Pulmonary Arterial Hypertension in Hospitalized Patients With Polycythemia Vera (from the National Inpatient Database)

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Polycythemia vera (P. vera) is a myeloproliferative neoplasm (MPN) originating from the clonal expansion of hematopoietic progenitor cells. The resulting increase in cellular mass, and the heightened platelet-derived inflammation and erythrocytic adhesion to the endothelium have a direct effect on the intravascular flow and endothelial microenvironment which may lead to vascular remodeling.[1] Multiple different mechanisms are linked to P. vera-associated PH and distinguishing the pathophysiologic mechanism is challenging. Correctly identifying pulmonary arterial hypertension (PAH) has important clinical and therapeutic implications. Small-scale studies and case series provide the majority of evidence for the association between MPN, PAH, and mortality. We aim to establish the prevalence and association of PAH in patients with P. vera using the Nationwide Inpatient Sample (NIS) database.

Methods

Data were obtained from the 2009 to 2010 NIS databases. The NIS is the largest publicly available all−payer inpatient care database in the United States. It is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project. It contains discharge−level data provided by states (n = 45 in 2010) that participate in the Healthcare Cost and Utilization Project. The NIS includes data from approximately 8 million hospital stays from about 1,000 hospitals designed to approximate a 20% stratified sample of all community hospitals in the United States. Criteria used for stratified sampling of hospitals include hospital ownership, patient volume, teaching status, urban or rural location, and geographic region. Inpatient hospital stays records in the NIS include clinical and resource use information available from discharge abstracts derived from state−mandated hospital discharge reporting. Discharge weights, provided for each patient discharge record, were used to obtain national estimates.

We used the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD−9−CM) code 238.4 to identify all patients ≥18 years of age with a discharge diagnosis of P. vera (n = 38,395). Patients with a concomitant diagnosis of PAH were identified using the ICD−9−CM code 416.0. Patients were stratified into 2 groups: patients with P. vera and PAH, and patients with PAH alone (without P. vera). Baseline patient characteristics including demographics (age, gender) and other clinically relevant co-morbidities such as diabetes mellitus, hypertension, current and previous tobacco use, previous history of any cancer, previous history of pulmonary embolism, chronic kidney disease, and chronic lung disease were identified using their corresponding ICD−9−CM codes. Clinical in-hospital outcomes such as in-hospital mortality were identified among both the groups.

Categorical variables were presented as percentage, and continuous variables as mean ± standard deviation (SD) for normally distributed variables and median (IQR) for others. Weighted data were used for all analyses. We used the Mantel-Haenszel chi-square test of linear association for categorical variables and linear regression for continuous variables to examine if there were significant differences between the groups. Unadjusted and multivariate adjusted logistic regression analyses were performed to determine if presence of P. vera predicted PAH after adjusting for demographic, and other clinically relevant confounding risk factors. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATA 14.0 MP (Stata Statistical Software: Release 14; StataCorp LP, College Station, TX).

Results

The prevalence of P. vera was 0.1% (n = 38,395 patients) of all hospital discharge records. PAH was more prevalent in patients with P. vera compared with the control population (7.9% vs 1.9%, $p < 0.0001$). Patients with P. vera and PAH were younger (63.9 ± 0.1 vs 70.9 ± 0.04 years; $p < 0.001$) and were more likely to be male (45% vs 61%; $p < 0.0001$) compared with patients with PAH alone. Patients with P. vera and PAH had increased prevalence of risk factors associated with pulmonary hypertension (PH) such as hypertension (61% vs 46%; $p < 0.0001$), tobacco use (25.6% vs 12.8%; $p < 0.0001$), previous history of

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pulmonary embolism (2.2% vs 0.8%; p <0.0001), chronic lung disease (5.9% vs 1.4%; p <0.0001) and chronic kidney disease (12.3% vs 8.4%; p <0.0001). There was no significant difference in previous history of malignancy between the 2 groups (1.7% vs 1.6%; p = 0.44; Table 1). Inpatient mortality was higher in P. vera and PAH group compared with those without P. vera (6.9% vs 4.9%, p = 0.02).

The presence of P. vera was a determinant of PAH in unadjusted analysis (odds ratio 4.4 [4.1 to 4.8]; p <0.001). After adjusting for age, gender, race, diabetes, tobacco use, previous history of tumor, previous history of pulmonary embolism, chronic lung disease, and chronic kidney disease, P. vera was associated with a higher risk of PAH (2.98 [2.7 to 3.2], p <0.001; Table 2). There was a greater risk for in-patient mortality in patients with P. vera and PAH compared with patients with PAH without associated P. vera (3.6% vs 2.2%, p <0.0001). Risk for in-hospital cardiac arrest was also higher in the PAH and P. vera group (0.6% vs 0.45%, p = 0.001).

Discussion

The rationale for our study was to determine the prevalence of PAH in the P. vera population, potential associated risk factors, and inpatient clinical outcomes. In our analysis, the prevalence of PAH in patients with P. vera was higher compared with the general population, and P. vera was associated with nearly a 3-fold higher risk for PAH after adjusting for several risk factors for PH.

P. vera is a type of MPN resulting in erythropoietin-independent red cell proliferation and, to a lesser extent, leukocyte and megakaryocyte expansion. Several mechanisms of P. vera-associated PH have been described, but the precise pathophysiologic process has not been clearly defined. The increased red cell mass is associated with hyperviscosity, increased intravascular blood flow turbulence, and the formation of adhesive cellular aggregates. These microvascular disturbances facilitate platelet and endothelial cell activation, and prompt the release of platelet-derived inflammatory cytokines, growth factors, and endothelial procoagulant factors leading to vascular remodeling, promotion of angiogenesis, and ultimately PAH.[2,3] Other causes of polycythemia, such as Chuvash polycythemia (caused by a von Hippel-Lindau gene mutation), have been linked to the development of PAH. Although the precise mechanism of PAH is not fully understood, the overexpression of inflammatory cytokines and vascular smooth muscle remodeling have been proposed as contributing events.[4] The prothrombotic phenotype of P. vera is attributed to the allele burden of Janus Kinase 2 (*JAK2)* V617F, excessive leukocyte and erythrocyte mass and platelet activation.[5–7] The vascular insult arising from the microvascular prothrombotic milieu causes small-vessel thrombosis, increased pulmonary vascular resistance and subsequent PH.[8] The elevated hematocrit also increases the pulmonary vascular resistance offering a contributing process for the development PH in this population.[9]

The incidence and prevalence of PAH in patients with MPN, especially in patients with P. vera are challenging to define due in part to the low prevalence of P. vera (approximately 22 per 100,000 residents), and the limited data available from small case series and single-center experiences.[10] Gupta et al identified 28 patients with MPN who underwent echocardiographic evaluation for PAH, defined as a right ventricular systolic pressure >35 mm Hg.[11] The prevalence of PAH in this study was 48%, of which only 5 patients had P. vera. A retrospective study of 24 patients with MPN (2 with P. vera) reported a prevalence of 41.7%.[12] A recent prospective analysis of 158 patients with MPN by Brabrand et al describes a prevalence of 3.8%, much lower than previously reported.[13] These studies combine all MPN, thus providing a limited description of the burden of PAH in P. vera alone.

PAH is an important risk factor for poor outcomes across a spectrum of chronic diseases, but it is less recognized as an important comorbid condition in patients with MPN. Pulmonary hypertension can be classified into 5 distinct groups according to the 2016 World Health Organization—group 1, PAH; group 2, secondary to left heart disease or failure; group 3, secondary to underlying pulmonary diseases; group 4, chronic thromboembolic PH; and group 5, a miscellaneous group comprising multifactorial disease processes which do not fit seamlessly into the previous categories.[14] MPN-associated PH has historically been included in the latter group. The multifactorial pathophysiologic and hemodynamic mechanisms of PH in MPN not only challenge optimal classification of P. vera-associated PH, it also limits the therapeutic targets in this population.[15]

Table 1
Demographics and risk factors in patients with polycythemia vera

Variable	P. vera n = 38,395 (0.1%)	No P. vera n = 39,395,521 (99.9%)	p value*
Pulmonary arterial hypertension	0.3%	0.05%	<0.0001
Demographic factors			
Age (years)	65.2±0.1	57±0.01	<0.001
Female	42.2%	57.8%	<0.0001
In-hospital clinical outcomes			
In-hospital death	3.6%	2.2%	<0.0001
Cardiac arrest	0.6%	0.45%	0.01
Risk factors			
Diabetes mellitus	18.6%	17.8%	0.09
Smoker	25.6%	12.8%	<0.0001
Hypertension	61.4%	46%	<0.0001
Prior history of tumor	1.7%	1.6%	0.44
Prior history of PE	2.2%	0.8%	<0.0001
Chronic lung disease	5.9%	1.4%	<0.0001
Chronic kidney disease	12.3%	8.4%	<0.0001

P. vera = polycythemia vera; PE = pulmonary embolism.
* p value calculated by chi-square test for categorical variables and *t* test for continuous variables.

Table 2
Unadjusted and multimodel-adjusted regression analysis of polycythemia vera in predicting the risk of pulmonary arterial hypertension

Model*	Odds ratio	p value
Unadjusted	4.4 (4.1-4.8)	<0.001
Multivariate adjusted	2.98 (2.7-3.2)	<0.001

* Model adjusted for age, gender, race, diabetes mellitus, hypertension, tobacco use, previous history of any tumor, previous history of pulmonary embolism, chronic lung disease, and chronic kidney disease.

Untreated PAH is associated with a high risk of death from ensuing right heart failure.[16] If left unrecognized and untreated, it may lead to a decline in functional status and overall quality of life. Approximately, 15% of patients with PAH die within the first year of diagnosis[17]; the 2-year mortality from PH in sickle cell disease patients is approximately 55%, as reported in a 2003 study.[18] Pulmonary hypertension due to other etiologies are equally burdened with an unacceptably high rate of death. However, the mortality associated with MPN, specifically P. vera has not yet been evaluated on a large-scale platform. Screening for PH is generally not recommended in patients with P. vera as it is for sickle cell disease.[19] Nevertheless, there may be a role for screening selected patients at higher risk.

To the best of our knowledge, this is the largest analysis demonstrating the association between PAH and P. vera as derived from the NIS. Despite the large sample size and nationally diverse cohort, our study has several important limitations. The NIS database provides details from a single inpatient hospitalization. This precludes any follow-up analysis regarding long-term morbidity and mortality as well as establishing causality. Additionally, these data represent an administrative discharge abstract, excluding many crucial laboratory values—hematocrit level, leukocyte and platelet counts, mutation testing, erythropoietin levels. The absence of diagnostic test results (echocardiogram and right-heart catheterization) prohibits us from confirming the diagnosis of PAH and differentiating those cases of PH caused by elevated pulmonary artery pressure and other etiologies. The inpatient focus of NIS data excludes patients with P. vera and PAH treated in the outpatient setting, admitted under observation status or discharged from the emergency department.

In conclusion, P. vera is associated with an increased prevalence of PAH compared with the general population. It was also found to be an independent predictor of PAH after accounting for other risk factors. Patients with P. vera and PAH have an increased risk for inpatient mortality and in-hospital cardiac arrest compared with those without P. vera. Large-scale studies of patients with P. vera are essential to better describe the mechanisms of PAH, evaluate potential risk factors, and ultimately improve patient outcomes.

Author Contribution

Jessica Maria Stempel, MD (corresponding author), is responsible for the conceptualization, methodology, project administration and supervision, writing and editing of the manuscript.

Akshaya Gopalakrishnan, MD, is responsible for the methodology, formal analysis, investigation, data curation, and reviewing/editing of the manuscript.

Parasuram Krishnamoorthy, MD, is responsible for the methodology, formal analysis, investigation, data curation, and review/editing of the manuscript.

Kevin Bryan Lo, MD, is responsible for the methodology, review/editing of the manuscript, and visualization of the project.

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Disclosures

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.

1. Wautier MP, El Nemer W, Gane P, Rain JD, Cartron JP, Colin Y, Le Van Kim C, Wautier JL. Increased adhesion to endothelial cells of erythrocytes from patients with polycythemia vera is mediated by laminin α5chain and Lu/BCAM. *Blood* 2007;110:894–901.
2. Landolfi R, Di Gennaro L, Falanga A. Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. *Leukemia* 2008;22:2020–2028.
3. Perros F, Montani D, Dorfmüller P, Durand-Gasselin I, Tcherakian C, Le Pavec J, Mazmanian M, Fadel E, Mussot S, Mercier O, Hervé P, Emilie D, Eddahibi S, Simonneau G, Souza R, Humbert M. Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008;178:81–88.
4. Hickey MM, Richardson T, Wang T, Mosqueira M, Arguiri E, Yu H, Yu QC, Solomides CC, Morrisey EE, Khurana TS, Christofidou-Solomidou M, Simon MC. The von Hippel-Lindau Chuvash mutation promotes pulmonary hypertension and fibrosis in mice. *J Clin Invest* 2010;120:827–839.
5. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, Tognoni G, Marchioli R. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. *Blood* 2007;109:2446–2452.
6. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, De Stefano V, Elli E, Iurlo A, Latagliata R, Lunghi F, Lunghi M, Marfisi RM, Musto P, Masciulli A, Musolino C, Cascavilla N, Quarta G, Randi ML, Rapezzi D, Ruggeri M, Rumi E, Scortechini AR, Santini S, Scarano M, Siragusa S, Spadea A, Tieghi A, Angelucci E, Visani G, Vannucchi AM, Barbui T. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med* 2013;368:22–33.
7. Vannucchi AM, Antonioli E, Guglielmelli P, Longo G, Pancrazzi A, Ponziani V, Bogani C, Ferrini PR, Rambaldi A, Guerini V, Bosi A, Barbui T. Prospective identification of high-risk polycythemia vera patients based on JAK2V617F allele burden. *Leukemia* 2007;21:1952–1959.
8. Dorfmüller P, Günther S, Ghigna MR, De Montpréville VT, Boulate D, Paul JF, Jaïs X, Decante B, Simonneau G, Dartevelle P, Humbert M, Fadel E, Mercier O. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. *Eur Respir J* 2014;44:1275–1288.
9. Vanderpool RR, Naeije R. Hematocrit-corrected pulmonary vascular resistance. *Am J Respir Crit Care Med* 2018;198:305–309.
10. Ma X, Vanasse G, Cartmel B, Wang Y, Selinger HA. Prevalence of polycythemia vera and essential thrombocythemia. *Am J Hematol* 2008;83:359–362.
11. Gupta R, Perumandla S, Patsiornik Y, Niranjan S, Ohri A. Incidence of pulmonary hypertension in patients with chronic myeloproliferative disorders. *J Natl Med Assoc* 2006;98:1779–1782.
12. Garypidou V, Vakalopoulou S, Dimitriadis D, Tziomalos K, Sfikas G, Perifanis V. Incidence of pulmonary hypertension in patients with chronic myeloproliferative disorders. *Haematologica* 2004;89:245–246.
13. Brabrand M, Nørregaard Hansen K, Laursen CB, Stauffer Larsen T, Vestergaard H, Abildgaard N. Frequency and etiology of pulmonary hypertension in patients with myeloproliferative neoplasms. *Eur J Haematol* 2019;102:227–234.
14. Galie N, Hunbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Sinonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez M, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard L, Trinidade P, Zompatori M, Hoeper M. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016;37:67–119.

15. Guilpain P, Montani D, Damaj G, Achouh L, Lefrère F, Le Pavec J, Marfaing-Koka A, Dartevelle P, Simonneau G, Humbert M, Hermine O. Pulmonary hypertension associated with myeloproliferative disorders: a retrospective study of ten cases. *Respiration* 2008;76:295–302.
16. Guazzi M, Naeije R. Pulmonary hypertension in heart failure: pathophysiology, pathobiology, and emerging clinical perspectives. *J Am Coll Cardiol* 2017;69:1718–1734.
17. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. *Eur Respir J* 2007;30:1103–1110.
18. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood* 2003;101:1257–1261.
19. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, Kato GJ, Ataga KI, Gibbs JS, Castro O, Rosenzweig EB, Sood N, Hsu L, Wilson KC, Telen MJ, DeCastro LM, Krishnamurti L, Steinberg MH, Badesch DB, Gladwin MT. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. *Am J Respir Crit Care Med* 2014;189:727–740.