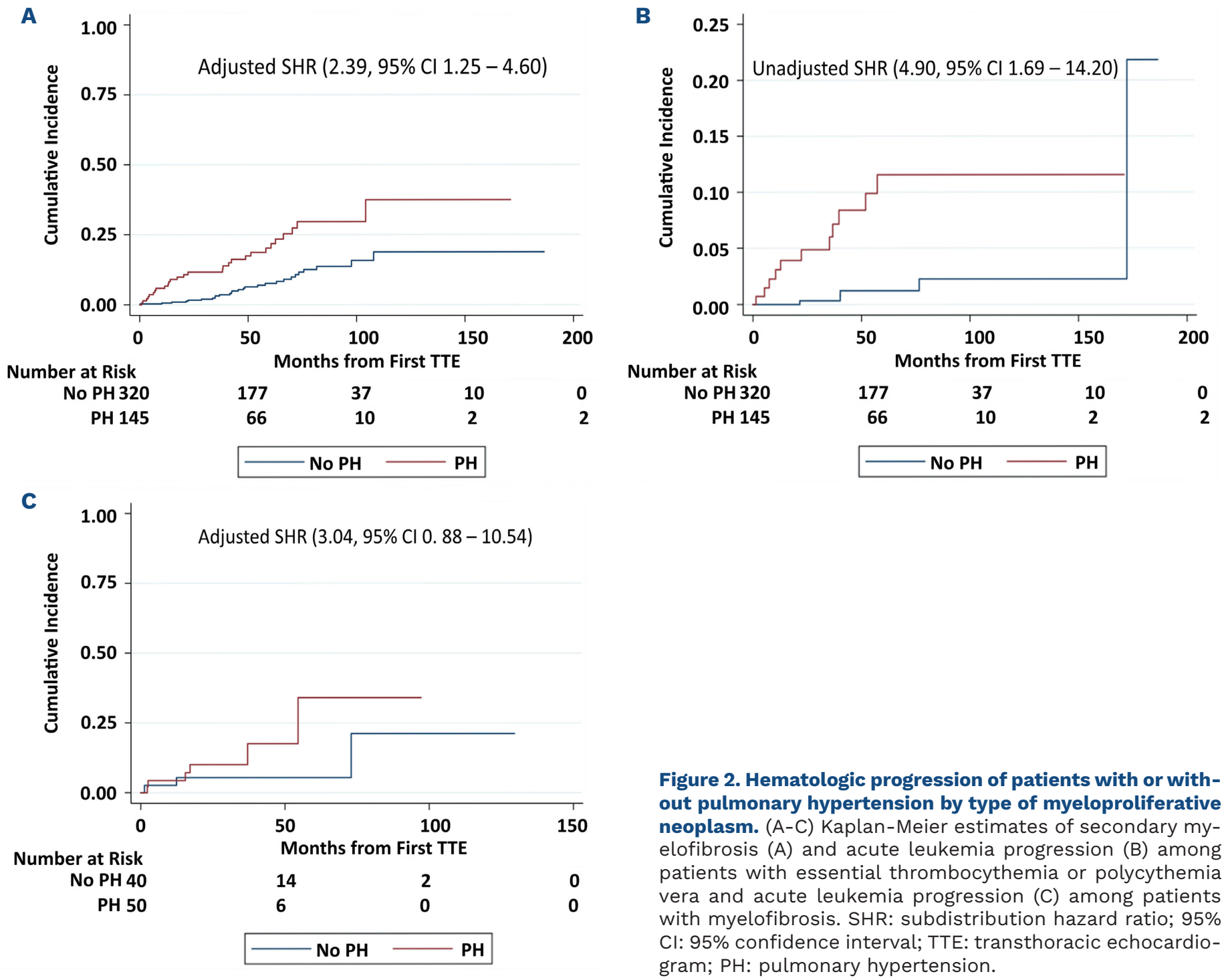

Figure 2. Hematologic progression of patients with or without pulmonary hypertension by type of myeloproliferative neoplasm. (A-C) Kaplan-Meier estimates of secondary myelofibrosis (A) and acute leukemia progression (B) among patients with essential thrombocythemia or polycythemia vera and acute leukemia progression (C) among patients with myelofibrosis. SHR: subdistribution hazard ratio; 95% CI: 95% confidence interval; TTE: transthoracic echocardiogram; PH: pulmonary hypertension.

after a median follow-up of 33.2 months (interquartile range, 13.8-62.7). The median time to disease progression from PH diagnosis was 14.9 months (interquartile range, 5.0-39.6) (*Online Supplementary Table S4*).

After backward stepwise competing-risk regression, spleen size ≥16.5 cm (adjusted SHR=2.40, 95% CI: 1.18-4.87), estimated cardiac output >7 L/min (adjusted SHR=2.40, 95% CI: 1.03-5.57), and hemoglobin <9 mg/dL (adjusted SHR=2.55, 95% CI: 1.29-5.03), and driver mutation variant allele frequency >50% (adjusted SHR=2.91, 95% CI:1.07-7.93) were associated with higher risk of disease progression (Figure 4).

Discussion

MPN are associated with PH, although the etiology and prognostic implications have not been characterized. Our study suggests that PH on echocardiography is associated with secondary MF progression, leukemia progression, and MACE. In a small subset of patients who underwent right heart catheterization, no patients without PH had MPN progression while 29.3% of those with PH did. Among patients with PH, the absence of LHD on echocardiography was associated with an increased risk of secondary MF progression among patients with ET or PV and leukemia progression among patients with MF. Patients with LHD had higher rates of MACE. Among patients with PH, anemia, elevated cardiac output, the presence of any non-phenotypic mutation, and driver mutation variant allele frequency >50% were associated with MPN disease progression to either leukemia or secondary MF.

In our study, PH on echocardiography was associated with

Table 3. Outcomes of patients with pulmonary hypertension with or without left heart disease at the time of pulmonary hypertension diagnosis.

Outcomes, N (%)	**All patients**	**No LHD**	**LHD**	***P***	**Hazard ratios (95% CI)**	
All MPN patients	**N=266**	**N=94**	**N=172**		**Unadjusted SHR or HR (95% CI)**	**Adjusted SHR or HR (95% CI)[b]**
MF progression	38 (14.3)	20 (21.3)	18 (10.5)	0.027	2.14 (1.13-4.07)	3.29 (1.45-7.45)
Leukemic progression	18 (9)	9 (9.6)	9 (5.2)	0.20	1.71 (0.69-4.28)	2.32 (0.91-5.90)
MACE[a]	138 (51.9)	39 (41.5)	99 (57.6)	0.015	0.56 (0.39-0.80)	0.56 (0.34-0.95)
All-cause death	149 (56.0)	52 (55.3)	97 (56.4)	0.90	0.76 (0.54-1.06)	1.02 (0.63-1.64)
ET or PV patients	**N=204**	**N=75**	**N=129**	***P***	**Unadjusted SHR or HR (95% CI)**	**Adjusted SHR or HR (95% CI)[c]**
MF progression	36 (17.6)	19 (25.4)	17 (13.2)	0.036	2.07 (1.09-3.95)	2.76 (1.19-6.38)
Leukemic progression	12 (5.9)	4 (5.3)	8 (6.2)	1.00	0.80 (0.25-2.63)	-
MACE[a]	110 (53.9)	33 (44.0)	77 (59.7)	0.041	0.57 (0.38-0.84)	0.70 (0.40-1.24)
All-cause death	111 (54.4)	40 (53.3)	71 (55.0)	0.88	0.74 (0.50-1.09)	1.09 (0.60-1.98)
MF patients	**N=62**	**N=19**	**N=43**	***P***	**Unadjusted SHR or HR (95% CI)**	**Adjusted SHR or HR (95% CI)[d]**
Leukemic progression	13 (21.0)	9 (47.4)	4 (9.3)	0.002	5.86 (1.83-18.78)	5.56 (1.41-21.94)
MACE[a]	28 (45.2)	6 (31.6)	22 (51.2)	0.18	0.48 (0.20-1.16)	0.51 (0.17-1.56)
All-cause death	38 (61.3)	12 (63.2)	26 (60.5)	1.00	0.92 (0.46-1.83)	1.25 (0.59-2.66)

[a]Composite of cardiovascular death, myocardial infarction, stroke, peripheral arterial thrombosis, venous thromboembolism, or hospitalization for heart failure. [b]Secondary MF adjusted for age, MPN type, driver mutation, HMR mutation, time from MPN to first TTE, white blood cell count at first TTE, spleen size; leukemia progression adjusted for DIPSS score, HMR mutation, and time from MPN to first TTE; MACE and all-cause death adjusted for the same variables as secondary MF progression in addition to DTA mutations, MPN treatment, hypertension, prior hospitalization for heart failure, prior atrial fibrillation, prior atherosclerotic cardiovascular disease, heart failure or dyspnea as the indication for TTE, setting of first TTE, aspirin use, anticoagulation, anti-hypertensive use, statin use, and creatinine. [c]Secondary MF adjusted for age, MPN type, driver mutation, HMR mutation, time from MPN to first TTE, white blood cell count at first TTE, spleen size; MACE and all-cause death adjusted for the same variables as the entire cohort. [d]All outcomes adjusted for age and MIPSS70 score. LHD: left heart disease; SHR: subdistribution hazard ratio; HR: hazard ratio; 95% CI: 95% confidence interval; MF: myelofibrosis; MACE: major adverse cardiovascular events; ET: essential thrombocythemia; PV: polycythemia vera; MPN: myeloproliferative neoplasm; HMR: high molecular risk; TTE: transthoracic echocardiography; DIPSS: Dynamic International Prognostic Scoring System; DTA: *DNMT3A, TET2* or *ASXL1* mutations; MIPSS70: Mutation-enhanced International Prognostic Scoring System.

increased risk of MPN disease progression. This association was primarily seen in PV or ET patients but not in those with MF, which may be due to the small number of MF patients. Prior studies have also suggested worse outcomes among patients with MPN and PH.[4,5,25] In one study of 301 patients with MPN, PH (PASP ≥35 mmHg) was associated with decreased overall survival, especially in patients with PASP ≥50 mmHg.[5] In a prior study of 197 patients with MPN and established cardiovascular disease, PH was associated with increased risk of all-cause death, cardiovascular death, as well as MPN disease progression.[4] Our current study included patients with or without prior cardiovascular disease and showed similar results, though confounding due to indication for TTE may still exist. Among patients with PH, more had TTE performed for heart failure or shortness of breath. Prospective studies are needed in order to systemically screen patients for PH to elucidate the role of preemptive TTE screening in MPN, although our study suggests that performing TTE for cardiovascular symptoms is a reasonable approach. Our study also sheds light on the mechanisms behind PH and possible characteristics unique to patients with MPN and PH that are associated with hematologic progression. Additionally, our data suggest that markers of more advanced MPN disease, including MF phenotype, driver mutation variant allele frequency, and presence of non-phenotypic driver mutations, were more prevalent among patients with PH in our cohort. LHD on TTE, and hence higher likelihood of having post-capillary PH, was common among patients with PH. However, our study suggests that patients with PH and without LHD are at increased risk of hematologic progression. This indicates that PH due to pre-capillary etiologies may be associated with disease progression in MPN. Pre-clinical and animal studies demonstrated increased circulating bone marrow-derived endothelial progenitor cells in both MPN (particularly MF) and patients with precapillary PH without MPN.[26-31] Additionally, bone marrow from patients with idiopathic PH has been shown to have myeloproliferative changes and reticulin fibrosis in the absence of MPN and mice transplanted with PH patient-derived endothelial progenitor cells have recapitulated a PH phenotype.[27,28,31]

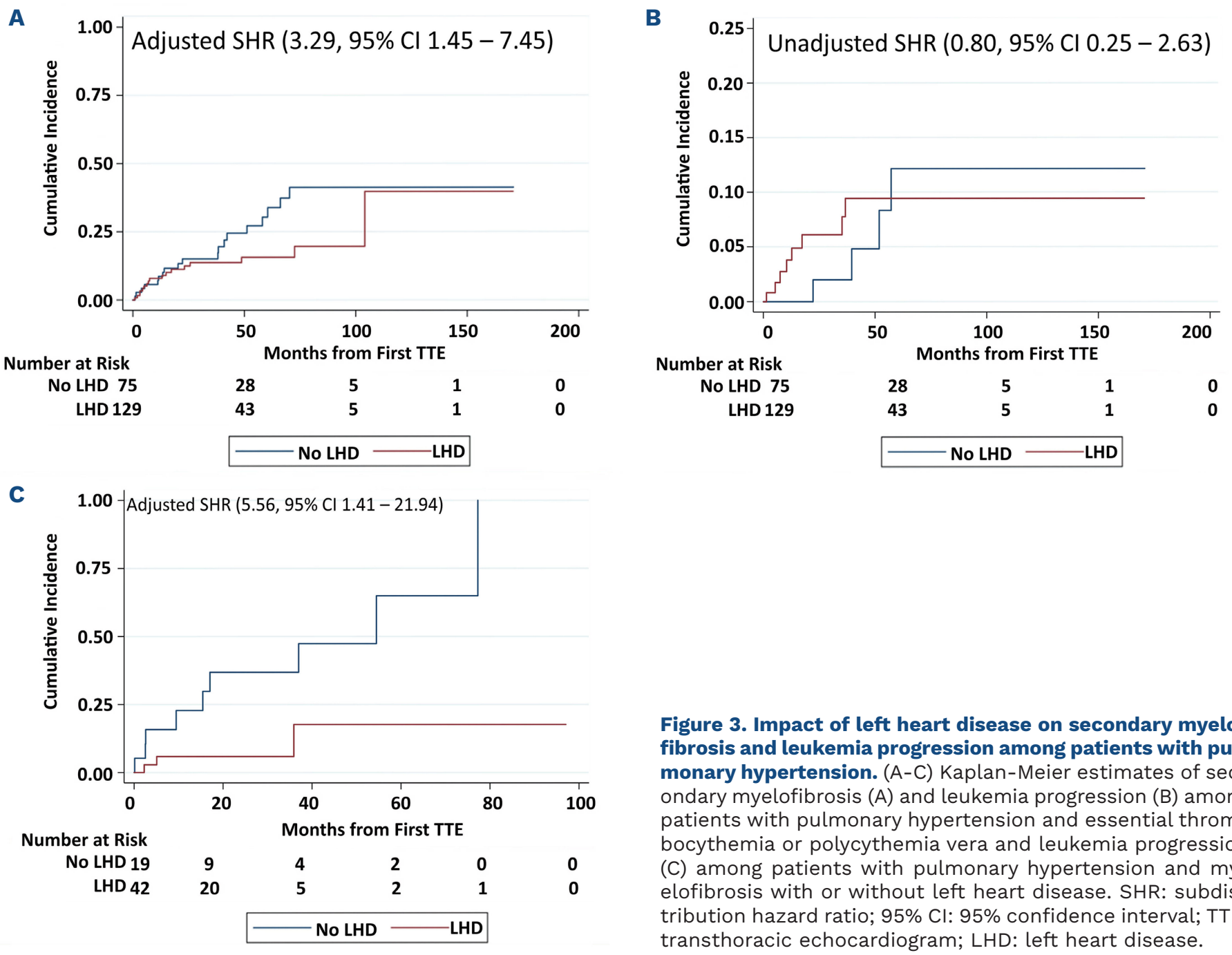

Figure 3. Impact of left heart disease on secondary myelofibrosis and leukemia progression among patients with pulmonary hypertension. (A-C) Kaplan-Meier estimates of secondary myelofibrosis (A) and leukemia progression (B) among patients with pulmonary hypertension and essential thrombocythemia or polycythemia vera and leukemia progression (C) among patients with pulmonary hypertension and myelofibrosis with or without left heart disease. SHR: subdistribution hazard ratio; 95% CI: 95% confidence interval; TTE: transthoracic echocardiogram; LHD: left heart disease.

Extramedullary hematopoiesis is another possible connection with PH and MPN and may explain the association between PH and disease progression.[32-38] Elevated estimated cardiac output was associated with increased risk of MPN disease progression among patients with PH independently of other MPN-specific risk factors, suggesting that high cardiac output is another contributor to the PH seen in patients with hematologic progression. This finding is concordant with studies demonstrating that MPN are associated with high-output heart failure, perhaps due to an increased metabolic demand of extramedullary hematopoiesis or inflammatory milieu and is additional evidence of an association between MPN disease progression and PH.[39,40] Our study suggests that PH may be a marker of advanced MPN disease, although further studies are needed to explore this. Another plausible explanation of increased risk of hematologic progression among patients without LHD is a competing risk of cardiovascular-related death in those with LHD. However, we utilized a competing-risk regression to account for this. Further studies are needed to confirm our findings. While our study has identified an association between PH and MPN progression, it still remains unclear whether management of PH improves MPN outcomes. PH is a diagnosis that requires right heart catheterization and only a small portion of our cohort underwent this procedure. Among the patients who were studied with right heart catheterization, most had isolated pre-capillary and combined pre- and post-capillary. PH-specific therapies were not utilized in our cohort and the data are sparse in the literature. However, a potential pre-capillary PH medication that may be of benefit in MPN is sotatercept. Sotatercept is a novel anti-proliferative therapy for pulmonary arterial hypertension which has been studied in MF.[41,42] Post-capillary PH is managed by treating the underlying LHD and cardiovascular risk factors. Prior literature suggests that among patients with PV and hypertension, treatment with angiotensin-converting enzyme inhibitors was associated with a lower need for cytoreductive chemotherapy.[43] Sodium-glucose co-transporter-2 inhibitors have become an important component of management of heart failure. Their use in MPN may be limited by worsening erythrocytosis in patients with ET or PV, although this may be beneficial in patients with MF.[44] More studies are needed to evaluate the hemodynamic phenotypes of PH using right heart catheterization, as well as the impact of pre- and post-capillary PH therapy on MPN outcomes. However, our study suggests that among patients with MPN at high risk of both cardiovascular disease and hematologic disease progression, TTE may be a useful tool for risk stratification and may identify patients who could benefit from further evaluation with right heart catheterization.

Our study has several limitations to consider. One limitation is the retrospective nature of the study, which lends to potential bias. Given that this was not a prospective study and included patients who underwent echocardiography for a variety of reasons, the study was likely enriched with patients with a higher pre-test probability of cardiovascular disease and this introduces selection bias. Additionally, echocardiography parameters were not adjudicated by a core laboratory and therefore variation in techniques between centers may be present. Right heart catheterization data were not available for the majority of patients in our cohort and therefore further investigation using the gold standard for diagnosing and categorizing PH is needed. Additionally, given that patients were not prospectively screened for MPN disease progression, it is possible that patients categorized as having ET or PV may have already progressed to MF prior to TTE but were undiagnosed at the time. Our study was retrospective in nature at two centers, therefore outcomes that occurred at other centers and those of patients lost to follow-up could not be captured, which is another limitation of our study.

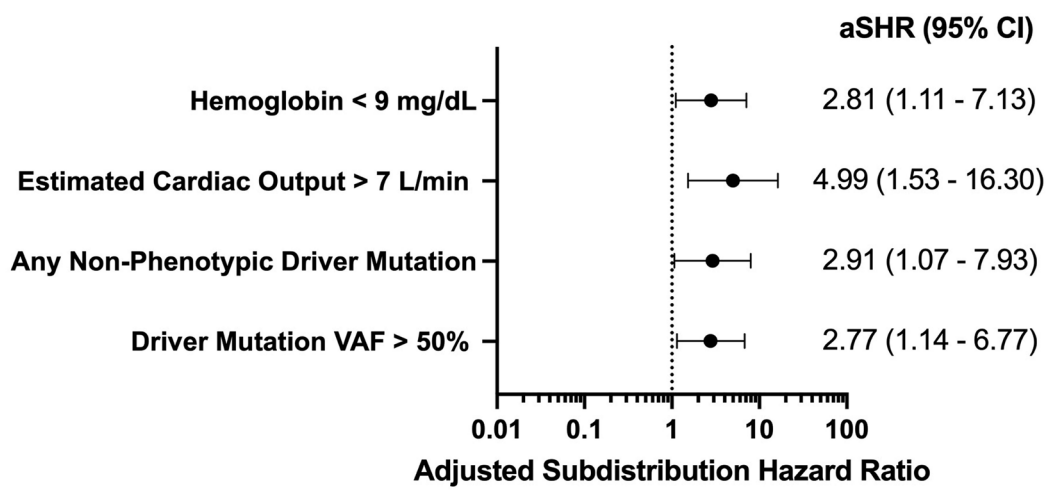

Figure 4. Risk factors for myeloproliferative neoplasm disease progression among patients with pulmonary hypertension. Forest plot of echocardiographic predictors of myeloproliferative neoplasm (MPN) disease progression among patients with pulmonary hypertension after backward stepwise regression. Risk factors also adjusted for age, type of MPN at time of diagnosis of pulmonary hypertension and MPN driver mutation. VAF: variant allele fraction; aSHR: adjusted subdistribution hazard ratio; 95% CI: 95% confidence interval.

In conclusion, our study suggests that PH on echocardiography is associated with an increased risk of hematologic progression, adverse cardiovascular events, and all-cause mortality among patients with MPN. Our study also suggests that PH is multifactorial and heterogenous in MPN, and LHD and diastolic dysfunction account for a significant portion of PH in MPN. Among patients with PH, the absence of LHD was associated with increased risk of hematologic progression. Additionally, among patients with PH, anemia, higher MPN driver mutation variant allele frequency, and high cardiac output were associated with hematologic progression. Prospective studies investigating the role of screening MPN patients for PH with echocardiography are needed to confirm our findings and further elucidate the interplay between PH and MPN disease progression.

Disclosures

NS reports consulting fees from Abbott and research funding from Abiomed and BioCardia. BS reports consultancy for Terumo Medical and advisory board membership for Philips Volcano. GH reports consulting fees from Pharmaxis and advisory board membership for Pfizer, BMS, GSK, Protagonist, Novartis, Morphosys and Cogen. The other authors have no conflicts of interest to disclose.

Contributions

OLe, SB, HR, NRS, BS, MHL, JH and GH contributed to the conception and design of the study. OLe, SS and OLi contributed to collecting data. OLe and OLi performed statistical analyses. OLe, JH, and GH drafted the manuscript. All authors contributed to the critical review of the manuscript and approved the final manuscript.

Data-sharing statement

Data can be shared upon reasonable request made to the authors for correspondence.

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