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In-Hospital and readmission outcomes of patients with myeloproliferative neoplasms and heart failure: Insights from the National Readmissions Database

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ABSTRACT

Background: Myeloproliferative neoplasms (MPNs) are chronic leukemias associated with increased risk of cardiovascular (CV) events. Prior studies suggest patients with MPN are at increased risk of HF. Additionally, preclinical murine models harboring the *JAK2* mutation, the most common driver mutation in MPNs, have shown accelerated adverse cardiac remodeling in myocardial infarction and pressure overload HF models. However, clinical outcomes, including in-hospital and readmission outcomes, of patients with MPN admitted for HF have not been well characterized.

Methods: Patients hospitalized for HF with and without MPN were identified using the 2017 and 2018 National Readmission Database. Propensity score matching (PSM) was performed to match 1 MPN with 10 non-MPN controls. Outcomes were in-hospital death, 90-day CV-related, HF-related, and all-cause readmissions. Logistic regression and Cox proportional hazards regression models were used to estimate risk of in-hospital death and 90-day readmission outcomes, respectively.

Results: After PSM, 4,626 patients with MPN were matched with 46,260 without. Patients with MPN were associated with increased risk of in-hospital death (OR 1.17, 95% CI 1.00 – 1.35), 90-day CV-related (HR 1.10, 95% CI 1.02 – 1.18) and all-cause (HR 1.24, 95% CI 1.17 – 1.31) but not HF-related (HR 1.05, 95% CI 0.97 – 1.14) readmissions.

Conclusion: Among patients hospitalized for HF, MPN was associated with increased risk of in-hospital death, and 90-day CV-related readmissions (driven primarily by thrombotic readmissions). Further investigation is needed in order to improve outcomes in patients with MPN and HF.

1. Introduction

Myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF), are a group of disorders of clonal hematopoiesis that have been associated with increased risk of cardiovascular (CV) disease including heart failure (HF) [1]. The most common driver mutations in MPNs are in the *JAK2*, *CALR*, *MPL* genes and lead to constitutive activation of the pro-inflammatory JAK/STAT signaling pathway. Experimental data suggest that mutations in the *JAK2* gene are associated with accelerated adverse cardiac remodeling and enhanced inflammatory response in mouse models of myocardial infarction and pressure overload-induced cardiomyopathy [2,3]. In a study of Medicare and Medicaid recipients, MPN was associated with a two-fold increased risk of HF compared to patients without MPN [4].

Among patients hospitalized for HF, readmissions after HF hospitalization are common [5,6]. However, in-hospital outcomes and readmission risk after HF hospitalization in patients with MPN has not been well characterized. Therefore, we investigated in-hospital and 90-day readmission outcomes among patients hospitalized for HF with and without MPN using the National Readmissions Database (NRD).

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2. Methods

2.1. Study design and population

Hospitalizations with a primary or secondary diagnosis of HF were identified using the NRD from 2017 and 2018 as previously validated in prior studies [5,6]. The NRD, sponsored by the Agency for Healthcare Research and Quality (AHRQ), is part of the Healthcare Cost and Utilization Project (HCUP) and captures approximately 50 % of hospitalizations in the United States. Unique identifiers are assigned to individual patients to track readmissions within a calendar year. Patients less than 18 years of age or unknown vital status were excluded. Patients with MPN were identified using ICD-10 codes. Co-morbidities and inpatient procedures (transfusion, mechanical circulatory support) during index hospitalization were identified using ICD-10 diagnostic and procedure codes, respectively, (Supplemental Table S1). Granular data is unavailable in the NRD, thus HF with reduced ejection fraction (HFrEF) was defined using ICD-10 codes. Our study was exempt by our Institutional Review Board given that the NRD is a publicly available database and is de-identified.

2.2. Outcomes

Our primary outcomes were index HF hospitalization in-hospital death and 90-day composite outcome of CV-related, and 90-day all-cause readmissions. Readmissions were deemed to be CV-related if the primary or secondary diagnoses were HF, arterial thrombosis (including acute myocardial infarction, ischemic stroke, or arterial thromboembolism), venous thromboembolism (VTE) or arrhythmia (including ventricular arrhythmias, atrial fibrillation, atrial flutter, and atrial arrhythmias). Secondary outcomes were HF-related, arterial thrombosis-related, and VTE-related readmissions at 90-days. Outcomes were identified using ICD-10 diagnostic codes (Supplemental Table S1). The NRD does not track patients across calendar years, thus admissions after September were excluded for primary outcome for 90-day readmission analyses.

2.3. Statistical analysis

In our primary analysis, propensity score (PS; the predicted probability of MPN status) was estimated using non-parsimonious multivariable logistic regression which included age, sex, smoking history, coronary artery disease (CAD), prior percutaneous coronary intervention (PCI), prior coronary artery bypass grafting (CABG), anemia, atrial fibrillation (AF), chronic lung disease, diabetes, hypertension, liver disease, prior stroke, peripheral arterial disease (PAD), chronic kidney disease (CKD), end-stage renal disease (ESRD), pulmonary arterial hypertension (PAH), valvular heart disease, do-not-resuscitate (DNR) status during index hospitalization, acute myocardial infarction or PCI during index hospitalization, ischemic cardiomyopathy, HF with reduced ejection fraction (HFrEF), biventricular HF, cardiogenic shock, mechanical circulatory support (MCS), vasopressors, hemodialysis, insurance status and hospital size as co-variables. We performed propensity score matching (PSM) without replacement (1 MPN patient to 10 non-MPN patient) using a greedy algorithm and a caliper size of 0.1 SD. Absolute standardized mean difference (SMD) was calculated for variables before and after PSM to assess for imbalances between groups. Imbalances between groups were considered insignificant if the SMD for a given co-variable was < 0.10. We used PSM cohort for our analyses. We utilized logistic regression analysis to estimate odds ratio (OR) of in-hospital death of patients with MPN compared with patients without MPN. For 90-day readmissions analyses, we employed a time-to-event analysis using a Cox proportional hazards regression model to estimate hazards ratio (HR).

Given the heterogeneous nature of MPNs, we performed subgroup analyses of individual MPN phenotypes (ET, PV and MF) and compared baseline characteristics and outcomes to patients without MPN. Multivariable logistic regression models were used to estimate OR of in-hospital death and Cox proportional regression hazard modeling was used to estimate HR of 90-day all-cause, CV-related and HF-related readmissions. Variables that were significantly different between non-MPN and MPN groups (SMD ≥ 0.10) were included as co-variables.

We also performed a subgroup of analysis of patients with MPN and compared patients with ET or PV with patients with MF given MF being a more aggressive and advanced MPN phenotype compared with ET or PV. Propensity scores (predicted probability of MF) were estimated using a non-parsimonious logistic regression in a similar fashion to the primary analysis. Propensity score weighting was performed with ET or PV patients given a weight of 1/(1-PS) and MF given a weight of 1/PS as previously described [7,8]. Logistic regression models were used to estimate OR of in-hospital death and Cox proportional regression hazard modeling was used to estimate HR of 90-day all-cause, CV-related and HF-related readmissions.

To identify risk factors for 90-day readmission for CV-related readmission among patients with MPN, we compared patients who had 90-day readmission with patients who did not. Patients admitted prior to October were included in this analysis given patients cannot be tracked across calendar years in the NRD. We performed a backward stepwise multivariable Cox proportional hazards regression starting with all co-

Table 1
Characteristics of Index Heart Failure Hospitalization After Propensity Score Matching.

	Non-MPN N = 46,260	MPN N = 4,626	SMD
Age, mean (SD)	76.0 (13.4)	74.9 (13.5)	0.079
Female Sex, N (%)	26,143 (56.5)	2,495 (53.9)	0.052
Smoking History, N (%)	16,929 (36.6)	1,827 (39.5)	0.060
Co-Morbidities, N (%)			
CAD	211,78 (45.8)	2,331 (50.4)	0.092
Prior PCI	3,993 (8.6)	480 (10.4)	0.060
Prior CABG	3,772 (8.2)	443 (9.6)	0.050
Prior MI	5,015 (10.8)	582 (12.6)	0.056
Anemia	21,172 (45.8)	2,238 (48.4)	0.052
Atrial Fibrillation	21,396 (46.3)	2,092 (45.2)	0.021
Chronic Lung Disease	16,627 (35.9)	1,744 (37.7)	0.036
Diabetes	15,562 (33.6)	1,630 (35.2)	0.034
Hypertension	3,311 (7.2)	417 (9.9)	0.068
Liver Disease	2,161 (4.7)	297 (6.4)	0.076
Prior Stroke	4,000 (8.6)	490 (10.6)	0.066
Peripheral Vascular Disease	3,948 (8.5)	497 (10.7)	0.075
Chronic Kidney Disease	22,110 (47.8)	2,242 (48.5)	0.013
ESRD	1,779 (3.8)	204 (4.4)	0.028
Pulmonary Arterial Hypertension	5,714 (12.4)	683 (14.8)	0.071
Valvular heart disease	7,401 (16.0)	866 (18.7)	0.072
DNR Status	8,877 (19.2)	925 (20.0)	0.020
Hospitalization Characteristics, N (%)			
AMI During Index	520 (1.1)	69 (1.5)	0.032
PCI During Index	394 (0.9)	56 (1.2)	0.036
Ischemic Cardiomyopathy	3,534 (7.6)	433 (9.4)	0.062
HFrEF	19,382 (41.9)	2,080 (45.0)	0.062
Biventricular HF	316 (0.7)	45 (1.0)	0.032
Cardiogenic Shock	1,022 (2.2)	140 (3.0)	0.051
MCS	225 (0.5)	32 (0.7)	0.027
Invasive Hemodynamic Monitoring	2,058 (4.4)	290 (6.3)	0.081
Mechanical Ventilation	939 (2.0)	126 (2.7)	0.046
Vasopressors	252 (0.5)	40 (0.9)	0.038
Hemodialysis	1,096 (2.4)	130 (2.8)	0.028
Medicare or Medicaid	41,235 (89.1)	4,044 (87.4)	0.053
Large or Medium Hospital	38,770 (83.8)	3,787 (81.9)	0.052

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DNR, do-not-resuscitate; ESRD, end-stage renal disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MCS, mechanical circulatory support; MI, myocardial infarction; MPN, myeloproliferative neoplasms; PCI, percutaneous coronary intervention; SD, standard deviation; SMD, standardized mean difference.

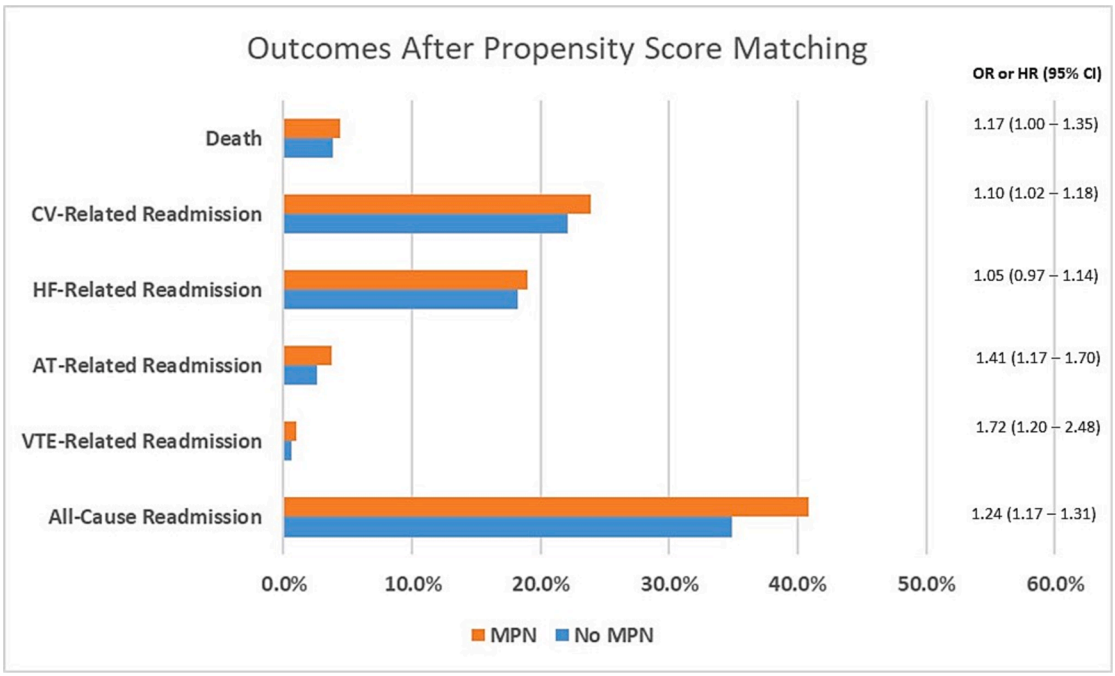

Fig. 1. In-Hospital Death and 90-Day Readmission Outcomes of Patients Admitted For HF With Versus Without MPN. Bar graph of in-hospital death and 90-day CV-related, HF, arterial thrombosis-related, VTE-related and all-cause readmissions after propensity score matching. Abbreviations: AT, arterial thrombosis; CV, cardiovascular; CI, confidence interval; HF, heart failure; HR, hazards ratio; MPN, myeloproliferative neoplasms; OR, odds ratio; VTE, venous thromboembolism.

variables and removing co-variables with $p > 0.10$. All analyses were two-tailed and a p value of < 0.05 was considered statistically significant. Analyses were conducted using Stata version 15 (STATA corporation) and SPSS version 29.0 (IBM).

3. Results

3.1. Baseline Characteristics of patients with and without MPN during index heart failure Hospitalization

A total of 1,045,920 patients were included, of whom 4,632 (0.4 %) had a diagnosis of MPN. Prior to PSM, patients with MPN were older (mean age 75.9 vs 72.2 years, SMD = 0.196), more likely to be female (54.0 % vs 48.1 %, SMD = 0.118), have anemia (34.2 % vs 48.4 %, SMD = 0.292) and pulmonary arterial hypertension (14.8 % vs 11.3 %, SMD = 0.104) compared with patients without MPN. However, patients with MPN were less likely to have classic cardiovascular comorbidities and risk factors including CAD (50.4 % vs 55.5 %, SMD = 0.103), diabetes (35.2 % vs 47.8 %, SMD = 0.259), and ESRD (4.4 % vs 8.6 %, SMD = 0.169). Patients with MPN were also less likely to have a diagnosis of HFrEF (44.9 % vs 51.6 %, SMD = 0.13), Supplemental Table S2. Additionally, patients with MPN had similar distribution of cardiomyopathy types (ischemic, hypertrophic, dilated, other) compared with patients without MPN. However, patients with MPN were less likely to have a history of prior implantable cardioverter defibrillator (ICD; 4.6 % vs 8.6 %, SMD = 0.163), Supplemental Table S3. After PSM 46,260 patients without MPN were matched with 4,626 patients with MPN. Variables were well balanced between patients with and without MPN after PSM, Table 1.

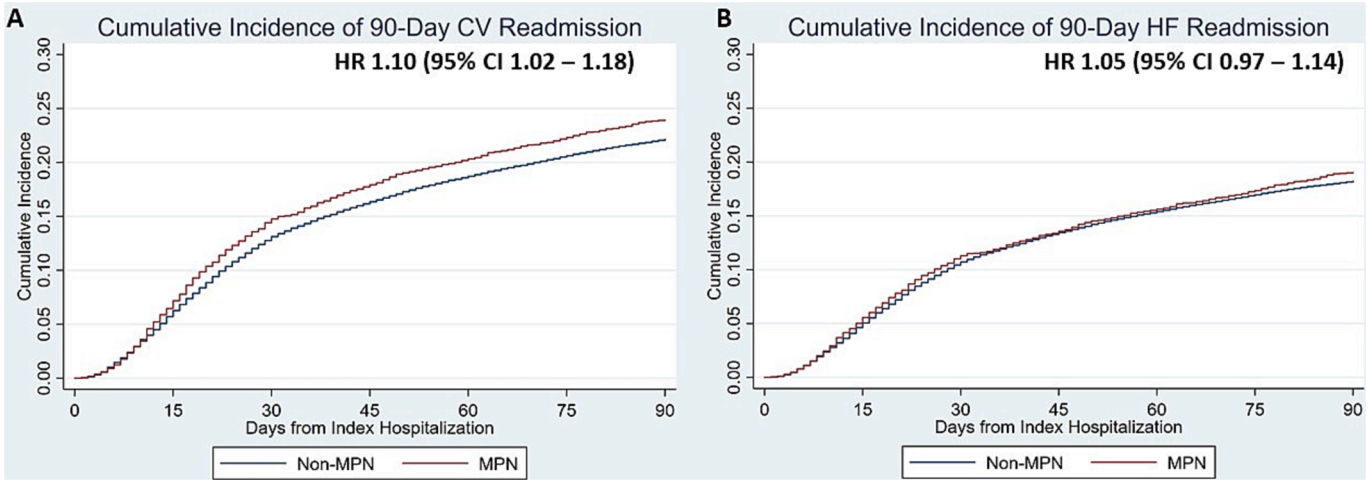

Fig. 2. Cumulative Incidence Curves for 90-Day CV-Related and HF-Related Readmissions After Propensity Score Matching. Cumulative incidence curves for 90-Day CV-related (A) and HF-related (B) readmissions of patients with and without MPN after propensity score matching.

Table 2
Unadjusted and Adjusted Logistic or Cox Proportional Hazards Regression by MPN Type.

	Unadjusted OR or HR (95 % CI)			Adjusted OR or HR (95 % CI) [a]		
	ET	PV	MF	ET	PV	MF
In-Hospital Death	1.07 (0.88 – 1.30)	0.95 (0.69 – 1.30)	1.75 (1.34 – 2.29)	1.01 (0.83 – 1.24)	0.84 (0.61 – 1.17)	1.33 (1.00 – 1.76)
CV-Related Readmission	1.03 (0.94 – 1.13)	0.82 (0.70 – 0.96)	1.13 (0.97 – 1.30)	1.03 (0.94 – 1.12)	0.90 (0.77 – 1.05)	1.10 (0.95 – 1.27)
HF-Related Readmission	0.94 (0.85 – 1.04)	0.83 (0.70 – 0.98)	1.10 (0.93 – 1.29)	0.94 (0.85 – 1.05)	0.93 (0.70 – 1.10)	1.08 (0.92 – 1.27)
Arterial Thrombosis Readmission	1.51 (1.23 – 1.85)	0.60 (0.36 – 0.99)	0.91 (0.58 – 1.42)	1.63 (1.33 – 1.99)	0.70 (0.42 – 1.17)	0.99 (0.63 – 1.56)
VTE Readmission	2.04 (1.33 – 3.13)	2.18 (1.13 – 4.19)	1.16 (0.43 – 3.08)	1.81 (1.18 – 2.78)	2.16 (1.12 – 4.16)	1.12 (0.42 – 2.98)
All-Cause Readmission	1.25 (1.17 – 1.34)	0.92 (0.81 – 1.04)	1.43 (1.28 – 1.59)	1.19 (1.11 – 1.27)	1.01 (0.90 – 1.27)	1.38 (1.20 – 1.49)

CV, cardiovascular; CI, confidence interval; ET, essential thrombocythemia; HF, heart failure; HR, hazards ratio; MF, myelofibrosis; OR, odds ratio; PV, polycythemia vera; VTE, venous thromboembolism;

[a] Adjusted for age, sex, smoking, CAD, prior PCI, prior CABG, anemia, diabetes, liver disease, CKD, ESRD, PAH, valvular heart disease, DNR status, systolic HF, hemodialysis during index hospitalization and insurance.

3.2. Index hospitalization and readmission outcomes in Propensity score matched cohort

After PSM, patients with MPN had increased rates of in-hospital death compared with patients without MPN (4.4 % vs 3.8 %, p = 0.031). Additionally, patients with MPN had longer LOS compared with patients without MPN (mean 6.6 vs 5.5 days, p < 0.001). Patients with MPN had higher rates of 90-day CV-related (23.9 % vs 22.1 %, p = 0.017), arterial thrombosis-related (3.7 % vs 2.6 %, p = 0.001), VTE-related (1.0 % vs 0.6 %, p = 0.006), and all-cause (40.9 % vs 34.9 %, p < 0.001) readmissions. There was no difference in 90-day HF readmissions between patients with and without MPN (19.0 % vs 18.2 %, p = 0.25), Fig. 1.

After Cox proportional hazards regression, MPN was associated with increased risk of CV-related readmissions (HR 1.10, 95 % CI 1.02 – 1.18), arterial thrombosis-related readmissions (HR 1.41, 95 % CI 1.17 – 1.70), VTE-related readmission (HR 1.72, 95 % CI 1.20 – 2.48) and all-cause readmission (HR 1.24, 95 % CI 1.17 – 1.31) but not HF-related readmissions (HR 1.05, 95 % CI 0.97 – 1.14), Fig. 1.

Among patients with 90-day CV-related readmissions, most CV-related readmissions were HF-related (84.8 % prior to PSM and 83.5 % after PSM). After PSM and among patients with 90-day CV-related

Table 3
Baseline Characteristics of Patients with MPN by MPN Type Before and After PS Weighting.

	Prior to Propensity Score Weighting			After Propensity Score Weighting		
	ET or PV N = 3,748	MF N = 884	SMD	ET or PV	MF	SMD
Age, mean (SD)	74.3 (14.1)	77.7 (9.6)	0.281	75.0 (13.8)	76.3 (10.4)	0.102
Female Sex, N (%)	2,103 (56.1)	397 (44.9)	0.225	54.0 %	54.9 %	0.018
Smoking History, N (%)	1,511 (40.3)	318 (36.0)	0.089	39.4 %	38.0 %	0.029
MPN Types, N (%)						
ET	2,639 (70.4)		N/A	70.5 %	0	N/A
PV	1,109 (29.6)		N/A	29.5 %	0	N/A
Co-Morbidities, N (%)						
CAD	1,875 (50.0)	459 (51.9)	0.038	50.3 %	50.1 %	0.004
Prior PCI	383 (10.2)	97 (11.0)	0.024	10.3 %	10.1 %	0.007
Prior CABG	350 (9.3)	93 (10.5)	0.040	9.5 %	9.7 %	0.007
Prior MI	462 (12.3)	120 (13.6)	0.039	12.4 %	12.8 %	0.012
Anemia	1,768 (47.2)	476 (53.8)	0.134	48.4 %	47.8 %	0.012
Atrial Fibrillation	1,702 (45.4)	390 (44.1)	0.026	45.2 %	45.9 %	0.014
Chronic Lung Disease	1,441 (38.4)	305 (34.5)	0.082	37.7 %	36.8 %	0.019
Diabetes	1,340 (35.8)	290 (32.8)	0.062	35.2 %	35.1 %	0.002
Hypertension	353 (9.4)	66 (7.5)	0.070	9.1 %	9.6 %	0.017
Liver Disease	221 (5.9)	76 (8.6)	0.104	6.4 %	6.0 %	0.017
Prior Stroke	404 (10.8)	88 (10.0)	0.027	10.6 %	11.2 %	0.019
Peripheral Vascular Disease	408 (10.9)	92 (10.4)	0.016	10.8 %	10.8 %	< 0.001
Chronic Kidney Disease	1,736 (46.3)	508 (57.5)	0.225	48.5 %	49.7 %	0.024
ESRD	152 (4.1)	52 (5.9)	0.084	4.4 %	4.5 %	0.005
Pulmonary Arterial Hypertension	549 (14.6)	137 (15.5)	0.024	14.8 %	16.2 %	0.039
Valvular heart disease	670 (17.9)	201 (22.7)	0.121	18.8 %	18.9 %	0.003
DNR Status	715 (19.1)	214 (24.2)	0.125	20.1 %	20.7 %	0.015
Hospitalization Characteristics, N (%)						
AMI During Index	57 (1.5)	13 (1.5)	0.004	1.5 %	1.2 %	0.026
PCI During Index	52 (1.4)	6 (0.7)	0.070	1.3 %	0.9 %	0.038
Ischemic Cardiomyopathy	337 (9.0)	96 (10.9)	0.063	9.3 %	9.7 %	0.014
Systolic HF	1,727 (46.1)	353 (39.9)	0.124	44.9 %	44.7 %	0.004
Biventricular HF	31 (0.8)	14 (1.6)	0.069	1.0 %	0.9 %	0.010
Cardiogenic Shock	126 (3.4)	14 (1.6)	0.115	3.0 %	2.9 %	0.006
MCS	31 (0.8)	1 (0.1)	0.105	0.7 %	0.6 %	0.012
Invasive Hemodynamic Monitoring	245 (6.5)	48 (5.4)	0.047	6.3 %	6.0 %	0.012
Mechanical Ventilation	108 (2.9)	18 (2.0)	0.055	2.7 %	2.4 %	0.019
Vasopressors	35 (0.9)	5 (0.6)	0.043	0.9 %	0.5 %	0.048
Hemodialysis	100 (2.7)	30 (3.4)	0.042	2.8 %	2.8 %	< 0.001
Medicare or Medicaid	3,250 (86.7)	799 (90.4)	0.115	87.5 %	88.7 %	0.037
Large or Medium Hospital	3,078 (82.1)	715 (80.9)	0.032	81.9 %	81.4 %	0.013

Abbreviations previously defined in Table 1.

readmissions, patients with MPN had similar proportion to HF-related (81.2 % vs 83.8 %, p = 0.061), arterial thromboembolism (0.4 % vs 0.1 %, p = 0.13), and VTE (1.3 % vs 0.9 %, p = 0.26) compared with patients without MPN. However, patients with MPN had higher proportion of STEMI (2.3 % vs 1.2 %, p = 0.013) and non-ST elevation acute coronary syndrome (NSTE-ACS, 9.3 % vs 6.6 %, p = 0.005), Supplemental Table S4. Cumulative incidence curve of 90-day CV-related and HF-related readmissions of patients with and without MPN shown in Fig. 2.

3.3. Index hospitalization mortality and readmission outcomes by MPN Type compared with Non-MPN

Among the 4,632 patients with MPN, 2,639 (57.0 %) had ET, 1,109 (23.9 %) had PV, and 884 (19.1 %) had MF. Baseline patient characteristics by MPN type are summarized in Supplemental Table S5. After multivariable logistic regression, there was no difference in index in-hospital mortality between non-MPN and ET (adjusted OR 1.01, 95 % CI 0.83 – 1.24) or PV patients (adjusted OR 0.84, 95 % CI 0.61 – 1.17). However, MF was associated with higher risk of in-hospital mortality compared with patients without MPN (adjusted OR 1.33, 95 % CI 1.00—1.76). There was no association between all MPN types and CV-related readmission and HF-related readmissions. ET was associated with increased risk of arterial thrombosis-related readmissions (adjusted HR 1.63, 95 % CI 1.33 – 1.99) while PV (adjusted HR 0.70, 95 % CI 0.42 – 1.17) and MF (adjusted HR 0.99, 95 % CI 0.63 – 1.56) were not. Both ET (adjusted OR 1.81, 95 % CI 1.18 – 2.78) and PV (adjusted OR 2.16, 95 % CI 1.12 – 4.16) were associated with increased risk of VTE-related readmission. ET (adjusted HR 1.19, 95 % CI 1.11 – 1.27) and MF (adjusted HR 1.38, 95 % CI 1.20 – 1.49) were associated with increased risk of all-cause readmission while PV (adjusted HR 1.01, 95 % CI 0.90 – 1.27) was not, Table 2.

3.4. Outcomes of patients with ET or PV compared with MF

Among the 4,632 patients with MPN, 3,748 had ET or PV and 884 had MF. Patients with MF were older (mean 77.7 vs 74.3 years, SMD = 0.281), less likely to be female (44.9 % vs 56.1 %, SMD = 0.225) and more likely to have liver disease (8.6 % vs 5.9 %, SMD = 0.104), CKD (57.5 % vs 46.3 %, SMD = 0.225), and valvular heart disease (22.7 % vs 17.9 %, SMD = 0.121). Patients with MF were also less likely to have systolic HF (39.9 % vs 46.1 %, SMD = 0.124) and have cardiogenic shock during index hospitalization (1.6 % vs 3.4 %, SMD = 0.115). After PS weighting, all variables were well balanced with the exception of age (76.3 vs 75.0 years, SMD = 0.102), Table 3.

Prior to PS weighting, patients with MF had higher rates of in-hospital death (6.4 % vs 3.9 %, p = 0.002), 90-day HF readmission (21.9 % vs 18.3 %, p = 0.037), and all-cause readmission (47.1 % vs 39.4 %, p < 0.001), Supplemental Table S6. After PS weighting, MF was associated with increased risk of death during index hospitalization (OR 1.67, 95 % CI 1.38 – 2.01), CV-related readmission (HR 1.18, 95 % CI 1.08 – 1.30), HF-related readmission (HR 1.24, 95 % CI 1.12 – 1.38) but lower risk of arterial thrombosis-related readmission (HR 0.62, 95 % CI 0.47 – 0.81), Fig. 3. Cumulative incidence curve of 90-day CV-related and HF-related readmissions shown in Fig. 4.

3.5. Risk factors for 90-Day CV-Related readmissions among patients with MPN

Among the 3,472 patients with MPN eligible for 90-day readmission analysis, 830 (23.9 %) had CV-related readmission at 90-days. More patients with 90-day CV-related readmissions had ET or MF (58 % and 21.7 % vs 57.2 % and 18.6 %, respectively, p = 0.008) compared with patients without CV-related readmission. Additionally, CAD (57.5 % vs 48.4 %, p < 0.001), anemia (52.5 % vs 48.5 %, p = 0.043), AF (51.2 % vs 42.5 %, p < 0.001), liver disease (8.2 % vs 5.7 %, p = 0.014), CKD (56.1 % vs 45.3 %, p < 0.001), and pulmonary arterial hypertension (14.6 % vs 11.9 %, p = 0.048) were more common among patients with 90-day

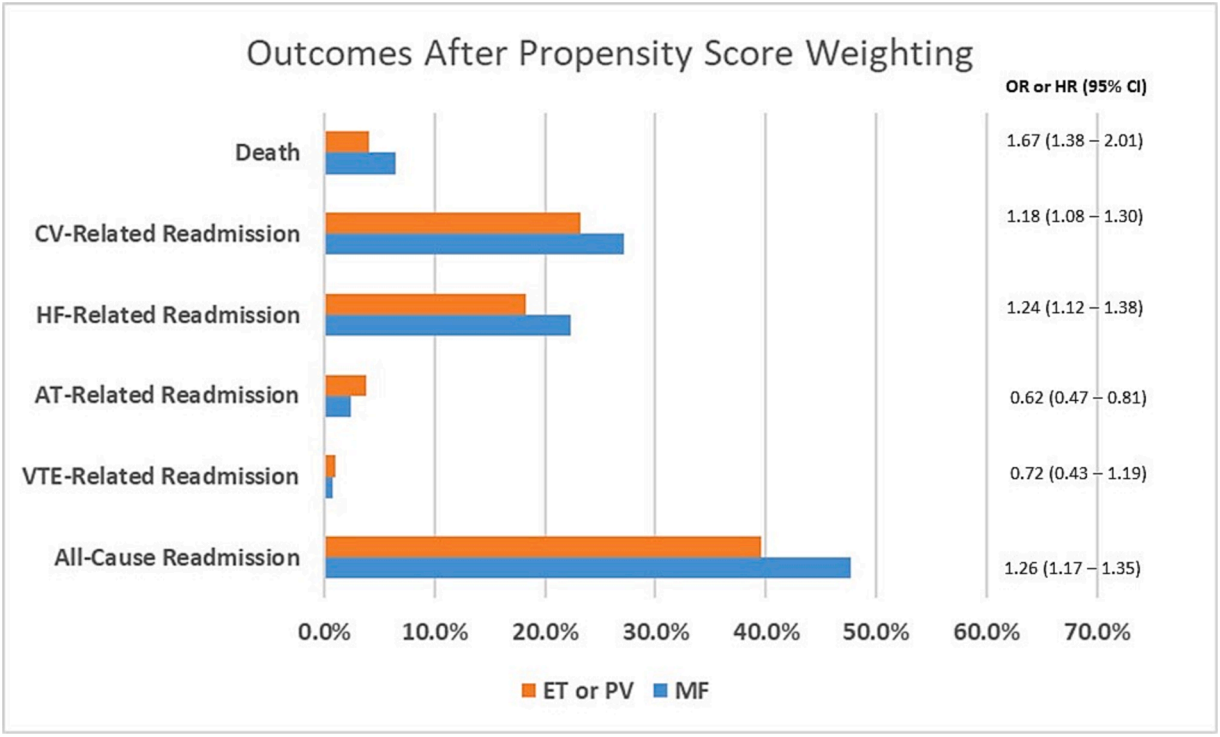

Fig. 3. In-Hospital Death and 90-Day Readmission Outcome of Patients with MPN Admitted for HF by MPN Type. Bar graph of in-hospital death and 90-day CV-related, HF-related, arterial thrombosis-related, VTE-related and all-cause readmissions after propensity score weighting.

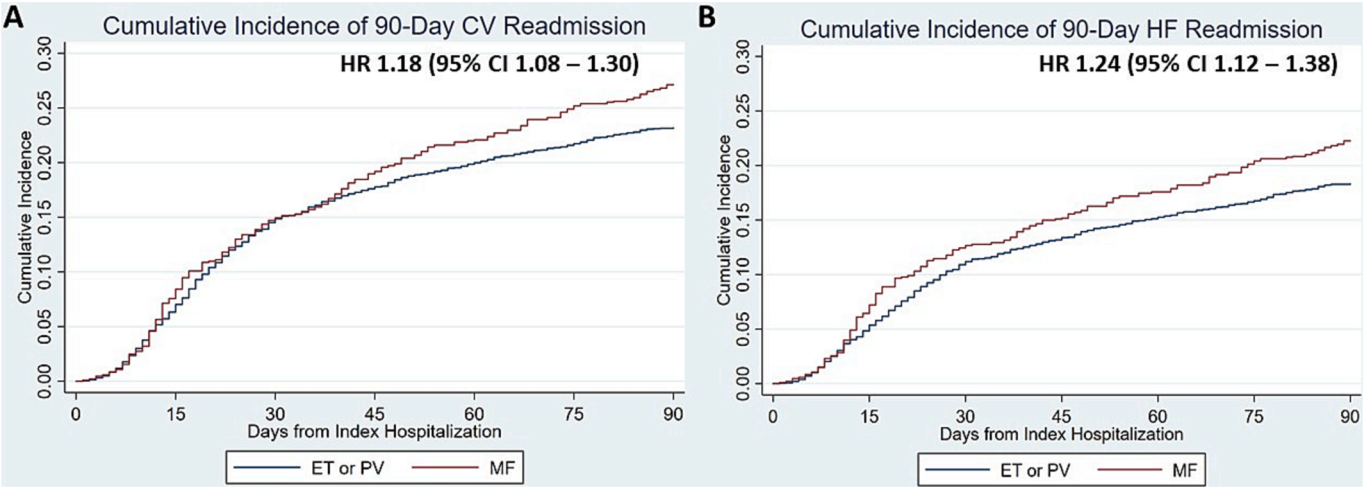

Fig. 4. Cumulative Incidence Curves for 90-Day CV-Related and HF-Related Readmissions Among Patients with MPN. Cumulative incidence curves for 90-Day CV-related (A) and HF-related (B) readmissions of patients with MPN (ET or PV versus MF) after propensity score weighting.

Table 4
Patient Characteristics of MPN Patients with and Without 90-Day Cardiovascular-Related Readmissions.

	No 90-Day CV Readmission N = 2,642	90-Day CV Readmission N = 830	P value
Age, mean (SD)	74.9 (13.5)	74.4 (13.6)	0.21
Female Sex, N (%)	1,420 (53.7)	445 (53.6)	0.97
Smoking History, N (%)	1,066 (40.3)	316 (38.1)	0.25
MPN Type, N (%)			0.008
ET	1,511 (57.2)	488 (58.8)	
PV	640 (24.2)	162 (19.5)	
MF	491 (18.6)	180 (21.7)	
Co-Morbidities, N (%)			
CAD	1,278 (48.4)	477 (57.5)	< 0.001
Anemia	1,281 (48.5)	436 (52.5)	0.043
Atrial Fibrillation	1,122 (42.5)	425 (51.2)	< 0.001
Chronic Lung Disease	993 (37.6)	330 (39.8)	0.27
Diabetes	906 (34.3)	316 (38.1)	0.050
Hypertension	249 (9.4)	75 (9.0)	0.78
Liver Disease	151 (5.7)	68 (8.2)	0.014
Peripheral Vascular Disease	271 (10.3)	86 (10.4)	0.95
Chronic Kidney Disease	1,198 (45.3)	466 (56.1)	< 0.001
ESRD	110 (4.2)	47 (5.7)	0.084
Pulmonary arterial hypertension	315 (11.9)	121 (14.6)	0.048
Valvular heart disease	502 (19.0)	148 (17.8)	0.47
Hospitalization Characteristics, N (%)			
AMI During Index	34 (1.3)	15 (1.8)	0.31
PCI During Index	31 (1.2)	6 (0.7)	0.33
Ischemic Cardiomyopathy	234 (8.9)	99 (11.9)	0.010
Systolic HF	1,141 (43.2)	415 (50.0)	0.001
Cardiogenic Shock	63 (2.4)	28 (3.4)	0.13
MCS	15 (0.6)	8 (1.0)	0.22
Mechanical Ventilation	54 (2.0)	24 (2.9)	0.18
Invasive Hemodynamic Monitoring	171 (6.5)	47 (5.7)	0.46
Vasopressors	16 (0.6)	8 (1.0)	0.33
Hemodialysis	52 (2.0)	33 (4.0)	0.002
Medicare or Medicaid	2,291 (86.7)	742 (89.4)	0.042
Large or Medium Hospital	2,161 (81.8)	690 (83.1)	0.41

ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.

CV-related readmissions, Table 4.

After backward step-wise Cox proportional hazards regression, female sex (HR 1.16, 95 % CI 1.00 – 1.34), ET (HR 1.21, 95 % CI 1.01 – 1.45) or MF (HR 1.33, CI 1.08 – 1.65), CAD (HR 1.35, 95 % CI 1.17 – 1.56), hemodialysis (HR 1.50, 95 % CI 1.05 – 2.14), AF (HR 1.39, 95 % CI 1.20 – 1.60), Medicare or Medicaid (HR 1.31, 95 % CI 1.03 – 1.60), liver disease (HR 1.29, 95 % CI 1.00 – 1.66), CKD (HR 1.38, 95 % CI 1.20 – 1.59), and systolic HF (HR 1.24, 95 % CI 1.08 – 1.43) were associated with increased risk of 90-day CV readmission, Fig. 5.

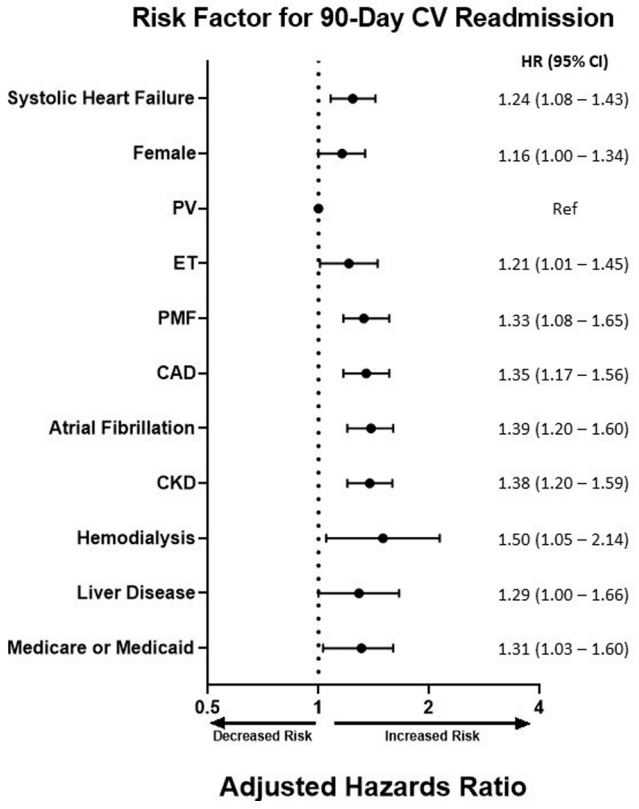

Fig. 5. Predictors of 90-Day CV-Related Readmissions Among Patients with MPN. Forest plot of predictors of 90-day CV-related readmissions among patients with MPN after backward stepwise Cox proportional hazards regression modeling.

4. Discussion

Despite prior studies suggesting an increased incidence of HF among patients with MPN and accelerated adverse cardiac remodeling in animal models of MPN, HF remains an underappreciated complication of MPN [1,2,4]. Our study examining in-hospital and readmission outcomes of patients hospitalized with HF with and without MPN suggests that MPN was associated with increased risk of 90-day CV-related, arterial thrombosis-related, VTE-related, and all-cause readmission. In addition, unlike a prior study of in-hospital outcomes of patients hospitalized with AMI, patients with MPN also had increased risk of in-hospital death during index HF hospitalization [8]. Additionally, among patients with MPN, MF was associated with increased risk of in-hospital mortality, CV-related and HF-related readmission. Our study also identified potential risk factors for 90-day CV-related readmissions among patients with MPN including ET or MF phenotype, prior AF, female sex, CAD, CKD, and systolic HF.

Patients with MPN have unique pathophysiology that may predispose patients to HF [1]. Our findings suggest that patients with MPN were less likely to have HFrEF and classical cardiovascular risk factors including diabetes and CAD. This suggests that the pathophysiology for HF among patients with MPN may be different compared with patients without MPN. In a prior single-center retrospective study of patients with MPN admitted for HF, patients with persevered left ventricular ejection fraction (LVEF) were more common than patients with reduced LVEF [9]. High-output HF may contribute to HF in some patients with MPN with up to 8 % of high-output HF etiologies being attributed to MPNs [10]. Pulmonary hypertension is another possible contributor to the development of HF in patients with HF. The World Health Organization classifies MPN-associated pulmonary hypertension in group 5 [11–13]. Indeed, in our study, prior to PSM patients with MPN had numerically higher rates of pulmonary arterial hypertension compared to patients without MPN. In a single-center study of 197 patients with MPN and cardiovascular disease, the presence of pulmonary hypertension was associated with increased risk of CV-related death [14]. Thus pulmonary hypertension may contribute to CV and HF risk in patients with MPN and further studies are merited. More investigation is needed in order to elucidate the underlying pathophysiologic mechanisms in HF in patients with MPN.

In our study, MPN was associated with increased risk of 90-day CV-related readmissions with readmissions for arterial thrombosis (particularly acute myocardial infarction) and VTE likely being responsible for the increased risk. Importantly, there was no difference in HF readmissions suggesting the difference in CV-related readmissions between groups was driven by thrombotic complications. Additionally, when comparing individual MPN phenotypes to non-MPN patients, there was no difference in CV-related or HF-related readmissions among all MPN phenotypes though ET and PV were associated with increased VTE-related and ET with arterial thrombosis-related readmissions. Thrombotic complications of HF are not uncommon and there are data suggesting a prothrombotic phenotype among patients with HF [15]. Among patients hospitalized for HF, prior studies have suggested an increased risk of VTE and ischemic stroke post-discharge [16,17]. Thrombotic complications are also common among patients with MPN [18]. Among patients with MPN, those with *JAK2* mutations are at highest risk of thrombotic complications [1]. The NRD does not capture mutation status thus further investigation is needed in order to identify mutational risk factors for thrombosis among patients with MPN and HF. Importantly, aspirin is recommended in some patients with MPNs (particularly PV and high-risk ET) [19,20]. Whether treatment with aspirin or other MPN-specific therapy (including cytoreduction) is associated with improved CV and thrombotic outcomes after HF hospitalization in MPN patients is still unclear and merits further investigation.

Our study also identified potential risk factors for 90-day CV-related readmission for patients with MPN hospitalized for HF. Interestingly, compared with patients with PV, our study suggests that ET and MF are associated with increased risk of 90-day CV-related readmission. Additionally, compared with ET or PV, MF was associated with increased risk of 90-day HF-related readmission. In prior single-center retrospective cohort studies of patients with MPN and CV disease, patients with MF were associated with increased risk of CV death and pulmonary hypertension [9,13,21]. Additionally, patients with MF have increased extramedullary hematopoiesis and anemia which may contribute to increased high-output HF [10]. Therefore, among patients with HF, patients with MPN should be followed closely for CV complications especially patients with MF or those with risk factors including CAD, CKD or AF. The exact mechanisms of increased risk of CV-related readmissions after HF hospitalization in patients with ET or PV have yet to be elucidated and further investigation is needed.

Our study has limitations to consider when interpreting our results. The NRD relies on administrative ICD-10 codes and granular data including vital signs, laboratory values, echocardiographic values (including left ventricular ejection fraction), HF medications (including diuretics and guideline-directed medical therapy) are not available and may be a source of unmeasured confounding. Given the data in the NRD are abstracted from administrative ICD-10 codes which may be inaccurate, it is difficult to verify whether certain diagnoses that require granular data (including HFrEF, HFpEF, and high-output heart failure) and therefore a limitation to consider when interpreting our results. Information on MPN genetics and therapy (including aspirin and cytoreduction), which may influence cardiovascular and thrombotic risk, are not available in the NRD. Additionally, the NRD does not track admissions across calendar years thus for 90-day readmission analyses patients admitted after September, respectively, are omitted and therefore reduces our sample size and limit evaluation of long-term outcomes. Given that readmissions and outcomes were identified using administrative codes, further prospective studies are needed in this patient population.

5. Conclusions

Our study suggests that patients with MPN and HF are associated with increased risk of in-hospital death and 90-day CV-related readmission compared with patients without MPN. ET and MF was associated with increased risk of 90-day CV-related readmission compared with PV. Additionally, among patients with MPN, MF was associated with increased risk of 90-day CV and HF-related readmissions compared with ET or PV. Further investigation is needed to better characterize underlying pathophysiology of HF in patients with MPN, investigate long-term outcomes, and improve outcomes in this patient population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101304.

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