Heart & Lung 48 (2019) 34–38

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Thrombocytopenia independently predicts death in idiopathic PAH

Rachel J. Le, MD [a], Carolyn M. Larsen, MD [a], Eric R. Fenstad, MD [b], Robert B. McCully, MD [a], Robert P. Frantz, MD [a], Michael D. McGoon, MD [a], Garvan C. Kane, MD, PhD [a,*]

[a] Pulmonary Hypertension Clinic, Department of Cardiovascular Diseases, Gonda 6, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States
[b] Minneapolis Heart Institute, United States

ARTICLE INFO

Article history:
Received 28 June 2016
Received in revised form 8 August 2018
Accepted 19 August 2018
Available online 6 October 2018

Key words:
Thrombocytopenia
Mortality
Prediction
Pulmonary hypertension

ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a progressive vascular disorder with a high mortality. Clinical experience and small case series suggest thrombocytopenia may be frequent in this population and associated with a poor prognosis. We sought to estimate the prevalence of thrombocytopenia in patients with PAH and characterize its association with disease characteristics and patient outcome.
Methods: Single center cohort study of 714 incident adult patients with Group 1 PH who were evaluated for baseline platelet count at the time of diagnosis. Pts were stratified into three groups: normal platelet count (>150 × 10^9/L), Grade 1 thrombocytopenia (75–149 × 10^9/L) and Grade 2–4 thrombocytopenia (<75 × 10^9/L).
Results: The median platelet count was 209 × 10^9/L (IQR 163, 264). There were 572 (80%) pts without thrombocytopenia, 107 (15%) with Grade 1 and 35 (5%) with Grade 2–4 thrombocytopenia. The median pt age was 55 years (IQR 44–65) with no difference between platelet groups ($p = 0.85$). Men were more likely to have thrombocytopenia (62, 34%) than women (80, 15%, $p < 0.0001$). Thrombocytopenia was frequent with portopulmonary PAH (84%) as opposed to idiopathic PAH (iPAH; 14%) or connective tissue disease associated PAH (12%). Platelet counts were not associated with functional class symptoms, the degree of right ventricular enlargement or dysfunction or tricuspid regurgitation by echocardiography. Invasive hemodynamics of right atrial pressure, mean pulmonary artery pressure and pulmonary vascular resistance were also similar between platelet groups. Thrombocytopenia was associated with higher mortality in iPAH patients (age- and sex-adjusted 5 year mortality [HR 1.95 (1.20, 3.08) $p = 0.008$] but not in other etiology groups. In a multivariate model of iPAH patients (adjusted for age, sex, DLCO, PVR, creatinine and 6MW distance) thrombocytopenia was most predictive of 5-year mortality [HR 1.68 (1.32, 2.12), $p < 0.0001$].
Conclusion: Thrombocytopenia in the context of iPAH portends a poor prognosis and is a simple independent factor to consider in judging severity of disease.

Introduction

Pulmonary arterial hypertension (PAH) is a disease characterized by pulmonary vascular remodeling with clinical progression typically correlating with right heart failure. Thrombocytopenia in pulmonary hypertension has been described in the literature on few occasions in small retrospective case series. In the largest cohort study available Chin et al describe an independent association of thrombocytopenia with epoprostenol use that appears to be dose dependent in a study of 87 PAH patients.[1] Additionally, they note an independent association of thrombocytopenia with more severe hemodynamics. The latter finding may be a result of progressive right heart failure leading to portal hypertension, splenomegaly and platelet sequestration. Several cases of PAH associated with microangiopathic hemolytic anemia and thrombocytopenia have also been described in the literature.[2,3]

More recently, Mojadidi and colleagues have demonstrated an association of thrombocytopenia with poor prognosis in an echocardiographically defined cohort of severe pulmonary hypertension.[4] A smaller study of 65 idiopathic PAH patients suggested platelet count below the mean (200 × 10^9/L) was a significant prognostic variable.[5] Probably due to sample size limitations this study failed to confirm other traditional prognostic variables. As therapeutic options for PAH continue to progress, risk stratification of patients utilizing prognostic variables is imperative. The minimally invasive nature of laboratory testing with platelet counts is ideal given the universal availability of

Abbreviations: BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; PAH, pulmonary arterial hypertension; PFT, pulmonary function test(ing); RHC, right heart catheterization; WHO, World Health Organization

* Corresponding author.
E-mail address: kane.garvan@mayo.edu (G.C. Kane).

https://doi.org/10.1016/j.hrtlng.2018.08.009
0147-9563/$ - see front matter © 2018 Elsevier Inc. All rights reserved.

the test. In the present study we sought to estimate the prevalence of thrombocytopenia, characterize the clinical and hemodynamic factors of patients with this co-morbid diagnosis, and determine its association with outcome in patients diagnosed with PAH.

Methods

Study sample

This study was conducted with use of our institutional PAH registry. We identified all adult patients (≥18 years) diagnosed with PAH at our tertiary care referral-based academic practice between 1/1/1995 and 12/31/2009. Diagnosis of PAH was based on current practice criteria[6] and diagnosis date was set at the time of first clinic visit in which diagnosis at our center was confirmed. Patients were not on PH therapy. Data entry occurred after the complete initial patient evaluation. Data presented here were collected at, or near, diagnosis. The etiology of PAH was recorded for each patient: idiopathic or familial PAH (iPAH), PAH associated with connective tissue disease (cPAH), portopulmonary PAH (poPAH), PAH associated with congenital heart disease or other PAH.

Platelet count was assessed in all patients at the time of PAH diagnosis. Patients in whom a platelet count was not available within 6 months of diagnosis were excluded (n = 34). Classification of thrombocytopenia was based upon the Common Terminology Criteria for Adverse Events of the National Cancer Institute.[7] No thrombocytopenia was considered when platelet counts were $\geq 150 \times 10^9$/L. Thrombocytopenia grades were defined as platelet counts between $75-149 \times 10^9$/L as grade 1; $50-74 \times 10^9$/L as grade 2; $25-49 \times 10^9$/L as grade 3; and $<25 \times 10^9$/L as grade 4.

The primary endpoint of this study was 5-year mortality. Survival data was obtained from combined review of the medical record and cross referencing with the social security national death index. Patient data was censored at 5 years or at the time of heart/ heart-lung or liver organ transplantation. Mortality status at 5 years was available from the medical record in greater than 95% of the cohort. All patients agreed to the use of their medical information for research purposes and the study was approved by the Mayo Foundation Institutional Review Board.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as the absolute number and percentages. Variables were compared utilizing unpaired t-test, chi-squared tests or ANOVA. Linear regression analysis was used for correlation assessment of continuous variables. Cox-proportional hazard models were used to assess predictors of 5-year mortality. Results are presented as hazard ratios (HRs) with 95% CIs. Models were developed using stepwise techniques with consideration of clinically relevant variables having $p < 0.1$ by univariate analysis. Variables were retained in the model at a threshold of $p < 0.1$. For persons with incomplete data, additional categorical variables (test performed, test not performed) were included. Long-term follow-up of patients is presented based on the Kaplan-Meier product-limit method and compared between groups using the log-rank test. p values <0.05 were considered statistically significant. All data analyses were performed using JMP, version 10.0 (SAS Institute Inc., Cary, North Carolina).

Results

Clinical characteristics

There were 714 patients who met criteria for inclusion. Platelet count was obtained a mean of 8.6 days (SD 23.4 days) from PAH diagnosis. Thirty-four patients were excluded as no platelet count was available within 6 months of PAH diagnosis. The median platelet count was 209×10^9/L (IQR 163, 264). The majority of patients had no thrombocytopenia (572, 80.1%). Grade 1–4 thrombocytopenia was present in 107 (15.0%), 28 (3.9%), 5 (0.7%) and 2 (0.3%) patients, respectively. Given the small number of patients with Groups 2–4 thrombocytopenia, these groups were combined for analyses. The presence and severity of thrombocytopenia varied across etiology groups as shown in Fig. 1.

All patients were within 3 months of diagnosis. The majority (96%) were newly diagnosed and not on any pulmonary hypertension therapy. Twenty-nine patients had been diagnosed recently and referred to the Mayo PH clinic and had been commenced on some therapy when seen (8/29 on prostaglandin analogs, 11 on endothelin receptor antagonists and 17 on PDE 5 inhibitors). The use of therapy was not associated with platelet counts.

The median patient age was 55 years (IQR 44–65) with no difference between platelet groups (p = 0.85). The distribution of demographic, clinical, echocardiographic and hemodynamic variables by presence and grade of thrombocytopenia are presented in Table 1. The presence of thrombocytopenia was more common in men (62, 34%) than women (80, 15%, $p < 0.0001$). The differences in thrombocytopenia rates by sex were larger related to higher rates of thrombocytopenia in patients with idiopathic PAH (Table 2).

Six-minute walk testing was more frequently completed in patients without thrombocytopenia (78% vs. 65%, p = 0.009); in those who completed a walk, there was no difference in the mean distance walked. Moderate or greater right atrial enlargement was more common in patients without thrombocytopenia (67% vs 57%, p = 0.046). There was no difference in other right heart parameters by echocardiography. Cardiac index was lower in patients without thrombocytopenia (2.5 L/min/m^2 vs 2.7, p = 0.02) but no difference was seen in other factors assessed at right heart catheterization. There was no relationship between platelet count and right atrial pressure at cardiac catheterization (r^2 = 0.004; p = 0.11).

Factors associated with all-cause mortality

One, three and five-year survival were 81.9, 62.9 and 50.5% respectively for the study cohort. The presence of thrombocytopenia was associated with increased mortality (HR 1.56; 95% CI 1.20–2.00). When stratified by etiology, the presence of thrombocytopenia was associated with mortality only in iPAH patients (unadjusted HR 2.34; 95% CI 1.53–3.45). Kaplan-Meier survival curves for the iPAH patient cohort are shown in Fig. 2. Several predictors of increased mortality were observed in univariate risk assessment of the iPAH cohort (Table 3).

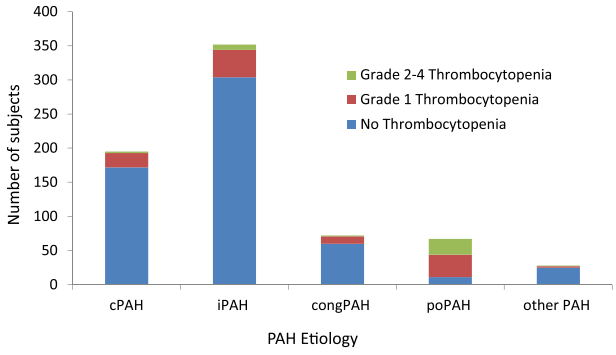

Fig. 1. Distribution of thrombocytopenia presence and severity by PAH etiology; $p < 0.0001$ for between group differences.

Table 1
Baseline clinical data by presence of absence of thrombocytopenia.

	No thrombocytopenia (n = 572)	Thrombocytopenia (n = 142)	p value
Age (years)	53.6, 15.2	52.8, 13.1	0.57
Gender (female, %)	450 (79%)	80 (56%)	<**0.0001**
NYHA FC 1–2	154 (27%)	49 (35%)	0.19
NYHA FC 3	333 (59%)	74 (53%)	
NYHA FC 4	75 (13%)	16 (12%)	
DLCO, % predicted	59.2, 23.6	61.1, 19.2	0.50
6MWD, meters (n = 445, 93)	326, 125	332, 106	0.69
Positive Vasodilator Response	48 (12%)	12 (13%)	0.88
RAP, mmHg (n = 466, 116)	11.9, 6.3	12.0, 6.3	0.92
mPAP, mmHg (n = 524, 129)	51.6, 13.1	53.3, 14.2	0.21
Cardiac Index, L/min/m^2 (n = 464, 119)	2.5, 0.8	2.7, 0.9	**0.02**
PVR, WU (n = 427, 118)	9.7, 5.2	8.8, 5.7	0.11
RAE, moderate or > (n = 367, 104)	247 (67%)	59 (57%)	**0.046**
RVE moderate or > (n = 367, 104)	264 (72%)	73 (70%)	0.73
RVD moderate or > (n = 367, 104)	212 (58%)	62 (60%)	0.74
TR moderate or > (n = 366, 104)	206 (56%)	51 (49%)	0.19

NYHA FC, New York Heart Association Functional Class; 6MWD, six-minute walk distance; DLCO, diffusion capacity for carbon monoxide; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAE, right atrial enlargement; RVE, right ventricular enlargement; RVD, right ventricular dysfunction; TR, tricuspid regurgitation.

Only a minority of patients in the cohort had simultaneous measures of brain natriuretic peptide (BNP) and platelet count (n = 259, 36%). In those in whom *no BNP* was available (n = 453), the univariate risk ratio per thrombocytopenia grade was 1.46 (1.16–1.80); p = 0.001 and in those that *BNP was available* (n = 259) the risk ratio per thrombocytopenia grade was 1.23 (0.83–1.72); p = 0.28. In a model that incorporated BNP elevation (presence or absence) and thrombocytopenia grade in these 256 patients with simultaneous measures, there appeared to be independent risk association with a risk ratio per thrombocytopenia grade of 1.34 (0.90–1.91); p = 0.14 and a risk ratio for elevation in BNP 2.38 (1.49–3.99); p = 0.0002.

When all variables of interest were incorporated into a multivariate model, the following variables remained predictive of outcome: 6MWD, pulmonary vascular resistance, DLCO, creatinine and progressive thrombocytopenia (Fig. 3). Increasing grade of thrombocytopenia (from none to grade 1 to grade 2–4) was the most predictive (HR 1.68; 95% CI 1.32–2.12).

Table 2
Association of patient sex and thrombocytopenia rates.

	Thrombocytopenia rates		
	% in men	% in women	
cPAH	3/28, 11%	20/167, 12%	0.85
iPAH	24/92, 26%	24/260, 9%	0.0001
congPAH	5/22, 23%	7/50, 14%	0.37
poPAH	28/32, 88%	28/35, 80%	0.40
Other PAH	2/10, 20%	1/18, 6%	0.25

cPAH, connective tissue disease related pulmonary hypertension; iPAH, idiopathic pulmonary arterial hypertension; congPAH, congenital systemic to pulmonary shunt related pulmonary arterial hypertension; poPAH, portopulmonary Hypertension; other PAH, other pulmonary arterial hypertension.

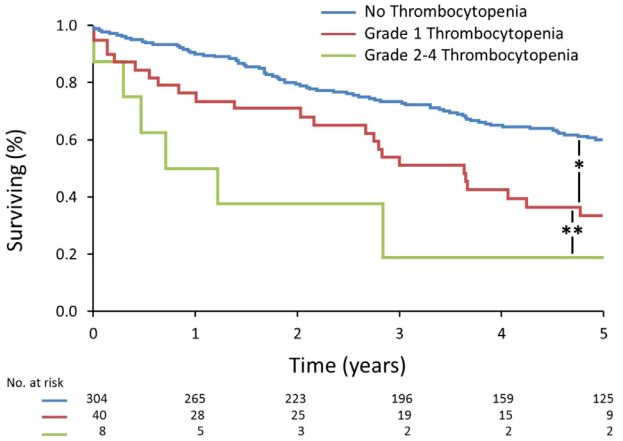

Fig. 2. Kaplan–Meier five-year survival assessed by presence and degree of thrombocytopenia in iPAH patients.

Discussion

Thrombocytopenia occurs in up to 20% of patients with PAH. Not unexpectedly, thrombocytopenia is common in poPAH (>80%) and relatively uncommon in other PAH etiology groups (<20%). The frequency of thrombocytopenia in poPAH is slightly greater than the 64% reported in cirrhotic patients.[8] Thrombocytopenia grade was not predictive of survival in our poPAH cohort. Men tended to have higher rates of thrombocytopenia in iPAH, but the reasons of this are unclear.

Multiple factors may lead to thrombocytopenia in PAH patients. Progressive right heart failure resulting in congestive hepatopathy and associated splenomegaly with platelet sequestration is one prominent theory. We found no relationship between right atrial pressure and platelet count in the present study. Neither were typical indicators of progressive right heart failure associated with thrombocytopenia in our analysis. These findings raise the hypothesis that unlike most novel biomarkers in PAH, platelet count is not a marker of right ventricular systolic function. Measures such as (NT-pro) brain natriuretic peptide, and even variables such as sodium and creatinine all likely reflect RV systolic function, which make them useful measures in establishing prognosis in pulmonary arterial hypertension. So if thrombocytopenia does not predict right ventricular systolic

Table 3
Age- and gender- adjusted predictors of 5-year mortality in iPAH patients.

	Univariate hazard ratio	95% Confidence intervals	p-value
Age (per 10 years)	1.11	0.99, 1.25	**0.08**
Gender (female favored)	0.70	0.49, 1.00	**0.05**
Thrombocytopenia, by grade	2.10	1.50, 2.84	<**0.0001**
Thrombocytopenia, presence	2.34	1.53, 3.45	**0.0002**
Functional class (1–2, 3, 4)	1.68	1.28, 2.19	**0.0001**
DLCO (per 10% decline)	1.33	1.21, 1.48	<**0.0001**
6MWD (by 50 m decline)	1.27	1.17, 1.38	<**0.0001**
Positive vasodilator response	1.48	0.77, 3.32	0.26
RAP (by 5 mmHg)	1.34	1.17, 1.53	<**0.0001**
mPAP (by 10 mmHg)	1.12	0.98, 1.27	0.10
Cardiac index (per 1 L/min/m^2)	0.63	0.48, 0.83	**0.0006**
PVR (by 5 WU)	1.30	1.10, 1.54	**0.003**
RAE (mod or >)	1.38	0.93, 2.09	0.11
RVE (mod or >)	1.51	0.99, 2.37	**0.05**
RVD (mod or >)	1.12	0.78, 1.62	0.55
TR (mod or >)	1.21	0.84, 1.77	0.31
REVEAL score by groups	1.41	1.24, 1.60	<**0.0001**

DLCO, diffusion capacity for carbon monoxide; 6MWD, six minute walk distance; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAE, right atrial enlargement; RVE, right ventricular enlargement; RVD, right ventricular dysfunction; TR, tricuspid regurgitation.

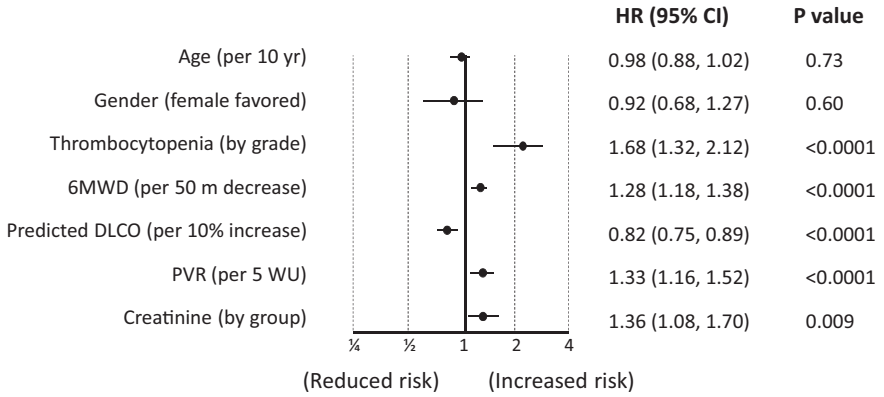

Fig. 3. Multivariate predictors of survival in iPAH. (cPAH, connective tissue disease related pulmonary hypertension; iPAH, idiopathic pulmonary arterial hypertension; congPAH, congenital systemic to pulmonary shunt related pulmonary arterial hypertension; poPAH, portopulmonary hypertension; other PAH, other pulmonary arterial hypertension).

function, what are they a marker of and why do they associate with prognosis? Plausibly, the platelet count may actually be a variable that reflects the vascular pathobiology in the lung. It has been suggested, the thrombocytopenia may originate as result of defects in platelet production or as a result of peripheral platelet clearance.[9] Some reports have suggested thrombocytopenia may arise from sequestration and fragmentation, which may result with hemodynamic pulmonary vascular stress in the plexiform lesions characteristic of PAH.[2,3] These lesions are atypical in PH associated with left heart disease or chronic hypoxia. Our study was restricted to PAH, but further study of thrombocytopenia in other PH etiologies compared to PAH patients would be of interest. Significant perturbations in a variety of stimulatory and inhibitory pulmonary vascular signals are recognized in patients with pulmonary arterial hypertension, many of which affect platelet activation, including enhanced thromboxane A2, and down regulated endothelial derived prostacyclin and nitric oxide.[9–12] Drug therapy has also been thought to contribute to thrombocytopenia in PAH patients. Our study assessed platelet count at the time of PAH diagnosis and hence treatment cannot explain the results seen.

In our patient cohort, survival was slightly less than that of other recently published cohorts.[13–15] This is likely explained by the different proportion of patients with cPAH and poPAH in our cohort compared to the other studies. The results from recent cohorts, ours included, show significant progress in pulmonary hypertension treatment with survival markedly improved compared to initial data from three decades ago.[16]

Multiple prognostic factors are utilized by clinicians when individualizing patient treatment recommendations.[13,17,18] In a recent analysis Mojadidi and colleagues suggested an independent prognostic role of moderate-severe thrombocytopenia in an echocardiographically defined PH group.[4] Our study only assessed group 1 PH with similar findings restricted to iPAH patients. This same finding was not appreciated in patients with other etiologies of PAH. Our data are consistent with the results of Taguchi et al who reported a survival difference in patients with iPAH and a platelet count above versus below the mean (200×10^9/L).[5] Our study added to their data by providing a large cohort of patients. We were able to demonstrate the independent negative impact of thrombocytopenia on survival in iPAH patients while confirming other traditional adverse prognostic variables. We also show no prognostic value of thrombocytopenia in other etiologies of PAH. This may reflect alternative mechanisms for the development of thrombocytopenia in patients with cPAH and poPAH rather than reflecting increased severity of PAH.

Limitations

Our study is a single-center retrospective analysis. The practice patterns specific to our center may influence the results. Additionally, the study is of patients evaluated at a PH Care Center and as a result may be prone to survival bias. These factors are unlikely to substantially affect the study conclusions given the similarities between our study and other published cohorts. Whether platelet counts vary over time including in response to chronic drug therapy and whether any changes in platelet counts are associated with disease progression and outcome could not be assessed in this study and warrants further investigation. Plausibly, serial changes in platelet counts over time may serve as a marker of changes in the patients' underlying pulmonary vascular pathobiology. Further studies should assess serial platelet counts in patients with PAH. All patients included were newly diagnosed. Whether platelet counts have similar relationship to disease characteristics or outcome in patients on therapy with chronic disease needs to be tested. These questions all warrant further investigation. Finally, we are unable to comment on potential implications of different platelet counting systems, as there was no standardization in the specific method of platelet count measurements across patients.

Conclusion

While survival in PAH has improved significantly in the modern era, PAH remains a disease characterized by high mortality in a relatively young population. Continued improvement in treatment with new therapies will be advanced by accurate assessment of patient risk. The development of novel prognostic markers in PAH should remain a priority. In patients with iPAH, we show that thrombocytopenia is independently associated with reduced 5-year survival. Our study demonstrates the prognostic role of platelet testing in patients with newly diagnosed iPAH.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2018.08.009.

References

1. Chin KM, Channick RN, de Lemos JA, Kim NH, Torres F, Rubin LJ. Hemodynamics and epoprostenol use are associated with thrombocytopenia in pulmonary arterial hypertension. *Chest*. 2009;135:130–136.
2. Stuard ID, Heusinkveld RS, Moss AJ. Microangiopathic hemolytic anemia and thrombocytopenia and primary pulmonary hypertension. *New Engl J Med*. 1972;287:869–870.

3. Jubelirer SJ. Primary pulmonary hypertension. Its association with microangiopathic hemolytic anemia and thrombocytopenia. *Arch Intern Med*. 1991;151:1221–1223.
4. Mojadidi MK, Goodman-Meza D, Eshtehardi P, et al. Thrombocytopenia is an independent predictor of mortality in pulmonary hypertension. *Heart Lung*. 2014;43:569–573.
5. Taguchi H, Kataoka M, Yanagisawa R, et al. Platelet level as a new prognostic factor for idiopathic pulmonary arterial hypertension in the era of combination therapy. *Circ J*. 2012;76:1494–1500.
6. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc. and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573–1619.
7. Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 National Cancer Institute.
8. Benza RL, Gomberg-Maitland M, Miller DP, et al. The reveal registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest*. 2012;141:354–362.
9. Bashour FN, Teran JC, Mullen KD. Prevalence of peripheral blood cytopenias (hypersplenism) in patients with nonalcoholic chronic liver disease. *Am J Gastroenterol*. 2000;95:2936–2939.
10. Herve P, Humbert M, Sitbon O, et al. Pathobiology of pulmonary hypertension. The role of platelets and thrombosis. *Clin Chest Med*. 2001;22:451–458.
11. Christman BW, McPherson CD, newman JH, King. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med*. 1992;327:70–75.
12. Klinger JR, Abman SH, Gladwin MT. Nitric oxide deficiency and endothelial dysfunction and pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2013;188:639–646.
13. Lannan KL, Phipps RP, White RJ. Thrombosis, platelet, microparticles and PAH: more than a clot. *Drug Discov Today*. 2014;19:1230–1235.
14. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL registry. *Chest*. 2012;142:448–456.
15. Humbert M, Sitbon O, Yaïci A. et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;36:549–555.
16. Korsholm K, Andersen A, Kirkfeldt RE, Hansen KN, Mellemkjñr S, Nielsen-Kudsk JE. Survival in an incident cohort of patients with pulmonary arterial hypertension in Denmark. *Pulm Circ*. 2015;5:364–369.
17. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med*. 1987;107:216–223.
18. Fenstad ER, Le RJ, Sinak LJ, et al. Pericardial effusions in pulmonary arterial hypertension: characteristics, prognosis, and role of drainage. *Chest*. 2013;144:1530–1538.