

Survival in Severe Pulmonary Hypertension Due to Chronic Lung Disease: Influence of In-Hospital Platelet Distribution Width

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Research

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Abstract

BACKGROUND: Platelet distribution width (PDW) has been recognized as risk predictors of idiopathic pulmonary arterial hypertension. This study aims to investigate whether in-hospital PDW would be useful to predict all-cause death in patients with severe pulmonary hypertension due to chronic lung diseases (CLD-PH).

METHODS: Early in-hospital PDW was measured in 67 severe CLD-PH patients who were confirmed by right heart catheterization and followed up. Event-free survival was estimated using the Kaplan–Meier method and analyzed with the log-rank test. Cox proportional hazards models were performed to determine the association between the PDW level and all-cause death.

RESULTS: Pulmonary function test and echocardiography parameters were different among patients divided by 17% (the upper reference range of the PDW). There were no significant differences in both clinical variables and RHC parameters among patients with $PDW \geq$ or $<$ 17%. During median of 2.4 (2.5, 3.7) years of follow-up, 44 patients died. A significant association was noted between in-hospital PDW level and the adjusted risk of all-cause mortality (hazard ratio [HR], 1.245; 95% confidence interval [CI], 1.099-1.409). Compared with those with $PDW <$ 17%, the HR for all-cause death increased to 5.067 (95% CI: 2.420-10.609, $P <$ 0.001) among patients with $PDW \geq$ 17 %. Higher levels of PDW were also associated with increased risk of all-cause death.

CONCLUSIONS: In-hospital PDW was independently associated with all-cause death in patients with severe CLD-PH. This potentially could be used to estimate the severity of severe CLD-PH.

Introduction

Pulmonary hypertension (PH) is a common complication of chronic lung diseases (CLD) and often progresses to right heart failure (RHF) and death[1, 2]. According to the hemodynamics[2, 3], PH in CLDs is classified into mild PH (mean pulmonary artery pressure [mPAP] \geq 25 mm Hg) and severe PH (mPAP \geq 35 mm Hg or 25 mm Hg $<$ mPAP $<$ 35 mm Hg with cardiac index [CI] $<$ 2.0 l/min/m² or pulmonary vascular resistance [PVR] $>$ 6 Wood units). Although accounting for only a minority of CLD-PH, severe CLD-PH patients generally have progressive vascular remodeling accompanying parenchymal disease that develops independently from pulmonary functional impairment, and generally progress to RHF and death [2, 4]. Currently, studies regarding severe CLD-PH survival are sparse. It makes all the difference that we explore the risk factors which may affect the prognosis of severe CLD-PH.

Recently, Looney MR et al[5] identified that the lungs made substantial contribution as a primary site of terminal platelet production and an organ with considerable hematopoietic potential, accounting for approximately 50% of total platelet production or 10 million platelets per hour. Idiopathic pulmonary arterial hypertension (IPAH) patients with a lower platelet level before treatment had a higher mortality rate compared to those with a higher level[6, 7]. Platelet distribution width (PDW), in addition to serving as

a marker of platelet activation, has been reported to increase in PAH associated with congenital heart diseases[8–10] and IPAH[11], and could help to predict disease severity as well.

Therefore, the objective of this study is to investigate the value of PDW predicting the survival in patients with severe CLD-PH.

Methods

Study Design and Patients

This is a retrospective study. Sixty-seven patients with severe CLD-PH were enrolled in Shanghai Pulmonary Hospital from 2009 to 2014. The established diagnosis of “severe PH” was in accordance with the following criteria: $mPAP \geq 35$ mm Hg or 25 mm Hg $< mPAP < 35$ mm Hg with $CI < 2.0$ L/min/m² or $PVR \geq 6$ Wood units[2]. Patients were excluded if: (1) other Group PH; (2) on anticoagulant or antiplatelet drug therapy including aspirin on admission.

This study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Ethics Committee of Shanghai Pulmonary Hospital approved the protocol (K08-015C), and written informed consent was obtained from all patients.

Assessment of patients

Demographic variables such as sex, age, body mass index (BMI), pulmonary function test (PFT), echocardiography and RHC parameters were obtained at baseline. RHC was performed as described previously[12]. All patients were admitted to the catheterization laboratory at Shanghai Pulmonary Hospital, where they were in room air and without additional oxygen supply. An 8 F introducer sheath was placed in the left antecubital vein or left subclavian vein, and a 7 F Swan-Ganz catheter (Edwards Lifesciences Co., Ltd, USA) was advanced into the pulmonary artery. Transducers were positioned at the midaxillary line and zeroed at atmospheric pressure. Cardiac output (CO) was measured in triplicate by the thermodilution technique (Cardiac Output Computer; GE, USA) with iced normal saline. mPAP, pulmonary artery wedge pressure (PAWP) and CO were measured at baseline. The CI was calculated by dividing CO by body surface area (BSA). Pulmonary vascular resistance (PVR) was calculated as $mPAP$ minus PAWP divided by CO. The heart rate and the transcutaneous arterial oxygen saturation were monitored continuously. Transthoracic echocardiography was underdone as described previously[13].

Blood sample

Blood samples were obtained in the non-fasting state when admitted into hospital. The blood sample for PDW measurement was collected in dipotassium EDTA tubes. Whole blood samples were processed via an automatic blood counter (ACL top 700; Beckman Corporation, USA). A technician who was blinded to patients' data performed the blood test within 30 minutes. The reference values for PDW ranged between 9.0% and 17.0%.

Outcomes

The main outcome was the time from the date of blood sampling to the occurrence of all-cause death. All patients were followed up until death, or through April 30, 2019, whichever occurred first. Specific events were confirmed through medical records, death certificates or based on confirmation provided by immediate family members.

Statistical Analysis

Results are expressed as mean with standard deviation (SD) or medians (and interquartile range) for continuous variables and absolute number for categorical variables. Comparisons were performed using independent-sample t-test or Mann–Whitney U test for continuous variables and chi-square test for categorical variables among patients grouped by the upper reference range of PDW (17%). Pearson or Spearson correlation test was performed to assess correlations between variables of interest and the PDW level. Cox proportional hazards models were performed to determine the predictors of independent all-cause death. First univariate Cox procedure was used to screen the predicting factors, then, a stepwise selection procedure was used to find independent predictors of all-cause mortality with p-to-enter of 0.10 or less and p-to-remove of 0.15 or more. 95% confidence intervals (CIs) were calculated to assess the significance of the estimates at a level of 0.05. Survival curves were plotted using Kaplan–Meier method and analyzed with the log-rank test.

In all univariate analyses, $P \leq 0.05$ was considered statistically significant. All statistical methods were performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5.04 software (GraphPad Software, Inc., San Diego, California).

Results

Characteristics of the studies

A total of 67 patients with severe CLD-PH matched inclusion criteria. The mean age at diagnosis was 58.0 ± 1.6 years with a male preponderance of 56.7% (Table 1). PDW ranged from 10.0% to 21.3% (median, 14.3%; interquartile range, 12.2% to 16.8%; mean, $14.7 \pm 0.4\%$), and 16 (23.9%) had a PDW level above the normal range of 9.0% to 17.0%. The median follow-up was 2.4 (2.5,3.7) years with the a maximal duration of 7.1 years. During follow-up, 44 (65.7%) patients died, and no patients underwent lung transplantation. No patient was lost to follow-up, giving us a 100% follow-up rate. In-hospital PDW was significantly higher in no-survivors ($n = 44$) than survivors ($n = 23$) ($15.6 \pm 3.3\%$ vs. $13.0 \pm 1.8\%$, $P = 0.004$; Figure 1). The reference values for PDW ranged between 9.0% and 17.0%, so all the patients were divided into two groups: PDW $\geq 17\%$ group ($n = 16$) and PDW $< 17\%$ group ($n = 51$). Table 1 presents the demographic, PFT, hemodynamic and echocardiographic data of the two groups. No statistically significant differences were observed in demography, etiology and hemodynamics between the two groups (Table 1). There were no differences in PFT, other than a lower FEV1/FVC ratio in patients with PDW $\geq 17\%$ [43.1 (32.1, 43.4)] than those with PDW $< 17\%$ [48.9 (43.8, 58.5)] ($P = 0.013$). RATD was higher in patients with PDW $\geq 17\%$ than those with PDW $< 17\%$ [5.3 (4.7, 6.3) vs. 4.7 (4.0, 5.5), $P = 0.016$].

Correlation between in-hospital PDW Level and PFT, hemodynamic and echocardiographic parameters and all-cause death

Table 2 illustrates correlation between PDW and PFT, hemodynamic and echocardiographic parameters. Right atrial transverse dimension and end-systolic stage eccentricity index (ENDSEI) showed positive correlation with PDW in severe CLD-PH patients. Univariate Cox regression analysis revealed that in-hospital PDW (hazard ratio [HR] = 1.238, 95% CI: 1.095-1.400, P = 0.001), CO (HR = 0.803, 95% CI: 0.647-0.996, P = 0.046), CI (HR = 0.659, 95% CI: 0.454-0.958, P = 0.029) and ENDSEI (HR = 2.332, 95% CI: 1.089-4.992, P = 0.029) was found to be a predictor of risk of all-cause death in patients with severe CLD-PH. In multivariate cox regression analysis, after factoring CO, CI, and ENDSEI, PDW (HR = 1.238, 95% CI: 1.095-1.400, P = 0.001) and CI (HR = 0.667, 95% CI: 0.455-0.978, P = 0.038) were independently associated with all-cause death, respectively (Table 3).

PDW difference in survival assessment

There were 44 all-cause death events during a median follow-up period of 2.4 (2.5, 3.7) years. The overall event-free survival rate was found to be 80.3%, 37.5% for the 1st year; 70.6%, 25% during the 2nd year, and 66.7%, 0% for the 3rd year, respectively, for PDW < 17% and PDW ≥ 17% subgroups.

The over event-free survival rate were statistically different between the two groups with log-ranked P-value ≤ 0.001 (Figure 2).

Discussions

PDW reflects variability in the size of circulating platelet and is routinely reported by automated laboratory equipment. We found an independent association between early in-hospital PDW value and the risk of all-cause death in patients with severe PH-CLD, most of whom had PDW levels within the normal range. Adjustment for multiple potential confounders did not eliminate the association between higher PDW levels and all-cause death. These findings are notable given that PDW is widely available to clinicians as part of the complete blood count.

PDW is a convenient indicator to assess platelet function and to reflect the platelet production rate and activation. Activation of platelets causes morphological changes, including pseudopodia formation. Progressively activated platelets with pseudopodia formation have heterogeneous sizes, and may increase PDW accordingly[14].

The association of PDW with survival may be hypothetically linked with hypercoagulation, which plays a significant role in conditions associated with survival in COPD[15] and acute myocardial infarction[16, 17]. Previously, PDW has been found to increase in tumors (cervical and hepatocellular carcinoma[18, 19], breast and gastric cancer[20, 21]) and inflammatory disorders (sepsis[22] acute pancreatitis[23]), and identified as a predictor for survival. Similarly, PDW has also been reported an elevation in IPAH patients[11]. However, instead of predicting prognosis in PAH, it could partially reflect disease severity.

Conversely, in the present study, PDW predicted prognosis in patients with severe CLD-PH, but did not correlate with CI, mPAP and PVR. This could be explained by the heterogeneity between severe CLD-PH and IPAH[4, 24]. To the best of our knowledge, this is the first demonstration that higher PDW could predict mortality in patients with severe CLD-PH.

The cause for the enhanced PDW in pulmonary diseases is not well understood. The chronic state of activation of coagulation, partly due to platelets exposed to micro trauma in the pulmonary vasculature or yet unknown factors in CLD-PH, leads to an increase in PDW. Additionally, hypoxic pulmonary vasoconstriction with platelet activation which causes morphological changes including change in platelet size, further provokes micro trauma and platelet activation. Whether any component within these morphologically altered platelet, particularly thromboxane like compound which is known vasoconstrictors, plays a provocative role in increasing PDW can be a point of debate and is just speculation on our part as it is not a point of study for this paper. The mechanism of PAH is complex and has multiple etiologies. Platelets are involved in thrombotic pulmonary vascular lesions, chronic vasoconstriction and pulmonary vascular remodeling in PH. Inflammatory processes were increasingly recognized as major pathogenic components of pulmonary vascular remodeling[25]. Systemic inflammation, thrombotic microangiopathies and immune dysfunction which were reported in patients with PAH might also cause platelet activation[26]. However, Looney MR et al Identify the lungs as a primary site of terminal platelet production and an organ with considerable hematopoietic potential[5]. Despite, the chicken or the egg analogy, for now the exact cause of increased PDW in CLD-PH remains an interesting clinical debate.

While PDW is more significantly predictive for all-cause deaths in females than males. We do not have a clear explanation for the differences between genders. It should be noted that the analyzed population by gender is small.

Study limitations

Some potential limitations should be acknowledged. First, it was a clinical study and thus the underlying pathophysiological mechanisms might only be speculative. Second, we did not investigate the causes of the increased PDW values. Third, the study population is small. Further large-scale prospective studies are warranted to clarify the potential role of PDW to predict all-cause death events.

Conclusion

We found an independent relation between the high levels of PDW and the risk of all-cause death in severe CLD-PH patients. As it can be simply and rapidly measured from routine blood examination, should our results be confirmed in larger samples, it may prove to be a widely available, inexpensive, and repeatable prognostic marker.

Abbreviations

AUC

area under curve; CI:cardiac index; Cis:confidence intervals; CLD:chronic lung diseases; ENDSEI:end-systolic stage left ventricular eccentricity index; mPAP:mean pulmonary artery pressure; PAd:pulmonary artery dilation; PAH:pulmonary arterial hypertension; PASP:pulmonary artery systolic pressure; PAWP:pulmonary artery wedge pressure; PH:pulmonary hypertension; PVR:pulmonary vascular resistance; RALD:right atrial longitudinal dimension; RAP:right atrial pressure; RATD:right atrial transverse dimension; RHC:right heart catheterization; ROC:receiver operation characteristic; RV:right ventricle; RVEDLD:right ventricular end-diastolic longitudinal dimension; RVEDTD:right ventricular end-diastolic transverse dimension; TAPSE:tricuspid annular plane systolic excursion; TV:tricuspid regurgitation; WHO:World Health Organization.

Declarations

Acknowledgement

None.

Author Contribution Statement

Conception by R.J., B.P. L.W. Y-L.Z, Q-H.Z and J.H. analyzed clinical data. Clinical management performed by P.Y., S-G.G, H-L.Q, R.Z, C-J.L and J-M.L. Manuscript organization, writing and editing by B.P, L.S., Y-L.Z, and L.W. All authors had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent for publication

All clinical, radiological, and laboratory data were collected after obtaining approval from the Institutional Ethics Committee of Shanghai Pulmonary Hospital approved the protocol (K08-015C) and according to the international standards of good clinical practice. All medical data used in this study were irreversibly anonymized.

Consent for publication

Not applicable.

Conflicts of interest

None

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Tables

Table 1 Demographic Characteristics, Pulmonary Function Test Results, Hemodynamics and Echocardiography Parameters of Patients				
	All patients	PDW \geq 17%	PDW < 17%	P
	N = 67	N = 16	N = 51	
Age (years)	58.0 \pm 1.6	56.1 \pm 2.8	56.8 \pm 1.9	0.504
Male (n, %)	38 (56.7)	13 (81.3)	25 (49.0)	0.024
BSA (\bar{x})	1.58 \pm 0.03	1.64 \pm 0.05	1.57 \pm 0.03	0.248
COPD	37 (52.2)	12 (75.0)	25 (49.0)	0.070
Bronchiectasis	12 (17.9)	1 (6.3)	11 (21.6)	0.166
ILD	6 (9.0)	1 (6.3)	5 (9.8)	0.666
Others	12 (20.9)	2 (12.5)	10 (19.6)	0.521
<i>Pulmonary Function Test</i>				
FEV1% predicted	32.4 (24.0, 44.0)	35.0 (21.3, 43.7)	31.5 (24.0, 44.9)	0.905
FEV1/FVC % predicted	47.4 (42.8, 56.1)	43.1 (32.1, 43.4)	48.9 (43.8, 58.5)	0.013
RV % predicted	204.0 \pm 12.3	246.1 \pm 40.8	195.8 \pm 12.2	0.128
TLC % predicted	113.6 \pm 4.5	110.6 \pm 6.4	134.4 \pm 11.1	0.162
DLCO % predicted	40.9 (27.9, 56.2)	28.3 (24.9, 53.3)	41.7 (28.7, 58.1)	0.281
<i>Hemodynamics</i>				
mPAP, mm Hg	46.0 (42.0, 55.0)	51.0 (43.3, 62.0)	46.0 (41.0, 54.0)	0.088
PAWP, mm Hg	9.8 \pm 0.5	10.4 \pm 4.0	9.6 \pm 4.1	0.509
CO, L/min	4.6 (4.0, 5.7)	4.4 (3.7, 5.5)	4.7 (4.3, 6.2) \pm 0.3	0.211
CI, L/min/m ²	3.1 (2.6, 3.7)	2.8 (2.3, 3.7)	3.2 (2.7, 3.7)	0.149
PVR, Wood units	8.0 (6.3, 10.2)	9.4 (6.4, 11.3)	8.0 (6.0, 9.4)	0.196
<i>Echocardiography</i>				
LVEF, %	70.9 \pm 9.0	68.8 \pm 10.8	71.4 \pm 8.5	0.307
RATD, cm	4.8(4.3, 5.5)	5.3 (4.7, 6.3)	4.7 (4.0, 5.5)	0.016
RALD, cm	5.2(4.3, 5.9)	5.6 (5.1, 6.2)	5.1 (4.3, 5.9)	0.112
RVEDTD, cm	4.3(3.8, 5.0)	4.5 (4.3, 5.4)	4.2 (3.8, 4.9)	0.219
RVEDLD, cm	6.6 \pm 0.9	6.8 \pm 0.5	6.5 \pm 1.0	0.220

PASP, mmHg	76.2 ± 22.6	82.7 ± 27.6	74.2 ± 20.6	0.190
TAPSE, cm	1.7(1.5, 1.9)	1.6(1.4, 1.9)	1.7(1.6, 1.9)	0.178
ENDSEI	1.3(1.0, 1.5)	1.5(1.2, 1.9)	1.2(1.0, 1.4)	0.059

Values are mean ± SD, median (interquartile interval) or n (%). COPD: chronic obstructive pulmonary diseases; ILD: Interstitial lung disease; mPAP: mean pulmonary artery pressure; RAP: right atrium pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; DLCO: diffusion capacity for carbon monoxide of the lung; PDW: platelet distribution width. Others included pulmonary lobectomy, chest deformity, lung destruction due to tuberculosis, pneumoconiosis, combined pulmonary fibrosis and emphysema. RVEDTD: right ventricular end-diastolic transverse dimension; RVEDLD: right ventricular end-diastolic longitudinal dimension; RATD: right atrial transverse dimension; RALD: right atrial longitudinal dimension; PASP: pulmonary arterial systolic pressure; ENDSEI: end-systolic stage eccentricity index; TAPSE: tricuspid annular plane systolic excursion; LVEF: left ventricular ejection fraction.

Table 2 Correlation between demography, pulmonary function test, hemodynamics and PDW		
	All patients	
	n = 67	
	r	p
Age (years)	-0.121	0.328
Male (n, %)	-0.070	0.573
<i>Pulmonary Function Test</i>		
FEV1% predicted	-0.063	0.679
FEV1/FVC % predicted	-0.252	0.092
RV % predicted	0.224	0.149
TLC % predicted	0.261	0.091
DLCO % predicted	-0.114	0.529
<i>Hemodynamics</i>		
mPAP, mm Hg	0.204	0.097
PAWP, mm Hg	0.085	0.492
CO, L/min	-0.117	0.347
CI, L/min/m ²	-0.120	0.335
PVR, Wood units	0.137	0.267
<i>Echocardiography</i>		
LVEF, %	-0.004	0.977
RATD, cm	0.334	0.006§
RALD, cm	0.191	0.121
RVEDTD, cm	0.185	0.133
RVEDLD, cm	0.221	0.072
PASP, mmHg	0.173	0.161
TAPSE, cm	-0.158	0.203
ENDSEI	0.280	0.021*

Abbreviations: mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; DLCO: diffusion capacity for carbon monoxide of the lung; PDW: platelet distribution width; RVEDTD: right ventricular

end-diastolic transverse dimension; RVEDLD: right ventricular end-diastolic longitudinal dimension; RATD: right atrial transverse dimension; RALD: right atrial longitudinal dimension; PASP: pulmonary arterial systolic pressure; ENDSEI: end-systolic stage eccentricity index; TAPSE: tricuspid annular plane systolic excursion; LVEF: left ventricular ejection fraction. * $P < 0.05$, § < 0.01

Table 3 Cox regression analysis for all-cause death in patients with severe CLD-PH

	Univariate Analysis		Multivariate-Adjusted Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (years)	1.012 (0.987-1.037)	0.360		
Gender	0.696 (0.381-1.271)	0.239		
Red blood cell ($\times 10^{12}/L$)	1.187 (0.829-1.689)	0.350		
Hemoglobin (g/L)	1.008 (0.997-1.020)	0.167		
White blood cell ($\times 10^9/L$)	0.932 (0.840-1.033)	0.179		
Platelet ($\times 10^9/L$)	0.996 (0.991-1.001)	0.089		
Red blood cell distribution width (%)	1.027 (0.979-1.076)	0.273		
PDW (%)	1.238 (1.095-1.400)	0.001	1.245 (1.117, 1.386)	< 0.001
Platelet crit (%)	0.006 (0.000-0.881)	0.044		
Mean platelet volume (fl)	0.992 (0.934-1.053)	0.786		
FEV1/FVC % predicted	0.973 (0.935, 1.012)	0.177		
DLCO % predicted	0.999 (0.982, 1.016)	0.892		
mPAP (mmHg)	1.016 (0.986-1.047)	0.239		
PVR (wood units)	1.065 (0.994-1.141)	0.074		
CO (L/min)	0.803 (0.647-0.996)	0.046		
CI (L/min/m ²)	0.659 (0.454-0.958)	0.029	0.667 (0.455, 0.978)	0.038
RATD, cm	1.102 (0.837, 1.405)	0.491		

ENDSEI	2.332 (1.089, 4.992)	0.029
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HR: hazard ratios; CI: confidence intervals; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; CO: cardiac output; CI: cardiac index; CLD-PH: pulmonary hypertension due to chronic lung diseases; PDW: Platelet distribution width; PCT: platelet crit; MPV: mean platelet volume; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; DLCO: diffusion capacity for carbon monoxide of the lung; RATD: right atrial transverse dimension; ENDSEI: end-systolic stage eccentricity index.

Table 4 Multivariate adjusted hazard ratios for the association between PDW and all-cause death.

PDW category	Unadjusted				CI and EI adjusted		
	No. of events	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
PDW < 17 %	28/51	Ref.			Ref.		
PDW ≥ 17 %	16/16	5.896	2.889-12.031	< 0.001	5.067	2.420-10.609	< 0.001

PDW = Platelet distribution width; CI = confidence interval. * Hazard ratios in this table are adjusted for all the covariates in the study.

Figures

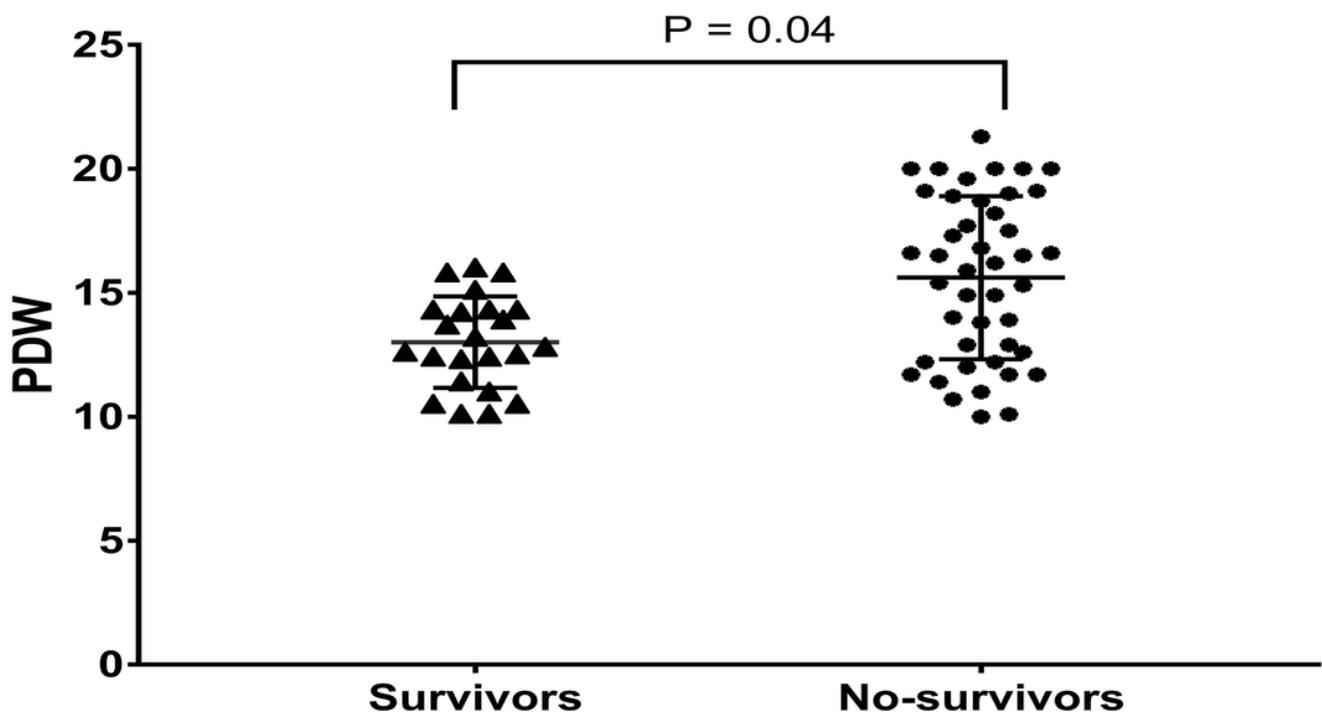


Figure 1

The box and whiskers of baseline PDW values between survivors and no-survivors. PDW: platelet distribution width.

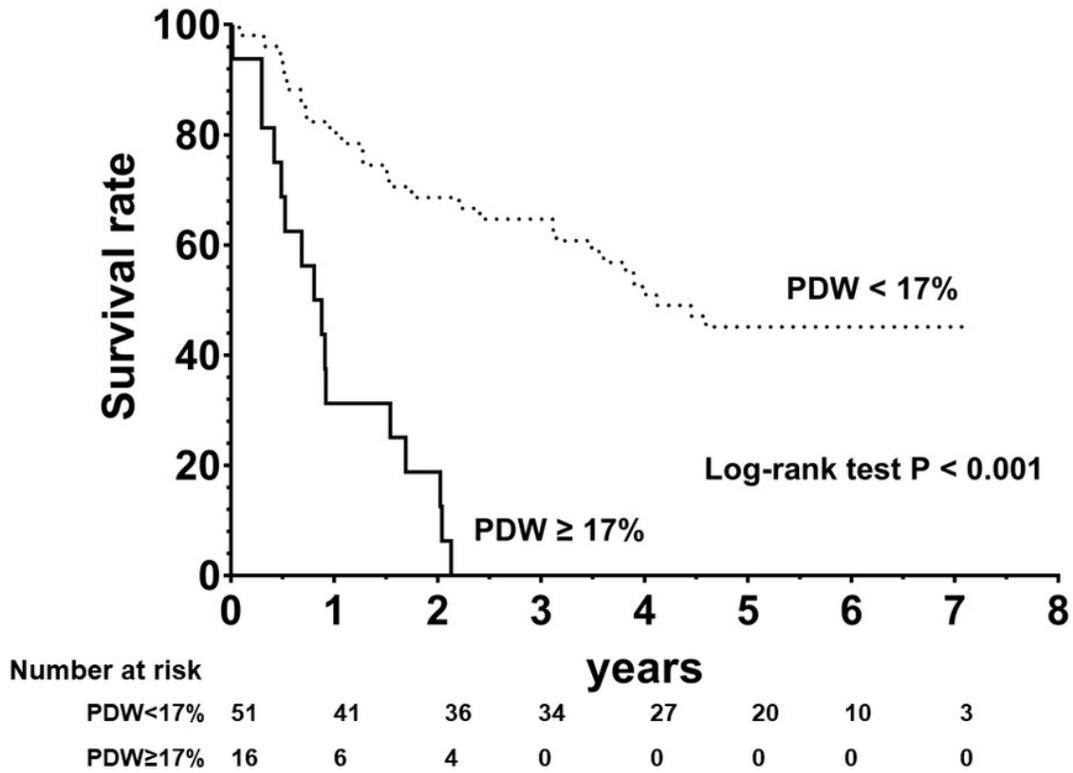


Figure 2

Kaplan-Meier all-cause mortality survival plots by the upper reference value of 17%.